PREFACE

In many ways 2021 has been a challenging year: the continued uncertainty surrounding the global pandemic, the burden on healthcare facilities, and the anxieties we all had to endure made adapting to a new way of life quite stressful. Yet ironically, despite the increases in physical distance, never in our lives did humanity come so closely together to face a common enemy. And little did we know that a global pandemic, challenging as it may be, would be a blessing in disguise for science... with the world's attention fixated on biology and public health, terms once considered esoteric jargon—R0, Ct value, mRNA, PCR, antigens, etc.—entered the common vernacular! ... and scientific inquiry captured the public's imagination.

Playing to our strength as a national academic medical center, the Sidra Research Branch made significant strides during the pandemic. On one end, our Core Genome Laboratory developed methods to detect viral infections that cleverly bypassed global shortages for testing reagents. On another, our scientists joined global consortia investigating penetrance and variability of COVID-19 in adults and children, leading to discoveries that impacted clinical care worldwide. As vaccines begin to roll out, our Deep Phenotyping Core developed an innovative serology assay, which detects antigens to a whole range of human Corona viruses. Even outside of COVID-19 projects, the Research Branch had a remarkably successful year. Reaching a milestone of 6,000 patients and family members enrolled in research studies. Sidra clinicians and scientists published nearly 300 papers, with almost 85% of Research Branch publications in the top 15% of international journals. Importantly, Sidra Medicine was awarded 12 national grants totaling QR 7.3M, demonstrating the growing recognition of the importance of academic medicine for translational discovery.

In terms of contribution to Qatar's knowledge economy, Sidra continued its mission to develop trainees in the fields of medicine and biomedical research. Almost 60% of Research Investigators have academic appointments at local and international institutions, and a total of 52 trainees and students were part of the Sidra Research family in 2021, including almost 20 MSc & PhD Students, supporting growth and development of the brightest talent to lead this growing field in the future. Finally, Sidra Research hosted its annual flagship 'Precision Medicine and Functional Genomics' symposium virtually this year, demonstrating our commitment to education and sustainability, and building a research enterprise in Qatar with strong links to the global scientific community.

In summary, 2021 ultimately became one of the most productive and innovative years at the Research Branch. We owe a most sincere gratitude to our hard-working research staff who braved the pandemic and worked around the clock to ensure that discovery and innovation remained strong, to our diverse clinical collaborators who were fundamental in devising studies and translating outcomes to patients, and, most importantly, to all the families and patients who entrust Sidra Medicine to deliver the highest-quality, research-driven care.

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المقـــدمـــة

لقد كانت سنة ٢٠٢١ مليئة بالتحديات على أصعدة متعددة: فلم يتعافَ العالم بعد من تبعات الوباء العالمي، وخيّم الشك على مستقبل الوباء، وما ترتب على ذلك من الأعباء الثقيلة الواقعة على مؤسسات الرعاية الصحية، بالإضافة إلى حالة القلق والحذر التي اكتنفت جميع أفراد المجتمع مما جعل التكيف مع أسلوب الحياة الجديد أمرًا مرهقًا للغاية. لكن من المفارقات التي شهدناها أنه وعلى الرغم من تباعد المسافات والآراء، فإن البشرية لم تتحد من قبل بهذا الشكل في مواجهة عدوٍ مشترك. ولم نكن نعلم أن محنة هذا الوباء العالمي، مهما وضعت من تحديات، ستكون منحة خفية لمجال العلوم الصحية والأبحاث الحيوية... ومع تركيز العالم على البيولوجيا وانصباب اهتمامه على الصحة العامة فقد أصبحت مصطلحات مثل عدد التكاثر الأساسي (0R)، وتفاعل البوليمريز المتسلسل اللحظي (RT-PCR)، وقيمة عتبة الدورة (Ct value)، والحمض النووي الريبي (RNA)، وغيرها، جزءا من الحوار العام بعد أن كانت من قبل مقتصرة على فئة محدودة من ذوي الاختصاص والعلوم! ... واستحوذ الفضول المعرفي والرغبة في التساؤل على انتباه الجمهور الذي أصبح على متابعة مستمرة لمجريات الدراسات العلمية ونتائجها.

وبصفتنا كمركز طبي أكاديمي وطني، حقق فرع سدرة للأبحاث إنجازات مهمة خلال فترة الوباء. فمن جهة، طور مختبر الجينوم الأساسي لدينا طرقًا مبتكرة لاستخلاص واكتشاف الحمض النووي الفيروسي، مكنتنا من تجاوز أزمة النقص العالمي في سلاسل التوريد لمواد الاختبار. ومن جهة أخرى، انضم علماؤنا إلى اتحادات عالمية وفرق بحثية مرموقة لدراسة انتشار وتنوع كوفيد- ١٩ لدى البالغين والأطفال، مما خلُص إلى اكتشافات تركت أثرًا على الرعاية السريرية في جميع أنحاء العالم. ومع بدء طرح اللقاحات، طورت وحدة التنميط الظاهري فحصًا مبتكرًا يكتشف مستضدات جميع أنواع فيروسات كورونا البشرية.

وبعيدًا عن مشروعات كوفيد- ١٩، حظي فرع الأبحاث بعام مليء بالنجاحات. فقد التحق أكثر من ٦٠٠٠ من المرضى وأسرهم بالدراسات البحثية. كما نشر أطباء سدرة وعلماؤها قرابة ٣٠٠ ورقة علمية؛ وكانت ٨٥٪ من هذه الابحاث منشورة في أفضل ١٥٪ من الدوريات العلمية العالمية. وعلى رأس هذه الانجازات، فإن سدرة للطب حصل على ١٢ منحة بحثية تقدر ب ٧.٣ ملايين ريال قطري، مما يُظهر أهمية الدور الرائد الذي تلعبه المراكز الطبية الأكاديمية في نمو البحث العلمي في دولة قطر.

وعلى صعيد المساهمة في الاقتصاد المعرفي، واصل سدرة للطب تنمية المتدربين في مجالات الطب والأبحاث الحيوية، حيث حظي ٦٠٪ تقريبًا من الباحثين على تعيين أكاديمي في مؤسسات محلية وعالمية، وأصبح ٥٢ فردًا من المتدربين والطلاب جزءًا من أسرة سدرة للبحوث في عام ٢٠٢١. واستضاف مركز الابحاث ما يقارب ٢٠ من طلاب الماجستير والدكتوراه في مختبراته لدعم نمو المواهب الصاعدة وتطويرها لقيادة هذا المجال في المستقبل. وأخيرًا، فقد استضاف سدرة للطب ندوته السنوية (الطب الدقيق وعلم الجينوم الوظيفي) في نسخته السابعة هذا العام بشكل افتراضي مُظهرين التزامنا بالتعليم والاستدامة وبناء مؤسسة بحثية في قطر تربطها روابط قوية مع المجتمع العلمي العالمي.

وفي الختام، فقد كان عام ٢٠٢١ أحد أكثر الأعوام إنتاجًا وابتكارًا بالنسبة لمركز الأبحاث في سدرة للطب. ونحن ندين بخالص الامتنان لفرق باحثينا الذين يعملون بجد ومثابرة، والذين تصدوا للوباء وعملوا بشكل دؤوب على مدار الساعة لضمان الحفاظ على جذوة الاكتشاف والابتكار، ولمختلف الزملاء السريريين الذين لعبوا دورًا أساسيًا في تطوير الدراسات وترجمة النتائج لمصلحة المرضى، ولجميع الأسر والمرضى الذين وضعوا ثقتهم في سدرة للطب لتقديم أجود رعاية قائمة على الطب الأكاديمي والأبحاث.
نتمنى أن تجدوا بين صفحات هذا التقرير قصصًا ملهمة واكتشافاتٍ رائدة ونقطة انطلاق الى مستقبل مشرق بإذن الله.

الدكتور خالد فخرو
رئيس قسم الأبحاث

نور فيصل
مدير التحرير

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Bhat *et al. Molecular Cancer* (2021) 20:2
https://doi.org/10.1186/s12943-020-01294-3

Molecular Cancer

REVIEW Open Access

Cytokine-chemokine network driven metastasis in esophageal cancer; promising avenue for targeted therapy

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Abstract

Esophageal cancer (EC) is a disease often marked by aggressive growth and poor prognosis. Lack of targeted therapies, resistance to chemoradiation therapy, and distant metastases among patients with advanced disease account for the high mortality rate. The tumor microenvironment (TME) contains several cell types, including fibroblasts, immune cells, adipocytes, stromal proteins, and growth factors, which play a significant role in supporting the growth and aggressive behavior of cancer cells. The complex and dynamic interactions of the secreted cytokines, chemokines, growth factors, and their receptors mediate chronic inflammation and immunosuppressive TME favoring tumor progression, metastasis, and decreased response to therapy. The molecular changes in the TME are used as biological markers for diagnosis, prognosis, and response to treatment in patients. This review highlighted the novel insights into the understanding and functional impact of deregulated cytokines and chemokines in imparting aggressive EC, stressing the nature and therapeutic consequences of the cytokine-chemokine network. We also discuss cytokine-chemokine oncogenic potential by contributing to the Epithelial-Mesenchymal Transition (EMT), angiogenesis, immunosuppression, metastatic niche, and therapeutic resistance development. In addition, it discusses the wide range of changes and intracellular signaling pathways that occur in the TME. Overall, this is a relatively unexplored field that could provide crucial insights into tumor immunology and encourage the effective application of modulatory cytokine-chemokine therapy to EC.

Keywords: Esophageal cancer, Cytokines, Chemokines, Inflammation, Tumor microenvironment, Epithelial-Mesenchymal transition, Drug targets, Immune evasion

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TLR3 controls constitutive IFN-β antiviral immunity in human fibroblasts and cortical neurons

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Human herpes simplex virus 1 (HSV-1) encephalitis can be caused by inborn errors of the TLR3 pathway, resulting in impairment of CNS cell-intrinsic antiviral immunity. Deficiencies of the TLR3 pathway impair cell-intrinsic immunity to vesicular stomatitis virus (VSV) and HSV-1 in fibroblasts, and to HSV-1 in cortical but not trigeminal neurons. The underlying molecular mechanism is thought to involve impaired IFN-α/β induction by the TLR3 recognition of dsRNA viral intermediates or by-products. However, we show here that human TLR3 controls constitutive levels of *IFNB* mRNA and secreted bioactive IFN-β protein, and thereby also controls constitutive mRNA levels for IFN-stimulated genes (ISGs) in fibroblasts. Tlr3$^{-/-}$ mouse embryonic fibroblasts also have lower basal ISG levels. Moreover, human TLR3 controls basal levels of IFN-β secretion and ISG mRNA in induced pluripotent stem cell–derived cortical neurons. Consistently, TLR3-deficient human fibroblasts and cortical neurons are vulnerable not only to both VSV and HSV-1, but also to several other families of viruses. The mechanism by which TLR3 restricts viral growth in human fibroblasts and cortical neurons in vitro and, by inference, by which the human CNS prevents infection by HSV-1 in vivo, is therefore based on the control of early viral infection by basal IFN-β immunity.

Introduction

TLR3 on endosomes recognizes double-stranded RNA (dsRNA) intermediates or by-products generated during viral infection. TLR3 signaling leads to the activation of IFN regulatory factor 3 (IRF3), NF-κB, and ATF/c-jun, promoting the induction of antiviral IFNs and downstream IFN-stimulated genes (ISGs) (1–4). The discovery of inborn errors of human TLR3 and its pathway in children with herpes simplex virus 1 (HSV-1) encephalitis (HSE) led to the suggestion that TLR3 serves as a key sensor for HSV-1 replication in the CNS (5–7). Childhood HSE is a rare, sporadic, and life-threatening complication of primary infection with HSV-1 in which the virus replicates in the CNS. HSV-1 infection is ubiquitous in the general population. The virus resides in the trigeminal (TG) ganglion, where it remains latent, but can later reactivate to cause benign herpes labialis or other rare complications, including HSE (8). The pathogenesis of HSE remained unexplained until our description of the first genetic etiologies for this disease (9, 10). Germline HSE-causing mutations have since been reported in 7 genes of the TLR3 pathway (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, *TBK1*, *IRF3*, *NEMO*) and 2 genes of the IFN-α/β receptor pathway (*IFNAR1*, *STAT1*) (9–17). UNC-93B is a membrane-bound molecule that regulates the signaling of endosomal TLR3, TLR7, TLR8, and TLR9 by binding to their transmembrane domains and

Authorship note: MJC, PZ, and OH contributed equally to this work. VB, MH, and JC contributed equally to this work. JLC and SYZ contributed equally to this work.
Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: October 24, 2019; **Accepted:** November 5, 2020;
Published: January 4, 2021.
Reference information: *J Clin Invest*. 2021;131(1):e134529.
https://doi.org/10.1172/JCI134529.

BMJ Open

Prospective validation study of prognostic biomarkers to predict adverse outcomes in patients with COVID-19: a study protocol

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To cite: Tang B, Shojaei M, Wang Y, *et al*. Prospective validation study of prognostic biomarkers to predict adverse outcomes in patients with COVID-19: a study protocol. *BMJ Open* 2021;**11**:e044497. doi:10.1136/bmjopen-2020-044497

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-044497).

Received 04 September 2020
Revised 17 November 2020
Accepted 15 December 2020

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ABSTRACT

Introduction Accurate triage is an important first step to effectively manage the clinical treatment of severe cases in a pandemic outbreak. In the current COVID-19 global pandemic, there is a lack of reliable clinical tools to assist clinicians to perform accurate triage. Host response biomarkers have recently shown promise in risk stratification of disease progression; however, the role of these biomarkers in predicting disease progression in patients with COVID-19 is unknown. Here, we present a protocol outlining a prospective validation study to evaluate the biomarkers' performance in predicting clinical outcomes of patients with COVID-19.

Methods and analysis This prospective validation study assesses patients infected with COVID-19, in whom blood samples are prospectively collected. Recruited patients include a range of infection severity from asymptomatic to critically ill patients, recruited from the community, outpatient clinics, emergency departments and hospitals. Study samples consist of peripheral blood samples collected into RNA-preserving (PAXgene/Tempus) tubes on patient presentation or immediately on study enrolment. Real-time PCR (RT-PCR) will be performed on total RNA extracted from collected blood samples using primers specific to host response gene expression biomarkers that have been previously identified in studies of respiratory viral infections. The RT-PCR data will be analysed to assess the diagnostic performance of individual biomarkers in predicting COVID-19-related outcomes, such as viral pneumonia, acute respiratory distress syndrome or bacterial pneumonia. Biomarker performance will be evaluated using sensitivity, specificity, positive and negative predictive values, likelihood ratios and area under the receiver operating characteristic curve.

Ethics and dissemination This research protocol aims to study the host response gene expression biomarkers in severe respiratory viral infections with a pandemic potential (COVID-19). It has been approved by the local ethics committee with approval number 2020/ETH00886. The results of this project will be disseminated in international peer-reviewed scientific journals.

Strengths and limitations of this study

- ► The study has a prospective study design, optimised to evaluate the performance of predictive biomarkers.
- ► Data generated from this study will enhance triage across a diverse range of clinical settings during COVID-19 pandemic.
- ► All outcomes are prespecified and have high clinical relevance to the management of patients with COVID-19.
- ► Study limitations include potential heterogeneity in management protocols of patients with COVID-19 across different countries (eg, medications administered to patients will vary depending on clinician preference or local institutional protocol).

INTRODUCTION

An enhanced ability to predict disease progression is central to the management of the current COVID-19 crisis. As the COVID-19 crisis escalates, health services can be overwhelmed by the rapid rise in infected cases. In some locations, such as northern Italy, Mexico, Brazil and some US states, hospital beds and ventilator requirements exceeded the maximum capacity at the peak of the outbreak. In these circumstances, clinicians are often confronted with difficult triage questions: (1) Which patients should be hospitalised? (2) Which patients will need

Cell and Tissue Research (2021) 383:445–456
https://doi.org/10.1007/s00441-020-03327-1

REVIEW

Odor coding in the mammalian olfactory epithelium

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Received: 14 September 2020 / Accepted: 27 October 2020 / Published online: 6 January 2021

Abstract
Noses are extremely sophisticated chemical detectors allowing animals to use scents to interpret and navigate their environments. Odor detection starts with the activation of odorant receptors (ORs), expressed in mature olfactory sensory neurons (OSNs) populating the olfactory mucosa. Different odorants, or different concentrations of the same odorant, activate unique ensembles of ORs. This mechanism of combinatorial receptor coding provided a possible explanation as to why different odorants are perceived as having distinct odors. Aided by new technologies, several recent studies have found that antagonist interactions also play an important role in the formation of the combinatorial receptor code. These findings mark the start of a new era in the study of odorant-receptor interactions and add a new level of complexity to odor coding in mammals.

Keywords Olfaction · Odor coding · Combinatorial code · Odorant · Receptor · Antagonist · Smell

Introduction

"I should think we might fairly gauge the future of biological science, centuries ahead, by estimating the time it will take to reach a complete, comprehensive understanding of odor. It may not seem a profound enough problem to dominate all the life sciences, but it contains, piece by piece, all the mysteries." — Lewis Thomas.

Smelling starts with a sniff. The process of breathing in air into the nose floods the nasal cavity with myriad odorous molecules, or simply put, odorants. These molecules may smell pleasant, repulsive, or act as carriers of critical biological or ecological messages.

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Odorants communicating vital biological information typically elicit behavioral and physiological changes in animals, thus playing a pivotal role in the survival and the propagation of the species (Li and Liberles, 2015). In some cases, the same odorant delivers different biological messages to animals of different species. In others, the identity of these ecologically-relevant odorants may vary greatly among different species, ultimately driving evolutionary adaptations to distinct ecological niches (Bear, et al., 2016; Li, et al., 2013; Manoel, et al., 2019).

A major challenge in studying smell and odor-guided behaviors has been the understanding of the biological mechanisms that enable the discrimination of a large number of odor cues, which are typically presented to the animal's nose in virtually infinite combinations of mixtures and concentrations.

This review presents a brief historical description of the key findings and early challenges surrounding odor coding in the mammalian nose. It discusses how recent advances in olfactory neurobiology fundamentally inform our understanding of the interactions between odorants and their receptors in the nose, and how this knowledge impacts theories of odor perception.

Organization of the mammalian olfactory system

The peripheral olfactory system of most mammalian species involves two major olfactory organs: the olfactory mucosa (OM) located at the top of the nasal cavity and the

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ARTICLE OPEN

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A map of copy number variations in the Tunisian population: a valuable tool for medical genomics in North Africa

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Copy number variation (CNV) is considered as the most frequent type of structural variation in the human genome. Some CNVs can act on human phenotype diversity, encompassing rare Mendelian diseases and genomic disorders. The North African populations remain underrepresented in public genetic databases in terms of single-nucleotide variants as well as for larger genomic mutations. In this study, we present the first CNV map for a North African population using the Affymetrix Genome-Wide SNP (single-nucleotide polymorphism) array 6.0 array genotyping intensity data to call CNVs in 102 Tunisian healthy individuals. Two softwares, PennCNV and Birdsuite, were used to call CNVs in order to provide reliable data. Subsequent bioinformatic analyses were performed to explore their features and patterns. The CNV map of the Tunisian population includes 1083 CNVs spanning 61.443 Mb of the genome. The CNV length ranged from 1.017 kb to 2.074 Mb with an average of 56.734 kb. Deletions represent 57.43% of the identified CNVs, while duplications and the mixed loci are less represented. One hundred and three genes disrupted by CNVs are reported to cause 155 Mendelian diseases/phenotypes. Drug response genes were also reported to be affected by CNVs. Data on genes overlapped by deletions and duplications segments and the sequence properties in and around them also provided insights into the functional and health impacts of CNVs. These findings represent valuable clues to genetic diversity and personalized medicine in the Tunisian population as well as in the ethnically similar populations from North Africa.

npj Genomic Medicine (2021)6:3 ; https://doi.org/10.1038/s41525-020-00166-5

INTRODUCTION

Copy number variations (CNVs) are considered as genomic structural variations ranging from 1 kb to multiple megabase pairs in length[1–3]. CNVs are likely caused by one single or a combination of multiple genomic rearrangements, such as unbalanced translocation, deletions, insertions, and duplications. Therefore, CNVs are generally observed as a gain or a loss of DNA segment copies that deviate from the normal diploid state. CNVs may influence phenotypes by changing gene dosage, interrupting coding sequences, creating novel fusion genes, or by altering the distance of a gene from its regulatory elements[4–6]. It has been assessed that up to 60% of the human genome encloses CNVs, which generally range in size from 100 to 500 kb[7]. These CNVs are major contributors to human genetic diversity.

Two models of CNV–phenotype associations have been suggested[8]. The first model encompasses common copy number polymorphisms (CNPs) with a frequency exceeding 1% in the general population. Genes spanned by CNPs are mainly enriched for biological functions and pathways related to drug response, immunity, and sensory perception[9,10]. They alter phenotypes by changing the dosage of genes or other functional elements, thus influencing complex traits such as HIV-1/AIDS susceptibility (MIM 609423), Crohn's disease (MIM 266600,) and glomerulonephritis in systemic lupus erythematosus (MIM 152700). CNVs also occur in genes encoding drug-metabolizing enzymes, including the cytochrome P450s (*CYP2B6* and *CYP2D6*), which are susceptible to structural variations due to highly homologous pseudogenes. CNV distribution influences drug metabolism and are important in pharmacogenomics screening[11]. The second model involves rare and highly penetrant CNVs. These CNVs are responsible for the deletion or the duplication of large genomic segments resulting in genomic disorders such as Prader–Willi syndrome/Angelman syndrome (MIM 176270/105830, 15q11-q13 deletion), Williams–Beuren syndrome (MIM: 194050, 7q11.23 deletion), Potocki–Lupski syndrome (MIM:610883, 17p11.2 duplication), and Charcot–Marie–Tooth disease, type 1A (MIM:610098, 17p12 duplication)[12].

In order to understand the extent to which CNVs influence phenotypes, deep analyses in both patient and healthy individuals are required. Different approaches, including quantification of hybridization to specific oligonucleotides[13], clone arrays[14], direct genome sequencing[15,16], and single-nucleotide polymorphism (SNP) array[17–19], allowed to explore CNVs, thus providing their global estimates of frequencies, distribution, and functional features in large population cohorts and HapMap samples[1,2,4,16,19–29]. Although medical and clinical genetic studies have been widely performed in the Arab World known to display high rates of consanguinity and endogamy, little attention has been paid to potential variations linked to health in the region[30,31]. Therefore, information related to molecular pathogenesis and knowledge of gene variants segregating in the Arab genome is lacking as well as genotype–phenotype correlation of genetic conditions for both monogenic and multifactorial diseases.

Studies focusing on the characterization of CNVs in the Arab World are not available, except one on the Qatari population[16]. In this study, we applied Affymetrix Genome-Wide Human SNP Array 6.0, which was designed for both SNP and CNV detection, to

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Published in partnership with CEGMR, King Abdulaziz University

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Journal of *Personalized Medicine*

MDPI

Article

A Whole-Genome Sequencing Association Study of Low Bone Mineral Density Identifies New Susceptibility Loci in the Phase I Qatar Biobank Cohort

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Abstract: Bone density disorders are characterized by a reduction in bone mass density and strength, which lead to an increase in the susceptibility to sudden and unexpected fractures. Despite the serious consequences of low bone mineral density (BMD) and its significant impact on human health, most affected individuals may not know that they have the disease because it is asymptomatic. Therefore, understanding the genetic basis of low BMD and osteoporosis is essential to fully elucidate its pathobiology and devise preventative or therapeutic approaches. Here we sequenced the whole genomes of 3000 individuals from the Qatar Biobank and conducted genome-wide association analyses to identify genetic risk factors associated with low BMD in the Qatari population. Fifteen variants were significantly associated with total body BMD ($p < 5 \times 10^{-8}$). Of these, five variants had previously been reported by and were directionally consistent with previous genome-wide association study data. Ten variants were new: six intronic variants located at six gene loci (MALAT1/TALAM1, FASLG, LSAMP, SAG, FAM189A2, and LOC101928063) and four intergenic variants. This first such study in Qatar provides a new insight into the genetic architecture of low BMD in the Qatari population. Nevertheless, more studies are needed to validate these findings and to elucidate the functional effects of these variants on low BMD and bone fracture susceptibility.

Keywords: bone mineral density; osteoporosis; whole-genome sequencing; genome-wide association; Qatar Biobank; Qatar

Citation: Younes, N.; Syed, N.; Yadav, S.K.; Haris, M.; Abdallah, A.M.; Abu-Madi, M. A Whole-Genome Sequencing Association Study of Low Bone Mineral Density Identifies New Susceptibility Loci in the Phase I Qatar Biobank Cohort. *J. Pers. Med.* **2021**, *11*, 34. https://doi.org/10.3390/jpm11010034

Received: 16 November 2020
Accepted: 15 December 2020
Published: 7 January 2021

1. Introduction

Bone density disorders are common systemic skeletal conditions characterized by a reduction in bone mass and density that increase the risk of bone fractures [1]. Loss of bone mass can be mild (osteopenia) or severe (osteoporosis). An estimated 200 million people suffer from osteoporosis worldwide, giving rise to ~9 million fractures each year [2]. Loss of bone mass is regarded as a clinically silent condition due to its gradual and asymptomatic nature, making its early diagnosis difficult and often only recognized after the occurrence of the first fracture [3]. The high prevalence of osteopenia and osteoporosis has a significant emotional and financial burden on patients and their families as well as the healthcare systems. Therefore, earlier identification and management of individuals suffering from low bone mineral density (BMD) and osteoporosis may help to curb the impeding societal burden of the disease. BMD serves as a predictor of osteoporotic fractures and is the primary measurement to assess bone health and the gold standard method for this measurement is dual-energy x-ray absorptiometry (iDXA).

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LETTER TO THE EDITOR

A Novel Point Mutation in the N Gene of SARS-CoV-2 May Affect the Detection of the Virus by Reverse Transcription-Quantitative PCR

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KEYWORDS COVID-19, SARS-CoV-2, RT-qPCR, N gene, point mutation

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, laboratory testing to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse transcription-quantitative PCR (RT-qPCR) has played a central role in mitigating the spread of the virus (1). Soon after the viral genome sequences were available, several RT-qPCR assays were developed and made available by the World Health Organization (WHO) for public use (https://www.who.int/docs/default-source/coronaviruse/whoinhouseassays.pdf). The primer and probe sequences for these assays were chosen from multiple target genes within the viral genome, such as the E gene, RdRp gene, ORF1ab, and N gene. Many commercial and laboratory-developed assays were developed for SARS-CoV-2 detection based on these primer and probe sequences. The large-scale sustained person-to-person transmission of SARS-CoV-2 has led to many mutational events, some of which may affect the sensitivity and specificity of available PCR assays (2). Recently, mutations in the E gene (C26340T) and N gene (C29200T) affecting the detection of target genes by two commercial assays were reported for 8 and 1 patients, respectively. Interestingly, both mutations are of the C→T type, a common single nucleotide polymorphism (SNP) that may be associated with strong host cell mRNA editing mechanisms known as apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminase (3, 4). Another study found a G→U substitution in position 29140 that affected the sensitivity of detection of N gene-based assays (5). Here, we report a novel N gene mutation (C29200A) seen in 3 patients which affected the detection of the SARS-CoV-2 N gene by a commercial assay.

Cepheid Xpert Xpress SARS-CoV-2 (Xpert) is an FDA-approved assay for COVID-19 under emergency use authorization (EUA). The Xpert assay is based on a multiplex PCR that includes both E gene and N gene targets for SARS-CoV-2 detection. The assay was implemented in our laboratory at Sidra Medicine, a pediatric referral center in Qatar, in June 2020. Since then, a total of 8,800 samples have been tested by Xpert, of which 365 (4.1%) were positive. Occasionally, discrepant results were seen (~2.5% of all positive results) for E gene and N gene targets, which were reported as "presumptive positive" by the Cepheid GeneXpert system. In the majority of these cases, RT-qPCR cycle threshold (C_T) values were >38 (Table 1). However, at the end of October 2020, a mutation in the SARS-CoV-2 N gene was suspected when Xpert failed to amplify the N gene target in a specimen, despite giving a strong positive result (C_T =19.8) for the E gene. Subsequently, 3 more samples showed similar results in the next 2 months (Table 1). All of these samples were confirmed to be positive by a second test method (QIAstat-Dx respiratory SARS-CoV-2 panel; Qiagen). The study involves the secondary

Citation Hasan MR, Sundararaju S, Manickam C, Mirza F, Al-Hail H, Lorenz S, Tang P. 2021. A novel point mutation in the N gene of SARS-CoV-2 may affect the detection of the virus by reverse transcription-quantitative PCR. J Clin Microbiol 59:e03278-20. https://doi.org/10.1128/JCM.03278-20.

Editor Alexander J. McAdam, Boston Children's Hospital

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Accepted manuscript posted online 20 January 2021

Published 19 March 2021

Clinical Imaging 74 (2021) 123–130

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Cardiothoracic Imaging

Utility of visual coronary artery calcification on non-cardiac gated thoracic CT in predicting clinical severity and outcome in COVID-19☆

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ARTICLE INFO

Keywords:
COVID-19
Coronary artery calcification
Clinical severity
CT chest severity score

ABSTRACT

Background: Assessment of visual-coronary artery calcification on non-cardiac gated CT in COVID-19 patients could provide an objective approach to rapidly identify and triage clinically severe patients for early hospital admission to avert worse prognosis.
Purpose: To ascertain the role of semi-quantitative scoring in visual-coronary artery calcification score (V-CACS) for predicting the clinical severity and outcome in patients with COVID-19.
Materials and methods: With institutional review board approval this study included 67 COVID-19 confirmed patients who underwent non-cardiac gated CT chest in an inpatient setting. Two blinded radiologist (Radiologist-1 &2) assessed the V-CACS, CT Chest severity score (CT-SS). The clinical data including the requirement for oxygen support, assisted ventilation, ICU admission and outcome was assessed, and patients were clinically subdivided depending on clinical severity. Logistic regression analyses were performed to identify independent predictors. ROC curves analysis is performed for the assessment of performance and Pearson correlation were performed to looks for the associations.
Results: V-CACS cut off value of 3 (82.67% sensitivity and 54.55% specificity; AUC 0.75) and CT-SS with a cut off value of 21.5 (95.7% sensitivity and 63.6% specificity; AUC 0.87) are independent predictors for clinical severity and also the need for ICU admission or assisted ventilation. The pooling of both CT-SS and V-CACS (82.67% sensitivity and 86.4% specificity; AUC 0.92) are more reliable in terms of predicting the primary outcome of COVID-19 patients. On regression analysis, V-CACS and CT-SS are individual independent predictors of clinical severity in COVID-19 (Odds ratio, 1.72; 95% CI, 0.99–2.98; $p = 0.05$ and Odds ratio, 1.22; 95% CI, 1.08–1.39; $p = 0.001$ respectively). The area under the curve (AUC) for pooled V-CACS and CT-SS was 0.96 (95% CI 0.84–0.98) which correctly predicted 82.1% cases.
Conclusion: Logistic regression model using pooled Visual-Coronary artery calcification score and CT Chest severity score in non-cardiac gated CT can predict clinical severity and outcome in patients with COVID-19.

1. Introduction

Corona Virus disease (COVID-19) is a viral infectious disease caused by a novel strain of the corona virus primarily causing pulmonary syndrome.[1] Its origin was reported in a cluster of patients in Wuhan city of Hubei Province, China. Due to a higher viral reproduction number and infectious nature of the disease, the virus transmitted rapidly out of China with WHO subsequently declaring this as a global pandemic. Despite quarantine rules and travel restrictions it has been difficult to contain the spread of COVID-19. Rapid testing and early identification are essential to diagnose and mitigate the spread of the disease.

The understanding of COVID-19 pathophysiology in relation to

Abbreviations: V-CACS, Visual Coronary artery calcification Score; CT-SS, CT Chest Severity Score; COVID-19, Corona Virus disease-2019; RT-PCR, Reverse Transcriptase Polymerase chain reaction.; ECMO, Extracorporeal membrane oxygenation.

☆ The authors have no disclosure or acknowledgements to be made.

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https://doi.org/10.1016/j.clinimag.2021.01.015
Received 3 November 2020; Received in revised form 28 December 2020; Accepted 15 January 2021
Available online 18 January 2021

JCI insight

RESEARCH ARTICLE

Distinct antibody repertoires against endemic human coronaviruses in children and adults

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Four endemic human coronaviruses (HCoVs) are commonly associated with acute respiratory infection in humans. B cell responses to these "common cold" viruses remain incompletely understood. Here we report a comprehensive analysis of CoV-specific antibody repertoires in 231 children and 1168 adults using phage immunoprecipitation sequencing. Seroprevalence of antibodies against endemic HCoVs ranged between approximately 4% and 27% depending on the species and cohort. We identified at least 136 novel linear B cell epitopes. Antibody repertoires against endemic HCoVs were qualitatively different between children and adults in that anti-HCoV IgG specificities more frequently found among children targeted functionally important and structurally conserved regions of the spike, nucleocapsid, and matrix proteins. Moreover, antibody specificities targeting the highly conserved fusion peptide region and S2′ cleavage site of the spike protein were broadly cross-reactive with peptides of epidemic human and nonhuman coronaviruses. In contrast, an acidic tandem repeat in the N-terminal region of the Nsp3 subdomain of the HCoV-HKU1 polyprotein was the predominant target of antibody responses in adult donors. Our findings shed light on the dominant species-specific and pan-CoV target sites of human antibody responses to coronavirus infection, thereby providing important insights for the development of prophylactic or therapeutic monoclonal antibodies and vaccine design.

Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: September 21, 2020
Accepted: January 13, 2021
Published: January 26, 2021

Reference information: *JCI Insight*. 2021;6(4):e144499. https://doi.org/10.1172/jci.insight.144499.

Introduction

Four endemic human-tropic coronaviruses (HCoVs) are commonly associated with respiratory illness in humans, namely HCoV-229E, -NL63, -OC43, and -HKU1 (1–4). Clinical outcomes of acute infection with these HCoVs range from mild upper respiratory tract infections in most patients, to viral bronchiolitis and pneumonia more rarely in patients, the latter requiring hospitalization (5). The ratio of more severe versus mild outcomes of acute infection with endemic HCoVs is largely comparable to that of other "common cold" viruses, such as human respiratory syncytial virus (HRSV), human rhinoviruses (HRVs), human adenoviruses, and human parainfluenza viruses, albeit with differences in seasonality and prevalence of the viruses depending on the species (5–7). In

doi:10.1093/brain/awaa420 BRAIN 2021: 144; 584–600 | 584

BRAIN
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An ancestral 10-bp repeat expansion in *VWA1* causes recessive hereditary motor neuropathy

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[‡]Appendix 1.

See Arribat (doi.10.1093/brain/awaa464) for a scientific commentary on this article.

The extracellular matrix comprises a network of macromolecules such as collagens, proteoglycans and glycoproteins. *VWA1* (von Willebrand factor A domain containing 1) encodes a component of the extracellular matrix that interacts with perlecan/collagen VI, appears to be involved in stabilizing extracellular matrix structures, and demonstrates high expression levels in tibial nerve. *Vwa1*-deficient mice manifest with abnormal peripheral nerve structure/function; however, *VWA1* variants have not previously been associated with human disease. By interrogating the genome sequences of 74 180 individuals from the 100K Genomes Project in combination with international gene-matching efforts and targeted sequencing, we identified 17 individuals from 15 families with an autosomal-recessive, non-length dependent, hereditary motor neuropathy and rare biallelic variants in *VWA1*. A single disease-associated allele p.(G25Rfs*74), a 10-bp repeat expansion, was observed in 14/15 families and was homozygous in 10/15. Given an allele frequency in European populations approaching 1/1000, the seven unrelated homozygote individuals ascertained from the 100K Genomes Project represents a substantial enrichment above expected. Haplotype analysis identified a shared 220 kb region suggesting that this founder mutation arose >7000 years ago. A wide age-range of patients (6–83 years) helped delineate the clinical phenotype over time. The commonest disease presentation in the cohort was an early-onset (mean 2.0 ± 1.4 years) non-length-dependent axonal hereditary motor neuropathy, confirmed on electrophysiology, which will have to be differentiated from other predominantly or pure motor neuropathies and neuronopathies. Because of slow disease progression, ambulation was largely preserved. Neurophysiology, muscle histopathology, and muscle MRI findings typically revealed clear neurogenic changes with single isolated cases displaying additional myopathic process. We speculate that a few findings of myopathic changes might be secondary to chronic denervation rather

Received June 18, 2020. Revised September 16, 2020. Accepted October 15, 2020. Advance access publication January 18, 2021

frontiers in Immunology

REVIEW
published: 14 January 2021
doi: 10.3389/fimmu.2020.589381

Proceedings From the First International Workshop at Sidra Medicine: "Engineered Immune Cells in Cancer Immunotherapy (EICCI): From Discovery to Off-the-Shelf Development", 15th–16th February 2019, Doha, Qatar

Bella Guerrouahen[1†], Muhammad Elnaggar[1†], Anjud Al-Mohannadi[1†], Dhanya Kizhakayil[1], Chiara Bonini[2], Reuben Benjamin[3], Renier Brentjens[4], Christian J. Buchholz[5], Giulia Casorati[6], Soldano Ferrone[7], Frederick L. Locke[8], Francisco Martin[9], Axel Schambach[10,11], Cameron Turtle[12], Paul Veys[13], Hans J. van der Vliet[14,15], Cristina Maccalli[1] and The EICCI Faculty Group*

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Edited by:
Yoshihiko Hirohashi,
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Reviewed by:
Bipulendu Jena,
Independent Researcher, San Diego, United States
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Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: 30 July 2020
Accepted: 30 November 2020
Published: 14 January 2021

Citation:
Guerrouahen B, Elnaggar M, Al-Mohannadi A, Kizhakayil D, Bonini C, Benjamin R, Brentjens R, Buchholz CJ, Casorati G, Ferrone S, Locke FL, Martin F, Schambach A, Turtle C, Veys P, van der Vliet HJ, Maccalli C and The EICCI Faculty Group (2021) Proceedings From the First International Workshop at Sidra Medicine: "Engineered Immune Cells in Cancer Immunotherapy (EICCI): From Discovery to Off-the-Shelf Development", 15th–16th February 2019, Doha, Qatar. Front. Immunol. 11:589381. doi: 10.3389/fimmu.2020.589381

The progress in the isolation and characterization of tumor antigen (TA)-specific T lymphocytes and in the genetic modification of immune cells allowed the clinical development of adoptive cell therapy (ACT). Several clinical studies highlighted the striking clinical activity of T cells engineered to express either Chimeric Antigen (CAR) or T Cell (TCR) Receptors to target molecularly defined antigens expressed on tumor cells. The breakthrough of immunotherapy is represented by the approval of CAR-T cells specific for advanced or refractory $CD19^+$ B cell malignancies by both the Food and Drug Administration (FDA) and the European Medicinal Agency (EMA). Moreover, advances in the manufacturing and gene editing of engineered immune cells contributed to the selection of drug products with desired phenotype, refined specificity and decreased toxicity. An important step toward the optimization of CAR-T cell therapy is the development of "off-the shelf" T cell products that allow to reduce the complexity and

the costs of the manufacturing and to render these drugs available for a broad number of cancer patients. The Engineered Immune Cells in Cancer Immunotherapy (EICCI) workshop hosted in Doha, Qatar, renowned experts, from both academia and industry, to present and discuss the progress on both pre-clinical and clinical development of genetically modified immune cells, including advances in the "off-the-shelf" manufacturing. These experts have addressed also organizational needs and hurdles for the clinical grade production and application of these biological drugs.

Keywords: cancer, immunotherapy, CAR-T cells, TCR engineered lymphocytes, CAR-NK cells, monoclonal antibody, clinical trial, off-the-shelf development

INTRODUCTION

Cancer immunotherapy is aimed at a driving patient's immune system to attack tumor cells. The great advances achieved in this field during the last two decades, lead to the emerging role of immunotherapy as the "fifth pillar" of cancer treatment, together with surgery, chemotherapy, radiotherapy and targeted therapy (1).

Adoptive cell therapy (ACT) with tumor antigen (TA)-specific T lymphocytes has been clinically developed at an unparalleled pace (2–4). In particular, the approach of the genetic engineering of T or NK cells to target and destroy cancer cells, revealed as powerful and, in some cases, unprecedented in term of clinical success for the treatment of patients with aggressive malignancies, refractory to other therapeutic interventions (5–7).

T cells engineered with chimeric antigen receptors (CARs), that combine the antigen binding region of antibodies and T cell signaling domains responsible for activation (8), represented the breakthrough of cell-based immunotherapy (1, 2, 3). Different CARs have been engineered to target a variety of antigens expressed by either hematologic or solid tumors, that are listed by Sadelain and colleagues (9). The initial clinical application of CAR-T cells was quite disappointing in terms of patients' responses, due to the inefficient expansion and persistence of CAR-T cells *in vivo* (10–12). Additional modifications of the structure of CARs, by including co-stimulatory domains allowed the achievement of clinical benefit through the treatment of patients with B cell malignancies overexpressing CD19 (13–18). Strikingly response rates in the range of 57%–82%, with complete response rate of 52-60%, were detected upon the infusion of CD19-CAR-T cells in patients with B cell malignancies refractory to prior treatments (7, 8, 9). These results led to the accelerated approval by both FDA and EMA of two drug products: 1. tisagenlecleucel/Kymriah for the treatment of children and young adult with acute lymphoblastic leukemia (ALL) (13, 14, 19–21), and for the treatment of adults with relapsed/refractory Diffuse Large B cell lymphoma (DLBCL) (22).

Axicabtagene Ciloleucel/Yescarta for the Treatment of Adult Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL), including **Table 1** (14, 16, 18).

More recently, a third product, brexucabtagene autolucel (Tecartus) has been approved for the treatment of relapsed or refractory mantle cell lymphoma. This approval was granted based on the results of the ZUMA-2 (NCT02601313) clinical trial, showing 87% of ORR, with a complete remission (CR) rate of 62% (23).

CAR-T cells represent promising therapeutic options also for solid tumors, although they are still under clinical development and do not yet have proven their clinical efficacy (**Table 1**) (24). The principal limitations for their clinical activity are: i. paucity of tumor specific antigens and ii. the low efficiency of T cells in penetrating the tumor microenvironment and homing to the tumor site, and iii. their limited functional activity within the tumor (24).

In addition, efforts are ongoing at different leading groups to develop allogeneic CAR-T cell therapies, in order to simplify the manufacturing process, to reduce the costs and rendering these drugs available to larger cohorts of patients (**Table 1**).

Abbreviations: AAV, Adeno-Associated Virus; ACT, Adoptive Cell Therapy; ADCC, Antibody-Dependent Cell-Mediated Cytotoxicity; BMT, Bone Marrow Transplant; CAR, Chimeric Antigen Receptor; CCR7, C-C Chemokine Receptor Type 7; CD1 a, b, c, d, family of glycoproteins expressed on the surface of various human antigen-presenting cells and related to HLA class I molecules; CD19, IgSF surface glycoprotein of 95 kDa expressed on B cells; CD20, B-lymphocyte antigen CD20; CD22, B-lymphocyte cell adhesion molecule; Sialic acid-binding Ig-like lectin 2 (SIGLEC-2); CD28, Cluster of Differentiation 28, T-cell-specific surface glycoprotein; CD40/CD40L, Cluster of differentiation 40/Ligand of CD40; CD52, Campath-1 antigen; CD54, Cluster of Differentiation 54 or Intercellular Adhesion Molecule 1 (ICAM-1); CD58, Lymphocyte function-associated antigen 3 (LFA-3) CD70, Cluster of Differentiation 70; CXCR4, C-X-C Chemokine Receptor Type 4; CD80, Cluster of differentiation 80 (also B7-1); CD86, Cluster of differentiation 86 (also B7-2); Cy, Cyclophosphamide; COSMID, Database of Genomic Structural Variation; CRC, Colorectal Cancer; CRISPR/Cas9, (Clustered Regularly Interspaced Short Palindromic Repeats) and CRISPR-associated (Cas9); CTLA-4, Cytotoxic T lymphocyte Antigen 4; EGFR, Epidermal Growth Factor, Fas, Death Receptor that regulate apoptosis; FcγR, Fc Gamma Receptor; Flu, Fludarabine; GMP, Good Manufacturing Practice; GvHD, Graft versus Host Disease; HLA, Human Leukocyte Antigen; HSCT, Allogenic Hematopoietic Stem Cell Transplant; IL-6, Interleukin 6; IL-7, Interleukin 7; IL-18, Interleukin 18; KO, Knock out; LAG-3, Lymphocyte Activation Gene-3; LDH, Lactate Dehydrogenase; LV, Lentiviral vector; MCP-1, Monocyte Chemoattractant Protein-1; MEGATAL, Meganucleases that have been fused with a Transcription Activator-Like (TA) containing Repeat Variable Residues (RVD); NK, Natural Killer; OS, Overall Survival; PD-/PD-L1, Programmed Cell Death-1/Ligand; RAS, Rat Sarcoma; RV, Retroviral vectors; scFV, Single-Chain Variable Fragment; TAA, Tumor-Associated Antigen; TCGA, The Cancer Genome Atlas; Tp53, Tumor Protein 53; TSCM, T Cell Memory Stem; TCR, T Cell Receptor; TCRαβ, T Cell Receptor alpha beta; TME, Tumor Microenvironment; TRAC, T-cell receptor α constant locus; TRBC1, T Cell Receptor Beta Constant 1; TRBC2, T Cell Receptor Beta Constant 2; TIM3, T cell immunoglobulin and mucin domain- containing protein 3; UCAR, Universal Chimeric Antigen Receptor; UCB, Umbilical Cord Blood; 4-1BB, activation-induced costimulatory molecule (CD137).

frontiers in Nutrition

REVIEW
published: 28 January 2021
doi: 10.3389/fnut.2020.612115

The Interplay Between Diet and the Epigenome in the Pathogenesis of Type-1 Diabetes

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The autoimmune disease, Type 1 Diabetes Mellitus (T1DM), results in the destruction of pancreatic β-cells, and the International Diabetes Federation reports that its incidence is increasing worldwide. T1DM is a complex disease due to the interaction between genetic and environmental factors. Certain dietary patterns and nutrients are known to cause epigenetic modifications in physiological conditions and diseases. However, the interplay between diet and epigenetics is not yet well-understood in the context of T1DM. Several studies have described epigenetic mechanisms involved in the autoimmune reactions that destroy the β-cells, but few explored diet components as potential triggers for epigenetic modifications. Clarifying the link between diet and epigenome can provide new insights into the pathogenesis of T1DM, potentially leading to new diagnostic and therapeutic approaches. In this mini review, we shed light on the influence of the diet-epigenome axis on the pathophysiology of T1DM.

Keywords: type 1 diabetes, diet, epigenetics, histone modifications, DNA methylation, micro-RNA

OPEN ACCESS

Edited by:
Rosita Gabbianelli,
University of Camerino, Italy

Reviewed by:
Melita Vidakovic,
University of Belgrade, Serbia
Sharon Ross,
National Cancer Institute (NCI),
United States

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Specialty section:
This article was submitted to Nutrigenomics, a section of the journal Frontiers in Nutrition

Received: *30 September 2020*
Accepted: *22 December 2020*
Published: *28 January 2021*

Citation:
Kohil A, Al-Asmakh M, Al-Shafai M and Terranegra A (2021) The Interplay Between Diet and the Epigenome in the Pathogenesis of Type-1 Diabetes. Front. Nutr. 7:612115. doi: 10.3389/fnut.2020.612115

INTRODUCTION

T1DM is a metabolic disease resulting from chronic autoimmune destruction of the insulin-producing pancreatic β-cells (1). It primarily affects children and adolescents and can lead to complications including ocular damage, stroke, diabetic ketoacidosis, coma, and kidney failure (2). The disease's incidence is increasing worldwide, with approximately one million cases annually [International Diabetes Federation (IDF) Diabetes Atlas 2014]. This may be due to recent advances in early diagnosis and monitoring of T1DM (1). However, the sedentary lifestyle predominant worldwide and especially in westernized countries has a strong impact toward developing autoimmune disorders, including T1DM (3). This lifestyle, characterized by a high-fat/low-fiber diet and lack of physical activity, is known to strongly modulate the immune system and can lead to T1DM primarily through its impact on T-cells. For example, in the United states, T1DM incidence increased by 21% among young adults (<20 years old) from 2001 to 2009 (4). Moreover, T1DM is highly prevalent among those <19 years of age in countries with a crescent economy and a shift toward a western-like lifestyle, as in the Middle East region, including Kuwait (44.5%), Saudi Arabia (33.5%), and Qatar (12.2%) (5). Similarly, in India the prevalence of T1DM is 31.9 per 100,000, with higher prevalence seen in urban areas compared to rural areas (6). In Korea between 2007 and 2013, the annual incidence of T1DM increased from 2.73 to 5.02 per 100,000 (7). These numbers illustrate the increasing worldwide prevalence of T1DM and indicate a noticeable impact in countries that have recently adopted a westernized lifestyle.

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Distinctive Microbial Signatures and Gut-Brain Crosstalk in Pediatric Patients with Coeliac Disease and Type 1 Diabetes Mellitus

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Citation: Singh, P.; Rawat, A.; Al-Jarrah, B.; Saraswathi, S.; Gad, H.; Elawad, M.; Hussain, K.; Hendaus, M.A.; Al-Masri, W.; Malik, R.A.; et al. Distinctive Microbial Signatures and Gut-Brain Crosstalk in Pediatric Patients with Coeliac Disease and Type 1 Diabetes Mellitus. *Int. J. Mol. Sci.* **2021**, *22*, 1511. https://doi.org/10.3390/ijms22041511

Academic Editor: Francesco Chiarelli
Received: 11 January 2021
Accepted: 25 January 2021
Published: 3 February 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Coeliac disease (CD) and Type 1 diabetes mellitus (T1DM) are immune-mediated diseases. Emerging evidence suggests that dysbiosis in the gut microbiome plays a role in the pathogenesis of both diseases and may also be associated with the development of neuropathy. The primary goal in this cross-sectional pilot study was to identify whether there are distinct gut microbiota alterations in children with CD (n = 19), T1DM (n = 18) and both CD and T1DM (n = 9) compared to healthy controls (n = 12). Our second goal was to explore the relationship between neuropathy (corneal nerve fiber damage) and the gut microbiome composition. Microbiota composition was determined by 16S rRNA gene sequencing. Corneal confocal microscopy was used to determine nerve fiber damage. There was a significant difference in the overall microbial diversity between the four groups with healthy controls having a greater microbial diversity as compared to the patients. The abundance of pathogenic proteobacteria *Shigella* and *E. coli* were significantly higher in CD patients. Differential abundance analysis showed that several bacterial amplicon sequence variants (ASVs) distinguished CD from T1DM. The tissue transglutaminase antibody correlated significantly with a decrease in gut microbial diversity. Furthermore, the Bacteroidetes phylum, specifically the genus *Parabacteroides* was significantly correlated with corneal nerve fiber loss in the subjects with neuropathic damage belonging to the diseased groups. We conclude that disease-specific gut microbial features traceable down to the ASV level distinguish children with CD from T1DM and specific gut microbial signatures may be associated with small fiber neuropathy. Further research on the mechanisms linking altered microbial diversity with neuropathy are warranted.

Keywords: gut microbiota; T1DM; coeliac disease; children; pediatric neuropathy; corneal confocal microscopy

1. Introduction

Type 1 diabetes (T1DM) [1] and coeliac disease (CD) [2] are two of the most frequent childhood autoimmune diseases [3,4]. T1DM is characterized by autoimmune destruction of β cells of the islets of Langerhans, causing insulin deficiency and hyperglycemia [5]. CD

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ARTICLE OPEN

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Ancestry-associated transcriptomic profiles of breast cancer in patients of African, Arab, and European ancestry

Jessica Roelands[1,2], Raghvendra Mall[3], Hossam Almeer[3], Remy Thomas[4], Mahmoud G. Mohamed[5,6], Shahinaz Bedri[7], Salha Bujassoum Al-Bader[8], Kulsoom Junejo[9], Elad Ziv[10], Rosalyn W. Sayaman[11,12], Peter J. K. Kuppen[2], Davide Bedognetti[6,13,14]✉, Wouter Hendrickx[1,14,15]✉ and Julie Decock[4,14,15]✉

Breast cancer largely dominates the global cancer burden statistics; however, there are striking disparities in mortality rates across countries. While socioeconomic factors contribute to population-based differences in mortality, they do not fully explain disparity among women of African ancestry (AA) and Arab ancestry (ArA) compared to women of European ancestry (EA). In this study, we sought to identify molecular differences that could provide insight into the biology of ancestry-associated disparities in clinical outcomes. We applied a unique approach that combines the use of curated survival data from The Cancer Genome Atlas (TCGA) Pan-Cancer clinical data resource, improved single-nucleotide polymorphism-based inferred ancestry assignment, and a novel breast cancer subtype classification to interrogate the TCGA and a local Arab breast cancer dataset. We observed an enrichment of BasalMyo tumors in AA patients (38 vs 16.5% in EA, $p = 1.30E-10$), associated with a significant worse overall (hazard ratio (HR) = 2.39, $p = 0.02$) and disease-specific survival (HR = 2.57, $p = 0.03$). Gene set enrichment analysis of BasalMyo AA and EA samples revealed differences in the abundance of T-regulatory and T-helper type 2 cells, and enrichment of cancer-related pathways with prognostic implications (AA: PI3K-Akt-mTOR and ErbB signaling; EA: EGF, estrogen-dependent and DNA repair signaling). Strikingly, AMPK signaling was associated with opposing prognostic connotation (AA: 10-year HR = 2.79, EA: 10-year HR = 0.34). Analysis of ArA patients suggests enrichment of BasalMyo tumors with a trend for differential enrichment of T-regulatory cells and AMPK signaling. Together, our findings suggest that the disparity in the clinical outcome of AA breast cancer patients is likely related to differences in cancer-related and microenvironmental features.

npj Breast Cancer (2021)7:10 ; https://doi.org/10.1038/s41523-021-00215-x

INTRODUCTION

As we enter an era of personalized medicine in oncology, large-scale studies have been instrumental in deciphering the pathogenesis and evolution of tumors. Public data repositories such as The Cancer Genome Atlas (TCGA) have enabled researchers to define the genomic landscape of different types of cancers, including breast cancer. The public availability of large-scale datasets has led to a surge in candidate drug targets and novel prognostic and/or predictive gene signatures. However, it is important to note that the majority of patients in public datasets are of European ancestry (EA), and, hence, the knowledge gained from such studies might not be applicable to patients of a different ancestry[1]. Given the global disparities in clinical behavior of breast cancer, it has become imperative to investigate ancestry-associated differences in tumor biology.

Breast cancer in women of African ancestry (AA) presents at a younger age, and is associated with more advanced disease and higher mortality rates as compared to breast cancer in age-matched patients of EA or Asian ancestry (AsA)[2–10]. Several reports have demonstrated an increased frequency of the more aggressive triple-negative breast cancer (TNBC) subtype and of the PAM50-molecular basal subtype in AA women[7–16]. Moreover, African-American women with early-stage TNBCs have been shown to exhibit a lower pathological complete response to neoadjuvant chemotherapy[17]. Interestingly, this discrepancy in clinical outcome remains after correcting for socioeconomic factors, suggesting the presence of molecular differences by ancestry[18,19]. The African-American breast cancer epidemiology and risk consortium identified few rare germline single-nucleotide polymorphisms (SNPs) that are associated with an increased risk of hormone receptor-negative breast cancer and/or TNBC in African-American women[20,21]. Analysis of genotypic traits revealed that most somatic mutations and copy number variations are subtype-specific rather than ancestrally determined[22,23]. Very few mutations showed dissimilar frequencies across African, African-American, or European-American patient subgroups when considering a specific breast cancer subtype. Likewise, numerous differentially expressed genes have been identified between breast tumors of patients of AA and EA[24–28]; however, there is little to no evidence linking these findings to differences in breast

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ARTICLE OPEN

Ethnic-specific association of amylase gene copy number with adiposity traits in a large Middle Eastern biobank

Niccolo' Rossi[1,5], Elbay Aliyev[2,5], Alessia Visconti[1], Ammira S. A. Akil[2], Najeeb Syed[2], Waleed Aamer[2], Sujitha S. Padmajeya[2], Mario Falchi[1,6] and Khalid A. Fakhro[2,3,4,6]✉

Studies assessing the impact of amylase genes copy number (CN) on adiposity report conflicting findings in different global populations, likely reflecting the impact of ancestral and ethnic-specific environment and lifestyle on selection at the amylase loci. Here, we leverage population size and detailed adiposity measures from a large population biobank to resolve confounding effects and determine the relationship between salivary (*AMY1*) and pancreatic (*AMY2A*) amylase genes CN and adiposity in 2935 Qatari individuals who underwent whole-genome sequencing (WGS) as part of the Qatar Genome Programme. We observe a negative association between *AMY1* CNs and trunk fat percentage in the Qatari population ($P = 7.50 \times 10^{-3}$) and show that Qataris of Arab descent have significantly lower CN at *AMY1* ($P = 1.32 \times 10^{-10}$) as well as less favorable adiposity and metabolic profiles ($P < 1.34 \times 10^{-8}$) than Qataris with Persian ancestry. Indeed, lower *AMY1* CN was associated with increased total and trunk fat percentages in Arabs ($P < 4.60 \times 10^{-3}$) but not in Persians. Notably, overweight and obese Persians reported a significant trend towards dietary restraint following weight gain compared to Arabs ($P = 4.29 \times 10^{-5}$), with *AMY1* CN showing negative association with dietary self-restraint ($P = 3.22 \times 10^{-3}$). This study reports an association between amylase gene CN and adiposity traits in a large Middle Eastern population. Importantly, we leverage rich biobank data to demonstrate that the strength of this association varies with ethnicity, and may be influenced by population-specific behaviors that also contribute to adiposity traits.

npj Genomic Medicine (2021)6:8 ; https://doi.org/10.1038/s41525-021-00170-3

INTRODUCTION

Salivary (AMY1) and pancreatic (AMY2A) amylase enzymes are responsible for starch digestion, which begins in the oral cavity and continues in the small intestine. The *AMY1 and AMY2A* genes show extensive copy number (CN) variability in humans, with a reported number of gene copies ranging from 2 to 18 for *AMY1*, and from 0 to 8 for *AMY2A*[1–4]. It has been shown that CN distribution at the salivary amylase gene is significantly variable between populations, with the number of copies of *AMY1* reflecting a biological adaptation to traditionally high-starch or low-starch diets throughout evolution[5].

In 2014, we first reported an association between reduced *AMY1* CN and increased body mass index (BMI) and obesity risk using 6200 individuals of European and Asian ancestries[6], although subsequent studies attempting to replicate this association yielded conflicting results. For instance, association with *AMY1* CN was not replicated in 4000 individuals of European ancestry, including people selected for being at the extremes of the BMI distribution[3], as well as in a case-control study of 932 Chinese and 145 Malay samples[7], and in 1400 participants from the UK 1958 Birth Cohort[8]. On the other hand, studies specifically analyzing obesity in children and young adults supported the association of BMI with amylase gene copy number in French[9], Mexican[10], and Italian children[11], as well as in females with early-onset obesity from Finland[12].

These studies highlight the complexity of studying an endpoint which has both genetic and environmental components, and suggest that differences in ethnicity, environment and food preferences may further influence the manifestation of this complex phenotype in the setting of genetic susceptibility. Indeed, previous works exploring the relationship between *AMY1* CN and diet revealed a significant effect of the interaction between *AMY1* CN and starch intake on BMI in 4800 nondiabetic adults from Sweden[13], and greater weight and central adiposity loss following randomized low-calorie diet interventions among carriers of the allele rs11185098-A (a proxy of higher *AMY1* CN and activity[3]), compared to noncarriers, among 692 Europeans from The POUNDS Lost Trial[14]. Taken together, these studies suggest that environmental factors, and particularly dietary choices, may play a role in modulating the observed association between *AMY1* CN and adiposity.

Here, we report a large-scale association study between CN at the amylase genes (*AMY1* and *AMY2A*) and adiposity traits in a large Middle Eastern cohort. Specifically, we combined CN inference from high-coverage (30×) whole-genome sequencing (WGS) with phenotypic traits related to adiposity traits and behaviors, collected for almost 3000 subjects as part of the Qatar Biobank[15]. Our findings help explain trans-ethnic differences in the effect of amylase CN on adiposity and introduce a role for subpopulation-specific traditional dietary and lifestyle choices in determining the strength of association between amylase and adiposity in global populations.

RESULTS

Distribution of adiposity traits in the Qatari population

The Qatar Biobank (QBB) collected a wide range of traits, biochemical measurements, and lifestyle questionnaires from adult Qatari nationals and long-term residents[15]. While many of these traits will be available for future studies, we focused this first

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Germline genetic contribution to the immune landscape of cancer

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(Affiliations continued on next page)

SUMMARY

Understanding the contribution of the host's genetic background to cancer immunity may lead to improved stratification for immunotherapy and to the identification of novel therapeutic targets. We investigated the effect of common and rare germline variants on 139 well-defined immune traits in ~9000 cancer patients enrolled in TCGA. High heritability was observed for estimates of NK cell and T cell subset infiltration and for interferon signaling. Common variants of *IFIH1, TMEM173 (STING1),* and *TMEM108* were associated with differential interferon signaling and variants mapping to *RBL1* correlated with T cell subset abundance. Pathogenic or likely pathogenic variants in *BRCA1* and in genes involved in telomere stabilization and Wnt-β-catenin also acted as immune modulators. Our findings provide evidence for the impact of germline genetics on the composition and functional orientation of the tumor immune microenvironment. The curated datasets, variants, and genes identified provide a resource toward further understanding of tumor-immune interactions.

INTRODUCTION

Immunotherapy with monoclonal antibodies that target immune inhibitory signaling (immune checkpoints) (Ishida et al., 1992; Leach et al., 1996) has emerged as the standard of care for many solid tumors, with an objective response rate up to ~40% in some cancer types (e.g., melanoma) (Chamoto et al., 2020; Sweis and Luke, 2017). However, overall, it has been estimated that fewer than ~15% of cancer patients might currently respond to such treatments (Haslam and Prasad, 2019). The density,

Moosa *et al. BioData Mining* (2021) 14:15
https://doi.org/10.1186/s13040-021-00237-y

BioData Mining

RESEARCH Open Access

DASSI: differential architecture search for splice identification from DNA sequences

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Abstract

Background: The data explosion caused by unprecedented advancements in the field of genomics is constantly challenging the conventional methods used in the interpretation of the human genome. The demand for robust algorithms over the recent years has brought huge success in the field of Deep Learning (DL) in solving many difficult tasks in image, speech and natural language processing by automating the manual process of architecture design. This has been fueled through the development of new DL architectures. Yet genomics possesses unique challenges that requires customization and development of new DL models.

Methods: We proposed a new model, DASSI, by adapting a differential architecture search method and applying it to the Splice Site (SS) recognition task on DNA sequences to discover new high-performance convolutional architectures in an automated manner. We evaluated the discovered model against state-of-the-art tools to classify true and false SS in Homo sapiens (Human), Arabidopsis thaliana (Plant), Caenorhabditis elegans (Worm) and Drosophila melanogaster (Fly).

Results: Our experimental evaluation demonstrated that the discovered architecture outperformed baseline models and fixed architectures and showed competitive results against state-of-the-art models used in classification of splice sites. The proposed model - DASSI has a compact architecture and showed very good results on a transfer learning task. The benchmarking experiments of execution time and precision on architecture search and evaluation process showed better performance on recently available GPUs making it feasible to adopt architecture search based methods on large datasets.

Conclusions: We proposed the use of differential architecture search method (DASSI) to perform SS classification on raw DNA sequences, and discovered new neural network models with low number of tunable parameters and competitive performance compared with manually engineered architectures. We have extensively benchmarked DASSI model with other state-of-the-art models and assessed its

(Continued on next page)

Relecom *et al. Journal of Experimental & Clinical Cancer Research* (2021) 40:74
https://doi.org/10.1186/s13046-021-01872-3

Journal of Experimental & Clinical Cancer Research

REVIEW Open Access

Emerging dynamics pathways of response and resistance to PD-1 and CTLA-4 blockade: tackling uncertainty by confronting complexity

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Abstract

Immune checkpoint inhibitors provide considerable therapeutic benefit in a range of solid cancers as well as in a subgroup of hematological malignancies. Response rates are however suboptimal, and despite considerable efforts, predicting response to immune checkpoint inhibitors ahead of their administration in a given patient remains elusive. The study of the dynamics of the immune system and of the tumor under immune checkpoint blockade brought insight into the mechanisms of action of these therapeutic agents. Equally relevant are the mechanisms of adaptive resistance to immune checkpoint inhibitors that have been uncovered through this approach. In this review, we discuss the dynamics of the immune system and of the tumor under immune checkpoint blockade emanating from recent studies on animal models and humans. We will focus on mechanisms of action and of resistance conveying information predictive of therapeutic response.

Keywords: Dynamics biomarkers, Immune checkpoint inhibitors, PD-1, CTLA-4, Tregs, MDSCs

Background

Immune checkpoint inhibitors (ICIs) are at the forefront of a therapeutic revolution in the treatment of cancer. Acting by modifying the anti-tumoral immune response, they offer the attractive prospect of long-lasting and self-sustained responses, having proven their potential to elicit considerable tumor control in a range of solid tumors as well as in a subgroup of hematological malignancies. Five year overall survival rates reaching 44 % in stage IV melanoma patients treated with an anti-PD-1 monotherapy in first line is in bold contrast with the 8 % 5 year overall survival rates observed under chemotherapy in the same pathology [1, 2], illustrating the considerable potential of these therapeutic agents. Reported response rates to ICIs are however limited, ranging from 10 to 40 % in monotherapy [3, 4]. Despite this large disparity in patient outcome, ICIs are, with very few exceptions, administered on a one treatment fits all basis. Moving towards a more potent and tailored approach to ICI prescription calls for a better understanding of the mechanisms underlying the action of these agents.

Several parameters influencing the probability of response to ICIs have been identified and recently reviewed elsewhere [5]. These can be subdivided into features of the tumor genome [6, 7], host immune-related traits [8] and the microbiota [9–11]. These multiple and diverse factors shape the complex interaction of the tumor and the immune system. Furthermore,

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Review

MOLECULAR METABOLISM

Role of NAD^+ in regulating cellular and metabolic signaling pathways

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ABSTRACT

Background: Nicotinamide adenine dinucleotide (NAD^+), a critical coenzyme present in every living cell, is involved in a myriad of metabolic processes associated with cellular bioenergetics. For this reason, NAD^+ is often studied in the context of aging, cancer, and neurodegenerative and metabolic disorders.

Scope of review: Cellular NAD^+ depletion is associated with compromised adaptive cellular stress responses, impaired neuronal plasticity, impaired DNA repair, and cellular senescence. Increasing evidence has shown the efficacy of boosting NAD^+ levels using NAD^+ precursors in various diseases. This review provides a comprehensive understanding into the role of NAD^+ in aging and other pathologies and discusses potential therapeutic targets.

Major conclusions: An alteration in the NAD^+/NADH ratio or the NAD^+ pool size can lead to derailment of the biological system and contribute to various neurodegenerative disorders, aging, and tumorigenesis. Due to the varied distribution of NAD^+/NADH in different locations within cells, the direct role of impaired NAD^+-dependent processes in humans remains unestablished. In this regard, longitudinal studies are needed to quantify NAD^+ and its related metabolites. Future research should focus on measuring the fluxes through pathways associated with NAD^+ synthesis and degradation.

Keywords NAD^+; Aging; Cancer; Metabolism; Neurodegeneration; Sirtuins

1. INTRODUCTION

Since the discovery of nicotinamide adenine dinucleotide (NAD), researchers have progressively learned more about its roles in cellular function. NAD^+ has emerged as a critical modulator of cell signaling and survival pathways [1]. Cellular NAD exists in two forms, oxidized (NAD^+) and reduced (NADH) [2]. NAD^+ and another essential intracellular coenzyme flavin adenine dinucleotide (FAD^+) play essential roles in cellular oxidation-reduction (redox) reactions and are responsible for accepting high-energy electrons and carrying them to the electron transport chain (ETC) to synthesize adenosine triphosphate (ATP) [3]. Regulation and maintaining a proper balance of the NAD^+/NADH and $FADH_2$/FAD ratio is critical for normal cell function and viability [4]. NAD^+ acts as a cofactor for enzymes involved in cellular energy metabolism and various metabolic pathways such as glycolysis, fatty acid oxidation, and the citric acid cycle [5]. Both NAD^+ and NADH play important roles as coenzymes in redox reactions, and an imbalance in their ratio can impair flux through these pathways' reactions, resulting in dysregulated cellular metabolism.

However, ATP generated via glycolytic reactions is critical for NAD + regeneration from NADH [6]. The crucial role of NAD^+ in different biological functions such as aging, metabolism, mitochondrial function, immunological pathways, oxidative stress, gene expression, and apoptosis has been extensively investigated [7]. Many studies have found that altered NAD^+ levels play an important role in metabolic disorders, neurodegenerative disorders, and tumorigenesis [8,9]. In this review, we discuss the importance of cellular NAD^+ in aging, neurodegeneration, metabolic disorders, and cancer.

2. NAD^+ BIOSYNTHESIS PATHWAYS

The intracellular concentration of NAD^+ is a balance between NAD^+ consumption and synthesis. The biosynthetic pathways of NAD^+ play an important role in maintaining NAD^+ pools, which are not only

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Received December 14, 2020 • Revision received February 2, 2021 • Accepted February 15, 2021 • Available online 17 February 2021

https://doi.org/10.1016/j.molmet.2021.101195

frontiers in Cell and Developmental Biology

REVIEW
published: 05 February 2021
doi: 10.3389/fcell.2021.617281

Insights Into the Role of CircRNAs: Biogenesis, Characterization, Functional, and Clinical Impact in Human Malignancies

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Circular RNAs (circRNAs) are an evolutionarily conserved novel class of non-coding endogenous RNAs (ncRNAs) found in the eukaryotic transcriptome, originally believed to be aberrant RNA splicing by-products with decreased functionality. However, recent advances in high-throughput genomic technology have allowed circRNAs to be characterized in detail and revealed their role in controlling various biological and molecular processes, the most essential being gene regulation. Because of the structural stability, high expression, availability of microRNA (miRNA) binding sites and tissue-specific expression, circRNAs have become hot topic of research in RNA biology. Compared to the linear RNA, circRNAs are produced differentially by backsplicing exons or lariat introns from a pre-messenger RNA (mRNA) forming a covalently closed loop structure missing 3′ poly-(A) tail or 5′ cap, rendering them immune to exonuclease-mediated degradation. Emerging research has identified multifaceted roles of circRNAs as miRNA and RNA binding protein (RBP) sponges and transcription, translation, and splicing event regulators. CircRNAs have been involved in many human illnesses, including cancer and neurodegenerative disorders such as Alzheimer's and Parkinson's disease, due to their aberrant expression in different pathological conditions. The

OPEN ACCESS

Edited by:
Mingli Liu, Morehouse School of Medicine, United States

Reviewed by:
Yumin Wang, Central South University, China
Juni Sarkar, University of Southern California, Los Angeles, United States

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Specialty section:
This article was submitted to Molecular Medicine, a section of the journal Frontiers in Cell and Developmental Biology

Received: *14 October 2020*
Accepted: *04 January 2021*
Published: *05 February 2021*

Citation:
Nisar S, Bhat AA, Singh M, Karedath T, Rizwan A, Hashem S, Bagga P, Reddy R, Jamal F, Uddin S, Chand G, Bedognetti D, El-Rifai W, Frenneaux MP, Macha MA, Ahmed I and Haris M (2021) Insights Into the Role of CircRNAs: Biogenesis, Characterization, Functional, and Clinical Impact in Human Malignancies. Front. Cell Dev. Biol. 9:617281. doi: 10.3389/fcell.2021.617281

functional versatility exhibited by circRNAs enables them to serve as potential diagnostic or predictive biomarkers for various diseases. This review discusses the properties, characterization, profiling, and the diverse molecular mechanisms of circRNAs and their use as potential therapeutic targets in different human malignancies.

Keywords: circRNA, RNA binding protein, miRNA sponges, signaling pathways, tumor, drug resistance

INTRODUCTION

Circular RNAs (circRNAs) are single-stranded non-coding RNAs that are covalently linked to form a continuous closed-loop and participate in the regulation of transcriptional and post-transcriptional gene expression (Wang M. et al., 2017). In recent years, circRNA has become a hotspot in research due to its ability to regulate a myriad of processes that include transcription, translation, splicing and sequestering RNA binding proteins (RBPs) and microRNAs (miRNAs) from their targets (Bartsch et al., 2018). Apart from the widely accepted role of circRNAs as miRNA sponges, circRNAs are also found to act as protein sponges, scaffolds, decoys and recruiters (Huang A. et al., 2020). Studies have found that circRNAs promote tumor progression in cancers such as lung adenocarcinoma, gastric cancer and cervical cancer by acting as RNA sponge and binding to miRNA, thereby increasing downstream gene expression (Tang Q. et al., 2019; Zhang X. et al., 2019; Xu Y. et al., 2020). CircRNAs are formed in the circular transcript by backsplicing of premature messenger RNAs (mRNAs). During the transcription process in eukaryotic cells, there is always a competition between linear and backsplicing. The presence of long introns, RBPs and inverted repeat elements favor the backsplicing event during transcription, and the splice-donor site downstream is brought closer to the splice-acceptor site upstream either by RBP dimerization or by base pairing between inverted repeat elements (Kristensen et al., 2019). The backsplicing event can result in the formation of different types of circRNA such as exon-intron circRNA (ElcircRNAs) (consists of both introns and exons), circular intronic RNAs (formed by introns), exonic circRNA (formed by the splicing of introns), and tRNA intronic circRNA (formed by pre-tRNA splicing) (Zhao X. et al., 2019). CircRNAs are presumably more stable than linear RNA because of the lack of 5′ and 3′ends, and ribonucleases do not easily digest them. The short half-life of linear RNA can be overcome by constructing engineered circRNAs and cyclizing mRNA, thereby promoting stable protein expression in eukaryotic cells (Wesselhoeft et al., 2018). The expression of circRNAs is disrupted in a wide range of diseases, including cancer. They have been proposed as potential biomarkers for cancer therapy as circRNAs can be easily detected in the patients' blood plasma (Wu Q. et al., 2019). circRNAs regulate cancer progression and are involved in various cancer signaling pathways such as PI3K/AKT, MAPL/ERK1/2, and Wnt/β-catenin signaling pathways due to their interaction with miRNAs (Yang Z. et al., 2017). The aberrant translation of circRNAs alters tumor malignancy, and in addition to the many described functions of circRNA, they can also be retro-transcribed and function as competitive RNA (Dong et al., 2016).

Circular RNAs were initially thought to be unable to translate through cap-dependent mechanisms due to their lack of 5′ cap structure and poly-A tail. But recent studies have shown the ability of circRNAs to translate in prokaryotes by mimicking DNA rolling circle amplification and association of circRNAs with translating ribosomes and the ability of circRNAs to generate proteins from circRNA minigenes (Abe et al., 2013; Pamudurti et al., 2017). The translations of circRNAs can be classified as an internal ribosome entry site (IRES) independent dependent and IRES dependent (Tatomer and Wilusz, 2017). IRES-independent translations are found in the circRNAs present in the HeLa cells (Abe et al., 2015). While IRES-dependent translations require additional non-canonical cellular factors to recruit ribosomes to the IRES element and are found in circZNF609 as the UTR element of circZNF609 drives the IRES-dependent translation process through splicing event (Legnini et al., 2017). Cap-dependent translation is inefficient and inhibited under stress conditions or viral infections. In contrast, mRNA translation can be initiated by an IRES-mediated cap-independent mechanism, which is known to be unaltered by these unfavorable conditions (Yang and Wang, 2019).

BIOGENESIS OF CircRNAs

Circular RNAs are produced by non- canonical splicing events commonly known as backsplicing, which is considered an alternative splicing event. Although back splicing is regarded as an alternative splicing event, the molecular mechanism underlying the circular RNAs' biogenesis remains elusive (Mao et al., 2018). CircRNAs are derived from canonical splice sites and depend on canonical splicing machinery, which is usually inefficient to generate linear RNAs (Salzman et al., 2012; Jeck et al., 2013; Memczak et al., 2013; Ashwal-Fluss et al., 2014). On the contrary, results obtained from studies on *Drosophila* showed inhibition of spliceosome components by U2snRNP depletion or inhibition that caused increased circRNA generation compared to its linear counterparts (Liang D. et al., 2017). Hence it is proven that, when pre-mRNA processing events are halted, nascent RNA can be redirected to different alternative pathways that can facilitate back splicing and, ultimately, circRNA generation (Kramer et al., 2015; Liang D. et al., 2017). Apart from the defective splicing machinery, looping of flanking intron sequences on both sides of exons, namely splice donor site and splice acceptor site can support efficient circularization of diverse exons across eukaryotes (Kramer et al., 2015). The looping can be mediated by base pairing of *Alu* repeats or any inverted repeat elements located in the upstream and downstream introns

Journal of Reproductive Immunology 145 (2021) 103293

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

Oral microbiome and pregnancy: A bidirectional relationship

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ARTICLE INFO

Keywords:
Pregnancy complications
Oral diseases
Sex hormones
Preterm birth

ABSTRACT

The oral cavity contains the second most complex microbial population within the human body, with more than 700 bacterial organisms. Recent advances in Next Generation Sequencing technology have unraveled the complexities of the oral microbiome and provided valuable insights into its role in health and disease. The human oral microbiome varies dramatically during the different stages of life, including pregnancy. The total viable microbial counts in pregnant women are known to be higher compared to non-pregnant women, especially in the first trimester of pregnancy. A balanced oral microbiome is vital for a healthy pregnancy, as perturbations in the oral microbiome composition can contribute to pregnancy complications. On the other hand, physiological changes and differences in hormonal levels during pregnancy, increase susceptibility to various oral diseases such as gingivitis and periodontitis. A growing body of evidence supports the link between the composition of the oral microbiome and adverse pregnancy outcomes such as preterm birth, preeclampsia, low birth weight among others. This review aims to summarize the dynamics of oral microbiome during pregnancy and to discuss the relationship between a dysbiotic oral microbiome and pregnancy complications.

1. Introduction

Humans carry numerous microbial symbionts forming a "holobiont" (Simon et al., 2019). The microbial component of the human holobiont is often referred to, as the "microbiome" (Sender et al., 2016). The use of Next Generation Sequencing technologies and ventures such as the Human Microbiome Project (Turnbaugh et al., 2007) have made it possible to characterize and understand the human microbiome. The human microbiota is a highly diverse ecosystem, that is extremely variable both within various body sites in a single subject and among different subjects (Costello et al., 2009; Turnbaugh et al., 2009; Anon, 2012).

The oral cavity including the teeth, gingival sulcus, tongue, cheeks, tonsils, hard and soft palates, represent a natural niche for up to 700 different species of *Streptococci, Lactobacilli, Staphylococci, Corynebacteria,* etc., (Dewhirst et al., 2010), and is considered to be one of the most clinically relevant habitats in humans (He et al., 2015). Many oral and systemic diseases have been associated with the various microorganisms within the oral cavity (Farrell et al., 2012; Griffen et al., 2012). The human oral microbiome dramatically varies from birth to adolescence and adulthood (Crielaard et al., 2011; Sampaio-Maia and Monteiro-Silva, 2014; Lif Holgerson et al., 2015; Dzidic et al., 2018). Similar, variations in the oral microbiome were observed during pregnancy.

It is well known that the female body undergoes a series of hormonal, metabolic, and immunological changes during pregnancy (Lain and Catalano, 2007; Wang et al., 2016), which may have a significant effect on the composition of the oral microbiome Multiple studies have examined the variation of various oral microorganisms in pregnant women as compared to non-pregnant women (Basavaraju et al., 2012; Borgo et al., 2014; Fujiwara et al., 2017). Studies have shown that the total viable oral microbial counts in all the stages of pregnancy were higher especially in the first trimester of pregnancy compared to non-pregnant women (Fujiwara et al., 2017). Moreover, the growth and proliferation of multiple bacterial taxa such as Lactobacillus, Bifidobacterium, Streptococcus, and *Escherichia coli* were found to be altered during pregnancy (Pelzer et al., 2012).

It is worth noting that the microbial changes occurring during pregnancy may be considered a natural consequence of a healthy pregnancy. However, imbalances in the oral microbial composition associated with a poor oral health status may predispose pregnant women to a higher risk of developing periodontal diseases (Balan et al., 2018). It has been shown that oral microbial dysbiosis combined with gingival inflammation leads to adverse outcomes of pregnancy, including low birth weight, preterm birth (PTB) (Moore et al., 2004; Liu et al., 2007), preeclampsia (Boggess et al., 2003), and miscarriages

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https://doi.org/10.1016/j.jri.2021.103293
Received 18 August 2020; Received in revised form 28 January 2021; Accepted 15 February 2021
Available online 19 February 2021

Author Manuscript Published OnlineFirst on October 13, 2020; DOI: 10.1158/1078-0432.CCR-20-1632
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Exploiting B Cell Receptor Stereotypy to design Tailored Immunotherapy in Chronic Lymphocytic Leukemia

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Running title: Immunotherapy for BcR stereotypy in CLL

Keywords: Chronic Lymphocytic Leukemia, Immunoglobulin receptors, VH CDR3 stereotypy, Immunotherapy

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The authors have no relevant conflicts of interest to disclose.

Author Manuscript Published OnlineFirst on October 13, 2020; DOI: 10.1158/1078-0432.CCR-20-1632
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Translational relevance

We here report *in vitro* and *in vivo* data showing that B cell receptor (BcR) stereotypy, a characteristic feature of chronic lymphocytic leukemia (CLL), whereby groups of patients share (quasi)identical BcR, can be exploited for immunotherapy approaches that can be quickly transferred into the clinical arena. We show that immunogenic epitopes can be isolated from the consensus VH CDR3 sequence of both human and murine stereotyped CLL, efficiently processed and presented by CLL cells and effectively recognized by specific T cells. Immunization of Eμ-TCL1 CLL mouse model reduced leukemia development and increased overall survival of the animals.

Our data highlights the immunogenicity of stereotyped VH CDR3 sequences and support the feasibility and efficacy of their use for novel cancer vaccines in CLL. The 'public' nature of stereotyped BcR implies that such approach has the advantage to generate "off-the-shelf" therapeutic vaccines targeting groups of patients with CLL rather than only individual cases.

Author Manuscript Published OnlineFirst on October 13, 2020; DOI: 10.1158/1078-0432.CCR-20-1632
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Abstract

Purpose: Approximately 30% of patients with chronic lymphocytic leukemia (CLL) can be grouped into subsets with stereotyped B cell receptor immunoglobulin (BcR IG) displaying remarkable similarity in the heavy complementarity-determining region 3 (VH CDR3). Here, we investigated whether the consensus VH CDR3 sequences from CLL stereotyped subsets can be exploited for immunotherapy approaches.

Experimental Design: Immunogenic epitopes from the consensus VH CDR3 sequence of the clinically aggressive subsets #1 and #2 and from Eμ-TCL1 mice, which spontaneously develop CLL with BcR IG stereotypy, were identified and used to generate specific HLA class I- and II-restricted T cells *in vitro*. T cell reactivity was assayed *in vitro* as IFN-γ production. Bone marrow derived-dendritic cells (BM-DC) loaded with the peptides were used as vaccination strategy to restrain leukemia development in the Eμ-TCL1 mouse model.

Results: These stereotyped epitopes were naturally processed and presented by CLL cells to the VH CDR3-specific T cells. Furthermore, we validated the efficacy of VH CDR3 peptide-based immunotherapy in the Eμ-TCL1 transplantable mouse model. Immunization of mice against defined VH CDR3 peptide epitopes, prior to the challenge with the corresponding leukemia cells, resulted in the control of CLL development in a significant fraction of mice, and increased overall survival.

Conclusions: Our data highlight the immunogenicity of stereotyped VH CDR3 sequences and support the feasibility and efficacy of their use for novel cancer vaccine in CLL. Such approach has the advantage to generate "off-the-shelf" therapeutic vaccines for relevant groups of patients belonging to stereotyped subsets.

JCI insight

RESEARCH ARTICLE

Dromedary camels as a natural source of neutralizing nanobodies against SARS-CoV-2

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The development of prophylactic and therapeutic agents for coronavirus disease 2019 (COVID-19) is a current global health priority. Here, we investigated the presence of cross-neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in dromedary camels that were Middle East respiratory syndrome coronavirus (MERS-CoV) seropositive but MERS-CoV free. The tested 229 dromedaries had anti–MERS-CoV camel antibodies with variable cross-reactivity patterns against SARS-CoV-2 proteins, including the S trimer and M, N, and E proteins. Using SARS-CoV-2 competitive immunofluorescence immunoassays and pseudovirus neutralization assays, we found medium-to-high titers of cross-neutralizing antibodies against SARS-CoV-2 in these animals. Through linear B cell epitope mapping using phage immunoprecipitation sequencing and a SARS-CoV-2 peptide/proteome microarray, we identified a large repertoire of *Betacoronavirus* cross-reactive antibody specificities in these dromedaries and demonstrated that the SARS-CoV-2–specific VHH antibody repertoire is qualitatively diverse. This analysis revealed not only several SARS-CoV-2 epitopes that are highly immunogenic in humans, including a neutralizing epitope, but also epitopes exclusively targeted by camel antibodies. The identified SARS-CoV-2 cross-neutralizing camel antibodies are not proposed as a potential treatment for COVID-19. Rather, their presence in nonimmunized camels supports the development of SARS-CoV-2 hyperimmune camels, which could be a prominent source of therapeutic agents for the prevention and treatment of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an increasing global threat to public health and economic development. SARS-CoV-2 differs from SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) by its rapid spread and virulent human-to-human transmission (1). Similar to its 2 predecessors, SARS-CoV-2 is a zoonotic virus, and there is a possibility that it has the same natural reservoir (bats) as SARS-CoV and MERS-CoV (2), with an unknown intermediate host (3).

Although SARS-CoV-2 vaccine development is progressing at a rapid pace, widespread vaccine availability must overcome various hurdles, including antigenic variation, low efficacy, and short-term immune responses (4). Until herd immunity against SARS-CoV-2 develops within communities, preferably by means of effective vaccines, the global population will remain at risk, and health care systems will continue to endure tremendous strain. Novel therapeutic and preventive approaches are being designed and tested worldwide. Passive antibody administration through the transfusion of plasma collected from donors who have recovered from COVID-19, known as COVID-19 convalescent plasma (CCP), has emerged as a promising therapy for the treatment of the disease (5). However, the potential benefits of CCP therapy are hampered by the short-term efficacy of the human polyclonal antibodies, the challenges of scaling up this

Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: November 4, 2020
Accepted: January 27, 2021
Published: February 2, 2021

Reference information: *JCI Insight*. 2021;6(5):e145785. https://doi.org/10.1172/jci.insight.145785.

nutrients

MDPI

Article

Akkermansia, a Possible Microbial Marker for Poor Glycemic Control in Qataris Children Consuming Arabic Diet—A Pilot Study on Pediatric T1DM in Qatar

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Abstract: In Qatar, Type 1 Diabetes mellitus (T1DM) is one of the most prevalent disorders. This study aimed to explore the gut microbiome's relation to the continuous subcutaneous insulin infusion (CSII) therapy, dietary habits, and the HbA1c level in the pediatric T1DM subjects in Qatar. We recruited 28 T1DM subjects with an average age of 10.5 ± 3.53 years. The stool sample was used to measure microbial composition by 16s rDNA sequencing method. The results have revealed that the subjects who had undergone CSII therapy had increased microbial diversity and genus *Akkermansia* was significantly enriched in the subjects without CSII therapy. Moreover, genus *Akkermansia* was higher in the subjects with poor glycemic control (HbA1c > 7.5%). When we classified the subjects based on dietary patterns and nationality, *Akkermansia* was significantly enriched in Qataris subjects without the CSII therapy consuming Arabic diet than expatriates living in Qatar and eating a Western/mixed diet. Thus, this pilot study showed that abundance of *Akkermansia* is dependent on the Arabic diet only in poorly controlled Qataris T1DM patients, opening new routes to personalized treatment for T1DM in Qataris pediatric subjects. Further comprehensive studies on the relation between the Arabic diet, ethnicity, and *Akkermansia* are warranted to confirm this preliminary finding.

Keywords: *Akkermansia*; T1DM; Arabic diet; ethnicity; HbA1c; CSII therapy

Citation: Lakshmanan, A.P.; Kohil, A.; El Assadi, F.; Al Zaidan, S.; Al Abduljabbar, S.; Bangarusamy, D.K.; Al Khalaf, F.; Petrovski, G.; Terranegra, A. *Akkermansia*, a Possible Microbial Marker for Poor Glycemic Control in Qataris Children Consuming Arabic Diet—A Pilot Study on Pediatric T1DM in Qatar. *Nutrients* **2021**, *13*, 836. https://doi.org/10.3390/nu13030836

Academic Editor: Lynnette Ferguson

Received: 10 February 2021
Accepted: 24 February 2021
Published: 4 March 2021

1. Introduction

Type 1 diabetes mellitus (T1DM) is a metabolic disorder, and it is caused by the autoimmune destruction of pancreatic beta cells resulting in insulin deficiency. T1DM affects all age groups irrespective of gender. Based on the International Diabetes Federation (IDF) Diabetes Atlas, the incidence of T1DM continues to increase worldwide, with approximately one million cases presented annually [1], and the diabetic prevalent rate in Qatar is around 17% [2]. T1DM is associated with various other complications, such as severe hypoglycemia, ketoacidosis, diabetic retinopathy, nephropathy, and cardiovascular complications [3]. Despite the severity and the incidence of the disease, the etiopathogenesis of T1DM is still not fully understood, involving a complex interaction between environmental and genetic factors [4].

In managing T1DM patients, the therapeutic goal is to manage glucose control, which is accomplished by different treatments, such as insulin therapy and medical nutrition therapy. Insulin therapy (basal-bolus regimen) is one of the recommended approaches in

frontiers in Cellular and Infection Microbiology

ORIGINAL RESEARCH
published: 04 March 2021
doi: 10.3389/fcimb.2021.639665

Vaginal Microbiota and Cytokine Levels Predict Preterm Delivery in Asian Women

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OPEN ACCESS

Edited by:
Irina Burd, Johns Hopkins University, United States

Reviewed by:
Mervi Gürsoy, University of Turku, Finland
Jianping Xie, Southwest University, China

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Specialty section:
This article was submitted to Bacteria and Host, a section of the journal Frontiers in Cellular and Infection Microbiology

Received: *09 December 2020*
Accepted: *28 January 2021*
Published: *04 March 2021*

Citation:
Kumar M, Murugesan S, Singh P, Saadaoui M, Elhag DA, Terranegra A, Kabeer BSA, Marr AK, Kino T, Brummaier T, McGready R, Nosten F, Chaussabel D and Al Khodor S (2021) Vaginal Microbiota and Cytokine Levels Predict Preterm Delivery in Asian Women. Front. Cell. Infect. Microbiol. 11:639665. doi: 10.3389/fcimb.2021.639665

Preterm birth (PTB) is the most common cause of neonatal morbidity and mortality worldwide. Approximately half of PTBs is linked with microbial etiologies, including pathologic changes to the vaginal microbiota, which vary according to ethnicity. Globally more than 50% of PTBs occur in Asia, but studies of the vaginal microbiome and its association with pregnancy outcomes in Asian women are lacking. This study aimed to longitudinally analyzed the vaginal microbiome and cytokine environment of 18 Karen and Burman pregnant women who delivered preterm and 36 matched controls delivering at full term. Using 16S ribosomal RNA gene sequencing we identified a predictive vaginal microbiota signature for PTB that was detectable as early as the first trimester of pregnancy, characterized by higher levels of *Prevotella buccalis*, and lower levels of *Lactobacillus crispatus and Finegoldia*, accompanied by decreased levels of cytokines including IFNγ, IL-4, and TNFα. Differences in the vaginal microbial diversity and local vaginal immune environment were associated with greater risk of preterm birth. Our findings highlight new opportunities to predict PTB in Asian women in low-resource settings who are at highest risk of adverse outcomes from unexpected PTB, as well as in Burman/Karen ethnic minority groups in high-resource regions.

Keywords: microbiota, microbiome, 16S rRNA gene sequencing, dysbiosis, vaginal cytokines, Nugent scoring, Asian, Preterm birth

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01004-8

ORIGINAL ARTICLE

Novel ORAI1 Mutation Disrupts Channel Trafficking Resulting in Combined Immunodeficiency

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Received: 30 November 2020 / Accepted: 19 February 2021

Abstract

Store-operated Ca^{2+} entry (SOCE) represents a predominant Ca^{2+} influx pathway in non-excitable cells. SOCE is required for immune cell activation and is mediated by the plasma membrane (PM) channel ORAI1 and the endoplasmic reticulum (ER) Ca^{2+} sensor STIM1. Mutations in the *Orai1* or *STIM1* genes abolish SOCE leading to combined immunodeficiency (CID), muscular hypotonia, and anhidrotic ectodermal dysplasia. Here, we identify a novel autosomal recessive mutation in ORAI1 in a child with CID. The patient is homozygous for p.C126R mutation in the second transmembrane domain (TM2) of ORAI1, a region with no previous loss-of-function mutations. SOCE is suppressed in the patient's lymphocytes, which is associated with impaired T cell proliferation and cytokine production. Functional analyses demonstrate that the p.C126R mutation does not alter protein expression but disrupts ORAI1 trafficking. Orai1-C126R does not insert properly into the bilayer resulting in ER retention. Insertion of an Arg on the opposite face of TM2 (L135R) also results in defective folding and trafficking. We conclude that positive side chains within ORAI1 TM2 are not tolerated and result in misfolding, defective bilayer insertion, and channel trafficking thus abolishing SOCE and resulting in CID.

Keywords Combined immunodeficiency · ORAI1 · store-operated Ca^{2+} entry · trafficking · integral membrane protein · channel · Ca^{2+} signaling · immune cell function · myotonia · anhidrosis

Introduction

Store-operated Ca^{2+} entry (SOCE) is ubiquitous Ca^{2+} influx pathway that regulates cellular signaling [1–4]. SOCE is triggered downstream of PLC-linked agonists that result in the production of IP_3 and Ca^{2+} release from stores. Intracellular Ca^{2+} stores depletion is sensed by the resident ER transmembrane protein STIM1, which clusters and migrates to ER-PM contact sites (ER-PM CS) that are in close apposition to the PM (within 25–30 nm) [1–3]. STIM1 recruits ORAI1 through diffusional trapping and gates it open to trigger Ca^{2+} influx [1–3].

Gain-of-function (GoF) and loss-of-function (LoF) mutations in either ORAI1 or STIM1 in humans lead to distinct pathologies [3, 5–7]. Autosomal dominant GoF mutations in ORAI1 that result in excessive Ca^{2+} influx including p.S97C, p.G98S, p.L138F, and p.P245L, develop TAM/Stormorken syndrome with no obvious immune phenotype [3, 8–10]. By contrast, recessive LoF mutations that abolish SOCE, including p.A88SfsX25, p.R91W, p.G98R, p.A103E/p.L194P (compound het.), p.H165PfsX1, p.V181SfsX8, and p.L194P, result in combined immunodeficiency (CID), anhidrotic ectodermal dysplasia (AED), and muscular hypotonia [3, 5–7, 11–15]. As the SOCE channel in lymphocytes is referred to as the Ca^{2+}-release activated Ca^{2+} channel

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Published online: 01 March 2021

Homo 72/1 (2021), 17–32
J. Comp. Hum. Biol.
Published online 23 February 2021, published in print March 2021

Bioarchaeology-related studies in the Arabian Gulf: potentialities and shortcomings

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Abstract: Archaeological studies provide a powerful tool to understand the prehistoric societies, especially when combined to cutting-edge morphological and molecular anthropological analyses, allowing reconstructing past population dynamics, admixture events, and socio-cultural changes. Despite the advances achieved in the last decades by archaeological studies worldwide, several regions of the World have been spared from this scientific improvement due to various reasons. The Arabian Gulf represents a unique ground to investigate, being the passageway for human migrations and one of the hypothesized areas in which Neanderthal introgression occurred. A number of archaeological sites are currently present in the Arabian Gulf and have witnessed the antiquity and the intensiveness of the human settlements in the region. Nevertheless, the archaeological and anthropological investigation in the Gulf is still in its infancy. Data collected through archaeological studies in the area have the potential to help answering adamant questions of human history from the beginning of the structuring of genetic diversity in human species to the Neolithisation process. This review aims at providing an overview of the archaeological studies in the Arabian Gulf with special focus to Qatar, highlighting potentialities and shortcomings.

Keywords: prehistoric societies; human skeletal remains; morphological analyses; molecular anthropological analyses; socio-cultural changes; Neolithisation process; Qatar

Introduction

Archaeological studies hold the promise of providing comprehensive frameworks of prehistoric societies especially when coupled with advanced molecular analyses. Bioarchaeology, defined independently by Clark and Buikstra in 1970s (Clark 1972; Clark 1973; Buikstra 1977; Wright & Yoder 2003; Knüsel 2010), represents a branch of archaeology which aims at studying human remains from archaeological sites. Human skeletal remains are considered part of the cultural heritage defined for the first time in 1954 in the Convention of Aja and then by the UNESCO in 1970 as "every artifacts or natural/biological formation considered important for religious, archaeological, historical, artistic, and scientific purposes" (Cattaneo & Gibelli 2014). Therefore, archaeological skeletal series have the potential to enhance the understanding of our history adding useful data for a more extensive comprehension of contemporary human beings.

Anthropological and bioarchaeological investigation helped answering lots of adamant questions that otherwise would remain still open. The analysis of skeletal remains plays an important role in the reconstruction of past population dynamics, lifestyles, dietary habits, admixture and migration events, as well as health status with possible implications even in the history of medicine (Armelagos & Van Gerven 2003; Knudson & Stojanowski 2008). Field anthropology along with mortuary archaeology allow the interpretation of the burial context, the funerary practices, and the decomposition modalities (Duday et al. 1990; Duday 2008; Willis & Tayles 2009) as well as their continuity and/or shifts amongst different pre-historic and/or historic periods in different countries (Duday et al. 1990; Duday 2008; Willis & Tayles 2009). Toward this aim, both the position of the skeletal remains and the taphonomic processes should be taken into account (Duday et al. 1990; Duday 2008). The changes occurred during the decomposition process (e.g. the

DOI: 10.1127/homo/2021/1282

Nano Today 38 (2021) 101136

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

2D MXenes with antiviral and immunomodulatory properties: A pilot study against SARS-CoV-2

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ARTICLE INFO

Article history:
Received 5 January 2021
Received in revised form 22 February 2021
Accepted 15 March 2021
Available online 18 March 2021

Keywords:
MXene
Toxicity
Immune system
Antiviral properties

ABSTRACT

Two-dimensional transition metal carbides/carbonitrides known as MXenes are rapidly growing as multimodal nanoplatforms in biomedicine. Here, taking SARS-CoV-2 as a model, we explored the antiviral properties and immune-profile of a large panel of four highly stable and well-characterized MXenes - $Ti_3C_2T_x$, $Ta_4C_3T_x$, $Mo_2Ti_2C_3T_x$ and $Nb_4C_3T_x$. To start with antiviral assessment, we first selected and deeply analyzed four different SARS-CoV-2 genotypes, common in most countries and carrying the wild type or mutated spike protein. When inhibition of the viral infection was tested in vitro with four viral clades, $Ti_3C_2T_x$ in particular, was able to significantly reduce infection only in SARS-CoV-2/clade GR infected Vero E6 cells. This difference in the antiviral activity, among the four viral particles tested, highlights the importance of considering the viral genotypes and mutations while testing antiviral activity of potential drugs and nanomaterials. Among the other MXenes tested, $Mo_2Ti_2C_3T_x$ also showed antiviral properties.

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https://doi.org/10.1016/j.nantod.2021.101136

Viral clades
Nanomedicine
Single cell mass cytometry

Proteomic, functional annotation analysis and comparison to the already published SARS-CoV-2 protein interaction map revealed that MXene-treatment exerts specific inhibitory mechanisms. Envisaging future antiviral MXene-based drug nano-formulations and considering the central importance of the immune response to viral infections, the immune impact of MXenes was evaluated on human primary immune cells by flow cytometry and single-cell mass cytometry on 17 distinct immune subpopulations. Moreover, 40 secreted cytokines were analyzed by Luminex technology. MXene immune profiling revealed i) the excellent bio and immune compatibility of the material, as well as the ability of MXene ii) to inhibit monocytes and iii) to reduce the release of pro-inflammatory cytokines, suggesting an anti-inflammatory effect elicited by MXene. We here report a selection of MXenes and viral SARS-CoV-2 genotypes/mutations, a series of the computational, structural and molecular data depicting deeply the SARS-CoV-2 mechanism of inhibition, as well as high dimensional single-cell immune-MXene profiling. Taken together, our results provide a compendium of knowledge for new developments of MXene-based multi-functioning nanosystems as antivirals and immune-modulators.

Introduction

From the very beginning of the coronavirus disease 2019 (COVID-19) pandemic, caused by the novel SARS-CoV-2, scientists with diverse backgrounds have converged in an effort to deal with this emergency [1–3]. In addition to extensive pre-clinical and clinical trials carried out for the design of drugs and vaccines, various research efforts are being conducted to achieve better viral inactivation strategies outside the patients, such as the development of self-disinfecting surfaces or personal protective equipment (PPE). In this view, we and others have recently highlighted how nanotechnology and 2D nanomaterials can offer new approaches to cope with the COVID-19 pandemic and infectious diseases in general, including future pandemics [4–17]. The fact that lipid nanoparticle-based vaccines have already obtained approval by the US Food and Drug Administration and European Medical Agency shows that expertise and knowledge developed in the field of nanomedicine has enabled nanoparticle-based vaccine trials to take place in the fight against COVID-19 [18–21]. Therefore, research to advance our understanding of nanomaterial behavior in biological systems is crucial to tackle any future life-threatening disease.

The rational design of nanomaterials, characterized by specific physicochemical properties, turns them into active platforms endowed with different activities exploitable in biomedicine [4,22–24]. In particular, two-dimensional (2D) nanomaterials have been investigated for a wide range of biomedical applications, including cancer theranostics, biosensors and antimicrobial platforms [25–29]. In 2011, the novel class of 2D materials was discovered; transition metal carbides/nitrides (MXenes) [30,31]. Since then, more than 30 stoichiometric members of this family have been successfully synthetized, along with tunable solid-solution MXenes, and more than 100 other forms of MXenes have been predicted *in silico* [32–34]. MXenes have the general formula $M_{n+1}X_nT_x$, where M is an early transition metal (Ti, Nb, V, etc.), X is C and/or N, n is 1–4, and T_x represents the surface terminations (typically, O, OH, F, and Cl) [33]. Due to their wet chemical etching route and surface terminations, MXenes are natively hydrophilic and negatively charged [35–37]. In particular – and almost unique among other 2D nanomaterials - the hydrophilic nature allows to easily integrate MXenes within common biomedical platforms without the need of any specific functionalization or surfactant.

It has been reported that 2D materials can show antimicrobial activity against bacteria, virus, and fungi [25,38–40]. For instance, numerous studies evaluated the antibacterial effectiveness of various graphene-based materials (GBMs), with different lateral size, thickness, functionalization and conjugation to polymers or metal nanoparticles [25], delineating the underlying mechanisms behind this activity (e.g., oxidative stress, inhibition of electron transports, direct contact with bacteria membrane and mechanical damage) [41–43]. To date, there have been numerous studies conducted on MXenes, showing their potential for a number of biomedical applications, including antibacterial properties [39,44–53], as we previously demonstrated for $Ti_3C_2T_x$ [49–51,54]. In addition to antibacterial activity, a few studies have demonstrated the potential application of 2D materials as antivirals [52,53,55–57]. However, no study so far has explored the antiviral activity of MXenes. Therefore, considering the intrinsic properties of MXenes and encouraged by our previous finding on their potential applications in the antimicrobial field, here we explore an in-depth antiviral behavior against four different SARS-CoV-2 genotypes on a large panel of MXenes in four different forms.

Moreover, in order to use any 2D material for biomedical applications, their biocompatibility and toxicity profile should be clearly and thoroughly assessed in order to envisage their potential applications [26,27]. Any exposure to these nanomaterials will result in immediate recognition by immune cells, the body's first line of defense against exogenous agents [58,59]. In this context, as we recently introduced by the nanoimmunity-by-design concept, the specific nanomaterial physicochemical properties can dictate their reactivity and interactions with immune cells [23]. This makes the assessment of the health and safety risks a challenging field, hampering their implementation into biomedical applications [23,60,61]. Moreover, the immune system reaction and cytokine storm syndrome are important factors in the progression of COVID-19 and as well as in other disease. It is therefore urgent to dissect the immune impact of MXene to foster its full potential. None of the studies present in literature reports a deep immune profile of MXenes at the single-cell level. In this study, simultaneously with its antiviral activity, we fully explored the immune cell compatibility of MXenes.

In this study, following material synthesis and characterization, we performed detailed antiviral and deep-immune profiling experimentation (Fig. 1A). We first delineated the antiviral activity simultaneously of four different highly stable MXenes: $Ti_3C_2T_x$, $Ta_4C_3T_x$, $Mo_2Ti_2C_3T_x$ and $Nb_4C_3T_x$. We selected four viral genotypes from the viral repository of the Microbiology References Laboratory in Turkey. We then assessed the viral inhibition by quantification of viral copy numbers and viability of Vero E6 cells. Based on this, we performed *in silico* molecular docking and proteomic analysis to reveal the mechanism of viral inhibition. Finally, because each immune subpopulation can play a different role with possible reactions to MXene-based clinical nanomedicine, we performed viability, activation assay by flow cytometry and a wide analysis on cytokine, chemokines production by Luminex. An in-depth analysis at the single-cell level towards 17 primary human immune cell subpopulations was then performed by single-cell mass cytometry looking at the impact on viability and their functionality by cytokine production.

European Journal of Human Genetics
https://doi.org/10.1038/s41431-021-00845-6

ARTICLE

Analysis of HLA gene polymorphisms in East Africans reveals evidence of gene flow in two Semitic populations from Sudan

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Received: 27 June 2020 / Revised: 28 November 2020 / Accepted: 25 February 2021

Abstract

Sudan, a northeastern African country, is characterized by high levels of cultural, linguistic, and genetic diversity, which is believed to be affected by continuous migration from neighboring countries. Consistent with such demographic effect, genome-wide SNP data revealed a shared ancestral component among Sudanese Afro-Asiatic speaking groups and non-African populations, mainly from West Asia. Although this component is shared among all Afro-Asiatic speaking groups, the extent of this sharing in Semitic groups, such as Sudanese Arab, is still unknown. Using genotypes of six polymorphic human leukocyte antigen (HLA) genes (i.e., *HLA-A*, *-C*, *-B*, *-DRB1*, *-DQB1*, and *-DPB1*), we examined the genetic structure of eight East African ethnic groups with origins in Sudan, South Sudan, and Ethiopia. We identified informative HLA alleles using principal component analysis, which revealed that the two Semitic groups (Gaalien and Shokrya) constituted a distinct cluster from the other Afro-Asiatic speaking groups in this study. The HLA alleles that distinguished Semitic Arabs co-exist in the same extended HLA haplotype, and those alleles are in strong linkage disequilibrium. Interestingly, we find the four-locus haplotype "C*12:02-B*52:01-DRB1*15:02-DQB1*06:01" exclusively in non-African populations and it is widely spread across Asia. The identification of this haplotype suggests a gene flow from Asia, and likely these haplotypes were brought to Africa through back migration from the Near East. These findings will be of interest to biomedical and anthropological studies that examine the demographic history of northeast Africa.

Introduction

The considerable level of cultural, linguistic, and genetic diversity of populations inhabiting East Africa and the Nile Valley reflects the complex demographic history of this part of the world. Such complexity demonstrates the large

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-021-00845-6.

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Published online: 22 March 2021

QMJ
A peer reviewed journal
QATAR MEDICAL JOURNAL

RESEARCH ARTICLE

Impact of attention deficit hyperactivity disorder and gender differences on academic and social difficulties among adolescents in Qatari Schools

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http://dx.doi.org/10.5339/qmj.2021.11
Submitted: 26 June 2020
Accepted: 20 September 2020

Cite this article as: Kamal M, Al-Shibli S, Shahbal S, Yadav SK. Impact of attention deficit hyperactivity disorder and gender differences on academic and social difficulties among adolescents in Qatari Schools, Qatar Medical Journal 2021:11 http://dx.doi.org/10.5339/qmj.2021.11

كيوساينس
QSCIENCE
دار جامعة حمد بن خليفة للنشر
HAMAD BIN KHALIFA UNIVERSITY PRESS

ABSTRACT

Background: To evaluate the social and academic impact of adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and gender differences compared with their non-ADHD peers.

Methods: A cross-sectional descriptive study using a standardized rating scale of teacher observations was conducted in the schools of Qatar from 7th to 12th grades. Teachers completed Swanson, Nolan, and Pelham (SNAP-IV) rating scale questionnaires for the ADHD core symptoms together with nine questions to evaluate the academic and social difficulties in all participants.

Results: A total of 1775 students (mean age: 15±1.5 years; boys/girls: 717/1058) were included in this study. Based on the SNAP-IV rating scale, 150 students were showing core symptoms of ADHD and classified as having ADHD (8.5%; boys/girls; 93/57) and 1625 students as non-ADHD peers (91.5%; boys/girls; 624/1001). Prevalence of ADHD among adolescent students is 8.5%, and it varied significantly between genders with 13% of boys and 5.4% of girls affected by this disorder. Adolescents with ADHD had more academic and social difficulties than their non-ADHD peers, the boys more so than the girls. Boys with inattentive subtype of ADHD had more academic difficulties than girls, while girls had more social difficulties than boys.

Conclusion: The results of this study revealed that ADHD among adolescents is substantially associated with academic and social difficulties in the school environment. Gender differences among students with ADHD should be considered in the school and clinical environment.

Keywords: ADHD, adolescents, academic performance, social difficulties, inattentive subtype

Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology REVIEW doi: 10.1111/cei.13600

Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review

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Accepted for publication 19 March 2021
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Summary

Cytotoxic T lymphocyte antigen 4 (CTLA-4) haploinsufficiency (CHAI) and lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency (LATAIE) are newly identified inborn errors of immunity with shared molecular pathomechanisms and clinical manifestations. In this review, we aimed to provide differential comparisons regarding demographic, clinical, immunological and molecular characteristics between these two similar conditions. A literature search was conducted in PubMed, Web of Science and Scopus databases and included studies were systematically evaluated. Overall, 434 (222 CHAI and 212 LATAIE) patients were found in 101 eligible studies. The CHAI patients were mainly reported from North America and western Europe, while LATAIE patients were predominantly from Asian countries. In CHAI, positive familial history ($P < 0{\cdot}001$) and in LATAIE, consanguineous parents ($P < 0{\cdot}001$) were more common. In CHAI patients the rates of granulomas ($P < 0{\cdot}001$), malignancies ($P = 0{\cdot}001$), atopy ($P = 0{\cdot}001$), cutaneous disorders ($P < 0{\cdot}001$) and neurological ($P = 0{\cdot}002$) disorders were higher, while LATAIE patients were more commonly complicated with life-threatening infections ($P = 0{\cdot}002$), pneumonia ($P = 0{\cdot}006$), ear, nose and throat disorders ($P < 0{\cdot}001$), organomegaly ($P = 0{\cdot}023$), autoimmune enteropathy ($P = 0{\cdot}038$) and growth failure ($P < 0{\cdot}001$). Normal lymphocyte subsets and immunoglobulins except low serum levels of $CD9^+$ B cells (14·0 *versus* 38·4%, $P < 0{\cdot}001$), natural killer (NK) cells (21 *versus* 41·1%, $P < 0{\cdot}001$), immunoglobulin (Ig)G (46·9 *versus* 41·1%, $P = 0{\cdot}291$) and IgA (54·5 *versus* 44·7%, $P = 0{\cdot}076$) were found in the majority of CHAI and LATAIE patients, respectively. The most frequent biological immunosuppressive agents prescribed for CHAI and LATAIE patients were rituximab and abatacept, respectively. Further investigations into the best conditioning and treatment regimens pre- and post-transplantation are required to improve the survival rate of transplanted CHAI and LATAIE patients.

Keywords: CHAI, CTLA-4, inborn errors of immunity, LATAIE, LRBA, primary immunodeficiency disease

Introduction

Inborn errors of immunity (IEIs) are a heterogeneous group of inherited disorders that affect the development and function of the immune system, and predispose patients to chronic susceptibility to recurrent infections, autoimmune disorders, allergy, lymphoproliferation and malignancy. In the last decade, due to the increased availability of genome sequencing, the spectrum of IEIs with immune dysregulation phenotype is rapidly expanding [1].

It has also been shown that the underpinning molecular pathomechanisms of some of these monogenic disorders are greatly overlapping. For instance, disorders of the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) pathway, including autosomal dominant CTLA-4 haploinsufficiency

SOFTWARE TOOL ARTICLE

REVISED An international virtual hackathon to build tools for the analysis of structural variants within species ranging from coronaviruses to vertebrates [version 2; peer review: 1 approved, 3 approved with reservations]

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v2 **First published:** 26 Mar 2021, **10**:246
https://doi.org/10.12688/f1000research.51477.1
Latest published: 03 Sep 2021, **10**:246
https://doi.org/10.12688/f1000research.51477.2

Abstract
In October 2020, 62 scientists from nine nations worked together remotely in the Second Baylor College of Medicine & DNAnexus hackathon, focusing on different related topics on Structural Variation, Pan-genomes, and SARS-CoV-2 related research. The overarching focus was to assess the current status of the field and identify the remaining challenges. Furthermore, how to combine the strengths of the different interests to drive research and method development forward. Over the four days, eight groups each designed and developed new open-source methods to improve the identification and analysis of variations among species, including humans and SARS-CoV-2. These included improvements in SV calling, genotyping, annotations and filtering. Together with advancements in benchmarking existing methods. Furthermore, groups focused on the diversity of SARS-CoV-2. Daily discussion summary and methods are available publicly at https://github.com/collaborativebioinformatics provides valuable insights for both participants and the research community.

Keywords
Structural variant, CNV, SARS-CoV-2, NextGeneration Sequencing

This article is included in the Sidra Medicine gateway.

Open Peer Review

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version 1 26 Mar 2021	? report	? report	? report	? report

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Any reports and responses or comments on the article can be found at the end of the article.

frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH
published: 19 March 2021
doi: 10.3389/fcell.2021.595156

Regulation of Circular RNA CircNFATC3 in Cancer Cells Alters Proliferation, Migration, and Oxidative Phosphorylation

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Specialty section:
This article was submitted to Molecular Medicine, a section of the journal Frontiers in Cell and Developmental Biology

Received: *15 August 2020*
Accepted: *26 February 2021*
Published: *19 March 2021*

Citation:
Karedath T, Al-Dasim FM, Ahmed I, Al-Qurashi A, Raza A, Andrews SS, Ahmed AA, Ali Mohamoud Y, Dermime S and Malek JA (2021) Regulation of Circular RNA CircNFATC3 in Cancer Cells Alters Proliferation, Migration, and Oxidative Phosphorylation. Front. Cell Dev. Biol. 9:595156. doi: 10.3389/fcell.2021.595156

Circular RNAs were once considered artifacts of transcriptome sequencing but have recently been identified as functionally relevant in different types of cancer. Although there is still no clear main function of circRNAs, several studies have revealed that circRNAs are expressed in various eukaryotic organisms in a regulated manner often independent of their parental linear isoforms demonstrating conservation across species. circNFATC3, an abundant and uncharacterized circular RNA of exon 2 and 3 from *NFATC3*, was identified in transcriptomic data of solid tumors. Here we show that circNFATC3 gain- and loss-of-function experiments using RNAi-mediated circRNA silencing and circular mini vector-mediated overexpression of circularized constructs in breast and ovarian cancer cell lines affect molecular phenotypes. The knockdown of circNFATC3 induces a reduction in cell proliferation, invasion, migration, and oxidative phosphorylation. Gain-of-function of circNFATC3 in MDA-MB-231 and SK-OV-3 cells show a significant increase in cell proliferation, migration, and respiration. The above results suggest that circNFATC3 is a functionally relevant circular RNA in breast and ovarian cancer.

Keywords: circRNA, RNA-seq, siRNA, circRNA mini vector, migration, invasion, oxidative phosphorylation

INTRODUCTION

Circular RNAs (circRNAs) were previously considered transcriptional byproducts, however, they drew attention after the functional characterization of a few circular RNAs such as *CDR1-AS* (*ciRS-7*), *SRY*, and *HIPK3* (Wilusz and Sharp, 2013; Jeck et al., 2013; Salzman, 2016). *ciRS-7*, one of the initially identified circRNAs and is known for its ability to sponge microRNAs, conceptually changed the understanding of the mechanisms of circRNA and RNA-mediated gene regulation (Hansen et al., 2013). The wide use of high throughput sequencing analysis has been instrumental in identifying novel circular RNAs in different disease phenotypes and tissues (Wang et al., 2014; Szabo and Salzman, 2016). circRNAs are formed during pre-mRNA splicing by non-canonical order which is referred to as backsplicing or head-to-tail splicing where a branch point upstream of an exon attacks a downstream splice donor. This could happen with a single exon or multiple exons

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Article

Machine learning workflows identify a microRNA signature of insulin transcription in human tissues

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SUMMARY

Dicer knockout mouse models demonstrated a key role for microRNAs in pancreatic β-cell function. Studies to identify specific microRNA(s) associated with human (pro-)endocrine gene expression are needed. We profiled microRNAs and key pancreatic genes in 353 human tissue samples. Machine learning workflows identified microRNAs associated with (pro-)insulin transcripts in a discovery set of islets (n = 30) and insulin-negative tissues (n = 62). This microRNA signature was validated in remaining 261 tissues that include nine islet samples from individuals with type 2 diabetes. Top eight microRNAs (miR-183-5p, -375-3p, 216b-5p, 183-3p, -7-5p, -217-5p, -7-2-3p, and -429-3p) were confirmed to be associated with and predictive of (pro-)insulin transcript levels. Use of doxycycline-inducible microRNA-overexpressing human pancreatic duct cell lines confirmed the regulatory roles of these microRNAs in (pro-)endocrine gene expression. Knockdown of these microRNAs in human islet cells reduced (pro-)insulin transcript abundance. Our data provide specific microRNAs to further study microRNA-mRNA interactions in regulating insulin transcription.

INTRODUCTION

Insulin production in pancreatic β-cells is an essential process required for the maintenance of normal glucose metabolism. Any decline in β-cell function is a common denominator to type 1 diabetes (T1D), as well as type 2 diabetes (T2D). Transcription of specialized genes, including (pro-)insulin, is dependent on several factors including chromatin organization, transcription factor assembly, as well as the expression of regulatory microRNAs (miRNAs/miRs). MicroRNAs are short, non-coding RNA molecules known to fine-tune gene expression via targeting multiple messenger RNAs (mRNAs). Biologically active (mature) microRNAs are generated through processing by dicer, an enzyme critical for the biogenesis of both canonical and non-canonical microRNAs (Wong et al., 2018). In mice, pancreatic *Dicer1* deletion demonstrated the essential role of microRNAs in the generation of pancreatic β-cells (Lynn et al., 2007) during embryonic development. Islet β-cell-specific (RIP-Cre) deletion of *Dicer1* in mice did not affect islet cell development but significantly reduced insulin transcription/production (Melkman-Zehavi et al., 2011) and promoted the development of diabetes (Kalis et al., 2011) in adult mice. Although these loss-of-function studies demonstrate, in general, the essential role of microRNAs in mouse islet biology, it is important to identify microRNAs associated with human (pro-)endocrine gene expression and more specifically those associated with (pro-) insulin gene transcription.

One of the very first studies in microRNA islet biology was the demonstration of a key role for miR-375 in mouse insulin secretion (Poy et al., 2004), followed by validation of its role in zebrafish (Kloosterman et al., 2007) and mouse (Poy et al., 2009) pancreatic islet development. These studies laid the foundation for

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Continued

Received: 7 February 2021 | Accepted: 8 March 2021

DOI: 10.1002/iub.2465

HYPOTHESIS

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Identification of mutation resistance coldspots for targeting the SARS-CoV2 main protease

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Abstract

Mutations in the novel coronavirus SARS-CoV2 are the major concern as they might lead to drug/vaccine resistance. In the host cell, the virus largely depends on the main protease (M^{pro}) to regulate infection hence it is one of the most attractive targets for inhibitor design. However, >19,000 mutations in the M^{pro} have already been reported. The mutations encompassing 282 amino acid positions and these "hotspots" might change the M^{pro} structure, activity and potentially delay therapeutic strategies targeting M^{pro}. Thus, here we identified 24 mutational "coldspots" where mutations have not been observed. We compared the structure–function relationship of these coldspots with several SARS-CoV2 M^{pro} X-ray crystal structures. We found that three coldspot residues (Leu141, Phe185, and Gln192) help to form the active site, while seven (Gly2, Arg4, Tyr126, Lys137, Leu141, Leu286, and Leu287) contribute to dimer formation that is required for M^{pro} activity. The surface of the dimer interface is more resistant to mutations compared to the active site. Interestingly, most of the coldspots are found in three clusters and forms conserved patterns when compared with other coronaviruses. Importantly, several conserved coldspots are available on the surface of the active site and at the dimer interface for targeting. The identification and short list of these coldspots offers a new perspective to target the SARS-CoV2 M^{pro} while avoiding mutation-based drug resistance.

KEYWORDS

dimer interface, mutation hotspot, mutation-based drug resistance, structure–function relationship, surface coldspots, X-ray structure

1 | INTRODUCTION

In SARS-CoV2, main protease (M^{pro}) or 3CL-protease ($3CL^{pro}$) is essential for proteolytic activity, production of structural proteins and host cell infection.[1] We already have access to high resolution 3D-structures of the SARS-CoV2 M^{pro}, which were developed with potential

Abbreviations: CoV, coronavirus; COVID-19, coronavirus disease 2019; GISAID, global Initiative on sharing all influenza data; MERS-CoV, middle east respiratory syndrome-related coronavirus; M^{pro}, main protease; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; $3CL^{pro}$, 3CL-protease.

Akil *et al. J Transl Med* (2021) 19:137
https://doi.org/10.1186/s12967-021-02778-6

Journal of Translational Medicine

REVIEW Open Access

Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era

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Abstract

Type 1 diabetes affects millions of people globally and requires careful management to avoid serious long-term complications, including heart and kidney disease, stroke, and loss of sight. The type 1 diabetes patient cohort is highly heterogeneous, with individuals presenting with disease at different stages and severities, arising from distinct etiologies, and overlaying varied genetic backgrounds. At present, the "one-size-fits-all" treatment for type 1 diabetes is exogenic insulin substitution therapy, but this approach fails to achieve optimal blood glucose control in many individuals. With advances in our understanding of early-stage diabetes development, diabetes stratification, and the role of genetics, type 1 diabetes is a promising candidate for a personalized medicine approach, which aims to apply "the right therapy at the right time, to the right patient". In the case of type 1 diabetes, great efforts are now being focused on risk stratification for diabetes development to enable pre-clinical detection, and the application of treatments such as gene therapy, to prevent pancreatic destruction in a sub-set of patients. Alongside this, breakthroughs in stem cell therapies hold great promise for the regeneration of pancreatic tissues in some individuals. Here we review the recent initiatives in the field of personalized medicine for type 1 diabetes, including the latest discoveries in stem cell and gene therapy for the disease, and current obstacles that must be overcome before the dream of personalized medicine for all type 1 diabetes patients can be realized.

Keywords: Type 1 diabetes, Autoimmunity, Personalized medicine, Personalized treatment, Genomic Risk Score, Insulin therapy, Stem cells, Gene polymorphism, Stem cells, Gene therapy, Pancreatic β cells

Introduction

Type 1 Diabetes (T1D) is a potentially life-threatening multifactorial autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β cells, resulting in a deficiency of insulin synthesis and secretion [1]. The incidence of T1D has been rising globally since the 1950s, with an average annual increase of 3–4% over the past three decades [2]. In particular, the incidence of childhood T1D is increasing, most rapidly in populations that previously had low incidence [3–5], and varying by ethnicity and race [4].

This worrying growth in T1D incidence has driven concerted research efforts to better understand the underlying risk factors, etiology, and pathology of the disease.

T1D has a largely heritable element, supported by a twin concordance rate of up to 70% [6] and of 8–10% sibling risk [7]. The bulk of risk is explained by difference at a several but strongly associated loci involving the HLA region "HLA class II, DQ and DR loci and HLA class I region" on chromosome 6p21 that account for ~ 50% of familial T1D [8, 9]. Genome-wide association (GWAS) and candidate gene association studies have produced an abundance body of evidence and provided convincing support about other genes and loci external to the HLA

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Hildebrand et al. *Cell Death and Disease* (2021)12:345
https://doi.org/10.1038/s41419-021-03636-5

Cell Death & Disease

ARTICLE Open Access

A family harboring an MLKL loss of function variant implicates impaired necroptosis in diabetes

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Abstract

Maturity-onset diabetes of the young, MODY, is an autosomal dominant disease with incomplete penetrance. In a family with multiple generations of diabetes and several early onset diabetic siblings, we found the previously reported P33T *PDX1* damaging mutation. Interestingly, this substitution was also present in a healthy sibling. In contrast, a second very rare heterozygous damaging mutation in the necroptosis terminal effector, MLKL, was found exclusively in the diabetic family members. Aberrant cell death by necroptosis is a cause of inflammatory diseases and has been widely implicated in human pathologies, but has not yet been attributed functions in diabetes. Here, we report that the MLKL substitution observed in diabetic patients, G316D, results in diminished phosphorylation by its upstream activator, the RIPK3 kinase, and no capacity to reconstitute necroptosis in two distinct *MLKL*$^{-/-}$ human cell lines. This MLKL mutation may act as a modifier to the P33T *PDX1* mutation, and points to a potential role of impairment of necroptosis in diabetes. Our findings highlight the importance of family studies in unraveling MODY's incomplete penetrance, and provide further support for the involvement of dysregulated necroptosis in human disease.

Introduction

Monogenic diabetes constitutes less than 5% of diabetes cases, of which the two main forms affect either newborns (NDM) or young adults (MODY)[1]. To date, there are 14 types of MODY named after the genes involved in each. MODY is inherited in an autosomal dominant mode, and despite being described as monogenic, it is not fully penetrant[2]. Families affected with the insulin promoter factor-1 (PDX1) MODY (or MODY4), for example, frequently do not segregate strictly with pathogenic PDX1 mutations, with unaffected carriers being common and some diabetic members lacking the mutations[3–7]. PDX1 is a transcription factor that regulates expression of key pancreatic genes, including those encoding insulin, somatostatin, glucokinase, islet amyloid polypeptide and glucose transporter type 2 genes[8]. Biallelic damaging mutations have been well characterized with severe consequences in humans and mice, involving pancreatic agenesis, NDM and death[9,10]. However, mice bearing a single allele knockout exhibit only a mild phenotype and do not develop diabetes[11]. Despite many of the reported MODY4 mutations studied in vitro and in vivo confirming a role in pathogenesis[3,4,6,7], these studies stop short of explaining the phenomenon of incomplete penetrance. Additional environmental or genetic factors are clearly acting alongside PDX1 mutations in the etiology of MODY. In support of this idea, the selective, inducible inhibition of IKK/NF-κB signaling in pancreatic β-cells could induce bona fide diabetes in pre-diabetic adult *Pdx1*$^{+/-}$ mice[12].

Family studies have greatly contributed to the identification of pathogenic mutations and continue to yield important new insights even in the era of large cohort sequencing. While genome-wide association (GWAS)

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Edited by B. Zhivotovsky

Review > Microrna. 2021;10(1):29-38. doi: 10.2174/2211536610666210412154455.

The Salivary miRNome: A Promising Biomarker of Disease

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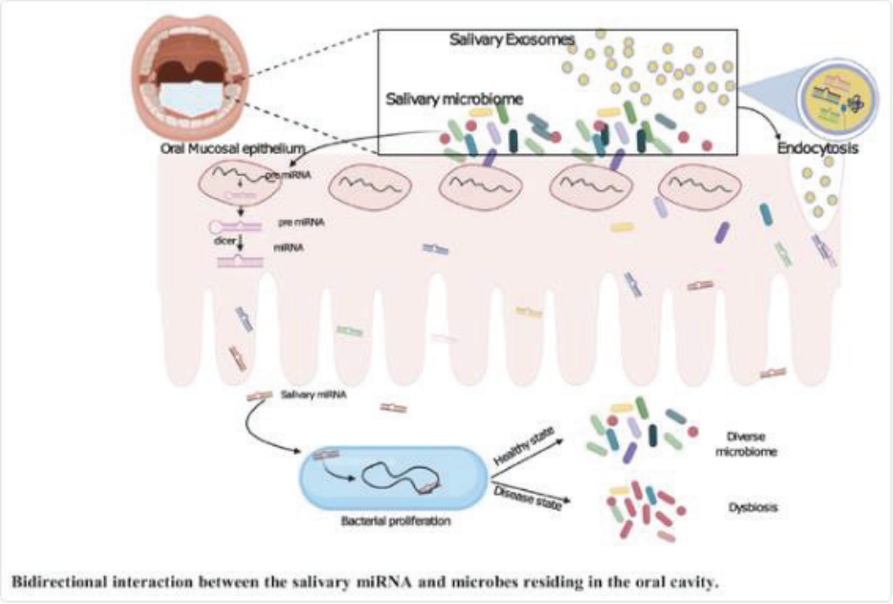
PMID: 33845754 DOI: 10.2174/2211536610666210412154455

Abstract

MicroRNAs (miRNAs) are non-coding RNAs ranging from 18-24 nucleotides, also known to regulate the human genome mainly at the post-transcriptional level. MiRNAs were shown to play an important role in most biological processes such as apoptosis and in the pathogenesis of many diseases such as cardiovascular diseases and cancer. Recent developments of advanced molecular high-throughput technologies have enhanced our knowledge of miRNAs. MiRNAs can now be discovered, interrogated, and quantified in various body fluids serving as diagnostic and therapeutic markers for many diseases. While most studies use blood as a sample source to measure circulating miRNAs as possible biomarkers for disease pathogenesis, fewer studies have assessed the role of salivary miRNAs in health and disease. This review aims at providing an overview of the current knowledge of the salivary miRNome, addressing the technical aspects of saliva sampling, and highlighting the applicability of miRNA screening to clinical practice.

Keywords: biomarkers; cancer; miRNA; microbiome.; saliva; sequencing.

Graphical Abstract



Bidirectional interaction between the salivary miRNA and microbes residing in the oral cavity.

frontiers in Immunology

ORIGINAL RESEARCH
published: 01 April 2021
doi: 10.3389/fimmu.2021.634119

Transcriptomic Profiling Identifies Neutrophil-Specific Upregulation of Cystatin F as a Marker of Acute Inflammation in Humans

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Cystatin F encoded by *CST7* is a cysteine peptidase inhibitor known to be expressed in natural killer (NK) and $CD8^+$ T cells during steady-state conditions. However, little is known about its expression during inflammatory disease states in humans. We have developed an analytic approach capable of not only identifying previously poorly characterized disease-associated genes but also defining regulatory mechanisms controlling their expression. By exploring multiple cohorts of public transcriptome data comprising 43 individual datasets, we showed that *CST7* is upregulated in the blood during a diverse set of infectious and non-infectious inflammatory conditions. Interestingly, this upregulation of *CST7* was neutrophil-specific, as its expression was unchanged in NK and $CD8^+$ T cells during sepsis. Further analysis demonstrated that known microbial products or cytokines commonly associated with inflammation failed to increase *CST7* expression, suggesting that its expression in neutrophils is induced by an endogenous serum factor commonly present in human inflammatory conditions. Overall, through the identification of *CST7* upregulation as a marker of acute inflammation in humans, our study demonstrates the value of publicly available transcriptome data in knowledge generation and potential biomarker discovery.

Keywords: neutrophil, transcriptome, cystatin F, data mining, meta-analysis, literature analysis

OPEN ACCESS

Edited by:
Antonio Cappuccio,
Mount Sinai Hospital, United States

Reviewed by:
Carlos Alberto Moreira-Filho,
University of São Paulo, Brazil
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Specialty section:
This article was submitted to Inflammation, a section of the journal Frontiers in Immunology

Received: *27 November 2020*
Accepted: *17 March 2021*
Published: *01 April 2021*

Citation:
Sawyer AJ, Garand M, Chaussabel D and Feng CG (2021) Transcriptomic Profiling Identifies Neutrophil-Specific Upregulation of Cystatin F as a Marker of Acute Inflammation in Humans. Front. Immunol. 12:634119. doi: 10.3389/fimmu.2021.634119

INTRODUCTION

Transcriptomic profiling has been widely used over the past two decades to uncover the expression and function of genes across the genome. Each transcriptomic profiling study generates enormous amounts of data, the bulk of which has been published in online repositories and is available for download free of charge. The NCBI Gene Expression Omnibus (GEO), for example, is an online database containing more than 58,000 series datasets from human studies, comprising 2 million individual samples. These include datasets from across the spectrum of human diseases, tissue types and cell types. Transcriptomic data generated from cells following stimulation or from gene-targeted cells provide additional insights into gene regulation. While transcriptomic datasets have typically been interrogated by the original researchers to identify pathways/genes of interest, most of

Inherited deficiency of stress granule ZNFX1 in patients with monocytosis and mycobacterial disease

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Contributed by Jean-Laurent Casanova, March 5, 2021 (sent for review February 11, 2021; reviewed by Marcel A. Behr and Anne Sophie Korganow)

Human inborn errors of IFN-γ underlie mycobacterial disease, due to insufficient IFN-γ production by lymphoid cells, impaired myeloid cell responses to this cytokine, or both. We report four patients from two unrelated kindreds with intermittent monocytosis and mycobacterial disease, including bacillus Calmette–Guérin-osis and disseminated tuberculosis, and without any known inborn error of IFN-γ. The patients are homozygous for *ZNFX1* variants (p.S959* and p.E1606Rfs*10) predicted to be loss of function (pLOF). There are no subjects homozygous for pLOF variants in public databases. ZNFX1 is a conserved and broadly expressed helicase, but its biology remains largely unknown. It is thought to act as a viral double-stranded RNA sensor in mice, but these patients do not suffer from severe viral illnesses. We analyze its subcellular localization upon overexpression in A549 and HeLa cell lines and upon stimulation of THP1 and fibroblastic cell lines. We find that this cytoplasmic protein can be recruited to or even induce stress granules. The endogenous ZNFX1 protein in cell lines of the patient homozygous for the p.E1606Rfs*10 variant is truncated, whereas ZNFX1 expression is abolished in cell lines from the patients with the p.S959* variant. Lymphocyte subsets are present at normal frequencies in these patients and produce IFN-γ normally. The hematopoietic and nonhematopoietic cells of the patients tested respond normally to IFN-γ. Our results indicate that human ZNFX1 is associated with stress granules and essential for both monocyte homeostasis and protective immunity to mycobacteria.

mycobacteria | monocytosis | inflammation | inborn error of immunity | ZNFX1

Significance

Mendelian susceptibility to mycobacterial disease (MSMD) is defined by selective vulnerability to weakly virulent mycobacteria. The 32 known inborn errors of IFN-γ immunity account for MSMD in about half of the patients, and for a smaller proportion of cases of tuberculosis (TB). We report homozygous *ZNFX1* variants in two families in which the index cases had MSMD or TB with intermittent monocytosis. Upon overexpression, the two variants encode truncated proteins. We show that human ZNFX1 is localized in ribonucleoprotein granules called stress granules. The patients' production of and response to IFN-γ are apparently intact, and the patients have not experienced severe viral illnesses. Inherited deficiency of stress granule-associated ZNFX1 is a genetic etiology of MSMD or TB with intermittent monocytosis.

Mycobacteria cause three major endemic illnesses—tuberculosis (TB), leprosy, and Buruli ulcer—and rarer illnesses caused by less virulent live bacillus Calmette–Guérin vaccines or "atypical" environmental mycobacteria (EM). Rare patients with a selective predisposition to clinical disease caused by bacillus Calmette–Guérin vaccine and EM have Mendelian susceptibility to mycobacterial disease (MSMD) (1, 2). These patients are also prone to disease caused by the more virulent *Mycobacterium tuberculosis*, and

Author contributions: T.L.V., J.-L.C., and J.B. designed research; T.L.V., A.-L.N., R.Y., J.R., M.O., M. Alshalan, F.A.A., T.K., M. Ata, C.G., D.B., N.M., F.A.M., V.B., and S.B.-D. performed research; M.R., M.C., S.-Y.Z., and S.B.-D. contributed new reagents/analytic tools; M. Alshalan, F.A.A., T.K., M. Ata, P.B., Y.S., F. Rapaport, B.B., L.B., N.B., L.A., N.M., F.A.M., D.W., and S.-Y.Z. analyzed data; T.L.V., J.-L.C., and J.B. wrote the paper; T.L.V., S.B.-D., and J.B. recorded the clinical data and created the figures; F.A., S.B., D.S., S.A.-M., A.B.-A., D.M., F.A.M., S.A.M., A.F., and B.R. provided samples and performed clinical diagnosis and follow-up of the kindreds; L.R. and A.D. recorded the clinical data; and F. Rozenberg performed viral serological analyses.

Reviewers: M.A.B., McGill International TB Centre; and A.S.K., Strasbourg University Hospital.

The authors declare no competing interest.

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This article contains supporting information online at https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2102804118/-/DCSupplemental.

Published April 5, 2021.

Review > Minerva Pediatr (Torino). 2021 Apr;73(2):98-110. doi: 10.23736/S2724-5276.20.06166-6.

Nutri-epigenetics: the effect of maternal diet and early nutrition on the pathogenesis of autoimmune diseases

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PMID: 33880901 DOI: 10.23736/S2724-5276.20.06166-6

Abstract

Autoimmune diseases comprise a wide group of diseases involving a self-response of the immune system against the host. The etiopathogenesis is very complex involving disease-specific factors but also environmental factors, among which the diet. Maternal diet during pregnancy as well as early nutrition recently attracted the interest of the scientists as contributing to the immune programming. In this paper, we reviewed the most recent literature on the effect of maternal diet and early nutrition in modulating the immune system in a selected subset of autoimmune diseases: type 1 diabetes, celiac disease, inflammatory bowel disease, juvenile idiopathic arthritis and rheumatoid arthritis. Particularly, we focused our narrative on the role of maternal and perinatal nutrition in the epigenetic mechanisms underlying the auto-immune response. Maternal diet during pregnancy as well as breastfeeding and early nutrition play a big role in many epigenetic mechanisms. Most of the nutrients consumed by the mother and the infant are known exerting epigenetic functions, such as folate, methionine, zinc, vitamins B12 and D, fibers, casein and gliadin, and they were linked to gene expression changes in the immune pathways. Despite the common role of maternal diet, breastfeeding and early nutrition in almost all the autoimmune diseases, each disease seems to have specific diet-driver epigenetic mechanisms that require further investigations. The research in this field is opening new routes to establishing a precision nutrition approach to the auto-immune diseases.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 12 April 2021
doi: 10.3389/fped.2021.646517

Hydronephrosis Classifications: Has UTD Overtaken APD and SFU? A Worldwide Survey

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Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Pediatric Urology, a section of the journal Frontiers in Pediatrics

Received: *27 December 2020*
Accepted: *23 February 2021*
Published: *12 April 2021*

Citation:
Vallasciani S, Bujons Tur A, Gatti J, Machado M, Cooper CS, Farrugia MK, Zhou H, El Anbari M and Lopez P-J (2021) Hydronephrosis Classifications: Has UTD Overtaken APD and SFU? A Worldwide Survey. Front. Pediatr. 9:646517. doi: 10.3389/fped.2021.646517

Objective: To collect baseline information on the ultrasonographic reporting preferences.

Method: A 13-multiple choice questionnaire was designed and distributed worldwide among pediatric urologists, pediatric surgeons, and urologists. The statistical analysis of the survey data consisted of 3 steps: a univariate analysis, a bivariate and a multivariate analysis.

Results: Three hundred eighty participants responded from all the continents. The bivariate analysis showed the significant differences in the geographical area, the years of experience and the volume of cases. Most of the physicians prefer the SFU and APD systems because of familiarity and simplicity (37 and 34%, respectively). Respondents noted that their imaging providers most often report findings utilizing the mild-moderate-severe system or the APD measurements (28 and 39%, respectively) except for North America (SFU in 50%). Multivariate analysis did not provide significant differences.

Conclusion: Our study evaluates the opinions regarding the various pediatric hydronephrosis classification systems from a large number of specialists and demonstrates that there is no single preferred grading system. The greatest reported shortcoming of all the systems was the lack of universal utilization. The observations taken from this study may serve as basis for the construction of a common worldwide system. As APD and SFU are the preferred systems and the UTD a newer combination of both, it is possible that with time, UTD may become the universal language for reporting hydronephrosis. This time, based on the result of this survey, seems not arrived yet.

Keywords: hydronephrosis, classification, survey, pediatric urology, ultrasound, pediatric radiology

Journal of *Personalized Medicine*

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Article

MicroRNA Expression Profile Distinguishes Glioblastoma Stem Cells from Differentiated Tumor Cells

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Abstract: Glioblastoma (GBM) represents the most common and aggressive tumor of the brain. Despite the fact that several studies have recently addressed the molecular mechanisms underlying the disease, its etiology and pathogenesis are still poorly understood. GBM displays poor prognosis and its resistance to common therapeutic approaches makes it a highly recurrent tumor. Several studies have identified a subpopulation of tumor cells, known as GBM cancer stem cells (CSCs) characterized by the ability of self-renewal, tumor initiation and propagation. GBM CSCs have been shown to survive GBM chemotherapy and radiotherapy. Thus, targeting CSCs represents a promising approach to treat GBM. Recent evidence has shown that GBM is characterized by a dysregulated expression of microRNA (miRNAs). In this study we have investigated the difference between human GBM CSCs and their paired autologous differentiated tumor cells. Array-based profiling and quantitative Real-Time PCR (qRT-PCR) were performed to identify miRNAs differentially expressed in CSCs. The Cancer Genome Atlas (TCGA) data were also interrogated, and functional interpretation analysis was performed. We have identified 14 miRNAs significantly differentially expressed in GBM CSCs ($p < 0.005$). MiR-21 and miR-95 were among the most significantly deregulated miRNAs, and their expression was also associated to patient survival. We believe that the data provided here carry important implications for future studies aiming at elucidating the molecular mechanisms underlying GBM.

Keywords: glioblastoma; microRNAs; cancer; qPCR; cancer stem cells

Citation: Tomei, S.; Volontè, A.; Ravindran, S.; Mazzoleni, S.; Wang, E.; Galli, R.; Maccalli, C. MicroRNA Expression Profile Distinguishes Glioblastoma Stem Cells from Differentiated Tumor Cells. *J. Pers. Med.* **2021**, *11*, 264. https://doi.org/10.3390/jpm11040264

Academic Editors: Alessandra Pulliero, Alberto Izzotti and Luigi Maria Larocca

Received: 24 January 2021
Accepted: 16 March 2021
Published: 1 April 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Glioblastoma is the deadliest malignant intracranial tumor in adults. In the United States its annual incidence is 3.2 cases per 100,000 people [1,2], while in Europe the incidence is 3–5 cases per 100,000 people [3]. Its progression is accompanied by a rapid spread, an infiltrative growth and high cellular heterogeneity [4,5]. The current management of Glioblastoma (GBM) patients includes surgical resection, radiotherapy, chemotherapy and tumor treating fields (TTFields) [4,6]. Among the chemotherapeutic agents, temozolomide (TMZ) is the most common alkylating agent employed in the clinical management of GBM patients. However, GBM has been shown to acquire resistance to TMZ, thus explaining GBM recurrence [4,6]. GBM prognosis is generally poor and the median survival is only 14 months, while the 5-year survival rate is unfortunately between 5%–10% [7–10].

cancers

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Review

Cancer Stem Cells Are Possible Key Players in Regulating Anti-Tumor Immune Responses: The Role of Immunomodulating Molecules and MicroRNAs

Sara Tomei [1], Ola Ibnaof [1,†], Shilpa Ravindran [1,†], Soldano Ferrone [2] and Cristina Maccalli [1,*]

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Simple Summary: This review provides a critical overview of the state of the art of the characterization of the immunological profile of a rare component of the tumors, denominated cancer stem cells (CSCs) or cancer initiating cells (CICs). These cells are endowed with the ability to form and propagate tumors and resistance to therapies, including the most innovative approaches. These investigations contribute to understanding the mechanisms regulating the interaction of CSCs/CICs with the immune system and identifying novel therapeutic approaches to render these cells visible and susceptible to immune responses.

Abstract: Cancer cells endowed with stemness properties and representing a rare population of cells within malignant lesions have been isolated from tumors with different histological origins. These cells, denominated as cancer stem cells (CSCs) or cancer initiating cells (CICs), are responsible for tumor initiation, progression and resistance to therapies, including immunotherapy. The dynamic crosstalk of CSCs/CICs with the tumor microenvironment orchestrates their fate and plasticity as well as their immunogenicity. CSCs/CICs, as observed in multiple studies, display either the aberrant expression of immunomodulatory molecules or suboptimal levels of molecules involved in antigen processing and presentation, leading to immune evasion. MicroRNAs (miRNAs) that can regulate either stemness properties or their immunological profile, with in some cases dual functions, can provide insights into these mechanisms and possible interventions to develop novel therapeutic strategies targeting CSCs/CICs and reverting their immunogenicity. In this review, we provide an overview of the immunoregulatory features of CSCs/CICs including miRNA profiles involved in the regulation of the interplay between stemness and immunological properties.

Keywords: cancer stem cells/cancer initiating cells; tumor microenvironment; immune responses; immunomodulating molecules; microRNAs

Citation: Tomei, S.; Ibnaof, O.; Ravindran, S.; Ferrone, S.; Maccalli, C. Cancer Stem Cells Are Possible Key Players in Regulating Anti-Tumor Immune Responses: The Role of Immunomodulating Molecules and MicroRNAs. *Cancers* **2021**, *13*, 1674. https://doi.org/10.3390/cancers13071674

Academic Editor: Shihori Tanabe

Received: 4 February 2021
Accepted: 9 March 2021
Published: 2 April 2021

1. Introduction

Tumors are composed of multiple and heterogeneous sub-populations of cells including those endowed with self-renewal and multipotency features, denominated as cancer stem cells (CSCs) or cancer initiating cells (CICs) [1–7]. Bonnet et al. reported for the first time the presence of CSCs/CICs in acute myeloid leukemia [8]. Later, cells endowed with stemness properties were isolated from solid tumors, such as brain, breast, colorectal (CRC) and ovarian cancer [9–12]. Various methods are used for the identification of CSCs/CICs, including the analysis of expression of markers using flow cytometry, the detection of side population by Hoechst method, the tumor sphere formation, the aldehyde dehydrogenase-1 (ALDH-1) activity assay and the tumorigenicity in in vivo immunodeficient mice [10,13–15].

International Journal of
Molecular Sciences

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Review

Chemokine-Cytokine Networks in the Head and Neck Tumor Microenvironment

Sabah Nisar [1,†], Parvaiz Yousuf [2,†], Tariq Masoodi [3], Nissar A. Wani [4], Sheema Hashem [1], Mayank Singh [5], Geetanjali Sageena [6], Deepika Mishra [7], Rakesh Kumar [8], Mohammad Haris [1,9], Ajaz A. Bhat [1,*] and Muzafar A. Macha [10,*]

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Abstract: Head and neck squamous cell carcinomas (HNSCCs) are aggressive diseases with a dismal patient prognosis. Despite significant advances in treatment modalities, the five-year survival rate in patients with HNSCC has improved marginally and therefore warrants a comprehensive understanding of the HNSCC biology. Alterations in the cellular and non-cellular components of the HNSCC tumor micro-environment (TME) play a critical role in regulating many hallmarks of cancer development including evasion of apoptosis, activation of invasion, metastasis, angiogenesis, response to therapy, immune escape mechanisms, deregulation of energetics, and therefore the development of an overall aggressive HNSCC phenotype. Cytokines and chemokines are small secretory proteins produced by neoplastic or stromal cells, controlling complex and dynamic cell–cell interactions in the TME to regulate many cancer hallmarks. This review summarizes the current understanding of the complex cytokine/chemokine networks in the HNSCC TME, their role in activating diverse signaling pathways and promoting tumor progression, metastasis, and therapeutic resistance development.

Keywords: head and neck squamous cell carcinomas; cytokines; chemokines; tumor microenvironment; apoptosis; invasion; metastasis; angiogenesis; response to therapy; immune evasion

Citation: Nisar, S.; Yousuf, P.; Masoodi, T.; Wani, N.A.; Hashem, S.; Singh, M.; Sageena, G.; Mishra, D.; Kumar, R.; Haris, M.; et al. Chemokine-Cytokine Networks in the Head and Neck Tumor Microenvironment. *Int. J. Mol. Sci.* **2021**, *22*, 4584. https://doi.org/10.3390/ijms22094584

Academic Editor: Susan Costantini

Received: 20 February 2021
Accepted: 5 April 2021
Published: 27 April 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is a very aggressive disease with a dismal prognosis. With an annual incidence of ~800,000 new cases and 350,000 deaths worldwide, HNSCC is the sixth most common cancer globally [1]. HNSCC includes tumors of the oral cavity, hypopharynx, oropharynx, larynx and, paranasal sinuses and is clinically, pathologically, phenotypically, and biologically a heterogeneous disease [2]. Oral squamous

Seminars in Cell and Developmental Biology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

miRNAs as novel immunoregulators in cancer

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ARTICLE INFO

Keywords:
MiRNAs
Immune modulation
Cancer
Exosomes
Immune evasion

ABSTRACT

The immune system is a well-known vital regulator of tumor growth, and one of the main hallmarks of cancer is evading the immune system. Immune system deregulation can lead to immune surveillance evasion, sustained cancer growth, proliferation, and metastasis. Tumor-mediated disruption of the immune system is accomplished by different mechanisms that involve extensive crosstalk with the immediate microenvironment, which includes endothelial cells, immune cells, and stromal cells, to create a favorable tumor niche that facilitates the development of cancer. The essential role of non-coding RNAs such as microRNAs (miRNAs) in the mechanism of cancer cell immune evasion has been highlighted in recent studies. miRNAs are small non-coding RNAs that regulate a wide range of post-transcriptional gene expression in a cell. Recent studies have focused on the function that miRNAs play in controlling the expression of target proteins linked to immune modulation. Studies show that miRNAs modulate the immune response in cancers by regulating the expression of different immune-modulatory molecules associated with immune effector cells, such as macrophages, dendritic cells, B-cells, and natural killer cells, as well as those present in tumor cells and the tumor microenvironment. This review explores the relationship between miRNAs, their altered patterns of expression in tumors, immune modulation, and the functional control of a wide range of immune cells, thereby offering detailed insights on the crosstalk of tumor-immune cells and their use as prognostic markers or therapeutic agents.

Abbreviations: MHC, major histocompatibility complex; APC, antigen presenting cells; NK cells, natural killer cells; DCs, dendritic cells; Tregs, regulatory T cells; MDSCs, myeloid derived suppressor cells; PD-1, programmed cell death protein; IL, interleukin; STAT, signal transducer and activator; JAK, janus kinase; TAM, tumor associated macrophages; miRNAs, microRNAs; TME, tumor microenvironment; APC, antigen-presenting cells; AP&P, antigen processing and presentation; APM, antigen processing machinery; TAP1, antigen peptide transporter 1; CTLs, cytotoxic T lymphocytes; HOTAIR, Hox antisense intergenic RNA; CIK cells, cytokine-induced killer cells; DAP12, DNAX activating protein; IDO, indoleamine 2,3-dioxygenase; CTLA4, cytotoxic T-lymphocyte-associated protein 4; iNKT, invariant Natural Killer T cells; NPC, nasopharyngeal carcinoma; PC, pancreatic Cancer; LC, lung Cancer; LiC, Liver cancer; BC, Breast cancer; CRC, colorectal cancer; OC, ovarian cancer; PCa, Prostate Cancer.

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https://doi.org/10.1016/j.semcdb.2021.04.013
Received 6 February 2021; Received in revised form 7 April 2021; Accepted 13 April 2021

Please cite this article as: Saife N. Lone, *Seminars in Cell and Developmental Biology*, https://doi.org/10.1016/j.semcdb.2021.04.013

Corneal confocal microscopy identifies a reduction in corneal keratocyte density and sub-basal nerves in children with type 1 diabetes mellitus

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Received 11 February 2021
Revised 10 April 2021
Accepted 20 April 2021

To cite: Gad H, Al-Jarrah B, Saraswathi S, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2021-319057

ABSTRACT

Purpose To assess whether alterations in stromal keratocyte density are related to loss of corneal nerve fibres in children with type 1 diabetes mellitus (T1DM).

Methods Twenty participants with T1DM and 20 age-matched healthy controls underwent corneal confocal microscopy. Corneal sub-basal nerve morphology and corneal keratocyte density (KD) were quantified.

Results Corneal nerve fibre density (CNFD) (p<0.001), corneal nerve branch density (p<0.001), corneal nerve fibre length (CNFL) (p<0.001) and inferior whorl length (IWL) (p<0.001) were lower in children with T1DM compared with healthy controls. Anterior (p<0.03) and mid (p=0.03) stromal KDs were lower with no difference in posterior KD (PKD) in children with T1DM compared with controls. Age, duration of diabetes, height, weight and body mass index did not correlate with anterior (AKD), mid (MKD) or PKD. Inverse correlations were found between glycated haemoglobin and PKD (r=−0.539, p=0.026), bilirubin with MKD (r=−0.540, p=0.025) and PKD (r=−0.531, p=0.028) and 25-hydroxycholecalciferol with MKD (r=−0.583, p=0.018). CNFD, CNFL and IWL did not correlate with AKD, MKD or PKD.

Conclusion This study demonstrates a reduction in corneal nerves and anterior and mid stromal KD in children with T1DM, but no correlation between corneal nerve and keratocyte cell loss.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) affects over half a million children worldwide.[1 2] Diabetic neuropathy is a major complication in adults with T1DM resulting in neuropathic pain and foot ulceration.[3 4] Although, clinical neuropathy is rare, there are reports of neuropathy in children with T1DM.[5–8] We have previously used corneal confocal microscopy (CCM) to identify significant corneal nerve loss in adults[9] and adolescents[10–12] with T1DM, even those without diabetic retinopathy[13] or microalbuminuria.[14] In adults, corneal nerve loss is associated with painful diabetic neuropathy,[15] has good diagnostic utility for diabetic neuropathy[9 16] and predicts incident diabetic neuropathy.[17 18] The mechanisms underlying corneal nerve loss are complex, however in adults with diabetes, corneal nerve loss has been associated with age, glycated haemoglobin (HbA1c), body mass index (BMI), blood pressure, low-density lipoprotein cholesterol and triglycerides.[19–21] Our previous studies in children have shown no association between corneal nerve loss and the duration of diabetes, HbA1c or lipids.[12 13] This suggests that other factors may be important in the development of early corneal nerve damage.

Corneal keratocytes are fibroblast-like cells within the stroma that maintain the integrity and mechanical stability of the cornea.[22–24] Stromal keratocytes and activated fibroblasts have recently been shown to produce multiple pro-inflammatory and neurotrophic factors which have a dose-dependent effect on neurite outgrowth.[25] We have previously used CCM to quantify alterations in the epithelium, stromal keratocytes and endothelium in adults[26] and adolescents[13] with diabetes. A reduction in anterior mid and posterior keratocyte density has been correlated with corneal nerve loss in adults with type 1 and type 2 diabetes.[23] However, corneal nerve loss was found with preserved keratocyte density in adults without diabetic retinopathy with a reduction in keratocyte density only occurring in patients with diabetic retinopathy.[26] Recently we have shown reduced corneal nerve and keratocyte densities in obese patients with and without diabetes with a correlation between corneal nerve fibre length and anterior keratocyte density and an improvement in both nerve and keratocyte densities and triglycerides and BMI, after bariatric surgery.[27]

In children with T1DM we and others have shown loss of corneal nerves,[11 14] but with normal[13] or increased[11] keratocyte densities. In the present study, we have assessed whether clinical and metabolic alterations are associated with a change in anterior, mid and posterior stromal keratocyte density and corneal nerve fibre morphology in children with T1DM and healthy controls.

MATERIALS AND METHODS

Study subjects

Twenty participants with T1DM (age 14±2 years, diabetes duration 4.08±2.91 years, HbA1c 9.3%±2.1%) and 20 age-matched healthy controls were recruited from outpatient clinics in Sidra Medicine and underwent CCM. Patients with a history of any other cause of neuropathy,

Please cite this article in press as: Manoel et al., Deconstructing the mouse olfactory percept through an ethological atlas, Current Biology (2021), https://doi.org/10.1016/j.cub.2021.04.020

Current Biology

CellPress
OPEN ACCESS

Article

Deconstructing the mouse olfactory percept through an ethological atlas

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https://doi.org/10.1016/j.cub.2021.04.020

SUMMARY

Odor perception in non-humans is poorly understood. Here, we generated the most comprehensive mouse olfactory ethological atlas to date, consisting of behavioral responses to a diverse panel of 73 odorants, including 12 at multiple concentrations. These data revealed that mouse behavior is incredibly diverse and changes in response to odorant identity and concentration. Using only behavioral responses observed in other mice, we could predict which of two odorants was presented to a held-out mouse 82% of the time. Considering all 73 possible odorants, we could uniquely identify the target odorant from behavior on the first try 20% of the time and 46% within five attempts. Although mouse behavior is difficult to predict from human perception, they share three fundamental properties: first, odor valence parameters explained the highest variance of olfactory perception. Second, physicochemical properties of odorants can be used to predict the olfactory percept. Third, odorant concentration quantitatively and qualitatively impacts olfactory perception. These results increase our understanding of mouse olfactory behavior and how it compares to human odor perception and provide a template for future comparative studies of olfactory percepts among species.

INTRODUCTION

How sensory cues translate into perceptual objects or complex behaviors remains a major unanswered question in neuroscience. Odor transduction in the nose leads to odor perception and to changes in behavior or physiology (e.g., aggression and feeding) that are key for survival and reproduction, making the olfactory system an attractive model to address this question.[1,2]

Many studies have used mice to elucidate molecular, cellular, and neural processes underlying mammalian olfaction.[1] The proliferation of annotated genomes and high-throughput sequencing technologies have yielded new clues into the functional logic and the evolutionary dynamics of mammalian olfaction more broadly.[3–5] However, our understanding of olfactory perception derives from large psychophysical datasets in humans combined with chemoinformatic, statistical, and machine-learning tools.[6–11] These studies have yielded three key findings regarding human olfactory perception. First, the first principal component of human olfactory perception is highly associated (r = 0.79) with a single dimension—odor valence.[6,7,12] Second, the human olfactory perceptual ratings for most odorous molecules can be predicted from chemical structure with surprising accuracy (r = 0.3–0.7), a value limited primarily by rater reliability.[8] Third, odorant concentration can qualitatively alter perceived odor intensity and character.[9,13] Do these principles also apply to olfactory perception in non-humans?

Characterizing olfactory perception in an animal relies on accurately quantifying multiple behaviors in response to large numbers of odorants, ideally at various concentrations. This assumes that visible mouse behaviors either encode for mouse perception or at least report something informative about the meaning of the stimulus. For example, mice may exhibit differential behavioral responses depending on odor valence (attractive versus aversive), odor novelty, or implications of the presence of an odor for a broader behavioral strategy (e.g., exploration of surroundings). They may also use behavior to communicate odor information to conspecifics. Despite recent efforts,[14–25] a systematic characterization of various mouse behaviors in response to a large panel of diverse odorants and several concentrations is still lacking. This prevents a systematic understanding of mouse olfactory behavior and how it relates to perception in humans and other species and limits our ability to study the neural computations underlying the transformation of odor stimuli at the nose to odor objects in the brain.

Here, we generated and investigated a mouse atlas of odor-guided behaviors in response to a diverse panel of odorants, at

frontiers in Microbiology

ORIGINAL RESEARCH
published: 23 April 2021
doi: 10.3389/fmicb.2021.603151

Azithromycin Exhibits Activity Against *Pseudomonas aeruginosa* in Chronic Rat Lung Infection Model

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Pseudomonas aeruginosa forms biofilms in the lungs of chronically infected cystic fibrosis patients, which are tolerant to both the treatment of antibiotics and the host immune system. Normally, antibiotics are less effective against bacteria growing in biofilms; azithromycin has shown a potent efficacy in cystic fibrosis patients chronically infected with *P. aeruginosa* and improved their lung function. The present study was conducted to evaluate the effect of azithromycin on *P. aeruginosa* biofilm. We show that azithromycin exhibited a potent activity against *P. aeruginosa* biofilm, and microscopic observation revealed that azithromycin substantially inhibited the formation of solid surface biofilms. Interestingly, we observed that azithromycin restricted *P. aeruginosa* biofilm formation by inhibiting the expression of *pel* genes, which has been previously shown to play an essential role in bacterial attachment to solid-surface biofilm. In a rat model of chronic *P. aeruginosa* lung infection, we show that azithromycin treatment resulted in the suppression of quorum sensing-regulated virulence factors, significantly improving the clearance of *P. aeruginosa* biofilms compared to that in the placebo control. We conclude that azithromycin attenuates *P. aeruginosa* biofilm formation, impairs its ability to produce extracellular biofilm matrix, and increases its sensitivity to the immune system, which may explain the clinical efficacy of azithromycin in cystic fibrosis patients.

Keywords: Gram-negative bacteria, PA-14, PAO1, multidrug resistance, respiratory tract infection, *pel* genes, extracellular biofilm matrix, quorum sensing molecule

OPEN ACCESS

Edited by:
Mark Smeltzer,
University of Arkansas for Medical Sciences, United States

Reviewed by:
Giuseppantonio Maisetta,
University of Pisa, Italy
Oana Ciofu,
University of Copenhagen, Denmark

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Specialty section:
This article was submitted to Antimicrobials, Resistance and Chemotherapy, a section of the journal Frontiers in Microbiology

Received: *05 September 2020*
Accepted: *15 March 2021*
Published: *23 April 2021*

Citation:
Kumar M, Rao M, Mathur T, Barman TK, Joshi V, Chaira T, Singhal S, Pandya M, Al Khodor S, Upadhyay DJ and Masuda N (2021) Azithromycin Exhibits Activity Against Pseudomonas aeruginosa in Chronic Rat Lung Infection Model. Front. Microbiol. 12:603151. doi: 10.3389/fmicb.2021.603151

INTRODUCTION

Pseudomonas aeruginosa is the most common bacterial pathogen that causes biofilm-mediated chronic lung infections among cystic fibrosis (CF) patients (Faure et al., 2018; Maurice et al., 2018). *P. aeruginosa* has an innate propensity to attach to different solid surfaces and form biofilms, which enables the bacteria to resist both the host's innate immune system and treatments with antibiotics (Mulcahy et al., 2014). The treatment options for nosocomial Gram-negative infections are very limited. The antibiotics of choice for Gram-negative pathogens are parenteral carbapenems, such asimipenem and meropenemor quinolones (Bassetti et al., 2018). However, the poor activities of these antibiotics on bacterial biofilms and the increasing prevalence of multidrug-resistant

Nano Today 38 (2021) 101136

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

2D MXenes with antiviral and immunomodulatory properties: A pilot study against SARS-CoV-2

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ARTICLE INFO

Article history:
Received 5 January 2021
Received in revised form 22 February 2021
Accepted 15 March 2021
Available online 18 March 2021

Keywords:
MXene
Toxicity
Immune system
Antiviral properties

ABSTRACT

Two-dimensional transition metal carbides/carbonitrides known as MXenes are rapidly growing as multimodal nanoplatforms in biomedicine. Here, taking SARS-CoV-2 as a model, we explored the antiviral properties and immune-profile of a large panel of four highly stable and well-characterized MXenes - $Ti_3C_2T_x$, $Ta_4C_3T_x$, $Mo_2Ti_2C_3T_x$ and $Nb_4C_3T_x$. To start with antiviral assessment, we first selected and deeply analyzed four different SARS-CoV-2 genotypes, common in most countries and carrying the wild type or mutated spike protein. When inhibition of the viral infection was tested in vitro with four viral clades, $Ti_3C_2T_x$ in particular, was able to significantly reduce infection only in SARS-CoV-2/clade GR infected Vero E6 cells. This difference in the antiviral activity, among the four viral particles tested, highlights the importance of considering the viral genotypes and mutations while testing antiviral activity of potential drugs and nanomaterials. Among the other MXenes tested, $Mo_2Ti_2C_3T_x$ also showed antiviral properties.

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https://doi.org/10.1016/j.nantod.2021.101136

Briefings in Bioinformatics, 00(0), 2021, 1–14

doi: 10.1093/bib/bbab168
Problem Solving Protocol

Network-based identification of key master regulators associated with an immune-silent cancer phenotype

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Abstract

A cancer immune phenotype characterized by an active T-helper 1 (Th1)/cytotoxic response is associated with responsiveness to immunotherapy and favorable prognosis across different tumors. However, in some cancers, such an intratumoral immune activation does not confer protection from progression or relapse. Defining mechanisms associated with immune evasion is imperative to refine stratification algorithms, to guide treatment decisions and to identify candidates for immune-targeted therapy. Molecular alterations governing mechanisms for immune exclusion are still largely unknown. The availability of large genomic datasets offers an opportunity to ascertain key determinants of differential intratumoral immune response. We follow a network-based protocol to identify transcription regulators (TRs) associated with poor immunologic antitumor activity. We use a consensus of four different pipelines consisting of two state-of-the-art gene regulatory network inference techniques, regularized gradient boosting machines and ARACNE to determine TR regulons, and three separate enrichment techniques, including fast gene set enrichment analysis, gene set variation analysis and virtual inference of protein activity by enriched regulon analysis to identify the most important

Raghvendra Mall is a scientist at QCRI. His expertise lies in machine learning and computational biology. His research focuses on inferring gene regulatory networks and differential network analysis in complex biological networks.
Mohamad Saad is a scientist at QCRI. His area of expertise is statistical genetics and bioinformatics. His research work focuses on GWAS and imputation of missing genotypes in population- and family-based designs.
Jessica Roelands is a PhD student affiliated with Sidra Medicine and Leiden University. Her research aims to define immunogenomic drivers of cancer immune responsiveness with a specific focus on colon cancer.
Darawan Rinchai is an expert in the fields of immunology and bioinformatics. Her research focuses on defining immune-biomarkers associated with immune checkpoint blockade administration.
Khalid Kunji is a software engineer at QCRI with a background in biophysics and mathematics. His work includes protein property prediction, family-based imputation and other work in bioinformatics.
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Submitted: 10 September 2020; **Received (in revised form):** 24 March 2021

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Omega-3 fatty acid-rich fish oil supplementation prevents rosiglitazone-induced osteopenia in aging C57BL/6 mice and in vitro studies

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Rosiglitazone is an effective insulin-sensitizer, however associated with bone loss mainly due to increased bone resorption and bone marrow adiposity. We investigated the effect of the co-administration of fish oil rich in omega-3 fatty acids (FAs) on rosiglitazone-induced bone loss in C57BL/6 mice and the mechanisms underlying potential preventive effect. Mice fed the iso-caloric diet supplemented with fish oil exhibited significantly higher levels of bone density in different regions compared to the other groups. In the same cohort of mice, reduced activity of COX-2, enhanced activity of alkaline phosphatase, lower levels of cathepsin k, PPAR-γ, and pro-inflammatory cytokines, and a higher level of anti-inflammatory cytokines were observed. Moreover, fish oil restored rosiglitazone-induced down-regulation of osteoblast differentiation and up-regulation of adipocyte differentiation in C3H10T1/2 cells and inhibited the up-regulation of osteoclast differentiation of RANKL-treated RAW264.7 cells. We finally tested our hypothesis on human Mesenchymal Stromal Cells differentiated to osteocytes and adipocytes confirming the beneficial effect of docosahexaenoic acid (DHA) omega-3 FA during treatment with rosiglitazone, through the down-regulation of adipogenic genes, such as adipsin and FABP4 along the PPARγ/FABP4 axis, and reducing the capability of osteocytes to switch toward adipogenesis. Fish oil may prevent rosiglitazone-induced bone loss by inhibiting inflammation, osteoclastogenesis, and adipogenesis and by enhancing osteogenesis in the bone microenvironment.

Thiazolidinediones (TZDs, also known as glitazones) are a class of antidiabetic agents that act as insulin sensitizers. Rosiglitazone (RSG) and pioglitazone are the most commonly used anti-diabetic drugs of this class and they work by binding to the peroxisome proliferator-activated receptors (PPAR)-γ in fat cells and making the cells more responsive to insulin[1].

TZDs are recommended in the algorithm of the American College of Endocrinologists for the treatment of Type 2 Diabetes (T2D), as per the latest consensus statement in January 2020[2]. They are the only antihyperglycemic agents able to reduce insulin resistance, in addition to potent A1C-lowering properties associated with low risk of hypoglycemia and durable glycemic effects[2–4]. Pioglitazone may also confer cardiovascular diseases (CVD) benefits[3,5,6], while RSG has a neutral effect on CVD risk[7,8]. However, the use of TZDs has been limited by the onset of side effects, such as weight gain, increased bone fracture risk in postmenopausal females and elderly males, and an elevated risk for chronic edema or heart failure[2,9–12].

RSG (Avandia®, GlaxoSmithKline) is a potent TZD insulin sensitizer that decreases hyperglycemia by reducing insulin resistance in patients with T2D[4]. It is used as a stand-alone drug or in combination with metformin or glimepiride. Despite RSG's effectiveness at decreasing blood sugar in T2D, its use decreased dramatically as studies showed apparent associations with increased risks of heart attacks and death[13]. Although extensive

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Biomedicine & Pharmacotherapy 140 (2021) 111736

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Original article

Bifidobacterium reduction is associated with high blood pressure in children with type 1 diabetes mellitus

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ARTICLE INFO

Keywords:
Microbiota
Pediatric
Diabetes
Hypertension
Blood pressure
Dysbiosis

ABSTRACT

Children with Type 1 diabetes mellitus (T1DM) have an elevated risk of abnormal blood pressure (BP) measurements and patterns. Both hypertension and T1DM are well-known risk factors for cardiovascular disease and kidney failure. The human microbiome has been linked to both diabetes and hypertension, but the relationship between the gut microbiome and BP in children with T1DM is not well-understood. In this cross-sectional study, we examined the relationship between resting office BP and gut microbiota composition, diversity, and richness in children with T1DM and healthy controls. We recruited 29 pediatric subjects and divided them into three groups: healthy controls (HC, n = 5), T1DM with normal BP (T1DM-Normo, n = 17), and T1DM with elevated BP (T1DM-HBP, n = 7). We measured the BP, dietary and clinical parameters for each subject. We collected fecal samples to perform the 16s rDNA sequencing and to measure the short-chain fatty acids (SCFAs) level. The microbiome downstream analysis included the relative abundance of microbiota, alpha and beta diversity, microbial markers using Linear Discriminant effect size analysis (LEfSe), potential gut microbial metabolic pathways using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) and metabolic pathways validation using Statistical Inference of Associations between Microbial Communities And host phenotype (SIAMCAT) machine learning toolbox. Our study results showed that T1DM-HBP group had distinct gut microbial composition (at multiple taxonomic levels) and reduced diversity (richness and abundance) compared with T1DM-Normo and HC groups. Children with T1DM-HBP showed a significant reduction of *Bifidobacterium* levels (especially *B. adolescentis*, *B. bifidum*, and *B. longum*) compared to the T1DM-Normo group. We also observed unique gut-microbial metabolic pathways, such as elevated lipopolysaccharide synthesis and glutathione metabolism in children with T1DM-HBP compared to T1DM-Normo children. We can conclude that the reduction in the abundance of genus *Bifidobacterium* could play a significant role in elevating the BP in pediatric T1DM subjects. More studies are needed to corroborate our findings and further explore the potential contributing mechanisms we describe.

Abbreviations: BMI, Body mass index; BP, Blood pressure; CSII, continuous subcutaneous insulin infusion; DBP, Diastolic blood pressure; DBPI, Diastolic blood pressure index; GPR41, G-protein coupled receptor 41; GPR43, G-protein coupled receptor 43; GPR109a, G-protein coupled receptor 109a; GSH, Glutathione; g_UC, genus_unclassified; g/day, gram/day; HbA1c, Glycated Hemoglobin A1c; HC, Healthy control; HDL, High-density lipoprotein; HTN, Hypertension; iNOS, Inducible nitric oxide; IQR, Interquartile range; IR, Inflammatory response; Kcal/day, Kilocalorie/day; LEfSe, Linear discriminant analysis effect size; LDL, Low-density lipoprotein; LPS, Lipopolysaccharide; mg/day, milligram/day; μg/day, microgram/day; mmHg, millimeter mercury; MUFA, monounsaturated fatty acid; NO, Nitric oxide; Olfr78, Olfactory receptor 78; OTUs, Operational taxonomic units; OW/OB, Overweight/Obese; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; PUFA, Polyunsaturated fatty acid; QIIME, Quantitative Insights Into Microbial Ecology; SBP, Systolic blood pressure; SBPI, Systolic blood pressure index; SEM, Standard error of the mean; SCFAs, Short-chain fatty acids; SIAMCAT, Statistical Inference of Associations between Microbial Communities And host phenoType; T1DM, Type 1 diabetes mellitus; T1DM-HBP, Type 1 diabetes mellitus-high blood pressure; T1DM-Normo, Type 1 diabetes mellitus-normal blood pressure; T2DM, Type 2 diabetes mellitus; TG, Triglyceride.

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https://doi.org/10.1016/j.biopha.2021.111736
Received 11 March 2021; Received in revised form 4 May 2021; Accepted 11 May 2021
Available online 23 May 2021

Journal of *Personalized Medicine*

MDPI

Article

Prescription Pattern of Antidepressants and the Potential for Personalized Medicine in the Qatari Population

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Abstract: Studying the prescription pattern of medications will help in understanding potential unnecessary prescriptions, due to the trial-and-error method of prescribing, and the need for personalized medicine in a population. Therefore, in this study, our aim was to explore the prescribing pattern and off-label use of antidepressants in the Qatari population. We conducted a retrospective study of Qatari patients who received prescriptions for antidepressants from the major healthcare providers in Qatar, for a period of 24 months between June 2018 and May 2020. The number of patients, prescriptions, and diagnostic indications were analyzed. The chi-square test was used for identifying statistically significant association of the number of individuals prescribed with age category or gender. Of the 14,601 Qatari patients who were prescribed antidepressants, the majority were female (61%, $p < 2.2 \times 10^{-16}$), and were at or above 60 years of age (27%, $p < 2.2 \times 10^{-16}$). More numbers of selective serotonin reuptake inhibitors (SSRIs) (22,085 out of 48,031; 46%), were dispensed than other classes of antidepressants, with escitalopram (26%) at the top of the list. Preponderance of prescription of antidepressants for non-mental health diseases was observed. Population-level prescription trends, as we reported here, when combined with patient genetic variability and outcome data, will have the power to predict the potential for treatment failures and adverse effects of these medications in the population. We also recommend educating non-mental health prescribers about the adherence to evidence and guidelines to ensure patient safety while prescribing antidepressants.

Keywords: antidepressants; prescription pattern; Middle East

Citation: Bastaki, K.; El Anbari, M.; Ghuloum, S.; Jithesh, P.V. Prescription Pattern of Antidepressants and the Potential for Personalized Medicine in the Qatari Population. *J. Pers. Med.* **2021**, *11*, 406. https://doi.org/10.3390/jpm11050406

Academic Editor: Roy C. Ziegelstein

Received: 28 March 2021
Accepted: 2 May 2021
Published: 13 May 2021

1. Introduction

The burden of mental illness is increasing across the world; more than one in ten are estimated to live with a mental health disorder (MHD) [1]. In the eastern Mediterranean region, Qatar ranked second for premature mortality from MHDs [2]. In Qatar, almost 37% of adults receiving healthcare from a primary healthcare setting met diagnostic criteria for at least one MHD, with depression being the most commonly diagnosed MHD (14%), followed by anxiety disorders (10.3%) [3]. Another study from Qatar identified that 20% of participants had a generalized anxiety disorder, while 19% had a depressive disorder, and both studies showed that women had a higher risk of MHD [4].

An increase in the usage of antidepressants over the years was observed. For example, the introduction of selective serotonin reuptake inhibitors (SSRIs) in the late 1980s resulted in increased prescriptions of antidepressants, which doubled in 10 years in western countries [5]. An increase in length of the prescribing period was also observed, putting patients at higher risk of adverse effects; this often leads to an increased rate of mortality, especially in elderly patients [6]. The use (and overuse) of antidepressants for mental illnesses are often debated (i.e., people are either for or against it) [7–9]. However, their use in treating non-mental health diseases have also become widespread, even without guidelines or evidence for their appropriateness in such conditions [10–12]. Thus, understanding the

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Molecular Sciences

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Immunomodulatory Effects of Vitamin D Supplementation in a Deficient Population

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Abstract: In addition to its canonical functions, vitamin D has been proposed to be an important mediator of the immune system. Despite ample sunshine, vitamin D deficiency is prevalent (>80%) in the Middle East, resulting in a high rate of supplementation. However, the underlying molecular mechanisms of the specific regimen prescribed and the potential factors affecting an individual's response to vitamin D supplementation are not well characterized. Our objective is to describe the changes in the blood transcriptome and explore the potential mechanisms associated with vitamin D3 supplementation in one hundred vitamin D-deficient women who were given a weekly oral dose (50,000 IU) of vitamin D3 for three months. A high-throughput targeted PCR, composed of 264 genes representing the important blood transcriptomic fingerprints of health and disease states, was performed on pre and post-supplementation blood samples to profile the molecular response to vitamin D3. We identified 54 differentially expressed genes that were strongly modulated by vitamin D3 supplementation. Network analyses showed significant changes in the immune-related pathways such as TLR4/CD14 and IFN receptors, and catabolic processes related to NF-kB, which were subsequently confirmed by gene ontology enrichment analyses. We proposed a model for vitamin D3 response based on the expression changes of molecules involved in the receptor-mediated intra-cellular signaling pathways and the ensuing predicted effects on cytokine production. Overall, vitamin D3 has a strong effect on the immune system, G-coupled protein receptor signaling, and the ubiquitin system. We highlighted the major molecular changes and biological processes induced by vitamin D3, which will help to further investigate the effectiveness of vitamin D3 supplementation among individuals in the Middle East as well as other regions.

Keywords: transcriptomic; 25-hydroxyvitamin D; 25(OH)D; immune system; immune response; vitamin D deficiency; Qatar

Citation: Garand, M.; Toufiq, M.; Singh, P.; Huang, S.S.Y.; Tomei, S.; Mathew, R.; Mattei, V.; Al Wakeel, M.; Sharif, E.; Al Khodor, S. Immunomodulatory Effects of Vitamin D Supplementation in a Deficient Population. *Int. J. Mol. Sci.* **2021**, *22*, 5041. https://doi.org/10.3390/ijms22095041

Academic Editor: Patrick Provost

Received: 11 March 2021
Accepted: 6 April 2021
Published: 10 May 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Vitamin D is well recognized for its functions in the homeostasis of calcium and bone mineralization [1]. In many Arab countries, including Qatar, a high prevalence of vitamin D deficiency is observed despite ample sunshine [2]. Women cover most of their skin for cultural reasons and are therefore especially affected [3–6]. Additionally, a high prevalence of vitamin D deficiency was reported among college-age women in Qatar [7]. Thus, vitamin D deficiency is a national interest to Qatar and needs to be better understood. Vitamin D supplementation (D2 or D3) is usually prescribed to treat those with suboptimal levels; however, the response to supplementation vary widely among individuals—with some individuals demonstrating virtually no absorption of oral D2/D3 [8–10]. The reason for

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Review

COVID-19 Infection during Pregnancy: Risk of Vertical Transmission, Fetal, and Neonatal Outcomes

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Abstract: The COVID-19 pandemic is a worldwide, critical public health challenge and is considered one of the most communicable diseases that the world had faced so far. Response and symptoms associated with COVID-19 vary between the different cases recorded, but it is amply described that symptoms become more aggressive in subjects with a weaker immune system. This includes older subjects, patients with chronic diseases, patients with immunosuppression treatment, and pregnant women. Pregnant women are receiving more attention not only because of their altered physiological and immunological function but also for the potential risk of viral vertical transmission to the fetus or infant. However, very limited data about the impact of maternal infection during pregnancy, such as the possibility of vertical transmission in utero, during birth, or via breastfeeding, is available. Moreover, the impact of infection on the newborn in the short and long term remains poorly understood. Therefore, it is vital to collect and analyze data from pregnant women infected with COVID-19 to understand the viral pathophysiology during pregnancy and its effects on the offspring. In this article, we review the current knowledge about pre-and post-natal COVID-19 infection, and we discuss whether vertical transmission takes place in pregnant women infected with the virus and what are the current recommendations that pregnant women should follow in order to be protected from the virus.

Keywords: SARS-CoV-2; coronavirus; pregnancy outcomes; ACE-2 receptor; immune response; placental antibody transfer

Citation: Saadaoui, M.; Kumar, M.; Al Khodor, S. COVID-19 Infection during Pregnancy: Risk of Vertical Transmission, Fetal, and Neonatal Outcomes. *J. Pers. Med.* **2021**, *11*, 483. https://doi.org/10.3390/jpm11060483

Academic Editor: Philip P. Foster

Received: 18 February 2021
Accepted: 20 May 2021
Published: 28 May 2021

1. Introduction

Pregnancy is an important and "formative period" governed by series of interconnected molecular and cellular mechanisms aimed to promote maternal homeostasis and maintain an optimal fetal-placental interaction while supporting fetal growth [1,2]. Despite being tightly regulated, many factors/events can disrupt this balance and lead to adverse pregnancy outcomes [3–5], which may result in failing the pregnancy and in few cases of maternal death [3,4] As per the UNICEF (United Nation United Nations International Children's Emergency Fund), one pregnant woman or newborn dies every 11 s worldwide [6]. This great risk on pregnant women and babies' health increases dramatically during pandemics [7].

Pregnant women are considered one of the most susceptible groups in a population, as changes during pregnancy, such as decreased functional residual capacity as well as changes in cellular immunity, can increase the risk of serious illness in response to viral infections and the risk of vertical transmission [8]. Vertical transmission is defined as the possibility of transmission from a mother to her fetus during the antepartum and intrapartum periods or to the neonate during the postpartum period, and it can occur via the placenta, body fluid contact during childbirth, or through direct contact owing to breastfeeding after birth [9]. During pregnancy, the placenta acts as a barrier set to avoid transmission of infectious pathogens from the mother to her fetus; however, some infectious agents can cross the placental barrier, leading, in some cases, to congenital infections [9,10].

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Review

Personalized Nutrition Approach in Pregnancy and Early Life to Tackle Childhood and Adult Non-Communicable Diseases

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Abstract: The development of childhood and adult non-communicable diseases (NCD) is associated with environmental factors, starting from intrauterine life. A new theory finds the roots of epigenetic programming in parental gametogenesis, continuing during embryo development, fetal life, and finally in post-natal life. Maternal health status and poor nutrition are widely recognized as implications in the onset of childhood and adult diseases. Early nutrition, particularly breastfeeding, also plays a primary role in affecting the health status of an individual later in life. A poor maternal diet during pregnancy and lack of breastfeeding can cause a nutrient deficiency that affects the gut microbiota, and acts as a cofactor for many pathways, impacting the epigenetic controls and transcription of genes involved in the metabolism, angiogenesis, and other pathways, leading to NCDs in adult life. Both maternal and fetal genetic backgrounds also affect nutrient adsorption and functioning at the cellular level. This review discusses the most recent evidence on maternal nutrition and breastfeeding in the development of NCD, the potentiality of the omics technologies in uncovering the molecular mechanisms underlying it, with the future prospective of applying a personalized nutrition approach to prevent and treat NCD from the beginning of fetal life.

Keywords: precision nutrition; pregnancy; breastfeeding; non-communicable diseases; gut microbiota; nutrigenetics; epigenetics; transcriptomics

Citation: Alabduljabbar, S.; Zaidan, S.A.; Lakshmanan, A.P.; Terranegra, A. Personalized Nutrition Approach in Pregnancy and Early Life to Tackle Childhood and Adult Non-Communicable Diseases. *Life* **2021**, *11*, 467. https://doi.org/10.3390/life11060467

Academic Editors: Giacomo Biasucci and Elvira Verduci

Received: 31 March 2021
Accepted: 11 May 2021
Published: 24 May 2021

1. Introduction

Nutrition plays an important role at all life stages—before and during pregnancy, lactation, infancy, and childhood, as well as during adult life. Maternal nutrition has a major impact on the infant, not only because the nutrient exchange through the placenta and breast milk is involved in fetal and infant growth, but it also plays a role in determining the offspring's risk of developing non-communicable diseases (NCDs) [1–3]. NCDs are defined as non-infectious diseases that progress slowly, but become chronic; they usually require long-term treatment. NCDs include cardiovascular disease (CVD), type 2 diabetes (T2D), metabolic syndrome, etc. [1]. Recent studies have investigated the roles of pregnancy and infancy as the most critical stages that influence the risks of NCDs in childhood and adult life. New nutritional recommendations were developed to reduce the burden of NCDs in future generations [4].

In the last few years, the food science have started to analyze the effects of nutrients and dietary behaviors on cellular functions and gene modulation This new approach is defined as precision nutrition, where genetic background as well as microbiota are taken into account, to understand the response to diet and to single nutrients intake, and to tackle metabolic diseases (e.g., NCDs) [5,6].

Since there is limited evidence for personalized nutrition in pregnancy and early life, this review aims to summarize current data and perspectives on the roles of diet, nutrigenetics, gut microbiome, epigenetics, and transcriptomics in pregnancy and breastfeeding, contributing to develop NCDs in the offspring.

frontiers in Oncology

REVIEW
published: 28 May 2021
doi: 10.3389/fonc.2021.635488

Cutaneous Melanoma Classification: The Importance of High-Throughput Genomic Technologies

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Cutaneous melanoma is an aggressive tumor responsible for 90% of mortality related to skin cancer. In the recent years, the discovery of driving mutations in melanoma has led to better treatment approaches. The last decade has seen a genomic revolution in the field of cancer. Such genomic revolution has led to the production of an unprecedented mole of data. High-throughput genomic technologies have facilitated the genomic, transcriptomic and epigenomic profiling of several cancers, including melanoma. Nevertheless, there are a number of newer genomic technologies that have not yet been employed in large studies. In this article we describe the current classification of cutaneous melanoma, we review the current knowledge of the main genetic alterations of cutaneous melanoma and their related impact on targeted therapies, and we describe the most recent high-throughput genomic technologies, highlighting their advantages and disadvantages. We hope that the current review will also help scientists to identify the most suitable technology to address melanoma-related relevant questions. The translation of this knowledge and all actual advancements into the clinical practice will be helpful in better defining the different molecular subsets of melanoma patients and provide new tools to address relevant questions on disease management. Genomic technologies might indeed allow to better predict the biological - and, subsequently, clinical - behavior for each subset of melanoma patients as well as to even identify all molecular changes in tumor cell populations during disease evolution toward a real achievement of a personalized medicine.

Keywords: melanoma, genomics, next-generation sequencing, DNA, mutations

OPEN ACCESS

Edited by:
Giuseppe Palmieri,
National Research Council (CNR), Italy

Reviewed by:
Panagiotis Paliogiannis,
Azienda Ospedaliero Universitaria Sassari, Italy
Camelia Quek,
Melanoma Institute Australia, Australia
Filippo Fraggetta,
Cannizzaro Hospital, Italy

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Specialty section:
This article was submitted to Skin Cancer, a section of the journal Frontiers in Oncology

Received: *30 November 2020*
Accepted: *30 March 2021*
Published: *28 May 2021*

Citation:
Scatena C, Murtas D and Tomei S (2021) Cutaneous Melanoma Classification: The Importance of High-Throughput Genomic Technologies. Front. Oncol. 11:635488. doi: 10.3389/fonc.2021.635488

INTRODUCTION ON CUTANEOUS MELANOMA

Cutaneous melanoma represents an aggressive tumor with a continuous increase in incidence, although mortality rates have begun to decline thanks to promising new targeted treatments (1). The incidence of cutaneous melanoma is increasing in white populations worldwide, in particular if people receive excessive sun exposure (2–4). In the United States the incidence is 20-30 cases per 100,000 inhabitants, while in Australia it is particularly high, with a rate of 50-60 cases per 100,000

Molecular Therapy
Oncolytics
Original Article

MicroRNA-sensitive oncolytic measles virus for chemovirotherapy of pancreatic cancer

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Advanced pancreatic cancer is characterized by few treatment options and poor outcomes. Oncolytic virotherapy and chemotherapy involve complementary pharmacodynamics and could synergize to improve therapeutic efficacy. Likewise, multimodality treatment may cause additional toxicity, and new agents have to be safe. Balancing both aims, we generated an oncolytic measles virus for 5-fluorouracil-based chemovirotherapy of pancreatic cancer with enhanced tumor specificity through microRNA-regulated vector tropism. The resulting vector encodes a bacterial prodrug convertase, cytosine deaminase-uracil phosphoribosyl transferase, and carries synthetic miR-148a target sites in the viral *F* gene. Combination of the armed and targeted virus with 5-fluorocytosine, a prodrug of 5-fluorouracil, resulted in cytotoxicity toward both infected and bystander pancreatic cancer cells. In pancreatic cancer xenografts, a single intratumoral injection of the virus induced robust *in vivo* expression of prodrug convertase. Based on intratumoral transgene expression kinetics, we devised a chemovirotherapy regimen to assess treatment efficacy. Concerted multimodality treatment with intratumoral virus and systemic prodrug administration delayed tumor growth and prolonged survival of xenograft-bearing mice. Our results demonstrate that 5-fluorouracil-based chemovirotherapy with microRNA-sensitive measles virus is an effective strategy against pancreatic cancer at a favorable therapeutic index that warrants future clinical translation.

INTRODUCTION

Patients with pancreatic ductal adenocarcinoma (PDAC) frequently present with unresectable tumors or develop metastases despite primary resection.[1] Treatment options for these patients are limited to palliative chemotherapy and best supportive care. Fluorinated pyrimidines were the first substances with clinical benefit in PDAC, leading to approval of gemcitabine (2,2-difluorodeoxycytidine) in 1996.[2] Outcomes have been improved with subsequent combination chemotherapies, several of which incorporate 5-fluorouracil (2,4-dioxo-5-fluoropyrimidine [5-FU]).[3] Today, systemic 5-FU with irinotecan and oxaliplatin (FOLFIRINOX) is the first-line regimen for advanced PDAC in patients with good performance status.[4] Fluoropyrimidine-based adjuvant chemotherapy includes dose-modified FOLFIRINOX or gemcitabine plus capecitabine (5-fluoro-*N*-[(pentyloxy)carbonyl]-deoxycytidine), a prodrug of 5-FU.[5,6] However, 5-year overall survival rates of ~9% underline that in most cases PDAC recurs and remains treatment-refractory despite multidisciplinary management.[7]

Oncolytic viruses (OVs) constitute a class of cancer therapeutics based on replication-competent viral vectors. Using multiple mechanisms of action, OVs may be capable of overcoming resistance to standard cancer therapies.[8–10] Clinical observations of measles virus (MeV) inducing anti-tumor effects in naturally infected hosts motivated the generation of oncolytic MeV from attenuated vaccine strains.[11] The MeV platform has since been developed toward clinical applicability in several tumor entities.[12–15] To this end, we and others have engineered MeV to express a wide range of therapeutic transgenes.[16–26]

Prodrug convertases catalyze the bioactivation of drugs from nontoxic precursors and can be used to enrich tumor tissue for active antineoplastics.[27] Well-studied examples include a fusion protein of two *Escherichia coli* enzymes, cytosine deaminase and uracil phosphoribosyl transferase (CD-UPRT), which converts 5-fluorocytosine (5-FC) into 5-FU and its active metabolite 5-fluorouridine monophosphate (5-FUMP).[28,29] We reasoned that the combination of

Received 12 November 2020; accepted 28 April 2021;
https://doi.org/10.1016/j.omto.2021.04.015.

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IMMUNOLOGICAL INVESTIGATIONS
https://doi.org/10.1080/08820139.2020.1770784

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Identifying Novel Mutations in Iranian Patients with LPS-responsive Beige-like Anchor Protein (LRBA) Deficiency

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ABSTRACT

LPS-responsive beige-like anchor protein (LRBA) deficiency is a monogenic primary immunodeficiency characterized by a heterogeneous spectrum of clinical manifestations associated with immune dysregulation. In this study, we reported clinical, immunologic, and genetic evaluation of two Iranian patients from unrelated families, both suffering from recurrent respiratory tract infections, failure to thrive, interstitial lung disease, autoimmune cytopenia, and hypogammaglobulinemia. Pulmonary abscess in one patient and persistent enteropathy in another were also observed. Further investigations revealed causative mutations in the exon (c.2166_2766del) and intron (c.4730–3 T > G) of the *LRBA* gene. These results may provide further elucidation of the clinical phenotypes and responsible genetic factors of LRBA deficiency.

KEYWORDS

LPS-responsive beige-like anchor protein deficiency; LRBA; immune dysregulation; autoimmunity; enteropathy

Introduction

LPS-responsive and beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by biallelic mutations in the *LRBA* gene leading to regulatory T cell defects and immune dysregulation (Azizi et al. 2018c). LRBA deficiency is characterized by a broad spectrum of clinical manifestations, predominantly including recurrent respiratory or gastrointestinal tract infections, autoimmunity, lymphoproliferative disorders, enteropathy, and allergic symptoms (Alkhairy et al. 2015; Gamez-Diaz et al. 2016).

The most frequent laboratory findings include hypogammaglobulinemia, normal T cell counts, diminished numbers of regulatory T cells (Tregs) and natural killer cells, and B-cell

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Supplemental data for this article can be accessed here.

Yadav et al. *Translational Psychiatry* (2021)11:349
https://doi.org/10.1038/s41398-021-01473-w

Translational Psychiatry

REVIEW ARTICLE Open Access

Genetic variations influence brain changes in patients with attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a neurological and neurodevelopmental childhood-onset disorder characterized by a persistent pattern of inattentiveness, impulsiveness, restlessness, and hyperactivity. These symptoms may continue in 55–66% of cases from childhood into adulthood. Even though the precise etiology of ADHD is not fully understood, it is considered as a multifactorial and heterogeneous disorder with several contributing factors such as heritability, auxiliary to neurodevelopmental issues, severe brain injuries, neuroinflammation, consanguineous marriages, premature birth, and exposure to environmental toxins. Neuroimaging and neurodevelopmental assessments may help to explore the possible role of genetic variations on ADHD neuropsychobiology. Multiple genetic studies have observed a strong genetic association with various aspects of neuropsychobiological functions, including neural abnormalities and delayed neurodevelopment in ADHD. The advancement in neuroimaging and molecular genomics offers the opportunity to analyze the impact of genetic variations alongside its dysregulated pathways on structural and functional derived brain imaging phenotypes in various neurological and psychiatric disorders, including ADHD. Recently, neuroimaging genomic studies observed a significant association of brain imaging phenotypes with genetic susceptibility in ADHD. Integrating the neuroimaging-derived phenotypes with genomics deciphers various neurobiological pathways that can be leveraged for the development of novel clinical biomarkers, new treatment modalities as well as therapeutic interventions for ADHD patients. In this review, we discuss the neurobiology of ADHD with particular emphasis on structural and functional changes in the ADHD brain and their interactions with complex genomic variations utilizing imaging genetics methodologies. We also highlight the genetic variants supposedly allied with the development of ADHD and how these, in turn, may affect the brain circuit function and related behaviors. In addition to reviewing imaging genetic studies, we also examine the need for complementary approaches at various levels of biological complexity and emphasize the importance of combining and integrating results to explore biological pathways involved in ADHD disorder. These approaches include animal models, computational biology, bioinformatics analyses, and multimodal imaging genetics studies.

Background

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous neurobiological disorder of inattention, impulsivity, and hyperactivity, affecting 5–7% of children worldwide[1–4]. Severity status and symptoms of ADHD vary throughout a person's lifespan; however,

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Article type : Original Article

Original article

The Epidemiology, Genetic Landscape and Classification of Childhood Diabetes Mellitus in the State of Qatar

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDI.13610

Word count- 3930

Abstract

Aims- To study the epidemiology, genetic landscape and causes of childhood diabetes mellitus (DM) in the State of Qatar.

Materials and methods- All patients (0-18 years) with DM underwent biochemical, immunological and genetic testing. ADA guidelines were used to classify types of DM. The incidence and prevalence of all the different types of DM were calculated.

Results- Total number of children with DM was 1325 (Type 1 (n=1096, ≥1 antibody), Type 2 (n=104), Type 1B (n=53), MODY (n=20), monogenic autoimmune (n=4), Neonatal Diabetes Mellitus (NDM) (n=10), syndromic DM (n=23) and double DM (n=15)). The incidence and prevalence of type 1 diabetes were 38.05 and 249.73 per 100,000 respectively and for type 2 were 2.51 and 23.7 per 100,000 respectively. Incidence of NDM was 34.4 per 1,000,000 live births and in indigenous Qataris incidence was 43.6. The prevalence of *type 1 diabetes* and *type 2 diabetes* in Qatari children was double to other nationalities. The prevalence of MODY in Qatar was 4.56 per 100,000.

Conclusions- This is the first prospective and comprehensive study to document the epidemiology and genetic landscape of childhood DM in this region. Qatar has the 4th highest incidence of type 1 DM with the incidence and prevalence being higher in Qatari compared to non-Qatari. The prevalence of type 2 DM is also higher in Qatar than the western countries. The incidence of NDM is the second highest in the world. *GCK* is the most common form of MODY and a large number of patients have type1B DM.

Key words- Epidemiology,Paediatric diabetes, type 1 diabetes, type 2 diabetes.

Introduction

Diabetes Mellitus (DM) is a chronic metabolic condition with hyperglycaemia resulting from inadequate production of insulin or resistance to insulin action. The chronic hyperglycaemia leads to macro and microvascular complications (1). The global burden of DM is rapidly increasing with an estimated average increase of 3-4% in

Received: 28 February 2020 | Revised: 3 September 2020 | Accepted: 4 May 2021

DOI: 10.1002/mgg3.1709

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Genetic evaluation of cardiomyopathies in Qatar identifies enrichment of pathogenic sarcomere gene variants and possible founder disease mutations in the Arabs

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Funding information
This work was supported by Sidra Medicine (SDR200038), a member of Qatar Foundation.

Abstract

Background: Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are serious inherited heart diseases with various causative mutations identified. The full spectrum of causative mutations remains to be discovered, especially in understudied populations.

Methods: Here, we established the DOHA Registry and Biobank for cardiomyopathies in Qatar, followed by sequencing of 174 genes on 51 HCM and 53 DCM patients, and 31 relatives.

Results: In HCM, the analysis of 25 HCM-associated genes showed that 20% of HCM cases had putative pathogenic variants for cardiomyopathy, mainly in sarcomere genes. Additional 49% of HCM cases had variants of uncertain significance, while 31% of HCM cases had likely benign variant(s) or had no variants identified within the analyzed HCM genes. In DCM, 56 putative DCM genes were analyzed. Eight percent of DCM cases had putative pathogenic variants for DCM, in the *TTN* gene while 70% of cases had variants of uncertain significance, in the analyzed DCM genes, that will need further pathogenicity assessment. Moreover, 22% of DCM cases remain unexplained, by having likely benign variant(s) or having no variants detected in any of the analyzed DCM genes.

Conclusion: We identified or replicated at least four recurrent variants among cardiomyopathy patients, which could be founder disease mutations in the Arabic population, including a frameshift variant (c.1371_1381dupTATCCAGTTAT) of unknown significance in the *FKTN* gene which seems to cause DCM in homozygosity, and HCM in heterozygosity. *In vivo* and/or *in vitro* functional validation need to be pursued in order to assess the pathogenicity of the identified variants.

KEYWORDS
cardiomyopathy, targeted sequencing, genetic variants, Qatar

HHS Public Access
Author manuscript
J Immunol. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:
J Immunol. 2021 July 01; 207(1): 133–152. doi:10.4049/jimmunol.2001451.

Genetic, immunological, and clinical features of 32 patients with autosomal recessive STAT1 deficiency

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Authorship contributions

Most of the experiments were performed by TLV under the supervision of JB and JLC. MB and LAb provided the founder effect data. AES, AS, BAS, HEG, GEE, PT, MC, YAT, SEB, IM,, MA, TC, RF, PDA, RB, LAl, MD, HAM, IH, CS, FH, LMK, ADM, NAK, MAH, SHA, SAM took care of the patients and participated in data collection. FR performed viral serological tests, NM performed PhIP-Seqanalysis. VJJ, AES, ANP, MR, ALN, COQ, JR, SBD contributed new reagents/analytical tools, MT, NS, SS, SF and SO made the *STAT1* plasmids and performed experiments in the overexpression system. JB and TLV recorded the clinical data and created the Figures. TLV, JLC and JB wrote the paper. All authors commented on and discussed the paper.

Disclosure of Conflicts of Interest

The authors have declared that no conflict of interest exists.

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Abstract

Autosomal recessive (AR) STAT1 deficiency is a severe inborn error of immunity disrupting cellular responses to type I, II, and III IFNs, and IL-27, conferring a predisposition to both viral and mycobacterial infections. We report the genetic, immunological, and clinical features of an international cohort of 32 patients from 20 kindreds: 24 patients with complete deficiency and 8 patients with partial deficiency. Twenty-four patients suffered from mycobacterial disease (BCG =13, environmental mycobacteria =10, or both in one patient). Fifty-four severe viral episodes occurred in 16 patients, mainly caused by *Herpesviridae* viruses. Attenuated live MMR and/or VZV vaccines triggered severe reactions in the five patients with complete deficiency. Seven patients developed features of hemophagocytic syndrome. Twenty-one patients died, and death was almost twice as likely in patients with complete STAT1 deficiency than in those with partial STAT1 deficiency. All but one of the eight survivors with AR complete deficiency underwent hematopoietic stem cell transplantation (HSCT). Overall survival after HSCT was 64%. A diagnosis of AR STAT1 deficiency should be considered in children with mycobacterial and/or viral infectious diseases. It is important to distinguish between complete and partial forms of AR STAT1 deficiency, as their clinical outcome and management differ significantly.

Introduction

STAT1 is a transcription factor governing cellular responses to to type I, II, and III interferons (IFN) and IL-27. Autosomal recessive (AR) STAT1 deficiency (OMIM #613796) is an inborn error of immunity (IEI) responsible for both viral and intramacrophagic bacterial diseases, including mycobacterial diseases in particular. AR complete STAT1 deficiency due to biallelic *STAT1* null mutations was first described in 2003 (1–6). Its clinical infectious phenotype is probably as severe as that of severe combined immunodeficiencies (SCID). It may be considered a “severe innate immunodeficiency”, but with the caveat that the defect is not restricted to innate leukocytes, instead also affecting adaptive leukocytes and even cell types other than leukocytes, as the receptors for type I and III IFNs are ubiquitously and broadly expressed, respectively, and control a major arm of non-leukocytic cell-intrinsic immunity. Loss-of-function (LOF) *STAT1* alleles result in a complete absence of STAT1 expression and function, in terms of the responses to type I, II, and III IFNs, and IL-27 (1, 4–6). Seven unrelated patients with AR complete STAT1 deficiency have been described to date. All suffered from disseminated mycobacterial infection and/or life-threatening viral infections within the first few months of life. The prognosis of this condition is clearly poor, as four of these patients died before the age of two years (1, 4, 7). Hematopoietic stem cell transplantation (HSCT) was performed in five patients, including the three survivors, all of whom were still well, up to nine years after HSCT, at their last reported follow-up visit (3–6). Some patients display AR partial STAT1 deficiency because they carry one (n=1) or two (n=4) hypomorphic mutant alleles

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01388-5

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Inherited PD-1 deficiency underlies tuberculosis and autoimmunity in a child

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The pathophysiology of adverse events following programmed cell death protein 1 (PD-1) blockade, including tuberculosis (TB) and autoimmunity, remains poorly characterized. We studied a patient with inherited PD-1 deficiency and TB who died of pulmonary autoimmunity. The patient's leukocytes did not express PD-1 or respond to PD-1-mediated suppression. The patient's lymphocytes produced only small amounts of interferon (IFN)-γ upon mycobacterial stimuli, similarly to patients with inborn errors of IFN-γ production who are vulnerable to TB. This phenotype resulted from a combined depletion of Vδ2$^+$ γδ T, mucosal-associated invariant T and CD56^{bright} natural killer lymphocytes and dysfunction of other T lymphocyte subsets. Moreover, the patient displayed hepatosplenomegaly and an expansion of total, activated and RORγT$^+$ CD4$^-$CD8$^-$ double-negative αβ T cells, similar to patients with *STAT3* gain-of-function mutations who display lymphoproliferative autoimmunity. This phenotype resulted from excessive amounts of STAT3-activating cytokines interleukin (IL)-6 and IL-23 produced by activated T lymphocytes and monocytes, and the STAT3-dependent expression of RORγT by activated T lymphocytes. Our work highlights the indispensable role of human PD-1 in governing both antimycobacterial immunity and self-tolerance, while identifying potentially actionable molecular targets for the diagnostic and therapeutic management of TB and autoimmunity in patients on PD-1 blockade.

About 25% of the global population is estimated to be infected with *Mycobacterium tuberculosis* (Mtb)[1], but only 5–10% of infected individuals develop TB in their lifetime[2]. Human genetics is a strong determinant of TB following infection with Mtb[3]. Two rare monogenic inborn errors of immunity (IEIs) have been reported to underlie TB in multiple kindreds: autosomal recessive (AR) complete interleukin-12 receptor β1 (IL-12Rβ1)[4] and tyrosine kinase 2 (TYK2)[5] deficiencies. Both disorders underlie TB by impeding IFN-γ production by T lymphocytes and natural killer (NK) lymphocytes in response to IL-12 and IL-23 (refs. [4,5]). We also recently described a common monogenic IEI, homozygosity for TYK2 P1104A, which selectively disrupts cellular responses to IL-23 (ref. [6]) and underlies about 1% of TB cases in humans of European descent[7]. The single P1104A allele originated in the ancestors of Western Europeans about 30,000 years ago, and its frequency has drastically decreased in Europe over the last 2,000 years due to the negative selection imposed by TB[8]. Autoimmunity is another substantial public health burden. Monogenic forms of autoimmunity have provided insight into genes governing self-tolerance in humans, including central T cell tolerance (for example, mutations in *AIRE*), regulatory T cells (T_{reg} cells; for example, *FOXP3*, *CTLA4* and *LRBA*), and the deletion of self-reactive CD4$^-$CD8$^-$ double-negative (DN) αβ T cells (for example, *FAS*). Only two IEIs to date have been shown to underlie both mycobacterial disease and autoimmunity, albeit with incomplete penetrance: heterozygosity for gain-of-function (GOF) variants of *STAT1* (ref. [9]) and *STAT3* (refs. [10–12]). The pathogenesis of mycobacterial diseases in patients with these conditions remains unexplained. Here, we studied a patient who suffered from life-threatening abdominal TB and died of pulmonary autoimmunity. The patient's older sibling also died of unexplained pneumonitis. We hypothesized that a single genetic lesion was responsible for the two unusually severe immunopathological phenotypes.

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Received: 15 September 2020 | Revised: 9 May 2021 | Accepted: 12 May 2021 | Published online: 5 June 2021

DOI: 10.1002/ctm2.434

CLINICAL AND TRANSLATIONAL MEDICINE Open Access

WILEY

RESEARCH ARTICLE

Integrated transcriptional-phenotypic analysis captures systemic immunomodulation following antiangiogenic therapy in renal cell carcinoma patients

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Funding information
Associazione Italiana per la Ricerca sul Cancro (AIRC) Special Program Innova-

Abstract

Background: The combination of immune checkpoint blockade (ICB) with standard therapies is becoming a common approach for overcoming resistance to cancer immunotherapy in most human malignancies including metastatic renal cell carcinoma (mRCC). In this regard, insights into the immunomodulatory properties of antiangiogenic agents may help designing multidrug schedules based on specific immune synergisms.

Methods: We used orthogonal transcriptomic and phenotyping platforms combined with functional analytic pipelines to elucidate the immunomodulatory effect of the antiangiogenic agent pazopanib in mRCC patients. Nine patients were studied longitudinally over a period of 6 months. We also analyzed transcriptional data from The Cancer Genome Atlas (TCGA) RCC cohort (N = 571)

Abbreviations: DC, dendritic cell; G-MDSC, granulocytic myeloid derived suppressor cells; ICB, immune checkpoint blockade; iDC, immature dendritic cell; IPA, ingenuity Pathway Analysis; mDC, myeloid dendritic cells; MDSC, myeloid-derived suppressor cells; M-MDSC, monocytic myeloid-derived suppressor cells; RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; NK, natural killer cell; PBMCs, peripheral blood mononuclear cells; PCA, principal component analysis; pDC, plasmacytoid dendritic cells; PHA, proportional hazard assumption; Tcm, central memory T cell; Tgd, T gamma delta cells; Th1 cells, T helper 1 cells; Th2 cells, T helper 2 cells; TKI, tyrosine-kinase inhibitor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor

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Review

Dexamethasone for Severe COVID-19: How Does It Work at Cellular and Molecular Levels?

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Abstract: The coronavirus disease 2019 (COVID-19) caused by infection of the severe respiratory syndrome coronavirus-2 (SARS-CoV-2) significantly impacted human society. Recently, the synthetic pure glucocorticoid dexamethasone was identified as an effective compound for treatment of severe COVID-19. However, glucocorticoids are generally harmful for infectious diseases, such as bacterial sepsis and severe influenza pneumonia, which can develop respiratory failure and systemic inflammation similar to COVID-19. This apparent inconsistency suggests the presence of pathologic mechanism(s) unique to COVID-19 that renders this steroid effective. We review plausible mechanisms and advance the hypothesis that SARS-CoV-2 infection is accompanied by infected cell-specific glucocorticoid insensitivity as reported for some other viruses. This alteration in local glucocorticoid actions interferes with undesired glucocorticoid to facilitate viral replication but does not affect desired anti-inflammatory properties in non-infected organs/tissues. We postulate that the virus coincidentally causes glucocorticoid insensitivity in the process of modulating host cell activities for promoting its replication in infected cells. We explore this tenet focusing on SARS-CoV-2-encoding proteins and potential molecular mechanisms supporting this hypothetical glucocorticoid insensitivity unique to COVID-19 but not characteristic of other life-threatening viral diseases, probably due to a difference in specific virally-encoded molecules and host cell activities modulated by them.

Keywords: glucocorticoids; glucocorticoid receptor (GR); inflammation; innate immunity; severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); type I interferons (IFNs)

Citation: Kino, T.; Burd, I.; Segars, J.H. Dexamethasone for Severe COVID-19: How Does It Work at Cellular and Molecular Levels? *Int. J. Mol. Sci.* **2021**, *22*, 6764. https://doi.org/10.3390/ijms22136764

Academic Editor: Omar Tliba

Received: 17 May 2021
Accepted: 18 June 2021
Published: 23 June 2021

1. Introduction

The viruses, intracellular parasites with limited amounts of genetic information, are major threats virtually for all organisms living on earth [1]. They are ancient but emerged as more significant concerns of humankind approximately 20,000–12,000 years ago, when their community density/population greatly increased following the introduction of a new life style "agriculture and pastoralism" [1]. This life style also enabled some viruses maintained in cultivating cattle contaminating into human communities and causing various zoonotic diseases (e.g., variola and influenza) [1]. Although invention of effective vaccinations against many of the pathogenic viruses dramatically reduced their outbreaks and associated diseases during the last century, "new" viruses are still our major threats, occasionally entering human communities [1].

From the beginning of the 21st century, humans encountered several outbreaks of "new" coronavirus [2]. Based on the data of the World Health Organization (WHO), the severe acute respiratory syndrome coronavirus (SARS-CoV) first entered the human community in China during 2003, and affected 8098 people worldwide of whom 774 died (~10% of total incidence) [3]. The less infectious but highly pathogenic middle east respiratory syndrome coronavirus (MERS-CoV) caused its outbreak in 2012 in the Arabian peninsula and subsequently in 2015 in South Korea, and affected a total of 2574 people with 845 associated deaths (~34%) [4]. In December 2019, highly infectious but less pathogenic

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439-P: A Promising Regulatory Role for MicroRNA-133b in Controlling Lipid Metabolism and Dyslipidemia Gene Expression in Diabetic Retinopathy: The 1000 Qataromics Cohort FREE

AMMIRA S. AKIL; SUJITHA SUBASH PADMAJEYA; LAILA A. JERMAN; TANWIR HABIB; ALYA AL-KURBI; ELBAY E. ALIYEV; MOHAMMED EL ANBARI; KHALID FAKHRO

Diabetes 2021;70(Supplement_1):439-P
https://doi.org/10.2337/db21-439-P

A number of hyperglycemia- and dyslipidemia- triggered pathways, and numerous protein-encoding genes boosting the diabetic retinopathy (DR) progression. Evolving data suggests vast number of microRNAs(miRNAs) which exhibit no protein-coding capacity, are expressed and play key roles in DR pathogenesis.

Purpose: of this pilot is to identify the miRNAs involved in pathways altered in lipid metabolism and dyslipidemia and to explore the association of dyslipidemia with the progression of DR.

Methodology: 460 patients with diabetes type 2 (T2D) aged 23-77 years including 37 with DR and 490 matched healthy controls age range 18-74, from Qatar biobank cohort. The circulating miRNA profile was assessed in this pilot study. Logistic regression analysis was performed on the phenotypic data to investigate the level of association between A1C, low-density lipoproteins (LDL) and Triglycerides (TG) covariants and the miRNA expression profile in T2D with and without DR.

Results: The most broadly characterized miRNAs in lipid metabolism are miR-33a/b; however, we identified another three miRNAs (miR-133b, miR-142-3p and miR-483-5p) shared between LDL and TG phenotypes. In particular, miR-133b appeared to be directly linked to retinal degeneration identified through our miRNA-target disease interaction network analysis. Our results indicated that all three miRNAs are significantly associated with VEGFR2 mediated vascular permeability, insulin signaling, apoptosis, EGFR, TGF-Beta signaling, cellular senescence and degradation pathways leading to the DR initiation than development.

Conclusions: miRNAs are not only small regulators of lipid metabolism, but vital influencers in lipid homeostasis and lipoproteins formation and secretion. Dysregulation of these regulatory elements most likely augment the underlying metabolic flaws perceived in lipid disorders and related microvascular

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Humans with inherited T cell CD28 deficiency are susceptible to skin papillomaviruses but are otherwise healthy

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SUMMARY

We study a patient with the human papilloma virus (HPV)-2-driven "tree-man" phenotype and two relatives with unusually severe HPV4-driven warts. The giant horns form an HPV-2-driven multifocal benign epithelial tumor overexpressing viral oncogenes in the epidermis basal layer. The patients are unexpectedly homozygous for a private *CD28* variant. They have no detectable CD28 on their T cells, with the exception of a small contingent of revertant memory CD4$^+$ T cells. T cell development is barely affected, and T cells respond to CD3 and CD2, but not CD28, costimulation. Although the patients do not display HPV-2- and HPV-4-reactive CD4$^+$ T cells *in vitro*, they make antibodies specific for both viruses *in vivo*. CD28-deficient mice are susceptible to cutaneous infections with the mouse papillomavirus MmuPV1. The control of HPV-2 and HPV-4 in keratinocytes is dependent on the T cell CD28 co-activation pathway. Surprisingly, human CD28-dependent T cell responses are largely redundant for protective immunity.

INTRODUCTION

Human papillomavirus (HPV) infections of cutaneous keratinocytes cause various types of lesions, including flat and common warts (Cubie, 2013). Common warts are typically caused by α-papillomavirus HPV-2 and γ-papillomavirus HPV-4. They are seen in the general population, in which they are typically localized and benign (Cubie, 2013). However, they can persist and spread in patients with various inherited or acquired T cell immunodeficiencies, who are also prone to a number of other infections (Béziat, 2020). "Cutaneous horns" are protrusions of keratotic material of various sizes and shapes that

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Human sample authentication in biomedical research: comparison of two platforms

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Samples used in biomedical research are often collected over years, in some cases from subjects that may have died and thus cannot be retrieved in any way. The value of these samples is priceless. Sample misidentification or mix-up are unfortunately common problems in biomedical research and can eventually result in the publication of incorrect data. Here we have compared the Fluidigm SNPtrace and the Agena iPLEX Sample ID panels for the authentication of human genomic DNA samples. We have tested 14 pure samples and simulated their cross-contamination at different percentages (2%, 5%, 10%, 25% and 50%). For both panels, we report call rate, allele intensity/probability score, performance in distinguishing pure samples and contaminated samples at different percentages, and sex typing. We show that both panels are reliable and efficient methods for sample authentication and we highlight their advantages and disadvantages. We believe that the data provided here is useful for sample authentication especially in biorepositories and core facility settings.

Abbreviations

ASP	Allele specific primer
CPM	Chip prep module
IFC	Integrated fluidic circuit
LSP	Locus specific primer
MALDI-TOF-MS	Matrix assisted laser desorption/ionization-time of flight mass spectrometry
PCR	Polymerase chain reaction
SAP	Shrimp alkaline phosphatase
SD	Standard deviation
SBE	Single base extension
SNP	Single nucleotide polymorphism
STA	Specific target amplification
STR	Single tandem repeat

Sample qualification is of paramount importance in biomedical research. Sample authentication is necessary to validate the data produced in any research project using human biosamples. Sample misidentification or mix-up are unfortunately common problems in biomedical research[1–5] and can eventually lead to the publication of incorrect results[1,2,6,7]

Despite the cross-contamination of biological samples being a widely recognized problem[8], only a minority of scientists perform tests to validate the identity of the samples analyzed prior to their studies[9,10]. Cell lines are considered "misidentified" when their genetic profile differs from that of the individual donors from whom they were initially established. Cell lines misidentification can be caused by the accidental substitution of culture samples or, perhaps most commonly, by cell line cross-contamination leading to the overgrowth of the contaminant cells resulting in cell mixtures[11]. Furthermore, during the growth of cell lines, genetic drift can occur due to their continued passage, making the identity testing not trivial to assess. It is estimated that between 10% and 35% of human cell lines are contaminated in some degree[12].

In biobanks, sample authentication is generally required for reasons of different nature as compared to cell lines. In fact, biobanks store and process mostly samples of primary origin that do not undergo extensive in vitro manipulation and whose genomic footprint does not change during the experimental processing. Samples in

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Human AGR2 Deficiency Causes Mucus Barrier Dysfunction and Infantile Inflammatory Bowel Disease

Short Title: AGR2 deficiency causes infantile IBD

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Synopsis:

This report describes the discovery of a human AGR2 deficiency causing monogenic infantile inflammatory bowel disease due to goblet cell depletion and mucus barrier defect.

Abstract

BACKGROUNDS AND AIM: The gastrointestinal epithelium plays a crucial role in maintaining homeostasis with the gut microbiome. Mucins are essential for intestinal barrier function and serve as a scaffold for antimicrobial factors. MUC2 is the major intestinal gel-forming mucin produced predominantly by goblet cells. Goblet cells express AGR2, a protein disulfide isomerase (PDI) that is crucial for proper processing of gel-forming mucins. Here, we investigated two siblings who presented with severe infantile onset inflammatory bowel disease. **METHODS:** We performed whole genome sequencing to identify candidate variants. We quantified goblet cell numbers using H&E histology and investigated the expression of gel-forming mucins, stress markers, and goblet cell markers using immunohistochemistry. AGR2-MUC2 binding was evaluated using co-immunoprecipitation. Endoplasmic reticulum (ER) stress regulatory function of mutant AGR2 was examined by expression studies in HEK293T using tunicamycin to induce ER stress. **RESULTS:** Both affected siblings were homozygous for a missense variant in *AGR2*. Patient biopsies showed reduced goblet cells, depletion of MUC2, MUC5AC, and MUC6, upregulation of AGR2, and elevated ER stress. The mutant AGR2 showed reduced capacity to bind MUC2 and alleviate tunicamycin-induced ER stress. **CONCLUSIONS:** Phenotype-genotype segregation, functional experiments, and the striking similarity of the human phenotype to the *AGR2*$^{-/-}$ mouse models suggest that the AGR2 missense variant is pathogenic. The Mendelian deficiency of AGR2, termed “Enteropathy caused by AGR2 deficiency, Goblet cell Loss, and ER Stress” (EAGLES), results in a mucus barrier defect, the inability to mitigate ER stress, and causes infantile onset IBD.

Key words: **AGR2; MUC2; ER stress; intestinal metaplasia; Goblet cells,**

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In vitro Interleukin-7 treatment partially rescues MAIT cell dysfunction caused by SARS-CoV-2 infection

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MAIT cells have been shown to be activated upon several viral infections in a TCR-independent manner by responding to inflammatory cytokines secreted by antigen-presenting cells. Recently, a few studies have shown a similar activation of MAIT cells in response to severe acute respiratory coronavirus 2 (SARS-CoV-2) infection. In this study, we investigate the effect of SARS-CoV-2 infection on the frequency and phenotype of MAIT cells by flow cytometry, and we test in vitro stimulation conditions on the capacity to enhance or rescue the antiviral function of MAIT cells from patients with coronavirus disease 2019 (COVID-19). Our study, in agreement with recently published studies, confirmed the decline in MAIT cell frequency of hospitalized donors in comparison to healthy donors. MAIT cells of COVID-19 patients also had lower expression levels of TNF-alpha, perforin and granzyme B upon stimulation with IL-12 + IL-18. 24 h' incubation with IL-7 successfully restored perforin expression levels in COVID-19 patients. Combined, our findings support the growing evidence that SARS-CoV-2 is dysregulating MAIT cells and that IL-7 treatment might improve their function, rendering them more effective in protecting the body against the virus.

Mucosal-associated invariant T (MAIT) cells are a sub-population of innate T lymphocytes with effector-like properties[1]. They are mainly found in the blood, lung, liver, and mucosa serving as sentinels against microbial and fungal infection[1,2]. Upon activation, they secrete pro-inflammatory cytokines and can kill bacteria or viral-infected cells by secretion of the cytolytic molecules granzyme B and perforin[3]. MAIT cells have been shown to be activated during human viral infections such as dengue virus, hepatitis C virus, and influenza virus[4]. MAIT cell activation correlates with disease severity in acute dengue infection[5], and the reconstitution of MAIT cell levels in peripheral blood was suggested to have a positive outcome in HIV patients[6]. MAIT cells can be activated in viral infections in response to IL-12 or IL-15 together with IL-18[7,8], and IL-7 is known to enhance the production of cytolytic molecules by these cells[8]. One study showed that the use of IL-7 alongside anti-retroviral therapy increased the number and frequency of MAIT cells in the peripheral blood of patients chronically infected with HIV[9].

The effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the immune system has been investigated in several studies; the most significant findings included a correlation between the severity

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PHYSIOLOGICAL GENOMICS

Physiol Genomics 53: 373–384, 2021.
First published July 12, 2021; doi:10.1152/physiolgenomics.00025.2021

SYSTEMATIC REVIEW

Frequency and management of medically actionable incidental findings from genome and exome sequencing data: a systematic review

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Abstract

The application of whole genome/exome sequencing technologies in clinical genetics and research has resulted in the discovery of incidental findings unrelated to the primary purpose of genetic testing. The American College of Medical Genetics and Genomics published guidelines for reporting pathogenic and likely pathogenic variants that are deemed to be medically actionable, which allowed us to learn about the epidemiology of incidental findings in different populations. However, consensus guidelines for variant reporting and classification are still lacking. We conducted a systematic literature review of incidental findings in whole genome/exome sequencing studies to obtain a comprehensive understanding of variable reporting and classification methods for variants that are deemed to be medically actionable across different populations. The review highlights the elements that demand further consideration or adjustment.

ACMG genes; incidental findings; whole exome/genome sequencing

INTRODUCTION

Extensive genomic information is generated using different technologies in both clinical and research settings, which has led to concerns surrounding the inevitable generation of incidental findings. The question of how to manage the incidental genomic findings has emerged as one of the most difficult challenges facing investigators in the clinical application of genome sequencing.

In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that, when reporting clinical whole genome/exome tests, laboratories should analyze and report pathogenic and likely pathogenic variants from a set of 56 genes (1). These recommendations were revised and updated in 2016, by removing one gene and adding four, to make the total number of recommended genes 59 (2). Patients should be aware that genetic sequencing could reveal incidental findings that are not related to the genetic test's primary purpose. Once testing is ordered, the laboratory should analyze this set of 59 genes, which are associated with highly penetrant diseases, and report findings that are deemed to be "medically actionable" regardless of the proband's phenotype or age.

Classifying incidental findings in diagnostic settings has been widely reported (3–6). The ACMG recommendation covers clinical genetic testing, therefore patients with a clinical indication for genetic evaluation. However, there is no obligation for WGS/WES performed in a research setting to report medically actionable variants, due to the large number of variants discovered by these technologies in apparently healthy participants and the unavailability of consensus guidelines of variant classification. Nonetheless, analyses of population-scale genome and exome sequences provide information about the prevalence, spectrum, penetrance, and expressivity of incidental findings in different populations, which can aid the detection of relevant variants and lead to early treatment of the associated conditions, thereby reducing overall healthcare system costs.

We conducted a systematic literature review and evaluated the reported frequencies of incidental findings using genome and exome sequencing technologies in different populations and clinical and research settings, focusing on the methods and filtering criteria used to analyze the data. The review highlights the effective elements of international recommendations and policy to identify the most relevant findings, and those that demand further consideration or adjustment.

METHODS

Search Strategy and Terms

An electronic literature search of the PubMed database was conducted to identify relevant articles written in English, published up to August 2020, about incidental findings from whole genome sequencing (WGS), and whole exome sequencing

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Submitted 11 March 2021 / Revised 20 June 2021 / Accepted 30 June 2021

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-24584-w OPEN

Development of a fixed module repertoire for the analysis and interpretation of blood transcriptome data

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As the capacity for generating large-scale molecular profiling data continues to grow, the ability to extract meaningful biological knowledge from it remains a limitation. Here, we describe the development of a new fixed repertoire of transcriptional modules, BloodGen3, that is designed to serve as a stable reusable framework for the analysis and interpretation of blood transcriptome data. The construction of this repertoire is based on co-clustering patterns observed across sixteen immunological and physiological states encompassing 985 blood transcriptome profiles. Interpretation is supported by customized resources, including module-level analysis workflows, fingerprint grid plot visualizations, interactive web applications and an extensive annotation framework comprising functional profiling reports and reference transcriptional profiles. Taken together, this well-characterized and well-supported transcriptional module repertoire can be employed for the interpretation and benchmarking of blood transcriptome profiles within and across patient cohorts. Blood transcriptome fingerprints for the 16 reference cohorts can be accessed interactively via: https://drinchai.shinyapps.io/BloodGen3Module/.

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Received: 2 May 2021 | Revised: 5 June 2021 | Accepted: 1 July 2021

DOI: 10.1111/all.15010

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Autoimmunity and Clinical Immunology

Evolution and long-term outcomes of combined immunodeficiency due to CARMIL2 deficiency

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Abbreviations: BPH, pleckstrin homolog; CARMA, CARD-Containing MAGUK Protein; CARMIL, capping protein regulator and myosin 1linker 2; CBR, C-terminal domain including a capping protein binding region; CP, capping protein; EBV, Epstein-Barr virus; HD, homodimerization domain; LRR, leucine-rich repeat; NF-κB, nuclear factor kappa; PKCθ, protein kinase C theta; PRR, proline-rich region; SMT, smooth muscle tumor.

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Funding information
Scientific and Technological Research Council of Turkey, Grant/Award Number: 318S202; National Institutes of Health, Grant/Award Number: R01AI065617 and R01AI128976; Sidra Precision Medicine Program, Grant/Award Number: SDR400013

Abstract

Background: Biallelic loss-of-function mutations in *CARMIL2* cause combined immunodeficiency associated with dermatitis, inflammatory bowel disease (IBD), and EBV-related smooth muscle tumors. Clinical and immunological characterizations of the disease with long-term follow-up and treatment options have not been previously reported in large cohorts. We sought to determine the clinical and immunological features of CARMIL2 deficiency and long-term efficacy of treatment in controlling different disease manifestations.

Methods: The presenting phenotypes, long-term outcomes, and treatment responses were evaluated prospectively in 15 CARMIL2-deficient patients, including 13 novel cases. Lymphocyte subpopulations, protein expression, regulatory T (Treg), and circulating T follicular helper (cT_{FH}) cells were analyzed. Three-dimensional (3D) migration assay was performed to determine T-cell shape.

Results: Mean age at disease onset was 38 ± 23 months. Main clinical features were skin manifestations (n = 14, 93%), failure to thrive (n = 10, 67%), recurrent infections (n = 10, 67%), allergic symptoms (n = 8, 53%), chronic diarrhea (n = 4, 27%), and EBV-related leiomyoma (n = 2, 13%). Skin manifestations ranged from atopic and seborrheic dermatitis to psoriasiform rash. Patients had reduced proportions of memory $CD4^+$ T cells, Treg, and cT_{FH} cells. Memory B and NK cells were also decreased. CARMIL2-deficient T cells exhibited reduced T-cell proliferation and cytokine production following CD28 co-stimulation and normal morphology when migrating in a high-density 3D collagen gel matrix. IBD was the most severe clinical manifestation, leading to growth retardation, requiring multiple interventional treatments. All patients were alive with a median follow-up of 10.8 years (range: 3–17 years).

Conclusion: This cohort provides clinical and immunological features and long-term follow-up of different manifestations of CARMIL2 deficiency.

KEYWORDS
CARMIL2, CD28 co-signaling, combined immune deficiency, inflammatory bowel disease, long-term follow-up

1 | INTRODUCTION

The capping protein regulator and myosin 1 linker 2 (CARMIL2) deficiency is an autosomal recessive inborn error of immunity (IEI) leading to combined T-cell, B-cell, and NK cell defects.[1,2] CARMIL2, also known as RGD motif, leucine-rich repeats, tropomodulin domain, and proline-rich containing protein (RLTPR), is a member of the CARMIL family. This family consists of three paralogous genes (*CARMIL1*, *CARMIL2*, *and CARMIL3*), producing multidomain proteins with high sequence homology. They contain an N-terminal pleckstrin homology (PH) domain, a leucine-rich repeat (LRR) domain, a homodimerization domain (HD), and a C-terminal domain including a capping protein binding region (CBR) and a proline-rich region (PRR). While all CARMILs have a capacity to bind to the capping proteins and regulate actin assembly, each protein also has a unique cellular function.[3] CARMIL1 activates the Trio-Rac1 pathway to enhance Arp2/3-mediated actin polymerization,[4,5] whereas CARMIL2 binds to cellular membranes via vimentin, and activates T cells by ligating CD28 and CARMA1 to mediate NF-$_k$B signaling.[6,7] Mice expressing mutated *Carmil2* gene are not able to conduct CD28-mediated activation of its effector protein kinase C theta (PKCθ), abrogating effector memory $CD4^+$ T and regulatory T cells (Treg) development.[7,8] CARMIL2 is also necessary for invadopodia formation, cell polarity, lamellipodial assembly, membrane ruffling, macropinocytosis, and cell migration.[3] The CARMIL3 is expressed mainly in the brain and spinal cord, and identified as oncofetal gene; however, recently, it was demonstrated as essential regulator of the proinflammatory cytokines in macrophages.[3,9]

The human *CARMIL2* gene was originally identified by Matsuzaka et al. and shown to be downregulated in affected skin

The American Journal of Pathology, Vol. ■, No. ■, ■ 2021

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The American Journal of
PATHOLOGY
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Myeloid Cells Are Enriched in Tonsillar Crypts, Providing Insight into the Viral Tropism of Human Papillomavirus

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Accepted for publication June 14, 2021.

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Viruses are the second leading cause of cancer worldwide, and human papillomavirus (HPV)—associated head and neck cancers are increasing in incidence in the United States. HPV preferentially infects the crypts of the tonsils rather than the surface epithelium. The present study sought to characterize the unique microenvironment within the crypts to better understand the viral tropism of HPV to a lymphoid-rich organ. Laser-capture microdissection of distinct anatomic areas (crypts, surface epithelium, and germinal centers) of the tonsil, coupled with transcriptional analysis and multiparameter immunofluorescence staining demonstrated that the tonsillar crypts are enriched with myeloid populations that co-express multiple canonical and noncanonical immune checkpoints, including *PD-L1*, *CTLA-4*, *HAVCR2* (*TIM-3*), *ADORA2A*, *IDO1*, *BTLA*, *LGALS3*, *CDH1*, *CEACAM1*, *PVR*, and C10orf54 (*VISTA*). The resident monocytes may foster a permissive microenvironment that facilitates HPV infection and persistence. Furthermore, the myeloid populations within HPV-associated tonsil cancers co-express the same immune checkpoints, providing insight into potential novel immunotherapeutic targets for HPV-associated head and neck cancers. *(Am J Pathol 2021, ■: 1—13; https://doi.org/10.1016/j.ajpath.2021.06.012)*

The Waldeyer tonsillar ring serves as the first line of defense against foreign pathogens entering the respiratory tract and/or oral cavity,[1] including high-risk human papillomavirus (HPV) that causes up to 80% of tonsil cancers diagnosed in the United States.[2,3] The surface squamous epithelium of the tonsil invaginates into the underlying lymphoid stroma to form tonsillar crypts that are lined by a highly specialized lymphoepithelium that lacks a contiguous basement membrane.[1,4] Tonsillar crypts represent an immune-privileged site because of localized expression of immune checkpoint programmed death ligand-1 (PD-L1).[5]

The present study aimed to further elucidate the natural regulatory mechanisms that support immune privilege and

Supported by NIH/National Institute of Dental and Craniofacial Research 1R01 DE025340 (S.I.P.) and NIH/National Cancer Institute P01 CA240239 (W.C.F., M.J.P., and S.I.P.).

A.K.M. and J.R. contributed equally to this work.

Disclosures: F.M.M. is an employee of Gilead Sciences, Inc., and serves on the advisory board at Calidi Biotherapeutics and Immunovative Therapies Corp. S.I.P. has received consultancy payments from Abbvie, Astrazeneca/MedImmune, Cue Biopharma, Fusion Pharmaceuticals, MSD/Merck, Newlink Genetics, Oncolys Biopharma, Replimmune, Scopus Biopharma, and Sensei Bio. S.I.P. has received grants/research support from Abbvie, Astrazeneca/MedImmune, Cue Biopharma, and Tesaro. M.J.P. has received consultancy payments from Aileron Therapeutics, AstraZeneca, Elstar Therapeutics, KSQ Therapeutics, MPM Capital, Siamab Therapeutics, Third Rock Ventures, and Tidal Therapeutics. All other authors declare no potential conflicts of interest.

https://doi.org/10.1016/j.ajpath.2021.06.012

JEM Journal of Experimental Medicine

ARTICLE

Human *STAT3* variants underlie autosomal dominant hyper-IgE syndrome by negative dominance

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Most patients with autosomal dominant hyper-IgE syndrome (AD-HIES) carry rare heterozygous *STAT3* variants. Only six of the 135 in-frame variants reported have been experimentally shown to be dominant negative (DN), and it has been recently suggested that eight out-of-frame variants operate by haploinsufficiency. We experimentally tested these 143 variants, 7 novel out-of-frame variants found in HIES patients, and other *STAT3* variants from the general population. Strikingly, all 15 out-of-frame variants were DN via their encoded (1) truncated proteins, (2) neoproteins generated from a translation reinitiation codon, and (3) isoforms from alternative transcripts or a combination thereof. Moreover, 128 of the 135 in-frame variants (95%) were also DN. The patients carrying the seven non-DN *STAT3* in-frame variants have not been studied for other genetic etiologies. Finally, none of the variants from the general population tested, including an out-of-frame variant, were DN. Overall, our findings show that heterozygous *STAT3* variants, whether in or out of frame, underlie AD-HIES through negative dominance rather than haploinsufficiency.

Introduction

Hyper-IgE syndrome (HIES) is an inborn error of immunity (IEI), initially described as Job's syndrome by Davis et al. in 1966 for patients with recurrent "cold" staphylococcal abscesses, eczema, and respiratory infections beginning at birth (Davis et al., 1966). In 1972, Buckley et al. reported high serum IgE levels in patients with this condition, which was renamed HIES (Buckley et al., 1972). These patients also have other clinical manifestations, including eosinophilia, low levels of inflammatory markers during infection, chronic mucocutaneous candidiasis (CMC), systemic allergic manifestations, and extra-hematopoietic features, including facial dysmorphism, deciduous tooth retention, osteopenia, hyperextensibility, scoliosis, and vascular abnormalities (Chandesris et al., 2012; Grimbacher et al., 1999; Tsilifis et al., 2021; Zhang et al., 2018b) The manifestations of HIES display variable expressivity. The estimated frequency of HIES is between 1 per 100,000 to 1,000,000 at

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https://doi.org/10.1093/brain/awab313 BRAIN 2021: 144; 3597–3610 | 3597

BRAIN
ORIGINAL ARTICLE

Biallelic *PI4KA* variants cause neurological, intestinal and immunological disease

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Phosphatidylinositol 4-kinase IIIα (PI4KIIIα/*PI4KA*/OMIM:600286) is a lipid kinase generating phosphatidylinositol 4-phosphate (PI4P), a membrane phospholipid with critical roles in the physiology of multiple cell types. PI4KIIIα's role in PI4P generation requires its assembly into a heterotetrameric complex with EFR3, TTC7 and FAM126. Sequence alterations in two of these molecular partners, TTC7 (encoded by *TTC7A* or *TCC7B*) and FAM126, have been associated with a heterogeneous group of either neurological (FAM126A) or intestinal and immunological (TTC7A) conditions.

Here we show that biallelic *PI4KA* sequence alterations in humans are associated with neurological disease, in particular hypomyelinating leukodystrophy. In addition, affected individuals may present with inflammatory bowel disease, multiple intestinal atresia and combined immunodeficiency. Our cellular, biochemical and structural modelling studies indicate that *PI4KA*-associated phenotypical outcomes probably stem from impairment of PI4KIIIα-TTC7-FAM126's organ-specific functions, due to defective catalytic activity or altered intra-complex functional interactions.

Together, these data define *PI4KA* gene alteration as a cause of a variable phenotypical spectrum and provide fundamental new insight into the combinatorial biology of the PI4KIIIα-FAM126-TTC7-EFR3 molecular complex.

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Received January 26, 2021. Revised July 14, 2021. Accepted August 1, 2021. Advance access publication August 20, 2021

Signal Transduction and Targeted Therapy www.nature.com/sigtrans

RESEARCH HIGHLIGHT OPEN

"*Armed for the future Coronavirus pandemic*": a promising use of the multimeric SARS-CoV-2 receptor binding domain nanoparticle as a new Pan-Coronavirus vaccine

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Signal Transduction and Targeted Therapy (2021)6:305 ; https://doi.org/10.1038/s41392-021-00721-1

In a recent article in *Nature*, Saunders et al. reported a new pan-coronavirus (CoVs) vaccine that elicited abundant neutralizing antibodies (nAbs) and was proven effective in protecting against a variety of coronavirus infections—including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), SARS-CoV-1, and other related bat-CoVs that could potentially cause the next pandemic.[1]

The SARS-CoV-2 caused Coronavirus Disease 2019 (COVID-19) outbreak has posed a severe threat to the global public health. SARS-CoV-2 is a new member of the pathogenic human coronavirus family, which also includes two common mild beta-coronaviruses; hCov-OC43 and hCoV-HKU1, as well as the life-threatening SARS-CoV-1 and MERS-CoV.[2] Like other beta-CoVs, SARS-CoV-2 harbors a single-strand positive-sense RNA, which encodes nucleocapsid (N), envelop (E), membrane (M), and spike (S) proteins. The S protein contains S1 and S2 subunits. Although the exact etiology of beta-CoVs infection remains elusive, the binding of these viruses to human cell via the receptor binding domain (RBD) of the S1 subunit appears to be the hallmark of their pathogenesis. Numerous studies have reported high titers of nAbs in patients who recovered from SARS-CoV-2 infection, with the majority of the isolated nAbs targeting viral S-protein, particularly the RBD,[3] highlighting the importance of RBD epitopes in priming the human immune system and mediating protection against SARS-CoV2 infection. As a result, the RBD is a promising target for developing vaccine candidates and boosting the immune system's ability to combat SARS-CoV-2 infection.

In this report, Saunders et al. designed a novel 24-mer SARS-CoV-2 RBD-sortase A conjugated nanoparticle (RBD-scNP) vaccine.[1] The recombinant RBD and ferritin nanoparticle were conjugated together by a sortase A reaction and combined with a small molecule adjuvant 3M-052 formulated with Alum, the toll-like receptor 7 and 8 agonists, to boost the immune response. Although, immunization of cynomolgus macaques with the RBD-scNP vaccine elicited high RBD-specific nAbs titers, which significantly neutralized viral infection, the most striking finding was that the neutralizing IgG induced by the RBD-scNP vaccine, not only covers the emerging variants of SARS-CoV-2 but was also able to cross-neutralize other coronaviruses, SARS-CoV-1 and beta-CoVs including BatCoV-WIV-1, and BatCoV-SHC014 with a range of potencies (Fig. 1). This suggests that the highly conserved RBD sequence encodes for a potent antigen capable of eliciting nAbs response that could provide pan-CoVs cross-protection. Competitive binding assays revealed that plasma Abs from RBS-scNP immunized macaques blocked the binding of angiotensin-converting enzyme-2 (ACE-2) and DH1047 nAb to SARS-CoV2, suggesting that RBS-scNP vaccine elicited DH1047-like antibodies. Interestingly, the RBD-scNP vaccine elicited a significantly higher magnitude of DH1047-like antibodies in immunized macaques than both the natural human SARS-CoV-2 infection and the mRNA-lipid nanoparticle (LNP) vaccine, which is similar to the licensed Pfizer/BNT162b2 mRNA-LNP SARS-CoV2 vaccine formulations. This work will pave the way towards developing a pan-CoVs vaccine that can protect from future coronavirus outbreaks.[4]

To further confirm the vaccine protection against natural CoV infection, Saunders et al. also challenged RBD-scNP vaccinated macaques with 10^5 plaque-forming units of SARS-CoV-2 virus via intratracheal and intranasal routes after their last vaccine boost. Interestingly, the vaccine exhibited a complete protection against SARS-CoV-2 infection as no detectable infectious virus was recovered from the nasal swab and bronchoalveolar lavage (BAL) fluid of vaccinated macaques four days after the challenge. In contrast, as expected, unimmunized macaques showed a high viral load in the range of 10^{4-5} copies/mL in their BAL fluids and nasal swabs. These findings were further supported by the hematoxylin and eosin staining of the lung tissues that showed a reduced inflammation in the immunized macaques compared to the unimmunized macaques infected with the virus.

Taken together, this study by Saunders *el al.* indicates that the RBD-scNP vaccine immunization triggers an ample protective titer of SARS-CoV-2 nAbs and confers a robust protection against SARS-CoV-2 in both upper and lower respiratory tracts. SARS-CoV-2 is a dynamic virus, and it has surprised the scientific world with its fast pace of adaptabilities and mutations. Emerging functional studies have demonstrated the increased infectivity and reduced sensitivity of new SARS-CoV-2 variants, B.1.1.7, B.1.351, and P.1 to some of the current vaccines, due to the mutations in the RBD domain at K417N, E484K and N501Y positions.[5] In this paper, Saunders et al. showed that three doses of the RBD-scNP vaccine elicited high levels of nAbs to neutralize all variants of SARS-CoV2, and that the binding of those antibodies to SARS-CoV2 was unaffected by mutations observed in B.1.1.7, B.1.351, and P.1 variants.

In summary, things were moving quickly in the last one year of the COVID-19 pandemic, and cutting-edge methodologies are being combined with advanced fundamental procedures by the pharmaceuticals and institutional researchers across the globe to identify new vaccine candidates in order to contain the SARS-CoV-2

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Received: 30 May 2021 Revised: 14 July 2021 Accepted: 30 July 2021
Published online: 17 August 2021

Kumar *et al. BMC Pregnancy and Childbirth* (2021) 21:570
https://doi.org/10.1186/s12884-021-04029-4

BMC Pregnancy and Childbirth

STUDY PROTOCOL Open Access

Omouma: a prospective mother and child cohort aiming to identify early biomarkers of pregnancy complications in women living in Qatar

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Abstract

Background: Pregnancy is governed by multiple molecular and cellular processes, which might influence pregnancy health and outcomes. Failure to predict and understand the cause of pregnancy complications, adverse pregnancy outcomes, infant's morbidity and mortality, have limited effective interventions. Integrative multi-omics technologies provide an unbiased platform to explore the complex molecular interactions with an unprecedented depth. The objective of the present protocol is to build a longitudinal mother-baby cohort and use multi-omics technologies to help identify predictive biomarkers of adverse pregnancy outcomes, early life determinants and their effect on child health.

Methods/design: : One thousand pregnant women with a viable pregnancy in the first trimester (6–14 weeks of gestation) will be recruited from Sidra Medicine hospital. All the study participants will be monitored every trimester, at delivery, and one-year post-partum. Serial high-frequency sampling, including blood, stool, urine, saliva, skin, and vaginal swabs (mother only) from the pregnant women and their babies, will be collected. Maternal and neonatal health, including mental health and perinatal growth, will be recorded using a combination of questionnaires, interviews, and medical records. Downstream sample processing including microbial profiling, vaginal immune response, blood transcriptomics, epigenomics, and metabolomics will be performed.

Discussion: It is expected that the present study will provide valuable insights into predicting pregnancy complications and neonatal health outcomes. Those include whether specific microbial and/or epigenomics signatures, immune profiles are associated with a healthy pregnancy and/or complicated pregnancy and poor neonatal health outcome. Moreover, this non-interventional cohort will also serve as a baseline dataset to understand how familial, socioeconomic, environmental and lifestyle factors interact with genetic determinants to influence health outcomes later in life. These findings will hold promise for the diagnosis and precision-medicine interventions.

Keywords: Birth cohort, Pregnancy, Multi-omics, Microbiome, Precision Medicine, Sidra Medicine, Qatar, Middle East

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Published in final edited form as:
Sci Immunol. 2021 August 19; 6(62): . doi:10.1126/sciimmunol.abl4348.

X-linked recessive TLR7 deficiency in 1% of men under 60 years with life-threatening COVID-19

A full list of authors and affiliations appears at the end of the article.

Abstract

Autosomal inborn errors of type I IFN immunity and autoantibodies against these cytokines underlie at least 10% of critical COVID-19 pneumonia cases. We report very rare, biochemically deleterious X-linked *TLR7* variants in 16 unrelated male individuals aged 7 to 71 years (mean: 36.7 years) from a cohort of 1,202 male patients aged 0.5 to 99 years (mean: 52.9 years) with unexplained critical COVID-19 pneumonia. None of the 331 asymptomatically or mildly infected male individuals aged 1.3 to 102 years (mean: 38.7 years) tested carry such *TLR7* variants ($p = 3.5 \times 10^{-5}$). The phenotypes of five hemizygous relatives of index cases infected with SARS-CoV-2 include asymptomatic or mild infection (n=2, 5 and 38 years), or moderate (n=1, 5 years), severe (n=1, 27 years), or critical (n=1, 29 years) pneumonia. Two boys (aged 7 and 12 years) from a cohort of 262 male patients with severe COVID-19 pneumonia (mean: 51.0 years) are hemizygous for a deleterious TLR7 variant. The cumulative allele frequency for deleterious *TLR7* variants in the male general population is $< 6.5\times10^{-4}$. We also show that blood B-cell lines and myeloid cell subsets from the patients do not respond to TLR7 stimulation, a phenotype rescued by wild-type *TLR7*. The patients' blood plasmacytoid dendritic cells (pDCs) produce low levels of type I IFNs in response to SARS-CoV-2. Overall, X-linked recessive TLR7 deficiency is a highly penetrant genetic etiology of critical COVID-19 pneumonia, in about 1.8% of male patients below the age of 60 years. Human TLR7 and pDCs are essential for protective type I IFN immunity against SARS-CoV-2 in the respiratory tract.

One Sentence Summary:

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Competing interests:

R.P.L a non-executive director of Roche. Because Roche is active in the diagnosis and treatment of SARS-CoV-2, this role could, in these contentious times, be construed as a conflict of interest, which I should disclose. V.S. has received speaker fees from GILEAD.

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01115-2

ORIGINAL ARTICLE

A Novel STK4 Mutation Impairs T Cell Immunity Through Dysregulation of Cytokine-Induced Adhesion and Chemotaxis Genes

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Received: 14 March 2021 / Accepted: 1 August 2021

Abstract

Purpose Human serine/threonine kinase 4 (STK4) deficiency is a rare, autosomal recessive genetic disorder leading to combined immunodeficiency; however, the extent to which immune signaling and host defense are impaired is unclear. We assessed the functional consequences of a novel, homozygous nonsense STK4 mutation (NM_006282.2:c.871C > T, p.Arg291*) identified in a pediatric patient by comparing his innate and adaptive cell-mediated and humoral immune responses with those of three heterozygous relatives and unrelated controls.

Methods The genetic etiology was verified by whole genome and Sanger sequencing. STK4 gene and protein expression was measured by quantitative RT-PCR and immunoblotting, respectively. Cellular abnormalities were assessed by high-throughput RT-RCR, RNA-Seq, ELISA, and flow cytometry. Antibody responses were assessed by ELISA and phage immunoprecipitation-sequencing.

Results The patient exhibited partial loss of STK4 expression and complete loss of STK4 function combined with recurrent viral and bacterial infections, notably persistent Epstein–Barr virus viremia and pulmonary tuberculosis. Cellular and molecular analyses revealed abnormal fractions of T cell subsets, plasmacytoid dendritic cells, and NK cells. The transcriptional responses of the patient's whole blood and PBMC samples indicated dysregulated interferon signaling, impaired T cell immunity, and increased T cell apoptosis as well as impaired regulation of cytokine-induced adhesion and leukocyte chemotaxis genes. Nonetheless, the patient had detectable vaccine-specific antibodies and IgG responses to various pathogens, consistent with a normal CD19 + B cell fraction, albeit with a distinctive antibody repertoire, largely driven by herpes virus antigens.

Conclusion Patients with STK4 deficiency can exhibit broad impairment of immune function extending beyond lymphoid cells.

Keywords Human serine/threonine kinase 4 (STK4) deficiency · Combined immunodeficiency · T cell lymphopenia · Interferon · Antibody repertoire · Transcriptomics

Introduction

Human serine/threonine kinase 4 (STK4) deficiency is a rare autosomal recessive (AR) genetic disorder leading to combined immunodeficiency with severe T cell lymphopenia. This condition is characterized by a predisposition to a wide range of bacterial and viral infectious diseases, mucocutaneous candidiasis, lymphomas, and congenital heart disease [1]. To date, STK4 deficiency has been reported in relatively few patients; therefore, the extent to which immune signaling and host defense mechanisms are impaired or

Andrea Guennoun, Salim Bougarn and Taushif Khan contributed equally.

Donald R. Love, Mohammed Yousuf Karim, Bernice Lo and Amel Hassan contributed equally. Mehdi Adeli and Nico Marr contributed equally.

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Published online: 24 August 2021

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Actionable genomic variants in 6,045 participants from the Qatar Genome Program

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/humu.24278.

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Abstract

In a clinical setting, DNA sequencing can uncover findings unrelated to the purpose of genetic evaluation. The American College of Medical Genetics and Genomics recommends evaluation and reporting of 59 genes from clinic genomic sequencing. While the prevalence of secondary findings is available from large population studies, these lack Arab and other Middle Eastern populations. The Qatar Genome Program (QGP) generates whole-genome sequencing (WGS) data and combines it with phenotypic information to create a comprehensive database for studying the Qatari and wider Arab and Middle Eastern populations at the molecular level. This study identified and analyzed medically actionable variants in the 59 ACMG genes using WGS data from 6,045 QGP participants. Our results identified a total of 60 pathogenic and likely pathogenic variants in 25 ACMG genes in 141 unique individuals. Overall, 2.3% of the QGP sequenced participants carried a pathogenic or likely pathogenic variant in one of the 59 ACMG genes. We evaluated the QGP phenotype-genotype association of additional not pathogenic ACMG variants. These variants were found in patients from the Hamad Medical Corporation or reported incidental findings data in Qatar. We found a significant phenotype association for two variants, c.313+3A>C in LDLR, and c.58C>T (p.Gln20*) in the TPM1.

Keywords

ACMG; medically actionable; genome sequencing; exome sequencing; Biobank; Qatar

biology

MDPI

Article

Transcriptome and Literature Mining Highlight the Differential Expression of ERLIN1 in Immune Cells during Sepsis

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Simple Summary: Sepsis is a disease affecting 19 million people worldwide, and accounts for 5 million deaths annually. Efforts in finding predictive markers of sepsis development have been difficult due to the complex clinical features of the disease. Public data repositories are valuable resources for mining gene expression changes across different studies. Using such resources, we observed a consistent increase in *ERLIN1*—a gene coding for an ER membrane prohibitin and regulator of cholesterol—in whole blood, and across a variety of immune cells, during sepsis or sepsis-like conditions. We verified this finding by exposing the whole blood of healthy volunteers to a combination of lipopolysaccharide and peptidoglycan in order to simulate sepsis. We observed an increase in ERLIN1 in whole-blood neutrophils and HL60 cell lines during sepsis; however, the protein was expressed differently in other immune blood cells. The current available studies on ERLIN1 and sepsis indicate a knowledge gap between the functions of ERLIN1, calcium balance, and cholesterol and fatty acid synthesis, and sepsis. Together with experimental data, we think that ERLIN1 is modulated differently in immune cells in response to infection, and has important implications for ER functions and/or ER membrane protein components during sepsis.

Abstract: Sepsis results from the dysregulation of the host immune system. This highly variable disease affects 19 million people globally, and accounts for 5 million deaths annually. In transcriptomic datasets curated from public repositories, we observed a consistent upregulation (3.26–5.29 fold) of *ERLIN1*—a gene coding for an ER membrane prohibitin and a regulator of inositol 1, 4, 5-trisphosphate receptors and sterol regulatory element-binding proteins—under septic conditions in healthy neutrophils, monocytes, and whole blood. In vitro expression of the ERLIN1 gene and proteins was measured by stimulating the whole blood of healthy volunteers to a combination of lipopolysaccharide and peptidoglycan. Septic stimulation induced a significant increase in *ERLIN1* expression; however, ERLIN1 was differentially expressed among the immune blood cell subsets. ERLIN1 was uniquely increased in whole blood neutrophils, and confirmed in the differentiated HL60 cell line. The scarcity of ERLIN1 in sepsis literature indicates a knowledge gap between the functions of ERLIN1, calcium homeostasis, and cholesterol and fatty acid biosynthesis, and sepsis. In combination with experimental data, we bring forth the hypothesis that ERLIN1 is variably modulated among immune cells in response to cellular perturbations, and has implications for ER functions and/or ER membrane protein components during sepsis.

Keywords: cholesterol biosynthesis; immunometabolism; leukocytes; calcium channel; bacteremia; sepsis; neutrophil; myeloid cells; innate immunity

Citation: Huang, S.S.Y.; Toufiq, M.; Saraiva, L.R.; Van Panhuys, N.; Chaussabel, D.; Garand, M. Transcriptome and Literature Mining Highlight the Differential Expression of ERLIN1 in Immune Cells during Sepsis. *Biology* **2021**, *10*, 755. https://doi.org/10.3390/biology10080755

Received: 8 July 2021
Accepted: 27 July 2021
Published: 5 August 2021

1. Introduction

Sepsis affects 19 million patients worldwide, with a mortality rate between 25% and 30%, rising to 50% when shock is present [1]. Compared with healthy adults, neonates

cells

MDPI

Review

Calcium Signaling Regulates Autophagy and Apoptosis

Pramod Sukumaran [1], Viviane Nascimento Da Conceicao [2], Yuyang Sun [2], Naseem Ahamad [2], Luis R Saraiva [3], Senthil Selvaraj [3] and Brij B Singh [2,*]

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Abstract: Calcium (Ca^{2+}) functions as a second messenger that is critical in regulating fundamental physiological functions such as cell growth/development, cell survival, neuronal development and/or the maintenance of cellular functions. The coordination among various proteins/pumps/Ca^{2+} channels and Ca^{2+} storage in various organelles is critical in maintaining cytosolic Ca^{2+} levels that provide the spatial resolution needed for cellular homeostasis. An important regulatory aspect of Ca^{2+} homeostasis is a store operated Ca^{2+} entry (SOCE) mechanism that is activated by the depletion of Ca^{2+} from internal ER stores and has gained much attention for influencing functions in both excitable and non-excitable cells. Ca^{2+} has been shown to regulate opposing functions such as autophagy, that promote cell survival; on the other hand, Ca^{2+} also regulates programmed cell death processes such as apoptosis. The functional significance of the TRP/Orai channels has been elaborately studied; however, information on how they can modulate opposing functions and modulate function in excitable and non-excitable cells is limited. Importantly, perturbations in SOCE have been implicated in a spectrum of pathological neurodegenerative conditions. The critical role of autophagy machinery in the pathogenesis of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases, would presumably unveil avenues for plausible therapeutic interventions for these diseases. We thus review the role of SOCE-regulated Ca^{2+} signaling in modulating these diverse functions in stem cell, immune regulation and neuromodulation.

Keywords: calcium signaling; calcium channels; autophagy; apoptosis; stem cells; neuronal and immune cell function

Citation: Sukumaran, P.; Nascimento Da Conceicao, V.; Sun, Y.; Ahamad, N.; Saraiva, L.R.; Selvaraj, S.; Singh, B.B. Calcium Signaling Regulates Autophagy and Apoptosis. *Cells* **2021**, *10*, 2125. https://doi.org/10.3390/cells10082125

Academic Editors: Maurizio Sorice and Fulvio Reggiori

Received: 22 July 2021
Accepted: 17 August 2021
Published: 18 August 2021

1. Introduction

Calcium is a prominent regulator for diverse processes such as gene transcription, proliferation, cell motility, cell signaling, neuronal regulation, autophagy and apoptosis [1]. To perform such a broad spectrum of functions, the cells have evolved multiple unique mechanisms that are modulated by different proteins that regulate cellular Ca^{2+} levels. In addition, the spatial and temporal regulation of Ca^{2+} levels that is maintained by various Ca^{2+} channels, transporters, pumps, and their binding to key proteins, play an essential role in maintaining a tight control on intracellular Ca^{2+} levels. The transient receptor potential (TRP) channels have been studied extensively and play a prominent role in regulating various cellular functions [2–4]. The TRPC subfamily consists of seven members (TRPC1-7) with diverse modes of regulation and physiological function. Intracellular Ca^{2+} plays a crucial role in both basal and induced autophagy [5,6]. Plenty of evidence has suggested a complex role of Ca^{2+} in the regulation of autophagy as well as in the regulation of apoptosis [7]. However, the mechanism by which Ca^{2+} controls autophagy and apoptosis remains controversial [8]. Previous studies have shown a negative role of Ca^{2+} on regulating

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Red Blood Cell derived Extracellular Vesicles during the process of autologous blood doping.

Abstract:

The purpose of this pilot study was to investigate the effects of the transfusion of one erythrocyte concentrate on the number of circulating Red Blood Cell Extracellular Vesicles (RBC-EVs) and their clearance time. Six, healthy volunteers donated their blood and were transfused with their Red Blood Cell concentrate after 35-36 days of storage. One K_2EDTA and one serum sample were collected before donation, at four timepoints after donation and at another six timepoints after transfusion. RBC-EVs were analysed on a Cytek Aurora flow-cytometer. A highly significant increase ($p<0.001$) of RBC-EVs from an average of 60.1±19.8 (10^3/µL) at baseline to 179.3±84.7 (10^3/µL) in the first 1-3 hours after transfusion could be observed. Individual differences in the response to transfusion became apparent with one volunteer showing no increase and another an increased concentration at one timepoint after donation due to an influenza infection. We concluded that in an individualized passport approach increased RBC-EVs might be considered as additional evidence when interpreting suspicious ABPs but for this additional research related to sample collection and transport processes as well as method development and harmonization would be necessary.

1. Introduction:

Autologous blood transfusion involves the collection and storage of blood and the re-transfusion to the same person when required, while homologous transfusion relies on the transfusion of blood from

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/dta.3157

Cellular Oncology (2021) 44:1209–1229
https://doi.org/10.1007/s13402-021-00634-9

REVIEW

The tumor microenvironment as driver of stemness and therapeutic resistance in breast cancer: New challenges and therapeutic opportunities

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Accepted: 30 August 2021 / Published online: 16 September 2021

Abstract

Background Breast cancer (BC), the second most common cause of cancer-related deaths, remains a significant threat to the health and wellness of women worldwide. The tumor microenvironment (TME), comprising cellular components, such as cancer-associated fibroblasts (CAFs), immune cells, endothelial cells and adipocytes, and noncellular components such as extracellular matrix (ECM), has been recognized as a critical contributor to the development and progression of BC. The interplay between TME components and cancer cells promotes phenotypic heterogeneity, cell plasticity and cancer cell stemness that impart tumor dormancy, enhanced invasion and metastasis, and the development of therapeutic resistance. While most previous studies have focused on targeting cancer cells with a dismal prognosis, novel therapies targeting stromal components are currently being evaluated in preclinical and clinical studies, and are already showing improved efficacies. As such, they may offer better means to eliminate the disease effectively.

Conclusions In this review, we focus on the evolving concept of the TME as a key player regulating tumor growth, metastasis, stemness, and the development of therapeutic resistance. Despite significant advances over the last decade, several clinical trials focusing on the TME have failed to demonstrate promising effectiveness in cancer patients. To expedite clinical efficacy of TME-directed therapies, a deeper understanding of the TME is of utmost importance. Secondly, the efficacy of TME-directed therapies when used alone or in combination with chemo- or radiotherapy, and the tumor stage needs to be studied. Likewise, identifying molecular signatures and biomarkers indicating the type of TME will help in determining precise TME-directed therapies.

Keywords Breast cancer · Tumor microenvironment · Targeted therapeutics · Cancer-associated fibroblasts · Tumor-associated macrophages · Immunotherapy · Cancer stemness

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JCI insight

RESEARCH ARTICLE

SLFN11 captures cancer-immunity interactions associated with platinum sensitivity in high-grade serous ovarian cancer

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Large independent analyses on cancer cell lines followed by functional studies have identified Schlafen 11 (SLFN11), a putative helicase, as the strongest predictor of sensitivity to DNA-damaging agents (DDAs), including platinum. However, its role as a prognostic biomarker is undefined, partially due to the lack of validated methods to score SLFN11 in human tissues. Here, we implemented a pipeline to quantify SLFN11 in human cancer samples. By analyzing a cohort of high-grade serous ovarian carcinoma (HGSOC) specimens before platinum-based chemotherapy treatment, we show, for the first time to our knowledge, that SLFN11 density in both the neoplastic and microenvironmental components was independently associated with favorable outcome. We observed SLFN11 expression in both infiltrating innate and adaptive immune cells, and analyses in a second, independent, cohort revealed that SLFN11 was associated with immune activation in HGSOC. We found that platinum treatments activated immune-related pathways in ovarian cancer cells in an SLFN11-dependent manner, representative of tumor-immune transactivation. Moreover, SLFN11 expression was induced in activated, isolated immune cell subpopulations, hinting that SLFN11 in the immune compartment may be an indicator of immune transactivation. In summary, we propose SLFN11 is a dual biomarker capturing simultaneously interconnected immunological and cancer cell–intrinsic functional dispositions associated with sensitivity to DDA treatment.

Authorship note: EL and GZ contributed equally to this work.

Conflict of interest: CW and JB are PostDoc Fellows of the AstraZeneca PostDoc program.

Submitted: December 1, 2020
Accepted: July 28, 2021
Published: September 22, 2021

Reference information: *JCI Insight*. 2021;6(18):e146098. https://doi.org/10.1172/jci.insight.146098.

Introduction

The putative DNA/RNA helicase Schlafen 11 (SLFN11) was independently reported by us (1) and others as the factor that best correlates with the response of cancer cells to DNA-damaging agents (DDAs) with different modes of action, such as topoisomerase I (e.g., topotecan and irinotecan) (2, 3), topoisomerase II inhibitors (e.g., epirubicin), and alkylating agents (e.g., cyclophosphamide or platinum) (4–6). Subsequently, a positive association between SLFN11 and sensitivity to Poly (ADP-ribose) polymerase (PARP) inhibitors was also described in preclinical models (6–9). After our discovery, several studies confirmed the causal role of SLFN11 in the process of cell death upon DDA treatment in cell lines (10, 11), organoids (5), and xenografts (3, 4, 6) from different tumor types. Moreover, SLFN11 has been recently studied in relation with the immune system (6, 12), especially in breast cancer (13), and for its potential role as an endogenous inhibitor of viral replication (14) and translation of DNA damage response proteins (15). Taken together, the available literature suggests that SLFN11 may play a so far incompletely understood role in an intertwined process of cancer and immune response to DDA-based chemotherapies. Indeed, it has been shown that SLFN11 is strictly correlated with immune-related transcripts in breast cancer (13), and its expression is regulated by IFN signaling in primary human cells (14, 16) as well as possibly in neoplastic cells (6, 12), hence pointing

Inherited human c-Rel deficiency disrupts myeloid and lymphoid immunity to multiple infectious agents

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We studied a child with severe viral, bacterial, fungal, and parasitic diseases, who was homozygous for a loss-of-function mutation of *REL*, encoding c-Rel, which is selectively expressed in lymphoid and myeloid cells. The patient had low frequencies of NK, effector memory cells reexpressing CD45RA (Temra) CD8$^+$ T cells, memory CD4$^+$ T cells, including Th1 and Th1*, Tregs, and memory B cells, whereas the counts and proportions of other leukocyte subsets were normal. Functional deficits of myeloid cells included the abolition of IL-12 and IL-23 production by conventional DC1s (cDC1s) and monocytes, but not cDC2s. c-Rel was also required for induction of CD86 expression on, and thus antigen-presenting cell function of, cDCs. Functional deficits of lymphoid cells included reduced IL-2 production by naive T cells, correlating with low proliferation and survival rates and poor production of Th1, Th2, and Th17 cytokines by memory CD4$^+$ T cells. In naive CD4$^+$ T cells, c-Rel is dispensable for early *IL2* induction but contributes to later phases of *IL2* expression. The patient's naive B cells displayed impaired *MYC* and *BCL2L1* induction, compromising B cell survival and proliferation and preventing their differentiation into Ig-secreting plasmablasts. Inherited c-Rel deficiency disrupts the development and function of multiple myeloid and lymphoid cells, compromising innate and adaptive immunity to multiple infectious agents.

Introduction

In humans, severe combined immunodeficiency (SCID) results from inborn errors of immunity causing a cell-intrinsic lack of autologous αβ and γδ T cells (1). Combined immunodeficiency (CID) results from inborn errors of αβ T cells, which are present, but in abnormally small numbers, or functionally compromised, at least in terms of their ability to proliferate in response to antigens in vitro. Patients also display a B cell defect in vivo that is either intrinsic or secondary to the T cell deficit (2). The T cell defect in patients with CID may be intrinsic or secondary to a deficiency of antigen-presenting cell (APC) function, such as inherited HLA class II deficiency (3, 4). Antigen-dependent T cell proliferation in vitro is normal for patients with other inborn errors of T cells not classified as CID (5). In the 2019 International Union of Immunological Societies (IUIS) classification of inborn errors of immunity, there were 57 CIDs with (syndromic CID) and 35 CIDs without (isolated CID) extrahematopoietic manifestations (5, 6). Patients with isolated or syndromic CID experience a broad range of infectious, autoimmune, autoinflammatory, allergic, and/or malignant phenotypes. Clinical manifestations vary among cases and are dependent on various host and environmental factors. These manifestations largely reflect the T and B cell phenotypes, which are dependent on the patient's genome, the gene mutated, and the mutant genotype itself. The severe infections observed in CID include a broad range of viral, bacterial, fungal, and parasitic diseases, in addition to pyogenic bacterial infections typically caused by the B cell defect (7). Age at onset and the range and severity of infections also depend on T and B cell phenotypes and the extent of abnormalities affecting other cell types, particular-

Authorship note: DL, VB, and FR contributed equally to this work. GR, TL, MB, and YJZ contributed equally to this work. LA, CSM, AAB, NM, JB, KL, PG, and FG contributed equally to this work. SGT, JLC, and AP contributed equally to this work.
Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: April 1, 2021; **Accepted:** July 8, 2021; **Published:** September 1, 2021.
Reference information: *J Clin Invest*. 2021;131(17):e150143.
https://doi.org/10.1172/JCI150143.

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Clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus among children in Qatar

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To describe the clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus (T1DM). Patients (0–18 years) with diabetes were recruited. Clinical data was collected, autoantibodies and c-peptide were measured. Whole Genome Sequencing was performed. Genomic data analysis was compared with the known genes linked with T1DM and HLA alleles were studied. 1096 patients had one or more antibody positivity. The incidence of T1DM in 2020 was 38.05 per 100,000 children and prevalence was 249.73. GADA was the most common autoantibody followed by IAA. Variants in *GSTCD*, *SKAP2*, *SLC9B1*, *BANK1* were most prevalent. An association of HLA haplotypes DQA1*03:01:01G (OR = 2.46, *p* value = 0.011) and DQB1*03:02:01G (OR = 2.43, *p* value = 0.022) was identified. The incidence of T1DM in Qatar is the fourth highest in the world, IA2 autoantibody was the most specific with some patients only having ZnT8 or IA2 autoantibodies thus underlining the necessity of profiling all 4 autoantibodies. The genes associated with T1DM in the Arab population were different from those that are common in the Caucasian population. HLA-DQ was enriched in the Qatari patients suggesting that it can be considered a major risk factor at an early age.

Type 1 diabetes mellitus is the most common form of diabetes observed in children. It is a chronic multifactorial disease with a strong genetic component, which, through interactions with specific environmental factors, triggers disease onset. Type 1 diabetes mellitus usually presents itselft in early to mid childhood as a defect in insulin production through the autoimmune destruction of pancreatic beta-cells[1]. There are two forms of type 1 diabetes mellitus (1A autoimmune and 1B idiopathic). In the autoimmune type there is antibody mediated beta-cell destruction resulting in metabolic abnormalities which is manifested as impaired glucose tolerance first and then progresses to symptomatic hyperglycaemia. Approximately 50% of the familial clustering of genes, which increase the susceptibility risk of inheriting type 1 diabetes mellitus, are located within or in the Human Leucocyte Antigen (HLA) complex on chromosome 6[2].

The performance of high-density Genome Wide Association Studies (GWAS) enabled by the advent of high-throughput single nucleotide polymorphism (SNP) genotyping array technologies, many additional type 1 diabetes mellitus susceptibility loci and genes have now been discovered[3]. Recent meta-analyses of multiple datasets from independent investigators have brought the total of genes implicated in type 1 diabetes mellitus to nearly 60[4].

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frontiers in Nutrition

EDITORIAL
published: 17 September 2021
doi: 10.3389/fnut.2021.705770

Editorial: The Triple Interaction: Diet, Microbiota and Epigenetics in the Onset and Management of Type 1 Diabetes

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Keywords: diet, microbiota, epigenetics, type 1 diabetes, therapy

Editorial on the Research Topic

The Triple Interaction: Diet, Microbiota and Epigenetics in the Onset and Management of Type 1 Diabetes

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease that leads to the destruction of pancreas ß-cells and insulin deficiency. The main determinant of T1D is genetic predisposition, although most children born carrying T1D genetic risk markers do not develop the disease and, as discussed in most of the papers in this collection, genetics cannot fully explain the disease pathogenesis (Hamilton-Williams et al.; Verduci et al.; Kohil et al.; Al Theyab et al.).

It becomes more and more apparent that T1D is a complex disease with intermediate phenotypes, many comorbidities, and heterogeneity in its therapeutic responses. This complexity can be due to interaction with diet and lifestyle that ultimately can affect the microbiota and host immune system *via* epigenetic mechanisms.

The Research Topic represented a fantastic opportunity for the scientific community to provide up-to-date knowledge and propose mechanisms explaining the role of gut microbiota as an epigenetics effector in T1D, and how diet and lifestyle can modulate this interaction, opening new opportunities in the diagnosis and management of T1D. Three key areas have been investigated:

1. Role of diet in T1D pathogenesis
2. Epigenetic function of microbiota
3. Therapeutic prospective.

DIET AND T1D PATHOGENESIS

Different types of diets may have a protective role against T1D, among those the gluten-free diet (Al Theyab et al.; Hamilton-Williams et al.) and the Mediterranean diet (MD), thanks to its anti-inflammatory properties (Calabrese et al.). On the contrary, a diet high in sugar can increase the risk of T1D, replacing fibers with sugar, which has a detrimental effect on the gut microbiota (Hamilton-Williams et al.). Confirmatory data comes from trials with high fiber diets that showed improvement in the BMI and blood pressure of T1D patients (Kohil et al.). Diets enriched in short-chain fatty acids

OPEN ACCESS

Edited and reviewed by:
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Specialty section:
This article was submitted to Nutrigenomics, a section of the journal Frontiers in Nutrition

Received: *06 May 2021*
Accepted: *11 August 2021*
Published: *17 September 2021*

Citation:
Terranegra A, Petrovski G and Verduci E (2021) Editorial: The Triple Interaction: Diet, Microbiota and Epigenetics in the Onset and Management of Type 1 Diabetes. Front. Nutr. 8:705770. doi: 10.3389/fnut.2021.705770

Biallelic variants in *SLC38A3* encoding a glutamine transporter cause epileptic encephalopathy

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Brain, Volume 145, Issue 3, March 2022, Pages 909–924,
https://doi.org/10.1093/brain/awab369
Published: 04 October 2021 **Article history** ▾

Abstract

The solute carrier (SLC) superfamily encompasses >400 transmembrane transporters involved in the exchange of amino acids, nutrients, ions, metals, neurotransmitters and metabolites across biological membranes. SLCs are highly expressed in the mammalian brain; defects in nearly 100 unique SLC-encoding genes (OMIM: https://www.omim.org) are associated with rare Mendelian disorders including developmental and epileptic encephalopathy and severe neurodevelopmental disorders.

Exome sequencing and family-based rare variant analyses on a cohort with neurodevelopmental disorders identified two siblings with developmental and epileptic encephalopathy and a shared deleterious homozygous splicing variant in *SLC38A3*. The gene encodes SNAT3, a sodium-coupled neutral amino acid transporter and a principal transporter of the amino acids asparagine, histidine, and glutamine, the latter being the precursor for the neurotransmitters GABA and glutamate. Additional subjects with a similar developmental and epileptic encephalopathy phenotype and biallelic predicted-damaging *SLC38A3* variants were ascertained through GeneMatcher and collaborations with research and clinical molecular diagnostic laboratories. Untargeted metabolomic analysis was performed to identify novel metabolic biomarkers.

Ten individuals from seven unrelated families from six different countries with deleterious biallelic variants in *SLC38A3* were identified. Global developmental delay, intellectual disability, hypotonia, and absent speech were common features while microcephaly, epilepsy, and visual impairment were present in the majority. Epilepsy was drug-resistant in half. Metabolomic analysis revealed perturbations of glutamate, histidine, and nitrogen metabolism in

plasma, urine, and CSF of selected subjects, potentially representing biomarkers of disease.

Our data support the contention that *SLC38A3* is a novel disease gene for developmental and epileptic encephalopathy and illuminate the likely pathophysiology of the disease as perturbations in glutamine homeostasis.

Received: 25 May 2021 | Revised: 29 August 2021 | Accepted: 20 September 2021

DOI: 10.1111/jcmm.16967

ORIGINAL ARTICLE

WILEY

Cancer testis antigen PRAME: An anti-cancer target with immunomodulatory potential

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Funding information
Qatar Biomedical Research Institute, Grant/Award Number: VR94; Qatar National Research Fund, Grant/Award Number: QRLP10-G-1803024

Abstract

PReferentially expressed Antigen in Melanoma (PRAME) is a cancer testis antigen with restricted expression in somatic tissues and re-expression in poor prognostic solid tumours. PRAME has been extensively investigated as a target for immunotherapy, however, its role in modulating the anti-tumour immune response remains largely unknown. Here, we show that PRAME tumour expression is associated with worse survival in the TCGA breast cancer cohort, particularly in immune-unfavourable tumours. Using direct and indirect co-culture models, we found that PRAME overexpressing MDA-MB-468 breast cancer cells inhibit T cell activation and cytolytic potential, which could be partly restored by silencing of *PRAME*. Furthermore, silencing of *PRAME* reduced expression of several immune checkpoints and their ligands, including PD-1, LAG3, PD-L1, CD86, Gal-9 and VISTA. Interestingly, silencing of *PRAME* induced cancer cell killing to levels similar to anti-PD-L1 atezolizumab treatment. Comprehensive analysis of soluble inflammatory mediators and cancer cell expression of immune-related genes showed that PRAME tumour expression can suppress the expression and secretion of multiple pro-inflammatory cytokines, and mediators of T cell activation, differentiation and cytolysis. Together, our data indicate that targeting of PRAME offers a potential, novel dual therapeutic approach to specifically target tumour cells and regulate immune activation in the tumour microenvironment.

KEYWORDS
breast cancer, immune activation, immune checkpoints, immunotherapy, PRAME

1 | INTRODUCTION

PReferentially expressed Antigen in Melanoma (PRAME) is a cancer testis antigen (CTA) also known as CT130. It is characterized by restricted expression in germ cells and a low expression in normal somatic tissues such as the testis, epididymis, endometrium, ovaries and adrenal glands.[1,2] PRAME expression has been demonstrated in a variety of solid and haematological malignancies.[3-6] High PRAME tumour expression has been associated with poor prognosis in several solid tumours, increased risk of metastases and shorter disease-free and overall survival,[7] whereas it has been found to predict a more favourable outcome in acute

Malik *et al. Hum Genomics* (2021) 15:61
https://doi.org/10.1186/s40246-021-00358-9

Human Genomics

PRIMARY RESEARCH Open Access

Seven novel glucose-6-phosphate dehydrogenase (G6PD) deficiency variants identified in the Qatari population

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Abstract

Background: Glucose-6-phosphate dehydrogenase deficiency (G6PDD) is the most common red cell enzymopathy in the world. In Qatar, the incidence of G6PDD is estimated at around 5%; however, no study has investigated the genetic basis of G6PDD in the Qatari population yet.

Methods: In this study, we analyzed whole-genome sequencing data generated by the Qatar Genome Programme for 6045 Qatar Biobank participants, to identify G6PDD variants in the Qatari population. In addition, we assessed the impact of the novel variants identified on protein function both in silico and by measuring G6PD enzymatic activity in the subjects carrying them.

Results: We identified 375 variants in/near *G6PD* gene, of which 20 were high-impact and 16 were moderate-impact variants. Of these, 14 were known G6PDD-causing variants. The most frequent G6PD-causing variants found in the Qatari population were p.Ser188Phe (*G6PD* Mediterranean), p.Asn126Asp (G6PD A+), p.Val68Met (G6PD Asahi), p.Ala335Thr (G6PD Chatham), and p.Ile48Thr (G6PD Aures) with allele frequencies of 0.0563, 0.0194, 0.00785, 0.0050, and 0.00380, respectively. Furthermore, we have identified seven novel *G6PD* variants, all of which were confirmed as G6PD-causing variants and classified as class III variants based on the World Health Organization's classification scheme.

Conclusions: This is the first study investigating the molecular basis of G6PDD in Qatar, and it provides novel insights about G6PDD pathogenesis and highlights the importance of studying such understudied population.

Keywords: *G6PD* deficiency, Whole-genome sequencing (WGS), Novel variants, Qatar Biobank (QBB), Qatar Genome Programme (QGP)

Background

Glucose-6-phosphate dehydrogenase (G6PD) is an omnipresent cytosolic enzyme that has an important housekeeping role in all cells. In red blood cells (RBCs), nicotinamide adenine dinucleotide phosphate (NADPH) is produced mainly by the action of G6PD in the first step of the pentose phosphate pathway [1]. NADPH, among other cellular functions, is particularly important in preventing the buildup of reactive oxygen species [2]. Normal activity of G6PD thus helps protect RBCs from oxygen-derived oxidative stress [3]. Gluscose-6-phosphate dehydrogenase deficiency (G6PDD) patients might develop symptoms after exposure to compounds that trigger oxidative stress in RBCs (favism and drug-induced hemolytic anemia), and it is inherited as X-linked recessive phenotype [4]. The WHO classifies G6PDD-causing variants into five classes: class I is the most severe causing chronic non-spherocytic hemolytic anemia (G6PD

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nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-25287-y OPEN

Thousands of Qatari genomes inform human migration history and improve imputation of Arab haplotypes

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Arab populations are largely understudied, notably their genetic structure and history. Here we present an in-depth analysis of 6,218 whole genomes from Qatar, revealing extensive diversity as well as genetic ancestries representing the main founding Arab genealogical lineages of Qahtanite (Peninsular Arabs) and Adnanite (General Arabs and West Eurasian Arabs). We find that Peninsular Arabs are the closest relatives of ancient hunter-gatherers and Neolithic farmers from the Levant, and that founder Arab populations experienced multiple splitting events 12–20 kya, consistent with the aridification of Arabia and farming in the Levant, giving rise to settler and nomadic communities. In terms of recent genetic flow, we show that these ancestries contributed significantly to European, South Asian as well as South American populations, likely as a result of Islamic expansion over the past 1400 years. Notably, we characterize a large cohort of men with the ChrY J1a2b haplogroup (n = 1,491), identifying 29 unique sub-haplogroups. Finally, we leverage genotype novelty to build a reference panel of 12,432 haplotypes, demonstrating improved genotype imputation for both rare and common alleles in Arabs and the wider Middle East.

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Immunology Notes and Resources

The Journal of Immunology

SysInflam HuDB, a Web Resource for Mining Human Blood Cells Transcriptomic Data Associated with Systemic Inflammatory Responses to Sepsis

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Sepsis develops after a dysregulated host inflammatory response to a systemic infection. Identification of sepsis biomarkers has been challenging because of the multifactorial causes of disease susceptibility and progression. Public transcriptomic data are a valuable resource for mechanistic discoveries and cross-studies concordance of heterogeneous diseases. Nonetheless, the approach requires structured methodologies and effective visualization tools for meaningful data interpretation. Currently, no such database exists for sepsis or systemic inflammatory diseases in human. Hence we curated SysInflam HuDB (http://sepsis.gxbsidra.org/dm3/geneBrowser/list), a unique collection of human blood transcriptomic datasets associated with systemic inflammatory responses to sepsis. The transcriptome collection and the associated clinical metadata are integrated onto a user-friendly and Web-based interface that allows the simultaneous exploration, visualization, and interpretation of multiple datasets stemming from different study designs. To date, the collection encompasses 62 datasets and 5719 individual profiles. Concordance of gene expression changes with the associated literature was assessed, and additional analyses are presented to showcase database utility. Combined with custom data visualization at the group and individual levels, SysInflam HuDB facilitates the identification of specific human blood gene signatures in response to infection (e.g., patients with sepsis versus healthy control subjects) and the delineation of major genetic drivers associated with inflammation onset and progression under various conditions. ***The Journal of Immunology*****, 2021, 207: 2195–2202.**

Sepsis and systemic inflammatory response syndrome (SIRS) are defined by systemic dysregulated host responses; the latter differs by having a noninfectious origin. These diseases are among the leading cause of morbidity and mortality, especially in pediatric and neonatal intensive care units. Sepsis is a serious clinical condition characterized by sequential organ dysfunction, after a dysregulated host response to a systemic infection (1). The relative contributions of clinical, genetic, and environmental factors toward sepsis susceptibility and outcomes remain unclear (2).

Current sepsis management relies on the prompt recognition and subsequent administration of broad-spectrum antibiotics, fluids, and vasopressors in case of life-threatening hypotension (shock). More than 19 million patients are affected by sepsis each year, resulting in around 5 million sepsis-related deaths, which occur predominately in low- and middle-income countries (3). Overall, the global sepsis mortality rate is between 25 and 30%, which increases to between 40 and 50% when shock occurs (4, 5).

By comparing transcriptomes between healthy and disease states, we can identify differentially expressed genes (DEGs) and the associated biological processes to evaluate potential gene biomarkers of specific phenotype (6). Advances in high-throughput transcriptomic platforms have driven a huge increase in the number of publicly available transcriptomic datasets in repositories, such as the NCBI Gene Expression Omnibus (GEO) (7, 8) and ArrayExpress (9, 10). These public resources represent an opportunity for mechanistic discoveries and confirmation of complex disease signatures across different studies. Different analytical approaches, such as GEO2R (7), ScanGEO (11), ImaGEO (12), BioJupies (13), and PulmonDB (14), have been used for large-scale omics investigations of human diseases.

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This work was supported by the Qatar Foundation and the Qatar National Research Fund Grant NPRP10-0205-170348 awarded to D.C.

M.T., D.C., and M.G. conceptualized the study. M.T., M.A., and S.B. performed software development and implementation. M.T. and M.G. performed data curation. M.T., S.S.Y.H., and M.G. performed analyses. M.T., S.S.Y.H., and M.G. wrote and D.R., L.R.S., and D.C. commented on the manuscript. All authors have read and approved the final manuscript.

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The online version of this article contains supplemental material.

Abbreviations used in this article: DEG, differentially expressed gene; FDR, false discovery rate; GEO, Gene Expression Omnibus; GO, Gene Ontology; GXB, Gene Expression Browser; NGS, next generation sequencing; RNA-seq, RNA sequencing; SIRS, systemic inflammatory response syndrome.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.2100697

Metabolic and Metabo-Clinical Signatures of Type 2 Diabetes, Obesity, Retinopathy, and Dyslipidemia

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Diabetes 2022;71:184–205 | https://doi.org/10.2337/db21-0490

Macro- and microvascular complications of type 2 diabetes (T2D), obesity, and dyslipidemia share common metabolic pathways. In this study, using a total of 1,300 metabolites from 996 Qatari adults (57% with T2D) and 1,159 metabolites from an independent cohort of 2,618 individuals from the Qatar BioBank (11% with T2D), we identified 373 metabolites associated with T2D, obesity, retinopathy, dyslipidemia, and lipoprotein levels, 161 of which were novel. Novel metabolites included phospholipids, sphingolipids, lysolipids, fatty acids, dipeptides, and metabolites of the urea cycle and xanthine, steroid, and glutathione metabolism. The identified metabolites enrich pathways of oxidative stress, lipotoxicity, glucotoxicity, and proteolysis. Second, we identified 15 patterns we defined as "metabo-clinical signatures." These are clusters of patients with T2D who group together based on metabolite levels and reveal the same clustering in two or more clinical variables (obesity, LDL, HDL, triglycerides, and retinopathy). These signatures revealed metabolic pathways associated with different clinical patterns and identified patients with extreme (very high/low) clinical variables associated with extreme metabolite levels in specific pathways. Among our novel findings are the role of *N*-acetylmethionine in retinopathy in conjunction with dyslipidemia and the possible roles of *N*-acetylvaline and pyroglutamine in association with high cholesterol levels and kidney function.

Metabolic association studies have successfully identified pathways perturbed in type 2 diabetes (T2D), a disease with complex etiology that is associated with diverse complications. In our previous study of subjects from the Middle East, an area with a high prevalence of T2D, we analyzed the plasma, saliva, and urine metabolic profiles of >350 individuals and revealed 94 metabolites significantly associated with T2D that were involved in metabolic pathways and different levels of glycemic control (1). We identified pathways involved in kidney function, glycosuria, lipolysis, proteolysis, brain function, and bile acids, among others.

Macro- and microvascular complications resulting from diabetes include cardiovascular conditions—the primary cause of diabetes-related mortality—and diabetic retinopathy. Both have various pathological mechanisms associated with dyslipidemia and abnormal lipoprotein levels. Other diabetes complications are associated with various risk factors, including hyperglycemia, hypertension, and dyslipidemia. Dyslipidemia is considered an independent risk factor for T2D (2): patients with T2D tend to have abnormal plasma lipid and lipoprotein levels, including decreased HDL cholesterol, a predominance of small dense LDL particles, and increased triglycerides (TRI) (3), despite having normal LDL-cholesterol levels. Furthermore, perturbed lipid metabolism and high glucose and insulin levels contribute to the development of atherosclerosis in patients with T2D (4,5). Impaired glucose tolerance and elevated free fatty acid levels in some patients suggest that insulin resistance occurs in those individuals before the onset of hyperglycemia (3,6). Insulin resistance is also associated with smaller and denser LDL particles and decreased HDL levels resulting from the hydrolysis of

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Received 7 June 2021 and accepted 25 October 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.16896382.

Chauhan *et al.*
Journal of Experimental & Clinical Cancer Research (2021) 40:356
https://doi.org/10.1186/s13046-021-02163-7

Journal of Experimental & Clinical Cancer Research

REVIEW Open Access

Ubiquitin-specific peptidase 37: an important cog in the oncogenic machinery of cancerous cells

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Abstract

Protein ubiquitination is one of the most crucial posttranslational modifications responsible for regulating the stability and activity of proteins involved in homeostatic cellular function. Inconsistencies in the ubiquitination process may lead to tumorigenesis. Ubiquitin-specific peptidases are attractive therapeutic targets in different cancers and are being evaluated for clinical development. Ubiquitin-specific peptidase 37 (USP37) is one of the least studied members of the USP family. USP37 controls numerous aspects of oncogenesis, including stabilizing many different oncoproteins. Recent work highlights the role of USP37 in stimulating the epithelial-mesenchymal transition and metastasis in lung and breast cancer by stabilizing SNAI1 and stimulating the sonic hedgehog pathway, respectively. Several aspects of USP37 biology in cancer cells are yet unclear and are an active area of research. This review emphasizes the importance of USP37 in cancer and how identifying its molecular targets and signalling networks in various cancer types can help advance cancer therapeutics.

Keywords: Ubiquitin, Deubiquitylating enzymes, Ubiquitin-specific peptidase, Ubiquitin-specific peptidase 37, Oncogene, Epithelial–mesenchymal transition

Background

Cancer is characterized by the complex evolution of a healthy cell to a cancerous cell in which the gradual accumulation of mutations provides a survival advantage for growth and nutrition. Douglas Hanahan and Robert Weinberg first described the hallmarks of cancer in 2000 and later updated them in 2011 [1, 2]. These hallmarks of cancer comprise evading apoptosis, sustaining angiogenesis, being insensitive to antigrowth signals, developing limitless replicative potential, reprogramming energy metabolism, evading immune responses, acquiring genome instability, and promoting inflammation. They characterized the complexity of cancer and emphasized that treatment failure is related to unknown facets of cancer biology that drive the uncontrolled growth of cancerous cells. Because of advances in research methodologies and the emergence of new technologies, multiple factors controlling cancer cell evolution are being discovered, and posttranslational modifications of oncoproteins have emerged as an important factor for cancer cell evolution. These protein modifications include ubiquitinylation, Phosphorylation etc. which often occur in response to extracellular stimulus and reversal of these modifications also happens rapidly on the removal of stimulus. Ubiquitination refers to the covalent attachment of a 76 aa peptide to substrate proteins that control the half-life of proteins in a cell, coordinating the cellular localization

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RESEARCH ARTICLE

Fasting-Mimicking Diet Is Safe and Reshapes Metabolism and Antitumor Immunity in Patients with Cancer

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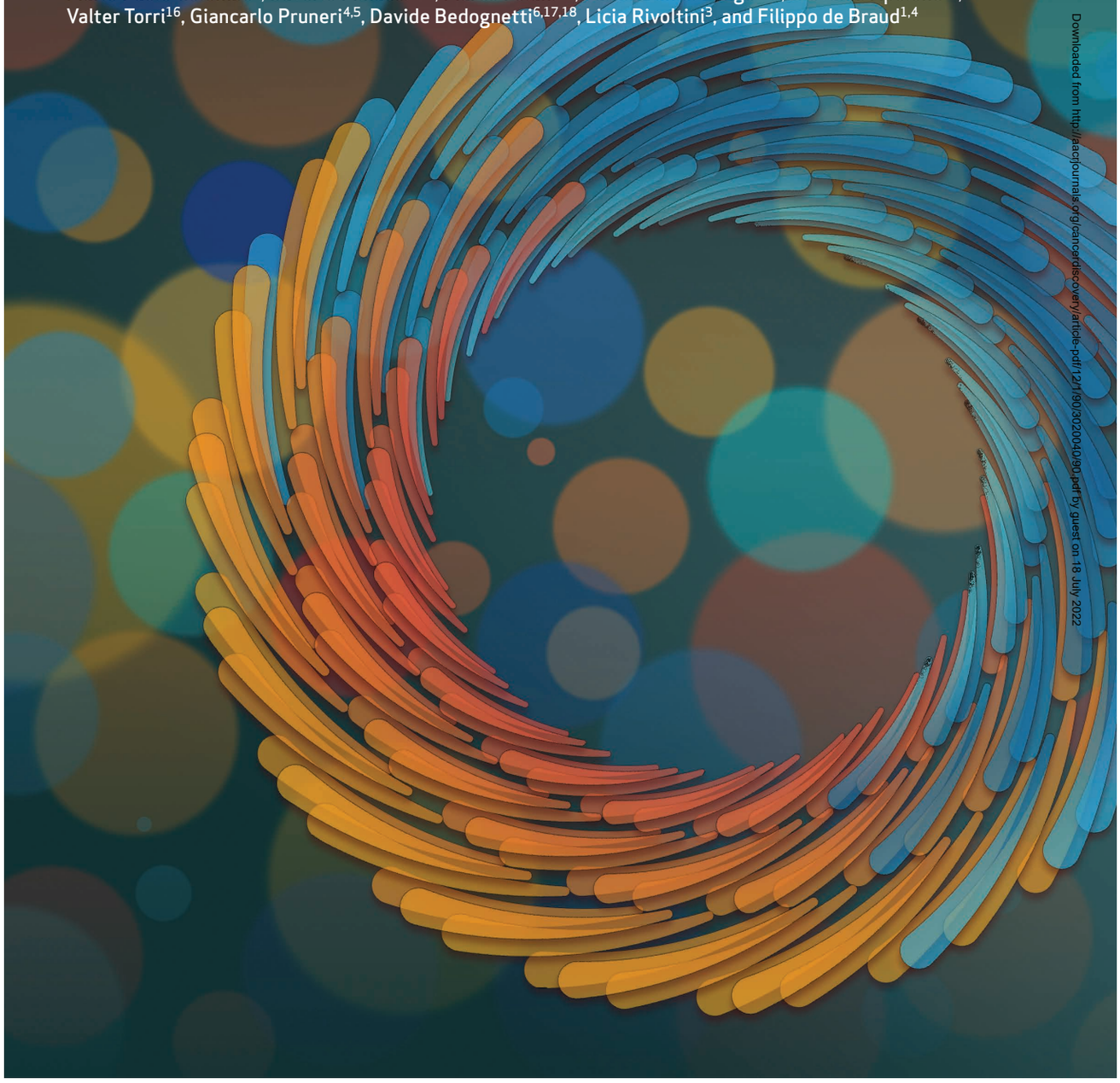

ABSTRACT In tumor-bearing mice, cyclic fasting or fasting-mimicking diets (FMD) enhance the activity of antineoplastic treatments by modulating systemic metabolism and boosting antitumor immunity. Here we conducted a clinical trial to investigate the safety and biological effects of cyclic, five-day FMD in combination with standard antitumor therapies. In 101 patients, the FMD was safe, feasible, and resulted in a consistent decrease of blood glucose and growth factor concentration, thus recapitulating metabolic changes that mediate fasting/FMD anticancer effects in preclinical experiments. Integrated transcriptomic and deep-phenotyping analyses revealed that FMD profoundly reshapes anticancer immunity by inducing the contraction of peripheral blood immunosuppressive myeloid and regulatory T-cell compartments, paralleled by enhanced intratumor Th1/cytotoxic responses and an enrichment of IFNγ and other immune signatures associated with better clinical outcomes in patients with cancer. Our findings lay the foundations for phase II/III clinical trials aimed at investigating FMD antitumor efficacy in combination with standard antineoplastic treatments.

SIGNIFICANCE: Cyclic FMD is well tolerated and causes remarkable systemic metabolic changes in patients with different tumor types and treated with concomitant antitumor therapies. In addition, the FMD reshapes systemic and intratumor immunity, finally activating several antitumor immune programs. Phase II/III clinical trials are needed to investigate FMD antitumor activity/efficacy.

INTRODUCTION

In tumor-bearing mice, cyclic fasting or calorie-restricted, low-carbohydrate, low-protein diets, collectively referred to as fasting-mimicking diets (FMD), have convincingly demonstrated additive or synergistic antitumor activity in combination with cytotoxic chemotherapy (ChT), immunotherapy, or endocrine therapies (1–6). These anticancer effects are mostly mediated by fasting/FMD-induced reduction of blood glucose, insulin, and insulin-like growth factor 1 (IGF1) concentration, which results in the inhibition of anabolic processes that sustain unrestrained growth/proliferation and the repair of chemotherapy-induced genotoxic and proteotoxic effects in cancer cells (2, 6). More recently, fasting and FMD were shown to boost tumor infiltration by $CD8^+$ T cells—the effectors of antitumor immune responses—and to reduce immunosuppressive regulatory T cells (Treg) in syngeneic mouse models (3, 5).

On the basis of this preclinical evidence, clinical trials have been initiated to investigate the feasibility and antitumor activity of cyclic FMD in combination with standard antitumor therapies in different clinical contexts (NCT03709147, NCT04248998, NCT03700437). The only study whose results have been reported so far is the phase II trial "DIRECT" (NCT02126449), which was prematurely interrupted because of poor patient compliance with the proposed FMD regimen and because the FMD failed to reduce ChT-induced adverse events (7).

Here we report on the final results of a first-in-human clinical trial (NCT03340935) that investigated the safety, feasibility, and metabolic and immunomodulatory effects of a severely calorie-restricted, five-day FMD regimen in patients with cancer. We also report on results of an interim analysis in which we investigated FMD-induced systemic and intratumor immune responses in 22 patients with breast cancer enrolled in the ongoing DigesT trial (NCT03454282).

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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Cancer Discov 2022;12:90–107

doi: 10.1158/2159-8290.CD-21-0030

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 01 November 2021
doi: 10.3389/fphar.2021.753845

Prescription Pattern and Off-Label Use of Antipsychotics in a Middle Eastern Population

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Background: Understanding the prescription pattern of medications in a population can help reveal the potential usage scenarios, including off-label prescriptions, and the need for precision medicine implementation. Therefore, the aim of this study was to assess the prescription pattern and off-label use of antipsychotics in the Qatari population.

Methods: We performed a cross-sectional study of Qatari patients who received antipsychotic prescriptions from the major healthcare providers in the country during the 2-year period between June 2018 and May 2020. The number of patients, prescriptions dispensed, and clinical indications were collected and statistical analysis using chi-square test was conducted.

Results: Among the 9,349 Qatari patients prescribed with antipsychotics during the study period, the majority were female (57%; $p < 0.001$) and were in the age categories 20–39 and 30–39 years (both 22%; $p < 0.001$). Among the 35,938 antipsychotic prescriptions dispensed, second-generation antipsychotics were the most highly prescribed (59%), specifically, quetiapine (16%) and olanzapine (12%), but the first-generation antipsychotic prochlorperazine (13%) was also highly prescribed. Most of the indications of antipsychotics (69%) were for off-label use such as for controlling chronic diseases, sleeping disorders, benign paroxysmal positional vertigo and irritable bowel syndrome.

Conclusion: Non-mental health and off-label prescriptions of several antipsychotics were observed. Integration of this data with pharmacogenomic and clinical outcome data will help in determining the course of action for implementing personalized and precision medicine in the country and beyond.

Keywords: antipsychotics, prescription pattern, Qatar, off-label, personalized medicine, electronic medical records, adverse drug effects

OPEN ACCESS

Edited by:
Luciane Cruz Lopes,
University of Sorocaba, Brazil

Reviewed by:
Benjamin Daniels,
University of New South Wales, Australia
Carlo Piccinni,
ReS Foundation, Italy

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Specialty section:
This article was submitted to Pharmacoepidemiology, a section of the journal Frontiers in Pharmacology

Received: *05 August 2021*
Accepted: *04 October 2021*
Published: *01 November 2021*

Citation:
Bastaki K, El Anbari M, Ghuloum S and Jithesh PV (2021) Prescription Pattern and Off-Label Use of Antipsychotics in a Middle Eastern Population. Front. Pharmacol. 12:753845. doi: 10.3389/fphar.2021.753845

Abbreviations: ASD, autism spectrum disorders; ATC, Anatomical Therapeutic Chemical classification; ADHD, attention-deficit hyperactivity disorder; BPPV, benign paroxysmal positional vertigo; CBT, cognitive behavioral therapy; EPS, extra-pyramidal symptom; FDA, U.S. Food and Drug Administration; FGAs, first-generation antipsychotics; HMC, Hamad Medical Corporation; IBS, irritable bowel syndrome; MDD, major depressive disorder; MHDs, mental health disorders; MHH, mental health hospital; MRC, Medical Research Centre; NICE, National Institute for Health and Care Excellence; OCD, obsessive compulsive disorder; PHCC, Primary Healthcare Corporation; PTSD, post-traumatic stress disorder; SGAs, second-generation antipsychotics; SSRI, selective serotonin reuptake inhibitors.

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CASE REPORT OPEN

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Homozygous duplication identified by whole genome sequencing causes *LRBA* deficiency

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In more than one-third of primary immunodeficiency (PID) patients, extensive genetic analysis including whole-exome sequencing (WES) fails to identify the genetic defect. Whole-genome sequencing (WGS) is able to detect variants missed by other genomics platforms, enabling the molecular diagnosis of otherwise unresolved cases. Here, we report two siblings, offspring of consanguineous parents, who experienced similar severe events encompassing early onset of colitis, lymphoproliferation, and hypogammaglobulinemia, typical of lipopolysaccharide-responsive and beige-like anchor (*LRBA*) or cytotoxic T lymphocyte antigen 4 (*CTLA4*) deficiencies. Gene-panel sequencing, comparative genomic hybridization (CGH) array, and WES failed to reveal a genetic aberration in relevant genes. WGS of these patients detected a 12.3 kb homozygous tandem duplication that was absent in control cohorts and is predicted to disrupt the reading frame of the *LRBA* gene. The variant was validated by PCR and Sanger sequencing, demonstrating the presence of the junction between the reference and the tandem-duplicated sequence. Droplet digital PCR (ddPCR) further confirmed the copy number in the unaffected parents (CN = 3, heterozygous) and affected siblings (CN = 4, homozygous), confirming the expected segregation pattern. In cases of suspected inherited immunodeficiency, WGS may reveal a mutation when other methods such as microarray and WES analysis failed to detect an aberration.

npj Genomic Medicine (2021)6:96 ; https://doi.org/10.1038/s41525-021-00263-z

INTRODUCTION

The *LRBA* gene encodes the lipopolysaccharide-responsive and beige-like anchor (LRBA) protein, which is highly conserved across species and widely expressed in human tissues[1,2]. Mutations in the *LRBA* gene cause an immunodeficiency encompassing autoimmune and lymphoproliferative features as well as antibody deficiency[2,3]. Commonly, these patients present in infancy or childhood with colitis, lymphadenopathy, and recurrent infections[4]. Most mutations described so far are localized throughout the gene and no correlation was found to the clinical presentation[4]. While most mutations resulted in a complete loss of LRBA protein, some had residual expression[5]. LRBA colocalizes with cytotoxic T lymphocyte antigen 4 (CTLA4) in endosomal vesicles and appears to control its turnover[5].

CTLA4 is expressed on activated and regulatory T cells[6] and provides an inhibitory proliferative signal by competing with the T cell co-stimulatory receptor CD28[7]. CTLA4 molecules are recycled by trafficking from the membrane to the cytoplasm, and back, through activation cycles[8]. Mutations in *LRBA* result in reduced CTLA4 expression, thus allowing for unchecked immune dysregulation, providing a plausible explanation for the autoimmune/lymphoproliferative nature of the disorder. Indeed, mutations in *CTLA4* result in a similar clinical spectrum to *LRBA* deficiency[9]. Moreover, patients with *LRBA* deficiency improve clinically when treated with the CTLA4–immunoglobulin fusion drug abatacept[10].

In a large published cohort with suspected *LRBA* deficiency, genetic analysis of the *LRBA* gene including whole-exome sequencing (WES) failed to show a mutation in a significant number of patients[4], suggesting this technique may fall short on identifying some genetic aberrations. We report here a similar case where whole-genome sequencing (WGS) was used in an attempt to define the diagnosis of *LRBA* deficiency, while gene-panel sequencing, comparative genomic hybridization (CGH) array, and WES failed to do so.

WGS can be effectively used to detect copy number variants (CNVs) and other structural variants that would be missed by exome sequencing or by genotyping or genome hybridization arrays[11,12], offering a tremendous opportunity to identify a molecular diagnosis for otherwise unresolved cases. Specifically, a pipeline that combines different methods based on read depth (CNVnator[13] and Estimation by Read Depth with Single-nucleotide variants (ERDS)[14]) was shown to be able to detect copy number gains and losses ranging from megabase to kilobase size range with high sensitivity and specificity[11].

RESULTS

Patients

Case 1 was born at term to consanguineous parents of Iraqi descent. Chronic watery diarrhea started at the age of 3 months and continued in spite of dietary changes, antibiotic therapy, and periodic management of *Clostridium difficile* when identified. An endoscopy performed at 18 months revealed complete villus atrophy, focal cryptitis, and chronic lamina propria inflammation.

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سدرة للطب Sidra Medicine

Graphene oxide activates B cells with upregulation of granzyme B expression: evidence at the single-cell level for its immune-modulatory properties and anticancer activity†

Marco Orecchioni,‡[a] Laura Fusco,‡[bcd] Raghvendra Mall,‡[e] Valentina Bordoni,[a] Claudia Fuoco,[f] Darawan Rinchai,[b] Shi Guo,[g] Raquel Sainz,§[g] Martina Zoccheddu,[a] Cansu Gurcan,[h] Acelya Yilmazer,[h] Barbara Zavan,[i] Cécilia Ménard-Moyon,[g] Alberto Bianco,[g] Wouter Hendrickx,*[bj] Davide Bedognetti*[bjk] and Lucia Gemma Delogu*[ac]

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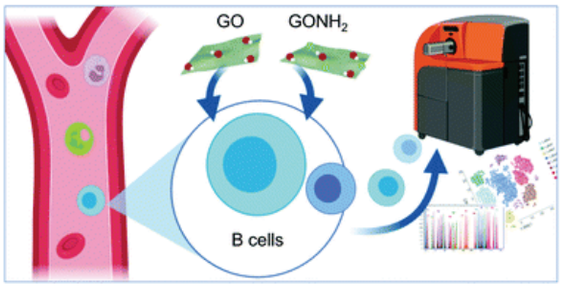
Abstract

We recently found by single-cell mass cytometry that *ex vivo* human B cells internalize graphene oxide (GO). The functional impact of such uptake on B cells remains unexplored. Here, we disclosed the effects of GO and amino-functionalized GO ($GONH_2$) interacting with human B cells *in vitro* and *ex vivo* at the protein and gene expression levels. Moreover, our study considered three different subpopulations of B cells and their functionality in terms of: (i) cytokine production, (ii) activation markers, (iii) killing activity towards cancer cells. Single-cell mass cytometry screening revealed the higher impact of GO on cell viability towards naïve, memory, and plasma B cell subsets. Different cytokines such as granzyme B (GrB) and activation markers, like CD69, CD80, CD138, and CD38, were differently regulated by $GONH_2$ compared to GO, supporting possible diverse B cell activation paths. Moreover, co-culture experiments also suggest the functional ability of both GOs to activate B cells and therefore enhance the toxicity towards HeLa cancer cell line. Complete transcriptomic analysis on a B cell line highlighted the distinctive GO and $GONH_2$ elicited responses, inducing pathways such as B cell receptor and CD40 signaling pathways, key players for GrB secretion. B cells were regularly left behind the scenes in graphene biological studies; our results may open new horizons in the development of GO-based immune-modulatory strategies having B cell as main actors.



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Molecular Case Studies

RESEARCH REPORT

Novel *MYO5B* mutation in microvillous inclusion disease of Syrian ancestry

Kamal Hassan,[1,5] Amal Robay,[2,5] Aljazi Al-Maraghi,[3] Nuha Nimeri,[1] Asmaa Basheer Azzam,[1] Alya Al Shakaki,[2] Eman Hamid,[1] Ronald G. Crystal,[4] and Khalid A. Fakhro[2,3]

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Abstract Microvillus inclusion disease (MVID) is a rare autosomal recessive condition characterized by a lack of microvilli on the surface of enterocytes, resulting in severe, life-threatening diarrhea that could lead to mortality within the first year of life. We identify two unrelated families, each with one child presenting with severe MVID from birth. Using trio whole-exome sequencing, we observed that the two families share a novel nonsense variant (Glu1589*) in the *MYO5B* gene, a type Vb myosin motor protein in which rare damaging mutations were previously described to cause MVID. This founder mutation was very rare in public databases and is likely specific to patients of Syrian ancestry. We present a detailed account of both patients' clinical histories to fully characterize the effect of this variant and expand the genotype–phenotype databases for MVID patients from the Middle East.

INTRODUCTION

Microvillus inclusion disease (MVID; MIM # 251850), also known as congenital microvillus atrophy, was first described by Davidson et al. (1978). It is a rare autosomal recessive disease that presents with an intractable life-threatening watery diarrhea either within the first days of life (early-onset form) or at several months of life (late-onset form) (Ruemmele et al. 2006). The hallmarks of MVID are a lack of microvilli on the surface of villous enterocytes, the occurrence of microvillous inclusions, and the cytoplasmic accumulation of periodic acid–Schiff-positive vesicles (Davidson et al. 1978; Cutz et al. 1989; Ruemmele et al. 2010). Müller et al. (2008) showed that mutations in *MYO5B* (MIM # 606540), encoding the unconventional type Vb myosin motor protein, were associated with MVID in an extended Turkish kindred. Since then, more mutations were described in different populations (Dhekne et al. 2018). In this report, we describe a novel mutation in two unrelated Syrian patients with MVID.

RESULTS

Patient 1 (MVID-1)

A Syrian girl was born at 36-wk gestation to consanguineous parents originally from the eastern part of Syria. The mother was 22-yr-old, gravida 7, para 3. Her previous three daughters died in Syria at 7, 10, and 30 d of age, following intractable diarrhea of unknown diagnosis.

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Ontology term: volvulus

Published by Cold Spring Harbor Laboratory Press

doi:10.1101/mcs.a006103

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 November 7; 27(41): 7065-7079

DOI: 10.3748/wjg.v27.i41.7065

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19

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Author contributions: García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Pérez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB, contributed equally to conceptualization and design, paper writing, critical review, and approved the final version of the paper.

Supported by Secretaría de Relaciones Exteriores México (SRE), No. SRE/027/2021; Agencia Mexicana de Cooperación Internacional para el Desarrollo

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Abstract

Coronavirus disease 2019 (COVID-19) is a disease produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it is currently causing a catastrophic pandemic affecting humans worldwide. This disease has been lethal for approximately 3.12 million people around the world since January 2020. Globally, among the most affected countries, Mexico ranks third in deaths after the United States of America and Brazil. Although the high number of deceased people might also be explained by social aspects and lifestyle customs in Mexico, there is a relationship between this high proportion of deaths and comorbidities

(AMEXCID), No. AMEXCID 2020-5; CONACyT for Doctoral Fellowships, No. 777953 (KC-C), No. 635676 (TB-G), No. 291236 (FH-Q), and No. 336296 (LEV-F); CONACyT for Master Fellowships, No. 997494 (NGZ-T), and No. 997152 (JMV-I); Fellows from the Sistema Nacional de Investigadores, Mexico, No. 43142 (PZ-S), No. 225525 (FB-G), No. 47399 (CP-C), and No. 19815 (JG-M).

Conflict-of-interest statement: The authors report no conflicts of interest.

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Mexico

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 1, 2021
Peer-review started: May 1, 2021
First decision: June 12, 2021
Revised: June 25, 2021
Accepted: September 30, 2021
Article in press: September 30, 2021
Published online: November 7, 2021

P-Reviewer: Verma AK, Wang CY
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

such as high blood pressure (HBP), type 2 diabetes, obesity, and metabolic syndrome. The official epidemiological figures reported by the Mexican government have indicated that 18.4% of the population suffers from HBP, close to 10.3% of adults suffer from type 2 diabetes, and approximately 36.1% of the population suffers from obesity. Disbalances in the gut microbiota (GM) have been associated with these diseases and with COVID-19 severity, presumably due to inflammatory dysfunction. Recent data about the association between GM dysbiosis and metabolic diseases could suggest that the high levels of susceptibility to SARS-CoV-2 infection and COVID-19 morbidity in the Mexican population are primarily due to the prevalence of type 2 diabetes, obesity, and metabolic syndrome.

Key Words: SARS-CoV-2; COVID-19; High blood pressure; Hypertension; Type 2 diabetes; Obesity; Metabolic syndrome; Gut microbiota; Immunity

Core Tip: This work reviews recent data about gut microbiota (GM) diversity in Mexico, a country in which more than 18.4% of adults present high blood pressure, 39.1% are overweight, 36.1% are obese, and more than 10.3% suffer from type 2 diabetes. This review highlights the link between GM dysbiosis and severe acute respiratory syndrome coronavirus 2 prevalence, which ranks Mexico third in cumulative coronavirus disease 2019 deaths in the world.

Citation: García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Perez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB. Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19. *World J Gastroenterol* 2021; 27(41): 7065-7079
URL: https://www.wjgnet.com/1007-9327/full/v27/i41/7065.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i41.7065

INTRODUCTION

Bacteria maintain the immune response in the gut

The human body harbors approximately 100 trillion cells belonging to commensal microorganisms[1], and they are primarily concentrated in the intestine[2]. The term gut microbiota (GM) refers to the symbiotic intestinal collection of bacteria, archaea, and some eukaryotes with an important influence on health and disease[3]. Among the several functions in the host, the GM participates in the synthesis of water-soluble vitamins, the supply of quinones[4], the metabolism of xenobiotics[5], neurotransmitter modulation[6], the production of energy substrates from dietary fiber[7] and the regulation of immune homeostasis[8].

A functional microbiota promotes the host's immunity[9]. For example, the polysaccharide A in *Bacteroides fragilis*' directs lymphoid organogenesis and corrects systemic T lymphocyte (TL) deficiencies and TL-helper Th1/Th2 imbalances through mechanisms such as interleukin (IL)-12/Stat4-mediated Th1 differentiation. Moreover, *B. fragilis*' polysaccharide A presentation by intestinal dendritic cells (DCs) activates clusters of differentiation in CD4+ TLs, eliciting appropriate cytokine production[10]. Commensal GM is also required for Th17 cell differentiation in the small intestine by activating the transforming growth factor (TGF)-β[11] and influences gut immunoglobulin (Ig) repertories and B lymphocyte (BL) development in the intestinal mucosa [12]. Elevated serum levels of IgE through BL isotype switching at mucosal sites have been reported for germ-free (GF) mice in a CD4+ TL- and IL-4-dependent manner, suggesting that a healthy GM is required to inhibit high IgE induction[13].

The GM plays a vital role in the innate immune system[14]. A total lack of TL and DC under GF conditions in the jejunum of piglets was reverted by *Escherichia coli* colonization, favoring the recruitment of both cell types to the lamina propria[15]. GM

Published in final edited form as:
Cell Genom. 2021 November 10; 1(2): . doi:10.1016/j.xgen.2021.100029.

GA4GH: International policies and standards for data sharing across genomic research and healthcare

A full list of authors and affiliations appears at the end of the article.

SUMMARY

The Global Alliance for Genomics and Health (GA4GH) aims to accelerate biomedical advances by enabling the responsible sharing of clinical and genomic data through both harmonized data aggregation and federated approaches. The decreasing cost of genomic sequencing (along with other genome-wide molecular assays) and increasing evidence of its clinical utility will soon drive the generation of sequence data from tens of millions of humans, with increasing levels of diversity. In this perspective, we present the GA4GH strategies for addressing the major challenges of this data revolution. We describe the GA4GH organization, which is fueled by the development efforts of eight Work Streams and informed by the needs of 24 Driver Projects and other key stakeholders. We present the GA4GH suite of secure, interoperable technical standards and policy frameworks and review the current status of standards, their relevance to key domains of research and clinical care, and future plans of GA4GH. Broad international participation in building, adopting, and deploying GA4GH standards and frameworks will catalyze an unprecedented effort in data sharing that will be critical to advancing genomic medicine and ensuring that all populations can access its benefits.

INTRODUCTION

The Universal Declaration of Human Rights states that everyone has the right to share in scientific advancement and its benefits.[1,2] In order to fully deliver the benefits from genomic science to the broad human population, researchers and clinicians must come together to agree on common methods for collecting, storing, transferring, accessing, and analyzing molecular and other health-related data. Otherwise, this information will remain siloed within individual disease areas, institutions, countries, or other jurisdictions, locking away its potential to contribute to research and medical advances.

The Global Alliance for Genomics and Health (GA4GH) is a worldwide alliance of genomics researchers, data scientists, healthcare practitioners, and other stakeholders. We are collaborating to establish policy frameworks and technical standards for responsible, international sharing of genomic and other molecular data as well as related health data. Founded in 2013,[3] the GA4GH community now consists of more than 1,000 individuals

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xgen.2021.100029.

Biomedicine & Pharmacotherapy 144 (2021) 112358

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Sanguinarine mediated apoptosis in Non-Small Cell Lung Cancer via generation of reactive oxygen species and suppression of JAK/STAT pathway

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ARTICLE INFO

Keywords:
Apoptosis
Antiproliferative
Alkaloids
Antioxidants
Cancer stem cells
Sanguinarine
ROS
STAT3

ABSTRACT

Effective treatment of lung cancer remains a significant clinical challenge due to its multidrug resistance and side effects of the current treatment options. The high mortality associated with this malignancy indicates the need for new therapeutic interventions with fewer side effects. Natural compounds offer various benefits such as easy access, minimal side effects, and multi-molecular targets and thus, can prove useful in treating lung cancer. Sanguinarine (SNG), a natural compound, possesses favorable therapeutic potential against a variety of cancers. Here, we examined the underlying molecular mechanisms of SNG in Non-Small Cell Lung Cancer (NSCLC) cells. SNG suppressed cell growth and induced apoptosis via downregulation of the constitutively active JAK/STAT pathway in all the NSCLC cell lines. siRNA silencing of STAT3 in NSCLC cells further confirmed the involvement of the JAK/STAT signaling cascade. SNG treatment increased Bax/Bcl-2 ratio, which contributed to a leaky mitochondrial membrane leading to cytochrome c release accompanied by caspase activation. In addition, we established the antitumor effects of SNG through reactive oxygen species (ROS) production, as inhibiting ROS production prevented the apoptosis-inducing potential of SNG. In vivo xenograft tumor model further validated our in vitro findings. Overall, our study investigated the molecular mechanisms by which SNG induces apoptosis in NSCLC, providing avenues for developing novel natural compound-based cancer therapies.

1. Introduction

Lung cancer is one of the leading causes of cancer death, accounting for 1.4 million deaths per year. Non-Small Cell Lung Cancer (NSCLC), a subtype of lung cancer, accounts for nearly 80–85% of cases [1,2]. Surgical resection at the earlier stage and chemotherapy, radiotherapy, targeted therapy, etc., at the advanced stage, is the preferred mode of treatment with a 5-year survival rate of about 15% [3]. Significant adverse effects, high cytotoxicity, and therapeutic resistance limit these targeted therapies' long-term beneficial effects [3]. The search for newer therapeutic options against NSCLC with fewer side effects continues. Herbal drugs, alone or combined with chemotherapeutic agents, are preferred due to their higher potency with fewer side effects [4].

Many medicinal plants have anticancer properties due to secondary

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https://doi.org/10.1016/j.biopha.2021.112358
Received 8 August 2021; Received in revised form 8 October 2021; Accepted 19 October 2021
Available online 28 October 2021

J Hum Genet. 2022 May;67(5):253-259. doi: 10.1038/s10038-021-00995-x. Epub 2021 Dec 3.

Novel variants in the LRP4 underlying Cenani–Lenz Syndactyly syndrome

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PMID: 34857885 DOI: 10.1038/s10038-021-00995-x

Abstract

Cenani-Lenz syndrome (CLS) is a rare autosomal-recessive congenital disorder affecting development of distal limbs. It is characterized mainly by syndactyly and/or oligodactyly, renal anomalies, and characteristic facial features. Mutations in the LRP4 gene, located on human chromosome 11p11.2-q13.1, causes the CLS. The gene LRP4 encodes a low-density lipoprotein receptor-related protein-4, which mediates SOST-dependent inhibition of bone formation and Wnt signaling. In the study, presented here, three families of Pakistani origin, segregating CLS in the autosomal recessive manner were clinically and genetically characterized. In two families (A and B), microsatellite-based homozygosity mapping followed by Sanger sequencing identified a novel homozygous missense variant [NM_002334.3: c.295G>C; p.(Asp99His)] in the LRP4 gene. In the third family C, exome sequencing revealed a second novel homozygous missense variant [NM_002334.3: c.1633C>T; p.(Arg545Trp)] in the same gene. To determine the functional relevance of these variants, we tested their ability to inhibit canonical WNT signaling in a luciferase assay. Wild type LRP4 was able to inhibit LRP6-dependent WNT signaling robustly. The two mutants p.(Asp99His) and p.(Arg545Trp) inhibited WNT signaling less effectively, suggesting they reduced LRP4 function.

Received: 29 October 2021 | Revised: 5 December 2021 | Accepted: 6 December 2021

DOI: 10.1111/dom.14618

REVIEW ARTICLE

WILEY

Melanocortin-4 receptor complexity in energy homeostasis, obesity and drug development strategies

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Abstract

The melanocortin-4 receptor (MC4R) has been critically investigated for the past two decades, and novel findings regarding MC4R signalling and its potential exploitation in weight loss therapy have lately been emphasized. An association between MC4R and obesity is well established, with disease-causing mutations affecting 1% to 6% of obese patients. More than 200 MC4R variants have been reported, although conflicting results as to their effects have been found in different cohorts. Most notably, some MC4R gain-of-function variants seem to rescue obesity and related complications via specific pathways such as beta-arrestin (ß-arrestin) recruitment. Broadly speaking, however, dysfunctional MC4R dysregulates satiety and induces hyperphagia. The picture at the mechanistic level is complicated as, in addition to the canonical G stimulatory pathway, the ß-arrestin signalling pathway and ions (particularly calcium) seem to interact with MC4R signalling to contribute to or alleviate obesity pathogenesis. Thus, the overall complexity of the MC4R signalling spectra has broadened considerably, indicating there is great potential for the development of new drugs to manage obesity and its related complications. Alpha-melanocyte-stimulating hormone is the major endogenous MC4R agonist, but structure-based ligand discovery studies have identified possible superior and selective agonists that can improve MC4R function. However, some of these agonists characterized in vitro and in vivo confer adverse effects in patients, as demonstrated in clinical trials. In this review, we provide a comprehensive insight into the genetics, function and regulation of MC4R and its contribution to obesity. We also outline new approaches in drug development and emerging drug candidates to treat obesity.

KEYWORDS
Ca^{2+}, drug design, G_s, MC4R, obesity, ß-arrestin

1 | INTRODUCTION

Obesity is characterized by excess fat mass, which affects physical health and increases the complexity of many associated diseases and conditions, including type 2 diabetes, cardiovascular complications and cancer.[1] The associated healthcare costs are huge, and obesity is accompanied by significant morbidity and mortality. Obesity is defined in terms of body mass index (BMI), that is, weight (kg)/height (m^2);

Received: 26 September 2021 | Revised: 9 November 2021 | Accepted: 16 November 2021

DOI: 10.1002/ccr3.5141

CASE REPORT

Clinical Case Reports Open Access WILEY

Maturity-onset diabetes of the young (MODY) due to PDX1 mutation in a sib-pair diabetes family from Qatar

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Funding information
This research was supported by the Qatar National Research Fund [QNRF-NPRP 10-6100017-AXX] awarded to Professor Khalid Hussain.

Abstract

Maturity-onset diabetes of young (MODY) is an autosomal dominant genetic disorder that causes insulin deficiency without autoimmunity. We present the first family with pancreatic duodenal homeobox 1 *(PDX1)* mutation causing diabetes from Qatar. Routine genetic screening of all antibody-negative diabetic patients with diabetes should be offered to avoid misdiagnosis.

KEYWORDS

MODY, PDX1, pediatric diabetes mellitus

1 | INTRODUCTION

Maturity-onset diabetes of the young (MODY) is an autosomal dominant genetic disorder characterized by impaired insulin secretion causing hyperglycemia at an early age, most commonly before 25 years of age. There is minimal or no defect in insulin action, absence of autoimmunity or insulin resistance.[1] Serum insulin and/or c-peptide with some residual pancreatic function is usually present. In the family history, typically multiple members will have diabetes.[2] MODY is the most common form of monogenic diabetes affecting 1%–5% of all patients with diabetes mellitus (DM).[3] However, these figures are based on studies in European and other western countries, with limited information about MODY in Middle Eastern countries.[2,3] MODY subjects are often misdiagnosed as type 1 or type 2 diabetes; however, they have different treatment modalities and prognosis. Diagnosis of MODY should be considered in subjects with autoantibody negative atypical diabetes with multiple affected family members.[1]

14 subtypes of MODY have been described in the literature, the most common being MODY due to glucokinase *(GCK)*, hepatocyte nuclear factor 1A *(HNF1A)*, and hepatocyte nuclear factor 4A *(HNF4A)* gene mutations.[4]

frontiers in Microbiology

ORIGINAL RESEARCH
published: 10 December 2021
doi: 10.3389/fmicb.2021.772736

Can the Salivary Microbiome Predict Cardiovascular Diseases? Lessons Learned From the Qatari Population

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Background: Many studies have linked dysbiosis of the gut microbiome to the development of cardiovascular diseases (CVD). However, studies assessing the association between the salivary microbiome and CVD risk on a large cohort remain sparse. This study aims to identify whether a predictive salivary microbiome signature is associated with a high risk of developing CVD in the Qatari population.

Methods: Saliva samples from 2,974 Qatar Genome Project (QGP) participants were collected from Qatar Biobank (QBB). Based on the CVD score, subjects were classified into low-risk (LR < 10) ($n = 2491$), moderate-risk (MR = 10–20) ($n = 320$) and high-risk (HR > 30) ($n = 163$). To assess the salivary microbiome (SM) composition, 16S-rDNA libraries were sequenced and analyzed using QIIME-pipeline. Machine Learning (ML) strategies were used to identify SM-based predictors of CVD risk.

Results: *Firmicutes* and *Bacteroidetes* were the predominant phyla among all the subjects included. Linear Discriminant Analysis Effect Size (LEfSe) analysis revealed that *Clostridiaceae* and *Capnocytophaga* were the most significantly abundant genera in the LR group, while *Lactobacillus* and *Rothia* were significantly abundant in the HR group. ML based prediction models revealed that *Desulfobulbus, Prevotella*, and *Tissierellaceae* were the common predictors of increased risk to CVD.

Conclusion: This study identified significant differences in the SM composition in HR and LR CVD subjects. This is the first study to apply ML-based prediction modeling using the SM to predict CVD in an Arab population. More studies are required to better understand the mechanisms of how those microbes contribute to CVD.

Keywords: CVD, salivary microbiome, precision medicine, machine learning, QGP

OPEN ACCESS

Edited by:
Florence Carrouel, Université Claude Bernard Lyon 1, France

Reviewed by:
Ina Saliasi, Université Claude Bernard Lyon 1, France
Frédéric Denis, Université de Nantes, France

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Specialty section:
This article was submitted to Microbial Symbioses, a section of the journal Frontiers in Microbiology

Received: *08 September 2021*
Accepted: *17 November 2021*
Published: *10 December 2021*

Citation:
Murugesan S, Elanbari M, Bangarusamy DK, Terranegra A and Al Khodor S (2021) Can the Salivary Microbiome Predict Cardiovascular Diseases? Lessons Learned From the Qatari Population. Front. Microbiol. 12:772736. doi: 10.3389/fmicb.2021.772736

INTRODUCTION

Non-communicable Diseases (NCDs) are the leading cause of death globally (Allen et al., 2017). According to the World Health Organization [WHO] (2013) report, the global burden of non-communicable diseases (NCDs) raised to 82% by 2020. The most common NCDs are cardiovascular diseases (CVD), cancer, respiratory disorders, and diabetes (Balakumar et al., 2016).

frontiers in Oncology

ORIGINAL RESEARCH
published: 08 December 2021
doi: 10.3389/fonc.2021.734959

Bulk and Single-Cell Profiling of Breast Tumors Identifies TREM-1 as a Dominant Immune Suppressive Marker Associated With Poor Outcomes

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Background: Triggering receptor expressed on myeloid cells (TREM)-1 is a key mediator of innate immunity previously associated with the severity of inflammatory disorders, and more recently, the inferior survival of lung and liver cancer patients. Here, we investigated the prognostic impact and immunological correlates of *TREM1* expression in breast tumors.

Methods: Breast tumor microarray and RNAseq expression profiles (n=4,364 tumors) were analyzed for associations between gene expression, tumor immune subtypes, distant metastasis-free survival (DMFS) and clinical response to neoadjuvant chemotherapy (NAC). Single-cell (sc)RNAseq was performed using the 10X Genomics platform. Statistical associations were assessed by logistic regression, Cox regression, Kaplan-Meier analysis, Spearman correlation, Student's t-test and Chi-square test.

Results: In pre-treatment biopsies, *TREM1* and known TREM-1 inducible cytokines (IL1B, IL8) were discovered by a statistical ranking procedure as top genes for which high expression was associated with reduced response to NAC, but only in the context of

OPEN ACCESS

Edited by:
Mariana Segovia, National Autonomous University of Mexico, Mexico

Reviewed by:
Camila O Dos Santos, Cold Spring Harbor Laboratory, United States
Samantha Henry, Cold Spring Harbor Laboratory, United States, contributed to the review of CDS
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Specialty section:
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

Received: *01 July 2021*
Accepted: *15 November 2021*
Published: *08 December 2021*

Citation:
Pullikuth AK, Routh ED, Zimmerman KD, Chifman J, Chou JW, Soike MH, Jin G, Su J, Song Q, Black MA, Print C, Bedognetti D, Howard-McNatt M, O'Neill SS, Thomas A, Langefeld CD, Sigalov AB, Lu Y and Miller LD (2021) Bulk and Single-Cell Profiling of Breast Tumors Identifies TREM-1 as a Dominant Immune Suppressive Marker Associated With Poor Outcomes. Front. Oncol. 11:734959. doi: 10.3389/fonc.2021.734959

JC-10 probe as a novel method for analyzing the mitochondrial membrane potential and cell stress in whole zebrafish embryos

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Nadin Younes, Bana S Alsahan, Asmaa J Al-Mesaifri, Sahar I Da'as, Gianfranco Pintus, Amin F Majdalawieh, Gheyath K Nasrallah

Toxicology Research, Volume 11, Issue 1, February 2022, Pages 77–87,
https://doi.org/10.1093/toxres/tfab114
Published: 21 December 2021 **Article history**

Views Cite Permissions Share

Abstract

Background

A sensitive method to investigate cellular stress and cytotoxicity is based on measuring mitochondrial membrane potential. Recently, JC-10, was developed to measure mitochondrial membrane potential *in vitro* and used as an indicator for cytotoxicity. Yet, JC-10 has never been used *in vivo* (whole organism). In normal cells, JC-10 concentrates in the mitochondrial matrix, where it forms red fluorescent aggregates. However, in apoptotic/necrotic cells, JC-10 diffuses out of the mitochondria, changes to monomeric form, and stains cells in green. Here, we aimed to develop and optimize a JC-10 assay to measure cytotoxicity in zebrafish embryo. We also investigated the effectiveness of JC-10 assay by comparing it to common cytotoxicity assays.

Methods

Zebrafish embryos were exposed to a toxic surfactant AEO-7 at no observed effect concentration (6.4 μg/L), and then cytotoxicity was measured using (i) JC-10 mitochondrial assay, (ii) acridine orange (AO), (iii) TUNEL assay, and (iv) measuring the level of Hsp70 by western blotting.

Results

As compared to the negative control, embryos treated with NOEC of AEO-7 did not show significant cytotoxicity when assessed by AO, TUNEL or western blotting. However, when JC-10 was used under the same experimental conditions, a significant increase of green:red fluorescent ratio signal was

J Knee Surg
DOI: 10.1055/s-0040-1721790

Original Article

Does Treatment with Dexmedetomidine Intra-articularly Improve Postoperative Pain and Rehabilitation after Anterior Cruciate Ligament Reconstruction?

Ayşe Ülgey , Adnan Bayram , Recep Aksu , Resul Altuntaş , Ahmet Güney , Gülen Güler

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› Further Information

Abstract

This study aims to evaluate the analgesic efficacy of dexmedetomidine added to levobupivacaine following anterior cruciate ligament (ACL) surgery. Fifty patients undergoing ACL reconstruction were included. Group DL (dexmedetomidin-levobupivacaine) received 20 mL 0.5% levobupivacaine plus 1 mL (100 µg) dexmedetomidine. Group L (levobupivacaine) patients received 20 mL 0.5% levobupivacaine plus 1 mL saline 10 minutes before tourniquet release. A patient-controlled analgesia (PCA) pump was then connected, delivering 0.5 mg at every 10 minutes and 1-mg morphine and 75-mg diclofenac sodium was used as a rescue analgesic. Postoperative pain was evaluated 0, 2, 4, 6, 12, and 24 hours after extubation at rest and during movement. A rehabilitation program was started after surgery. Postoperative continuous passive motion (CPM) starting time, postoperative leg flexion angle, and straight leg lifting time were evaluated for each group. There were no significant differences between the groups in terms of demographic data and operation time. Morphine consumption, analgesic requirements, and visual analogue scale (VAS) assessments were significantly lower in group DL during the 24-hour period after surgery. The time to start CPM in the postoperative period was significantly shorter in group DL. Passive joint flexion angle was significantly higher in group DL. Postoperative straight leg lifting time was significantly shorter in group DL. Adding dexmedetomidine to the intra-articular levobupivacaine provided better postoperative pain control and improved rehabilitation period after ACL surgery.

Keywords

anesthesia - pain therapy - postoperative analgesia

Publication History

Received: 21 March 2020

Accepted: 12 November 2020

Article published online:
03 January 2021

Thieme Medical Publishers, Inc.
333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

Journal of Clinical Immunology (2021) 41:603–609
https://doi.org/10.1007/s10875-020-00952-x

ORIGINAL ARTICLE

Differential Expression of Interferon-Alpha Protein Provides Clues to Tissue Specificity Across Type I Interferonopathies

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Received: 23 October 2020 / Accepted: 22 December 2020 / Published online: 7 January 2021

Abstract

Whilst upregulation of type I interferon (IFN) signaling is common across the type I interferonopathies (T1Is), central nervous system (CNS) involvement varies between these disorders, the basis of which remains unclear. We collected cerebrospinal fluid (CSF) and serum from patients with Aicardi-Goutières syndrome (AGS), STING-associated vasculopathy with onset in infancy (SAVI), presumed monogenic T1Is (pT1I), childhood systemic lupus erythematosus with neuropsychiatric features (nSLE), non-IFN-related autoinflammation (AI) and non-inflammatory hydrocephalus (as controls). We measured IFN-alpha protein using digital ELISA. Eighty-two and 63 measurements were recorded respectively in CSF and serum of 42 patients and 6 controls. In an intergroup comparison (taking one sample per individual), median CSF IFN-alpha levels were elevated in AGS, SAVI, pT1I, and nSLE compared to AI and controls, with levels highest in AGS compared to all other groups. In AGS, CSF IFN-alpha concentrations were higher than in paired serum samples. In contrast, serum IFN was consistently higher compared to CSF levels in SAVI, pT1I, and nSLE. Whilst IFN-alpha is present in the CSF and serum of all IFN-related diseases studied here, our data suggest the primary sites of IFN production in the monogenic T1I AGS and SAVI are, respectively, the CNS and the periphery. These results inform the diagnosis of, and future therapeutic approaches to, monogenic and multifactorial T1Is.

Keywords Interferon · cerebrospinal fluid · Aicardi-Goutières syndrome · STING-associated vasculopathy with onset in infancy · systemic lupus erythematosus

Introduction

Beyond their function in mediating an antiviral state, type I interferons (IFN) play an important role in the pathogenesis of several human diseases [1]. In 2011, the term type I interferonopathy (T1I) was coined to define a novel set of Mendelian inborn errors [2], the neuroinflammatory disorder Aicardi-Goutières syndrome (AGS) being the first identified [3]. Since that time, there has been the expansion of this grouping [4] including STING-associated vasculopathy with onset in infancy (SAVI), proteasome-associated autoinflammatory syndromes (PRAAS), and COPA syndrome. By definition, these monogenic disorders share the common feature of upregulated type I IFN signaling, which is considered central to disease pathogenesis (i.e. not merely representing a biomarker). Furthermore, enhanced type I IFN is also observed in several multifactorial disorders, including systemic lupus erythematosus (SLE) and dermatomyositis (DM) [5]. Although some features are shared across certain of these phenotypes (for example intracranial calcification (ICC) and vasculitic-like skin involvement), phenotypic differences are also notable (for example severe pulmonary

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European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-020-04108-y

ORIGINAL ARTICLE

Epidemiological, molecular, and clinical features of rotavirus infections among pediatrics in Qatar

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Received: 23 June 2020 / Accepted: 20 November 2020

Abstract

Acute gastroenteritis (AGE) remains a major cause of diarrhea in developing and developed countries. Rotavirus (RV) is a leading cause of severe pediatric diarrhea worldwide. Here we report on the prevalence of circulating genotypes in association with demographics and clinical manifestations outcomes in Qatar. A total of 231 RV-positive fecal samples were collected from children suffering from AGE during 3 years study period between June 2016 and June 2019. The age of the subjects ranged between 2 months and 14 years (median of 16 months). The VP4 and VP7 were amplified and sequenced. Phylogenetic analyses were performed using MEGA7.0. Pearson's chi-squared test was used to determine significant differences for comparisons of general categorical variables. RV infections were most common in children between 1 and 3 years of age (49%), followed by those < 1 year and > 3 years of age (33% and 28%, respectively). RV infections were more frequent in males than females, with a ratio of 1.4:1. RV infections occurred throughout the year, with a noticeable increase in summer (42.8%) and a drop in winter (20.1%). RV genotypes G3P[8] (30.8%), G2P[8] (12.3%), G4P[8] (11.7%), and G1P[8] (10.4%) were the common genotypes during the study period. The G3P[8] strain detected in our study revealed similarities to the equine-like G3P[8] (10.3%; 24/231) (KT988229.1), Wa-like genomic constellation (9%; 21/231) (MF563894.1), and DS-1-like strains (6.4%; 15/231) (LC386081.1). Based on the Vesikari score system, severe clinical illness including diarrhea and vomiting (average frequency: 4 to 5 times/day) was recorded for G3P[8] group, followed by G9P[8], G4P[8], and G1P[8]. Higher incidence for G3P[8], G2P[8], G4P[8], and G1P[8] were reported in Qatari subjects compared to other nationalities. The multinational status of a small country explains the wide diversity of circulating RV genotypes in Qatar. The highest prevalence and severe illnesses were recorded to G3P[8], which is different from other surrounding countries/global levels.

Keywords Rotavirus · Genotyping · Vaccination · Age-specific

Introduction

Rotavirus (RV) infections are a leading global cause of severe gastroenteritis (GE) and severe diarrheal disease among infants and children worldwide [1]. According to the 2016 World Health Organization (WHO) estimates, around 215,000 children aged under 5 years die from vaccine-preventable rotavirus infections every year [2]. Although the incidence rate of RV infections represents a high burden in both low- and high-income countries, the mortality rate due to RV infections is higher in low-income countries [3]. It is estimated that by the age of 5 years, most children will have had at least one episode of RV infections [4]. The primary source of the transmission of these viruses is through the fecal-oral route and possibly by contaminated surfaces, and hands [5]. Clinical symptoms associated with RV infections are diarrhea, vomiting, and fever in infants and young children.

RV, a member *Reoviridae* family, is a non-enveloped wheel-like double-stranded RNA virus with 11 viral genome segments [6] encoding for six non-structural proteins (NSP1-NSP6) that are involved in viral virulence and six structural viral proteins

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Published online: 07 January 2021

Original Research

Cost-effectiveness of Oral Versus Intravenous Ibuprofen Therapy in Preterm Infants With Patent Ductus Arteriosus in the Neonatal Intensive Care Setting: A Cohort-based Study

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ABSTRACT

Purpose: Use of ibuprofen for the patent ductus arteriosus (PDA) has become increasingly common. This study aimed to evaluate the clinical and economic impact of oral ibuprofen versus intravenous ibuprofen for PDA among preterm infants.

Methods: This retrospective, cohort-based pilot study examined the clinical and economic associations of oral versus intravenous ibuprofen for PDA. A decision-analytic model was constructed, from the hospital perspective, to follow the oral versus intravenous administrations of ibuprofen for PDA and their clinical and economic consequences. The course regimen of either formulation was an initial 10 mg/kg followed by 5 mg/kg at 24- and 48-h intervals. Clinical and resource utilization data were extracted from Cerner medical database, from 2014 through 2018, at the tertiary neonatal intensive care unit setting in Qatar. The primary outcome measures were the rate of successful closure based on the ductal diameter measure after the first course of treatment and the overall direct medical cost of PDA management. A population of 118 neonates was required for results with 80% power and 0.05 significance. Sensitivity analyses involving unit costs and a subgroup analysis based on gestational age and birth weight, added to a second-order probabilistic analysis of all model inputs, were performed.

Findings: Forty infants were available for inclusion in the oral ibuprofen study group, not achieving the desired sample size, with successful PDA closure reported in 64% of cases compared with a reduced success of 36% with intravenous ibuprofen (n = 59) (risk ratio = 0.56; 95% CI, 0.32–0.97; $P = 0.04$), which was associated with economic advantage to oral ibuprofen. The probabilistic analysis illustrated that oral ibuprofen costs less than intravenous ibuprofen in 72% of patient cases, with QAR 48,751 (US $13,356) (95% CI, QAR 47,500–50,000, US $13,014–$13,699) in mean savings. Sensitivity analyses confirmed the robustness of study conclusions and found that the rate of closure success versus failure was the most influential on results, followed by the occurrence of adverse drug events with both intravenous and oral ibuprofen. Although both ibuprofen formulations had similar safety profiles ($P = 0.16$), the intravenous formulation was associated with a larger number of adverse drug effects.

Accepted for publication December 7, 2020
https://doi.org/10.1016/j.clinthera.2020.12.004
0149-2918/$ - see front matter

J Appl Biomech. 2021 Apr 1;37(2):109-117. doi: 10.1123/jab.2020-0013. Epub 2021 Jan 15.

Obese Youth Demonstrate Altered Landing Knee Mechanics Unrelated to Lower-Extremity Peak Torque When Compared With Healthy Weight Youth

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Affiliations + expand

PMID: 33450728 DOI: 10.1123/jab.2020-0013

Abstract

Obese (OB) youth demonstrate altered knee mechanics and worse lower-extremity performance compared with healthy weight (HW) youth. Our objectives were to compare sagittal plane knee landing mechanics between OB and HW youth and to examine the associations of knee and hip extension peak torque with landing mechanics in OB youth. Twenty-four OB and 24 age- and sex-matched HW youth participated. Peak torque was measured and normalized to leg lean mass. Peak knee flexion angle and peak internal knee extension moment were measured during a single-leg hop landing. Paired t tests, Pearson correlation coefficients, and Bonferroni corrections were used. OB youth demonstrated worse performance and lower knee extension (OB: 12.76 [1.38], HW: 14.03 [2.08], P = .03) and hip extension (OB: 8.59 [3.13], HW: 11.10 [2.89], P = .005) peak torque. Furthermore, OB youth demonstrated lower peak knee flexion angles (OB: 48.89 [45.41 to 52.37], HW: 56.07 [52.59 to 59.55], P = .02) and knee extension moments (OB: -1.73 [-1.89 to -1.57], HW: -2.21 [-2.37 to -2.05], P = .0001) during landing compared with HW youth. Peak torque measures were not correlated with peak knee flexion angle nor internal knee extension moment during landing in either group (P > .01). OB youth demonstrated altered landing mechanics compared with HW youth. However, no associations among peak torque measurements and knee landing mechanics were present.

Keywords: childhood obesity; knee strength; landing mechanics; single-leg hop.

Online publiziert: 15.01.2021

Thieme

Augenärztliche Screening-Untersuchung bei Frühgeborenen (S2k-Level, AWMF-Leitlinien-Register-Nr. 024/010, März 2020)

Gemeinsame Empfehlung von Deutsche Ophthalmologische Gesellschaft (DOG), Retinologische Gesellschaft (RG), Berufsverband der Augenärzte Deutschlands (BVA), Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ), Berufsverband der Kinder- und Jugendärzte e.V. (BVKJ), Bundesverband „Das frühgeborene Kind“ e.V., Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI)

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online publiziert 15.01.2021

Bibliografie
Z Geburtsh Neonatol 2021; 225: 19–33
DOI 10.1055/a-1248-0649
ISSN 0948-2393

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Leitlinienreport

Redaktionskomitee

Federführende Fachgesellschaft

- Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin e.V. (GNPI)

Beteiligung weiterer AWMF-Gesellschaften

- Deutsche Ophthalmologische Gesellschaft e.V. (DOG)
- Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V. (DGKJ)

Beteiligung weiterer Fachgesellschaften/Organisationen

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- Berufsverband der Augenärzte Deutschlands
- Berufsverband der Kinder- und Jugendärzte e. V. (BVKJ)
- Bundesverband „Das frühgeborene Kind“ e.V.

* nach dem federführenden Autor in alphabetischer Reihenfolge

Mandatierung

- Prof. Dr. Rolf F. Maier für die GNPI (federführend)
- Prof. Dr. Helmut Hummler für die GNPI
- Prof. Dr. Ulrich Kellner für die RG
- Prof. Dr. Tim U. Krohne für den BVA
- Dr. Burkhard Lawrenz für den BVKJ
- Prof. Dr. Birgit Lorenz
- Barbara Mitschdörfer für den Bundesverband „Das frühgeborene Kind“ e.V.
- Prof. Dr. Claudia Roll für die GNPI und DGKJ
- Prof. Dr. Andreas Stahl für die DOG

Geltungsbereich und Zweck

- Begründung für die Auswahl des Leitlinienthemas: Sicherstellung einer rechtzeitigen Diagnose jeder interventionsbedürftigen Frühgeborenenretinopathie (ROP)
- Zielorientierung der Leitlinie: Rationale Handlungsempfehlungen zur Durchführung des ROP-Screenings bei Frühgeborenen, Vermeiden von Über- und Unterdiagnostik
- Patientenzielgruppe: Frühgeborene
- Versorgungsbereich: Früherkennung, spezialisierte und primärärztliche, stationäre und ambulante pädiatrische und ophthalmologische Einrichtungen
- Anwenderzielgruppe/Adressaten: Kinderärztinnen/-ärzte, Augenärztinnen/-ärzte

Zusammensetzung der Leitliniengruppe: Beteiligung von Interessensgruppen

- Repräsentativität der Leitliniengruppe: Beteiligte Berufsgruppen
  - Kinderärztinnen/-ärzte aus dem stationären und dem ambulanten Bereich
  - Augenärztinnen/-ärzte aus dem stationären und dem ambulanten Bereich
- Repräsentativität der Leitliniengruppe: Beteiligung von Patienten
  - Beteiligung des Bundesverbands „Das frühgeborene Kind“ e.V. als Patientenvertretung

Methodologische Exaktheit

Recherche, Auswahl und Bewertung wissenschaftlicher Belege (Evidenzbasierung)

- Formulierung von Schlüsselfragen
  - Bei welchen Kindern ist das ROP-Screening indiziert?
  - Wann soll die erste Untersuchung erfolgen?
  - In welchem zeitlichen Abstand sollen Folgeuntersuchungen erfolgen?
  - Wann kann das ROP-Screening beendet werden?
  - Wie soll die Untersuchung ablaufen?
  - Wie sollen die Befunde klassifiziert und dokumentiert werden?
  - Bei welchen Befunden soll therapeutisch interveniert werden?
- Verwendung existierender Leitlinien zum Thema
  - Erste Auflage dieser Leitlinie von 1999 (siehe unten)
  - Zweite Auflage dieser Leitlinie von 2007 (siehe unten)
  - Britische Leitlinie von 2008
  - Niederländische Leitlinie von 2013
  - Schwedische Leitlinie von 2012
  - US-Amerikanische Leitlinie von 2018
  - Kanadische Leitlinie von 2006
- Systematische Literaturrecherche
  - PubMed (Schwerpunkt 2000–2019, besonders relevante Literatur auch älter), ausgehend von dem MeSH-Begriff „retinopathy of prematurity“ allein und in Kombination mit weiteren Begriffen wie „VLBW infants“, „screening“, „ophthalmological examination“, „fundoscopy“, „guideline“, „recommendation“
  - weitere Ergebnisse aus Handsuche in ausgewählten Zeitschriften und Literaturverzeichnissen aufgefundener Literatur

Formulierung der Empfehlungen und strukturierte Konsensfindung

- Formale Konsensfindung: Verfahren und Durchführung
  - E-Mail-basierter Gruppenprozess mit mandatierten Teilnehmerinnen/Teilnehmern
  - Literaturrecherchen zu aufgeworfenen Themenkomplexen, gefolgt von einer anonymisierten (06.03.–15.04.2019) und 2 offenen E-Mail-basierten Delphi-Runden (GNPI-Delphikonferenz)
  - die finale Fassung wurde mit allen Empfehlungen einstimmig angenommen (starker Konsens (>95 % der Stimmberechtigten) laut AWMF-Regelwerk
- Berücksichtigung von Nutzen, Nebenwirkungen, relevanten Outcomes
  - Der Nutzen für die Kinder wie auch für die Gesellschaft besteht in der Verhinderung von Erblindung.
- Formulierung der Empfehlungen
  - Entsprechend dem aktuellen Literaturstand wurde die vorhergehende Fassung der Leitlinie zunächst vom federführenden Autor und dann von den beteiligten Koautorinnen/-autoren überarbeitet.
  - Die endgültige Formulierung ist das Ergebnis von mehreren Überarbeitungsschritten u. a. auch in mehreren Telefonkonferenzen der Autorinnen/Autoren.
  - Im Text der Leitlinie wurde die Empfehlungsstärke mit den Verben ‚sollen‘ (starke Empfehlung), ‚sollten‘ (Empfehlung) und ‚können‘ (offene Empfehlung) zum Ausdruck gebracht.

Externe Begutachtung und Verabschiedung

Pilottestung

Die beiden vorherigen Fassungen dieser Leitlinie können als Pilottestung gewertet werden.

Externe Begutachtung

Die Erfahrungen mit den vorherigen Fassungen der Leitlinie waren ein wesentlicher Gesichtspunkt bei der Formulierung der aktuellen Fassung. Hinzu kommt der o. g. Delphi-Prozess.

Verabschiedung durch die Vorstände der herausgebenden Fachgesellschaften/Organisationen

Einstimmig verabschiedet vom Vorstand der GNPI am 09.03.2020, danach konsentiert von den weiteren tragenden Gesellschaften und dem Bundesverband „Das frühgeborene Kind“ e.V. (bis 10.05.2020).

Received: 12 August 2020 | Revised: 4 January 2021 | Accepted: 5 January 2021

DOI: 10.1002/ijc.33476

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Characteristics and outcome of pediatric renal cell carcinoma patients registered in the International Society of Pediatric Oncology (SIOP) 93-01, 2001 and UK-IMPORT database: A report of the SIOP-Renal Tumor Study Group

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Abbreviations: 5y, five-year; AJCC, American Joint Committee on Cancer; EFS, event-free survival; MiT, microphthalmia transcription factor; MiT-RCC, translocation type renal cell carcinoma; NSS, nephron-sparing surgery; OS, overall survival; RCC, renal cell carcinoma; RTSG, Renal Tumor Study Group; SIOP, International Society of Pediatric Oncology; TFE3, transcription factor E3; TFEB, transcription factor EB; WHO, World Health Organization.

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Funding information
Children's Cancer and Leukaemia Group/Little Princess Trust, Grant/Award Number: CCLGA 2019 27B; Children's Cancer and Leukaemie Group/Bethany's Wish, Grant/Award Number: CCLGA 2017 02; Great Ormond Street Hospital Children's Charity, Grant/Award Number: W1090; Stichting Kinderen Kankervrij, Grant/Award Number: 341

Abstract

In children, renal cell carcinoma (RCC) is rare. This study is the first report of pediatric patients with RCC registered by the International Society of Pediatric Oncology-Renal Tumor Study Group (SIOP-RTSG). Pediatric patients with histologically confirmed RCC, registered in SIOP 93-01, 2001 and UK-IMPORT databases, were included. Event-free survival (EFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Between 1993 and 2019, 122 pediatric patients with RCC were registered. Available detailed data (n = 111) revealed 56 localized, 30 regionally advanced, 25 metastatic and no bilateral cases. Histological classification according to World Health Organization 2004, including immunohistochemical and molecular testing for transcription factor E3 (TFE3) and/or EB (TFEB) translocation, was available for 65/122 patients. In this group, the most common histological subtypes were translocation type RCC (MiT-RCC) (36/64, 56.3%), papillary type (19/64, 29.7%) and clear cell type (4/64, 6.3%). One histological subtype was not reported. In the remaining 57 patients, translocation testing could not be performed, or TFE-cytogenetics and/or immunohistochemistry results were missing. In this group, the most common RCC histological subtypes were papillary type (21/47, 44.7%) and clear cell type (11/47, 23.4%). Ten histological subtypes were not reported. Estimated 5-year (5y) EFS and 5y OS of the total group was 70.5% (95% CI = 61.7%-80.6%) and 84.5% (95% CI = 77.5%-92.2%), respectively. Estimated 5y OS for localized, regionally advanced, and metastatic disease was 96.8%, 92.3%, and 45.6%, respectively. In conclusion, the registered pediatric patients with RCC showed a reasonable outcome. Survival was substantially lower for patients with metastatic disease. This descriptive study stresses the importance of full, prospective registration including TFE-testing.

KEYWORDS
pediatric, renal cell carcinoma, survival, treatment

1 | INTRODUCTION

While renal cell carcinoma (RCC) is the most common renal tumor in adults, it accounts for 2% to 6% of malignant renal tumors in the pediatric population.[1-4] Our understanding of pediatric RCC has increased the past years; however, it still often remains based on knowledge of adult RCC.[3,5] From the few studies that have described pediatric RCC cohorts, it has become clear that compared to RCC in adult patients, childhood RCC has distinct clinical, histological and molecular characteristics.[3,6-8] In adults, clear cell RCC represents the predominant histological subtype, whereas in children distribution of subtypes is different.[5,9,10] Translocation-type RCC (MiT-RCC), officially recognized by the World Health Organization (WHO) in 2004, is characterized by translocations including transcription factor E3 (TFE3) or

What's new?

Pediatric renal cell carcinoma (RCC) is a rare malignancy, knowledge of which is based largely on adult RCC. Here, pediatric RCC was retrospectively studied using data from the International Society of Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG). Pediatric RCC patients had a 5-year overall survival rate of 84.5 percent, with notably lower survival for patients with metastatic disease. In pediatric RCC patients tested for transcription factor E3 and EB, 56.3 percent presented with translocation type. The findings highlight the importance of full registration of pediatric RCCs, with information on germline genetics and transcription factor testing.

Equity in coronavirus disease 2019 vaccine development and deployment

Neena Modi, MD; Diogo Ayres-de-Campos, PhD; Eduardo Bancalari, MD; Manon Benders, MD; Despina Briana, MD; Gian Carlo Di Renzo, MD; Eduardo Borges Fonseca, MD, PhD; Moshe Hod, MD; Liona Poon, MD; Magda Sanz Cortes, MD; Umberto Simeoni, MD; Charlotte Tscherning, MD; Maximo Vento, MD; Gerald H. A. Visser, MD; Liliana Voto, MD

The coronavirus disease 2019 pandemic exposed weaknesses in multiple domains and widened gender-based inequalities across the world. It also stimulated extraordinary scientific achievement by bringing vaccines to the public in less than a year. In this article, we discuss the implications of current vaccination guidance for pregnant and lactating women, if their exclusion from the first wave of vaccine trials was justified, and if a change in the current vaccine development pathway is necessary. Pregnant and lactating women were not included in the initial severe acute respiratory syndrome coronavirus 2 vaccine trials. Therefore, perhaps unsurprisingly, the first vaccine regulatory approvals have been accompanied by inconsistent advice from public health, governmental, and professional authorities around the world. Denying vaccination to women who, although pregnant or breastfeeding, are fully capable of autonomous decision making is a throwback to a paternalistic era. Conversely, lack of evidence generated in a timely manner, upon which to make an informed decision, shifts responsibility from research sponsors and regulators and places the burden of decision making upon the woman and her healthcare advisor. The World Health Organization, the Task Force on Research Specific to Pregnant Women and Lactating Women, and others have highlighted the long-standing disadvantage experienced by women in relation to the development of vaccines and medicines. It is uncertain whether there was sufficient justification for excluding pregnant and lactating women from the initial severe acute respiratory syndrome coronavirus 2 vaccine trials. In future, we recommend that regulators mandate plans that describe the development pathway for new vaccines and medicines that address the needs of women who are pregnant or lactating. These should incorporate, at the outset, a careful consideration of the balance of the risks of exclusion from or inclusion in initial studies, patient and public perspectives, details of "developmental and reproductive toxicity" studies, and approaches to collect data systematically from participants who are unknowingly pregnant at the time of exposure. This requires careful consideration of any previous knowledge about the mode of action of the vaccine and the likelihood of toxicity or teratogenicity. We also support the view that the default position should be a "presumption of inclusion," with exclusion of women who are pregnant or lactating only if justified on specific, not generic, grounds. Finally, we recommend closer coordination across countries with the aim of issuing consistent public health advice.

Key words: antibody-dependent enhancement, clinical trials, coronavirus disease 2019, gender-equity, lactation, neonatal immunity, pregnancy, randomized trials, research-equity, safety and efficacy, severe acute respiratory syndrome coronavirus 2, Task Force on Research Specific to Pregnant Women and Lactating Women, vaccine development, women, World Health Organization

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Received Dec. 29, 2020; revised Jan. 12, 2021; accepted Jan. 12, 2021.

N.M. is the immediate past-president of the United Kingdom Royal College of Paediatrics and Child Health, the current president of the United Kingdom Medical Women's Federation, and the president-elect of the British Medical Association. G.C.D.R. is the president of the International Foundation for Maternal, Periconceptional and Peri-Neonatal Medicine. All views expressed are their own.

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0002-9378/$36.00 • • https://doi.org/10.1016/j.ajog.2021.01.006

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Photobiomodulation: The Clinical Applications of Low-Level Light Therapy

Aesthetic Surgery Journal
2021, Vol 41(6) 723–738

DOI: 10.1093/asj/sjab025
www.aestheticsurgeryjournal.com
OXFORD UNIVERSITY PRESS

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Abstract

Background: Low-level light therapy (LLLT) is a recent addition to the pantheon of light-based therapeutic interventions. The absorption of red/near-infrared light energy, a process termed "photobiomodulation," enhances mitochondrial ATP production, cell signaling, and growth factor synthesis, and attenuates oxidative stress. Photobiomodulation is now highly commercialized with devices marketed directly to the consumer. In the gray area between the commercial and therapeutic sectors, harnessing the clinical potential in reproducible and scientifically measurable ways remains challenging.

Objectives: The aim of this article was to summarize the clinical evidence for photobiomodulation and discuss the regulatory framework for this therapy

Methods: A review of the clinical literature pertaining to the use of LLLT for skin rejuvenation (facial rhytids and dyschromias), acne vulgaris, wound healing, body contouring, and androgenic alopecia was performed.

Results: A reasonable body of clinical trial evidence exists to support the role of low-energy red/near-infrared light as a safe and effective method of skin rejuvenation, treatment of acne vulgaris and alopecia, and, especially, body contouring. Methodologic flaws, small patient cohorts, and industry funding mean there is ample scope to improve the quality of evidence. It remains unclear if light-emitting diode sources induce physiologic effects of compararable nature and magnitude to those of the laser-based systems used in most of the higher-quality studies.

Conclusions: LLLT is here to stay. However, its ubiquity and commercial success have outpaced empirical approaches on which solid clinical evidence is established. Thus, the challenge is to prove its therapeutic utility in retrospect. Well-designed, adequately powered, independent clinical trials will help us answer some of the unresolved questions and enable the potential of this therapy to be realized.

Editorial Decision date: November 4, 2020; online publish-ahead-of-print January 20, 2021.

Light and Skin Aging

As we age, so, inevitably, does our skin. Intrinsic skin aging occurs as a result of the relentless passage of time, whereas extrinsic aging arises as the cumulative result of our environmental exposures.[1] With age, progressive loss of telomere length leads to cellular senescence and a failure of cell-mediated tissue regeneration, the histopathologic manifestations of which include thinning of both the epidermis and dermis, flattening of the rete ridges, and decline in synthesis of type 1 collagen.[2] Changes in soft tissue volume and distribution and in the structure of the skeletal framework lead to age-associated facial aging.[3,4] Concurrently, extrinsic changes manifest as loss of tone and elasticity caused by fragmentation of collagen, elastin, and anchoring fibrils induced by alterations in the ratio of matrix metalloproteinase to metalloproteinase-inhibitor expression; loss of extracellular matrix glycosaminoglycans; and pigmentary variations (ephilides/freckles and lentigines) due to localized changes in melanocyte and melanosome activity.[5] The basis for extrinsic aging is free

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[Intervention Review]

Interventions for treating iron deficiency anaemia in inflammatory bowel disease

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Editorial group: Cochrane Gut Group.
Publication status and date: New, published in Issue 1, 2021.

Citation: Gordon M, Sinopoulou V, Iheozor-Ejiofor Z, Iqbal T, Allen P, Hoque S, Engineer J, Akobeng AK. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No.: CD013529. DOI: 10.1002/14651858.CD013529.pub2.

ABSTRACT

Background

Inflammatory bowel disease affects approximately seven million people globally. Iron deficiency anaemia can occur as a common systemic manifestation, with a prevalence of up to 90%, which can significantly affect quality of life, both during periods of active disease or in remission. It is important that iron deficiency anaemia is treated effectively and not be assumed to be a normal finding of inflammatory bowel disease. The various routes of iron administration, doses and preparations present varying advantages and disadvantages, and a significant proportion of people experience adverse effects with current therapies. Currently, no consensus has been reached amongst physicians as to which treatment path is most beneficial.

Objectives

The primary objective was to evaluate the efficacy and safety of the interventions for the treatment of iron deficiency anaemia in people with inflammatory bowel disease.

Search methods

We searched CENTRAL, MEDLINE, Embase, and two other databases on 21st November 2019. We also contacted experts in the field and searched references of trials for any additional trials.

Selection criteria

Randomised controlled trials investigating the effectiveness and safety of iron administration interventions compared to other iron administration interventions or placebo in the treatment of iron deficiency anaemia in inflammatory bowel disease. We considered both adults and children, with studies reporting outcomes of clinical, endoscopic, histologic or surgical remission as defined by study authors.

Data collection and analysis

Two review authors independently conducted data extraction and 'Risk of bias' assessment of included studies. We expressed dichotomous and continuous outcomes as risk ratios and mean differences with 95% confidence intervals. We assessed the certainty of the evidence using the GRADE methodology.

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LETTER TO THE EDITOR

A Novel Point Mutation in the N Gene of SARS-CoV-2 May Affect the Detection of the Virus by Reverse Transcription-Quantitative PCR

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KEYWORDS COVID-19, SARS-CoV-2, RT-qPCR, N gene, point mutation

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, laboratory testing to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse transcription-quantitative PCR (RT-qPCR) has played a central role in mitigating the spread of the virus (1). Soon after the viral genome sequences were available, several RT-qPCR assays were developed and made available by the World Health Organization (WHO) for public use (https://www.who.int/docs/default-source/coronaviruse/whoinhouseassays.pdf). The primer and probe sequences for these assays were chosen from multiple target genes within the viral genome, such as the E gene, RdRp gene, ORF1ab, and N gene. Many commercial and laboratory-developed assays were developed for SARS-CoV-2 detection based on these primer and probe sequences. The large-scale sustained person-to-person transmission of SARS-CoV-2 has led to many mutational events, some of which may affect the sensitivity and specificity of available PCR assays (2). Recently, mutations in the E gene (C26340T) and N gene (C29200T) affecting the detection of target genes by two commercial assays were reported for 8 and 1 patients, respectively. Interestingly, both mutations are of the C→T type, a common single nucleotide polymorphism (SNP) that may be associated with strong host cell mRNA editing mechanisms known as apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminase (3, 4). Another study found a G→U substitution in position 29140 that affected the sensitivity of detection of N gene-based assays (5). Here, we report a novel N gene mutation (C29200A) seen in 3 patients which affected the detection of the SARS-CoV-2 N gene by a commercial assay.

Cepheid Xpert Xpress SARS-CoV-2 (Xpert) is an FDA-approved assay for COVID-19 under emergency use authorization (EUA). The Xpert assay is based on a multiplex PCR that includes both E gene and N gene targets for SARS-CoV-2 detection. The assay was implemented in our laboratory at Sidra Medicine, a pediatric referral center in Qatar, in June 2020. Since then, a total of 8,800 samples have been tested by Xpert, of which 365 (4.1%) were positive. Occasionally, discrepant results were seen (~2.5% of all positive results) for E gene and N gene targets, which were reported as "presumptive positive" by the Cepheid GeneXpert system. In the majority of these cases, RT-qPCR cycle threshold (C_T) values were >38 (Table 1). However, at the end of October 2020, a mutation in the SARS-CoV-2 N gene was suspected when Xpert failed to amplify the N gene target in a specimen, despite giving a strong positive result (C_T =19.8) for the E gene. Subsequently, 3 more samples showed similar results in the next 2 months (Table 1). All of these samples were confirmed to be positive by a second test method (QIAstat-Dx respiratory SARS-CoV-2 panel; Qiagen). The study involves the secondary

Citation Hasan MR, Sundararaju S, Manickam C, Mirza F, Al-Hail H, Lorenz S, Tang P. 2021. A novel point mutation in the N gene of SARS-CoV-2 may affect the detection of the virus by reverse transcription-quantitative PCR. J Clin Microbiol 59:e03278-20. https://doi.org/10.1128/JCM.03278-20.

Editor Alexander J. McAdam, Boston Children's Hospital

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Accepted manuscript posted online 20 January 2021

Published 19 March 2021

Elsayed et al. *Cell Death and Disease* (2021)12:103
https://doi.org/10.1038/s41419-021-03390-8

Cell Death & Disease

ARTICLE Open Access

Aberrant development of pancreatic beta cells derived from human iPSCs with *FOXA2* deficiency

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Abstract

FOXA2 has been identified as an essential factor for pancreas development and emerging evidence supports an association between FOXA2 and diabetes. Although the role of FOXA2 during pancreatic development is well-studied in animal models, its role during human islet cell development remains unclear. Here, we generated induced pluripotent stem cells (iPSCs) from a patient with *FOXA2* haploinsufficiency (FOXA2$^{+/-}$ iPSCs) followed by beta-cell differentiation to understand the role of FOXA2 during pancreatic beta-cell development. Our results showed that *FOXA2* haploinsufficiency resulted in aberrant expression of genes essential for the differentiation and proper functioning of beta cells. At pancreatic progenitor (PP2) and endocrine progenitor (EPs) stages, transcriptome analysis showed downregulation in genes associated with pancreatic development and diabetes and upregulation in genes associated with nervous system development and WNT signaling pathway. Knockout of FOXA2 in control iPSCs (FOXA2$^{-/-}$ iPSCs) led to severe phenotypes in EPs and beta-cell stages. The expression of NGN3 and its downstream targets at EPs as well as INSUILIN and GLUCAGON at the beta-cell stage, were almost absent in the cells derived from FOXA2$^{-/-}$ iPSCs. These findings indicate that FOXA2 is crucial for human pancreatic endocrine development and its defect may lead to diabetes based on FOXA2 dosage.

Introduction

During human development, early endodermal tissue becomes specified toward a pancreatic fate before evagination of pancreatic buds, populated with pancreatic progenitors. All adult pancreatic cells are originated from the same progenitors expressing a group of transcription factors (TFs), including PDX1, SOX9, FOXA2, NKX6.1, HNF6, and PTF1A[1,2]. Monogenic diabetes (MD) is caused by a mutation or defect in a single gene-regulating beta-cell development and/or function[3]. Several heterozygous mutations in the TFs expressed during pancreatic development are associated with a specific form of MD, known as MODY. However, homozygous mutations of the same TFs lead to neonatal diabetes, which can be associated with pancreatic hypoplasia/agenesis in some mutations[4]. This indicates that the onset and severity of the diabetes phenotype are correlated with the dosage of the TF expression during pancreatic development.

FOXA2 is expressed in several tissues and performs distinct functions as evident in the phenotypes of mouse models[5]. *Foxa2* knockout mice die at an early embryonic stage and show developmental defects in the foregut (FG) and neural tube[6–8]. During pancreatic development, FOXA2 is expressed at early stages starting from the endoderm stage and its protein level is increased during the endocrine specification stage[1,9], while the exocrine and ductal cells express a low level of FOXA2[9]. Mouse studies showed that Foxa2 is important for islet development and beta-cell functionality[6,10–12] and its specific deletion in beta-cells leads to hyperinsulinemic hypoglycemic phenotype[13,14]. In human, previous reports demonstrated that patients with heterozygous *FOXA2* mutations develop hyperinsulinemia, hypoglycemia,

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Edited by A. Finazzi-Agrò

European Journal of Obstetrics & Gynecology and Reproductive Biology 258 (2021) 235–239

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Seasonal influenza during pregnancy

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ARTICLE INFO

Article history:
Received 29 October 2020
Received in revised form 26 December 2020
Accepted 4 January 2021

Keywords:
Influenza
Seasonal influenza
Influenza A
Influenza B
Pregnancy

ABSTRACT

Seasonal Influenza is an acute respiratory illness caused by Influenza A or B viruses. Its presentation is commonly with signs and symptoms of upper respiratory tract involvement such as cough, sore throat and runny nose, associated with generalized systemic symptoms such as fever, headaches, myalgia, and weakness. The severity of symptoms is very variable, ranging from mild self-limiting infection to severe acute respiratory illness requiring intensive interventions. It usually occurs during the winter season and can lead to outbreaks and epidemics worldwide. Influenza is associated with increased morbidity and mortality in high-risk populations including pregnant women and up to two weeks postpartum. Rapid and accurate diagnosis of Influenza is necessary for prompt treatment to reduce morbidity. General public health measures and vaccination are recommended to reduce morbidity and control the spread of the disease. There are many published articles on the several Influenza epidemics that have occurred in this century. In this article, we aim to review the epidemiology, clinical manifestations, diagnosis, treatment, and prevention of seasonal Influenza during pregnancy. We performed an electronic search on PubMed, Cochrane database, National guidelines clearing house and Google Scholar databases.

Introduction

Influenza is caused by a group of RNA viruses (A, B, and C) belonging to the Orthomyxoviridae family. Influenza A viruses are further characterized by the subtype of their surface glycoproteins-haemagglutinin (HA) and neuraminidase (NA). While many genetically distinct subtypes (16 for HA and 9 for NA) have been found in circulating Influenza A viruses, only three HA (H1, H2, and H3) and two NA (N1 and N2) subtypes have caused human epidemics [1]. Both Influenza A and B strains cause seasonal infections of viral Influenza (flu). Influenza C typically causes only a mild respiratory illness [2].

Epidemiology

The epidemiology of Influenza has been widely followed over this century [3].In 1918 there was an outbreak of Influenza A pandemic flu known as the Spanish flu. This was most likely attributed to an avian-like H1N1infection [2,3]. It affected one-third of the world's population, resulting in over 50 million deaths, with fatality rates greater than 2.5 % (compared with 0.1 % for a typical flu outbreak) [2]. In 1957 H2N2 caused the Asian flu pandemic. In 1976 there was an outbreak of swine H1N1 Influenza amongst soldiers in New Jersey, resulting in 230 confirmed cases and 1 death. A separate pandemic in 1968, the Hong Kong Influenza, was related to human/avian H3N2 virus [2]. In March and early April 2009 a new swine-origin Influenza virus (S-OIV) A (H1N1), emerged in Mexico and the USA [4,5]. The virus quickly spread worldwide through human-to-human transmission. Because of the number of countries and communities world-wide reporting human cases, the World Health Organization raised the Influenza pandemic alert to its highest level in June 2009 [6]. Seasonal Influenza continues to be a major health hazard. The Centres for Disease Control and Prevention (CDC) estimated that Influenza was associated with more than 35.5 million illnesses, more than 16.5 million medical visits, 490,600 hospitalizations and 34,200 deaths during the 2018–2019 Influenza seasons [7].

Transmission

A large quantity of Influenza viruses are often present in respiratory secretions of infected people. As a result, they can be transmitted through sneezing and coughing and as both large droplets (>5 microns) [8] and aerosols or small particles [9].The

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https://doi.org/10.1016/j.ejogrb.2021.01.005
0301-2115/

European Journal of Obstetrics & Gynecology and Reproductive Biology 258 (2021) 424–429

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Non invasive prenatal testing (NIPT) for common aneuploidies and beyond

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ARTICLE INFO

Article history:
Received 4 October 2020
Received in revised form 20 December 2020
Accepted 8 January 2021

Keywords:
Non invasive prenatal testing (NIPT)
Cell free fetal DNA (cffDNA)
Fetal chromosomal abnormalities
Fetal genetic abnormalities
Next generation sequencing (NGS)
Whole exome sequencing (WES)
Non invasive prenatal testing (NIPT) laboratory technologies
Clinical application of Non invasive prenatal testing (NIPT)
Psychological impact of Non invasive prenatal testing (NIPT)
NIPT in various healthcare systems

ABSTRACT

Non invasive prenatal Testing (NIPT) is changing the practice of prenatal diagnosis worldwide. It provides high sensitivity and specificity in screening for common aneuploidies. As a result, it has reduced the number of invasive procedures, thereby reducing their associated risk of pregnancy miscarriage. NIPT is based on the detection and analysis of cell free fetal DNA (cffDNA) that is obtained from a maternal peripheral blood sample.

Advanced laboratory detection and purification technology has improved the performance of NIPT and allowed the introduction of new applications in recent years. The introduction of Next Generation Sequencing (NGS) into clinical practice has rendered NIPT to have high sensitivity in the screening of aneuploidy. It has also allowed detecting and investigating the fetal genome from maternal plasma. Fetal Whole Exome Sequencing (WES) provides non invasive prenatal diagnosis of inherited monogenic disorders and can also offer a diagnosis of an underlying cause of fetal anomalies that have a normal karyotype.

The following will review the current and potential future applications of NIPT and discuss the advantages and disadvantages of the various NIPT techniques. The role of public healthcare system plays in the provision of the test, and the psychological impact of NIPT on the end-users will also be highlighted.

Introduction

Fetal congenital malformations remain the leading cause of perinatal mortality and morbidity. Most fetal anomalies will have a chromosomal or genetic underlying cause. Chromosomal abnormalities, including aneuploidy, translocations, duplications, and deletions are present in approximately 1 in 150 live births [1,2]. Invasive testing in the form of chorionic villous sampling and amniocentesis, followed by karyotyping and/or CGH microarray, are currently available diagnostic tests for chromosomal abnormalities. However, these tests carry a relatively small but significant risk of pregnancy miscarriage [3]. Traditionally, the combined or triple tests are used to identify high-risk groups that could benefit from and thus should be offered invasive testing [4,5]. Early attempts of non invasive prenatal testing have focused on fetal cells in maternal plasma; however due to the rarity of them and other technical difficulties, it was not possible to reuse fetal cells in clinical applications [6].

The discovery and ability to analyze Cell free fetal DNA (cffDNA) in maternal plasma have changed the field of prenatal screening and diagnosis [7]. cffDNA originates from the placenta, likely secondary to the apoptosis of the trophoblasts [8]. It can be detected at as early as 5 weeks of gestation, and its concentration in maternal plasma increases with gestational age. cffDNA is cleared from the maternal plasma within hours following the delivery of the placenta, which makes it pregnancy specific [9,10]. Fetal Fraction (FF), which is the ratio between fetal and total DNA in maternal plasma is variable and increases with gestational age. The FF is strongly linked to how reliable the NIPT results are [11,12].

Advanced cffDNA analysis techniques have provided a high positive and negative predictive value of fetal chromosomal and genetic abnormalities and hence have reduced the number of unnecessary invasive tests. The recent introduction of next-

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https://doi.org/10.1016/j.ejogrb.2021.01.008
0301-2115/

Journal of Pediatric Urology (2021) **17**, 393.e1–393.e7

Impact of bilateral ureteral reimplantation at the time of complete primary repair of bladder exstrophy on reflux rates, renogram abnormalities and bladder capacity

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Keywords
Bladder exstrophy; Ureteral reimplantation; Vesicoureteral reflux; Renal scar

Received 18 September 2020
Revised 11 January 2021
Accepted 15 January 2021
Available online 21 January 2021

Summary

Introduction
Bilateral ureteral reimplantation at the time of the complete primary repair of bladder exstrophy (BUR-CPRE) has been proposed and has demonstrated favorable outcomes in the past. However, the potential benefits, including prevention of vesicoureteral reflux (VUR) and renal scarring must be tempered with any risks of reimplantation, persistent VUR, and the potential for overtreatment. We aimed to determine the impact of BUR-CPRE on reflux rates, renogram findings and bladder capacity.

Methods
An IRB approved registry of children treated for bladder exstrophy epispadias complex (BEEC) during a long-term international collaboration hosted in a region with high prevalence of BEEC was queried. Children undergoing primary CPRE for bladder exstrophy (BE) were identified. Surgical procedure and outcome measures nuclear medicine dimercaptosuccinic acid (DMSA) scintigraphy scans, voiding cystourethrogram (VCUG), and urodynamic study (UDS) were assessed for presence and degree of VUR, renogram abnormalities, and bladder capacity.

Results
A total cohort of 147 patients with BEEC was queried; 52 children (37 males, 71%) underwent primary CPRE for BE between 2009 and 2019 at median age of 1.1 years (IQR 0.6—1.9 years) with median follow up 4.4 years (IQR 2.4—6.4 years). BUR-CPRE was performed in 22/52 (42%). After BUR-CPRE, children were less likely to have VUR (any VUR present in 9 of 20 with imaging (45%) compared to 23 of 26 with imaging (82%) in the CPRE alone group ($p = 0.007$)). VUR in the BUR-CPRE group tended to be unilateral and lower grade in comparison to the CPRE alone group. DMSA abnormalities were less common in the BUR-CPRE group (4/19 (21%) vs.12/27 (44%)), although the difference did not reach statistical significance ($p = 0.1$). At 4 years follow-up, the BUR-CPRE group had a larger bladder capacity ($p = 0.016$).

Discussion
After BUR-CPRE, children had a lower rate of VUR, and when present, VUR was more often unilateral and lower grade compared to the CPRE alone group. Fewer numbers of children in the BUR-CPRE group depicted DMSA abnormalities. No children developed obstruction after BUR-CPRE and none have undergone repeat reimplantation. We documented a larger bladder capacity at the time of maximum follow-up available (4 years)—but further data are needed to confirm this observation.

Conclusion
BUR-CPRE decreases the incidence and severity of VUR after CPRE, but the clinical significance of this remains unclear. We are encouraged by these initial results, but since BUR-CPRE does not uniformly eliminate VUR, we continue to proceed carefully in the well selected patient.

[1] Denotes co-first author.

https://doi.org/10.1016/j.jpurol.2021.01.020

JCI insight

RESEARCH ARTICLE

Distinct antibody repertoires against endemic human coronaviruses in children and adults

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Four endemic human coronaviruses (HCoVs) are commonly associated with acute respiratory infection in humans. B cell responses to these "common cold" viruses remain incompletely understood. Here we report a comprehensive analysis of CoV-specific antibody repertoires in 231 children and 1168 adults using phage immunoprecipitation sequencing. Seroprevalence of antibodies against endemic HCoVs ranged between approximately 4% and 27% depending on the species and cohort. We identified at least 136 novel linear B cell epitopes. Antibody repertoires against endemic HCoVs were qualitatively different between children and adults in that anti-HCoV IgG specificities more frequently found among children targeted functionally important and structurally conserved regions of the spike, nucleocapsid, and matrix proteins. Moreover, antibody specificities targeting the highly conserved fusion peptide region and S2′ cleavage site of the spike protein were broadly cross-reactive with peptides of epidemic human and nonhuman coronaviruses. In contrast, an acidic tandem repeat in the N-terminal region of the Nsp3 subdomain of the HCoV-HKU1 polyprotein was the predominant target of antibody responses in adult donors. Our findings shed light on the dominant species-specific and pan-CoV target sites of human antibody responses to coronavirus infection, thereby providing important insights for the development of prophylactic or therapeutic monoclonal antibodies and vaccine design.

Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: September 21, 2020
Accepted: January 13, 2021
Published: January 26, 2021

Reference information: *JCI Insight*. 2021;6(4):e144499. https://doi.org/10.1172/jci.insight.144499.

Introduction

Four endemic human-tropic coronaviruses (HCoVs) are commonly associated with respiratory illness in humans, namely HCoV-229E, -NL63, -OC43, and -HKU1 (1–4). Clinical outcomes of acute infection with these HCoVs range from mild upper respiratory tract infections in most patients, to viral bronchiolitis and pneumonia more rarely in patients, the latter requiring hospitalization (5). The ratio of more severe versus mild outcomes of acute infection with endemic HCoVs is largely comparable to that of other "common cold" viruses, such as human respiratory syncytial virus (HRSV), human rhinoviruses (HRVs), human adenoviruses, and human parainfluenza viruses, albeit with differences in seasonality and prevalence of the viruses depending on the species (5–7). In

Published online: 2021-03-03

Delayed Diagnosis of a Pyloric Web Causing Gastric Outlet Obstruction in a 13-Month-Old Girl

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Eur J Pediatr Surg Rep 2021;9:e20–e22.

Abstract

Pyloric web is a rare cause of gastric outlet obstruction. Classical pyloric web can be diagnosed by obtaining a patient history, physical examination, and plain abdominal X-ray, whereas a perforated web leads to incomplete intestinal obstruction. Delayed diagnosis is rare, and the definite diagnosis is made by upper endoscopy. In this report, we report a case of a girl in whom a pyloric web was diagnosed at the age of 13 months.

Keywords

- gastric outlet obstruction
- pyloric web
- atresia

New Insights and the Importance for the Pediatric Surgeon

Pyloric web is a rare entity of gastric outlet obstruction and can present with nonspecific symptoms that can cause a delay in diagnosis.

Thus, a high index of suspicion in addition to an upper gastrointestinal endoscopy can help achieve a definite diagnosis. Surgical intervention remains the best modality of treatment.

Introduction

Gastric outlet obstruction can be caused by prepyloric or pyloric abnormalities. Most of the cases reported in the literature refer to the gastric antral web as a cause of gastric outlet obstruction.[1] Pyloric web, the most common type of pyloric atresia (PA), is diagnosed during the neonatal period with nonbilious vomiting. Its delayed detection is very rare.[2] Hence, only a few cases report on pyloric web as a cause of gastric outlet obstruction in infancy.[1] We report a case of an infant with a delayed diagnosis of pyloric web, as well as the challenges in the diagnosis and management.

Case Report

The patient was a 13-month-old girl who was born full term with a birth weight of 3.1 kg. Her symptoms started with nonbilious vomiting on the second day of life; however, her growth and weight were not affected. After 6 months of age, her symptoms progressed, and occasional coffee ground vomiting started in addition to a plateau in her weight. Therefore, different milk formulas were tried without much improvement of the vomiting. Her weight was on the third percentile, and the blood tests were negative for food allergens, *Helicobacter pylori*, and celiac disease, but positive for occult stool blood. The abdominal ultrasound showed a distended stomach and a normal-looking pylorus (►Fig. 1A, B).

Consequently, upper gastrointestinal (UGI) contrast study showing delayed gastric emptying without anatomical filling defect (►Fig. 2).

Therefore, the child was treated conservatively for delayed gastric emptying and symptomatic gastroesophageal reflux. However, she continued to vomit beyond a certain volume of food especially solid food. Thus, an

received
August 3, 2020
accepted after revision
September 24, 2020

DOI https://doi.org/10.1055/s-0041-1723017.
ISSN 2194-7619.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.67.01.20200062

Does parental opinion differ from the health care team regarding cosmesis after hypospadias repair?

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SUMMARY

OBJECTIVE: Hypospadias is the most common malformation of the male genitalia. Surgical correction has traditionally focused on anatomic and functional outcomes, with less attention being paid to cosmetic results. Our purpose is to compare the cosmetic results of hypospadias repair among different groups of observers, namely the patient's family and the health care team, using photography and a simple rating scale.

METHODS: Prospective observational study included 9 boys undergoing Snodgrass hypospadias repair. Photographs of the penis taken before, immediately after, and six months after surgery were assessed by a panel of 15 observers (parents and health care team) and a scale including three questions with diagrams for comparison with the pictures was used. Observers also assigned an overall postoperative score for the cosmetic result.

RESULTS: Interobserver agreement was noted for the group of parents of other children with hypospadias regarding the shape of the glans (k=0.404; p=0.008) and for the group of pediatric surgeons regarding the degree of residual curvature (k=0.467; p=0.005). Two observers in the pediatrician group have indicated good performance in the assessment of residual curvature (k=0.609; P=0.024). In the overall assessment of cosmetic outcomes, the highest scores were assigned by observers in the parents group and in the pediatrician group, while the pediatric surgeons group has one of the lowest scores (p<0.001).

CONCLUSIONS: Photography appears to be suitable for documenting corrections of hypospadias regarding penile curvature, and postoperative cosmetic result. Surgeons seem more concerned about cosmesis than parents.

KEYWORDS: Hypospadias. Photography. Parents. Patient care team.

INTRODUCTION

Hypospadias is a common birth defect of the male genitalia, involving arrested development of the urethra, foreskin, and ventral surface of the penis[1]. In patients with hypospadias, the urethral meatus is located ventrally on the penis, with or without ventral penile curvature. The incidence of hypospadias is variable and depends on regional and ethnical differences. Some papers have shown increasing hypospadias rates and others have shown no increasing rates; but, currently, hypospadias is the most common malformation of the male genitalia[1-5].

Different surgical techniques can be used to repair hypospadias. The main goals of surgery are the construction of a urethral meatus in orthotopic (glandular) position and correction of penile curvature, if present[6]. The correction of hypospadias has traditionally focused on anatomic and functional outcomes. However, a growing concern with body image has led

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Conflicts of interest: the authors declare there are no conflicts of interest. Funding: none.
Received on August 10, 2020. Accepted on September 20, 2020.

Using clinical guidelines to assess the potential value of laboratory medicine in clinical decision-making

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Abstract

Introduction: It is often quoted that 70% of clinical decisions are based on laboratory results, but the evidence to substantiate this claim is lacking. Since clinical guidelines aim to document best-practice decision making for specific disease conditions, inclusion of any laboratory test means that the best available evidence is recommending clinicians use it. Cardiovascular disease (CVD) is the world's most common cause of mortality, so this study reviewed all CVD guidelines published by five national/international authorities to determine what proportion of them recommended laboratory testing.

Materials and methods: Five leading CVD guidelines were examined, namely the European Society of Cardiology (ESC), the UK National Institute for Health and Clinical Excellence (NICE), the American College of Cardiology (ACC), the Australian Heart Foundation (AHF) and the Cardiac Society of Australia and New Zealand (CSANZ).

Results: A total of 101 guidelines were reviewed. Of the 33 individual ESC guidelines relating to CVD, 24/33 made a direct reference to the use of clinical laboratory tests in either diagnosis or follow-up treatment. The same applied to 15/20 of NICE guidelines, 24/32 from the ACC and 15/16 from the AHF/CSANZ. Renal function and blood count testing were the most recommended (39 and 26 times), with lipid, troponin and natriuretic peptide measurement advocated 25, 19 and 19 times respectively.

Conclusions: This study has shown that laboratory testing is advocated by between 73% and 94% of individual CVD guideline recommendations from five national/international authorities. This provides an index to assess the potential value of laboratory medicine to healthcare.

Keywords: cardiovascular diseases; guideline; clinical laboratory testing

Submitted: May 12, 2020 *Accepted: September 23, 2020*

Introduction

The contribution of laboratory medicine to patient diagnosis, management and follow-up has proven difficult to quantify with systematic evidence of improved patient outcomes scarce (1). The phrase that 'laboratory medicine influences 70% of clinical decisions', or similar, has been published many times but the evidence to substantiate this claim is lacking. An editorial in the Annals of Clinical Biochemistry stated that the 70% figure was first published in 1996 and was based on anecdotal evidence and unpublished studies (2). The editorial lists various examples of the use of this phrase, albeit with slight modifications, for example; Lord Carter's report on the UK Pathology service, the First Report of the UK House of Commons Select Committee on Health, and in the UK Department of Health report "Modernizing Pathology Services" (2).

A related and also oft-quoted statistic is that 70% of the electronic patient record is composed of laboratory data, but the main limitation of this obser-

PLOS ONE

RESEARCH ARTICLE

Procalcitonin, C-reactive protein, neutrophil gelatinase-associated lipocalin, resistin and the APTT waveform for the early diagnosis of serious bacterial infection and prediction of outcome in critically ill children

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OPEN ACCESS

Citation: Nielsen MJ, Baines P, Jennings R, Siner S, Kolamunnage-Dona R, Newland P, et al. (2021) Procalcitonin, C-reactive protein, neutrophil gelatinase-associated lipocalin, resistin and the APTT waveform for the early diagnosis of serious bacterial infection and prediction of outcome in critically ill children. PLoS ONE 16(2): e0246027. https://doi.org/10.1371/journal.pone.0246027

Editor: Aleksandar R. Zivkovic, Heidelberg University Hospital, GERMANY

Received: February 1, 2020

Accepted: January 12, 2021

Published: February 5, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0246027

Data Availability Statement: The data that support the findings of this study are available on request

Abstract

Objective

Bacterial Infections remains a leading cause of death in the Paediatric Intensive Care Unit (PICU). In this era of rising antimicrobial resistance, new tools are needed to guide antimicrobial use. The aim of this study was to investigate the accuracy of procalcitonin (PCT), neutrophil gelatinase-associated lipocalin (NGAL), resistin, activated partial thromboplastin time (aPTT) waveform and C-reactive protein (CRP) for the diagnosis of serious bacterial infection (SBI) in children on admission to PICU and their use as prognostic indicators.

Setting

A regional PICU in the United Kingdom.

Patients

Consecutive PICU admissions between October 2010 and June 2012.

from the University of Liverpool, Institute of Infection, Veterinary and Ecological Sciences Head of Operations iveshoo@liverpool.ac.uk The data are not publicly available due to restrictions imposed by collection of patient data from a named hospital, and therefore contains information that could compromise the privacy of research participants.

Funding: The study was funded jointly by the NIHR Liverpool Biomedical Research Centre in Microbial Diseases and the Alder Hey Charity awarded to EC. MJN is supported by a Wellcome Trust Research Training Fellowship (award reference 203919/Z/16/Z). The funders had no role in the study design, data collection and analysis, decision to publics, or preparation of the manuscript.

Competing interests: The authors have read the journal's policy and have the following potential competing interest: LMcC is a paid employee of Select Statistics. This does not alter our adherence to PLOS ONE policies on sharing data and materials. There are no patents, products in development or marketed products associated with this research to declare. The other authors declare that they have no competing interests.

Abbreviations: aPTT, Activated Partial Thromboplastin Time; AUC, Area Under the Curve; CI, Confidence Interval; CRP, C-Reactive Protein; ICU, Intensive Care Unit; IPPV, Invasive positive pressure ventilatio; LR, Likelihood Rati; NGAL, Neutrophil Gelatinase Associated Lipocali; NPV, Negative Predictive Valu; NRI, Net Reclassification Improvemen; OR, Odds Rati; PCT, Procalcitoni; PICU, Paediatric Intensive Care Uni; PELOD, Paediatric Logistic Organ Dysfunction Scor; PPV, Positive Predictive Valu; ROC, Receiver Operator Curve; SBI, Serious Bacterial Infectio; SIRS, Systemic Inflammatory Response Syndrom.

Measurements

Blood samples were collected daily for biomarker measurement. The primary outcome measure was performance of study biomarkers for diagnosis of SBI on admission to PICU based on clinical, radiological and microbiological criteria. Secondary outcomes included durations of PICU stay and invasive ventilation and 28-day mortality. Patients were followed up to day 28 post-admission.

Main results

A total of 657 patients were included in the study. 92 patients (14%) fulfilled criteria for SBI. 28-day mortality was 2.6% (17/657), but 8.7% (8/92) for patients with SBI. The combination of PCT, resistin, plasma NGAL and CRP resulted in the greatest net reclassification improvement compared to CRP alone (0.69, p<0.005) with 10.5% reduction in correct classification of patients with SBI (p 0.52) but a 78% improvement in correct classification of patients without events (p <0.005). A statistical model of prolonged duration of PICU stay found log-transformed maximum values of biomarkers performed better than first recorded biomarkers. The final model included maximum values of CRP, plasma NGAL, lymphocyte and platelet count (AUC 79%, 95% CI 73.7% to 84.2%). Longitudinal profiles of biomarkers showed PCT levels to decrease most rapidly following admission SBI.

Conclusion

Combinations of biomarkers, including PCT, may improve accurate and timely identification of SBI on admission to PICU.

Introduction

Invasive bacterial infections account for over a quarter of all deaths in PICU [1] whilst up to 31% of paediatric sepsis survivors are affected by disability at discharge [2]. Early recognition of sepsis and prompt anti-microbial therapy reduce mortality and duration of organ dysfunction [3–5], but indiscriminate antimicrobial use contributes to resistance [6, 7]. Differentiation of infective and non-infective causes of the systemic inflammatory response syndrome (SIRS) is an ongoing challenge for clinicians. A reliable marker, or combination of markers, that change early in bacterial infection, correlate with real-time clinical progression and have a rapid laboratory turn-around time is an urgent unmet clinical need.

Procalcitonin (PCT) has been shown in comparatively small studies to be a better diagnostic marker of bacterial infection in PICU than C-reactive protein (CRP) [8, 9] and to be a prognostic marker in meningococcal disease [10]. The biphasic activated Partial Thromboplastin Time (aPTT) waveform is the optical profile generated from changes in light transmittance during clot formation. It has been found in adults to be a more useful marker of sepsis than CRP alone, correlating with increasing risk of clinical deterioration and disseminated intravascular coagulation (DIC) [11–13] and to be abnormal in children with meningococcal sepsis [14]. Neutrophil gelatinase- associated lipocalin (NGAL), measured in plasma or urine, is a marker of acute kidney injury but also a promising marker of sepsis and multi-organ dysfunction in adults [15, 16] and neonates [17]. Resistin an adipokine which contributes to inflammation-induced insulin resistance, has been shown to correlate with sepsis severity in adults [18,

International Journal of
Molecular Sciences

MDPI

Article

Distinctive Microbial Signatures and Gut-Brain Crosstalk in Pediatric Patients with Coeliac Disease and Type 1 Diabetes Mellitus

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Citation: Singh, P.; Rawat, A.; Al-Jarrah, B.; Saraswathi, S.; Gad, H.; Elawad, M.; Hussain, K.; Hendaus, M.A.; Al-Masri, W.; Malik, R.A.; et al. Distinctive Microbial Signatures and Gut-Brain Crosstalk in Pediatric Patients with Coeliac Disease and Type 1 Diabetes Mellitus. *Int. J. Mol. Sci.* **2021**, *22*, 1511. https://doi.org/10.3390/ijms22041511

Academic Editor: Francesco Chiarelli
Received: 11 January 2021
Accepted: 25 January 2021
Published: 3 February 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Coeliac disease (CD) and Type 1 diabetes mellitus (T1DM) are immune-mediated diseases. Emerging evidence suggests that dysbiosis in the gut microbiome plays a role in the pathogenesis of both diseases and may also be associated with the development of neuropathy. The primary goal in this cross-sectional pilot study was to identify whether there are distinct gut microbiota alterations in children with CD (n = 19), T1DM (n = 18) and both CD and T1DM (n = 9) compared to healthy controls (n = 12). Our second goal was to explore the relationship between neuropathy (corneal nerve fiber damage) and the gut microbiome composition. Microbiota composition was determined by 16S rRNA gene sequencing. Corneal confocal microscopy was used to determine nerve fiber damage. There was a significant difference in the overall microbial diversity between the four groups with healthy controls having a greater microbial diversity as compared to the patients. The abundance of pathogenic proteobacteria *Shigella* and *E. coli* were significantly higher in CD patients. Differential abundance analysis showed that several bacterial amplicon sequence variants (ASVs) distinguished CD from T1DM. The tissue transglutaminase antibody correlated significantly with a decrease in gut microbial diversity. Furthermore, the Bacteroidetes phylum, specifically the genus *Parabacteroides* was significantly correlated with corneal nerve fiber loss in the subjects with neuropathic damage belonging to the diseased groups. We conclude that disease-specific gut microbial features traceable down to the ASV level distinguish children with CD from T1DM and specific gut microbial signatures may be associated with small fiber neuropathy. Further research on the mechanisms linking altered microbial diversity with neuropathy are warranted.

Keywords: gut microbiota; T1DM; coeliac disease; children; pediatric neuropathy; corneal confocal microscopy

1. Introduction

Type 1 diabetes (T1DM) [1] and coeliac disease (CD) [2] are two of the most frequent childhood autoimmune diseases [3,4]. T1DM is characterized by autoimmune destruction of β cells of the islets of Langerhans, causing insulin deficiency and hyperglycemia [5]. CD

Psychiatric Quarterly
https://doi.org/10.1007/s11126-021-09888-w

REVIEW ARTICLE

Gender and Racial Disparities among US Psychiatry Residents: A Review of Trends

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Accepted: 25 January 2021

Abstract
Diversity provides better patient outcomes, reduces physician burnout, and therefore lessens the burden of the healthcare system. In this study, we explore the gender and racial trends in the recruitment of medical graduates into US psychiatry residency programs. Retrospective data analysis was performed utilizing the data from the Accreditation Council for Graduate Medical Education (ACGME) Data's annual Resource Books from the year 2007 to 2018. Demographic data, including gender and race, were extracted for psychiatry residents. Gender was categorized as Male, Female, and Not Reported. Race/ethnicity was categorized as White (Non-Hispanic), Asian/Pacific Islander, Hispanic, Black/African-American (Non-Hispanic), Native American/Alaskan, Others (not in the aforementioned categories), and Unknown. Female psychiatry residents relatively decreased by 2.6% whereas male psychiatry residents relatively increased by 15.5% from 2007 to 2018. Between the years 2011 and 2018, there was a relative increase in African American/Black and Native American/Alaskan psychiatry residents by 5.5% and 1%, respectively, whereas the Asian/Pacific Islanders, White (Non-Hispanic), and Hispanic/Latino psychiatry residents relatively decreased by 5.1%, 2.3%, and 1.7%, respectively. Despite the overall increase of women and ethnic minorities in US medical schools, women and racial minorities remain significantly under-represented in psychiatry residency programs in the US.

Keywords Gender · Race · Disparity · Difference · Psychiatry residency · Under-representation

Introduction

The diversity of medical faculty and professionals improves healthcare outcomes by providing culturally competent career to minority group populations [1]. Existing evidence suggests that diversity has a favorable association with patient satisfaction, team communication, and financial performance [2]. The homogenous composition of care teams has reflected significant inequalities in clinical care and decision making [2].

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Published online: 13 February 2021

Received: 17 July 2020 | Revised: 7 December 2020 | Accepted: 27 January 2021

DOI: 10.1002/ijc.33513

INFECTIOUS CAUSES OF CANCER

IJC International Journal of Cancer

Declining rates of cervical intraepithelial neoplasia in British Columbia, Canada: An ecological analysis on the effects of the school-based human papillomavirus vaccination program

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Funding information
BC Children's Hospital Foundation; Canadian Child Health Clinician Scientist Program; Canadian Immunization Research Network; Michael Smith Foundation for Health Research; Canadian Institutes of Health Research (CIHR), Grant/Award Number: FDN-143339

Abstract

Since 2008, girls in British Columbia (BC), Canada, have been offered HPV vaccination through a school-based, publicly funded immunization program. The oldest birth cohort eligible for the vaccination program was born in 1994 and uptake is on average 63%. To evaluate the impact of the HPV vaccine in BC, ecological trends in cervical intraepithelial neoplasia (CIN) rates were assessed in young women before and after the implementation of the HPV vaccination program. Information on all Pap smears and histopathological abnormalities, in calendar years 2004-2017 in women 16-28 years of age in BC were obtained from the population-based BC Cancer Cervix Screening Program database. Rates of CIN 2 and 3 were calculated as the number of cases divided by the number of cytology specimens for that period. Rate ratios (RR) were calculated by negative binomial piecewise regression. Age-centered incidence rates of CIN 2 and 3 in BC declined significantly among women 16-23 years of age after HPV vaccine introduction compared to before vaccine introduction. The overall reduction postvaccination for CIN2 and 3 in women 16-23 years was respectively 62% (95% CI 54-68%) and 65% (95% CI 58-71%). Age-specific rates for CIN2 significantly declined for those 18-22 years of age and for those 19, 20 and 23 years of age

Abbreviations: 95% CI, 95% confidence interval; AIS, Adenocarcinoma in situ; BC, British Columbia; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; PY, person-years; RR, rate ratio; y, years.

for CIN3. Among women 24-28 years of age no decline in CIN2 and 3 rate over time was observed. The observed reduction in CIN 2 and 3 rates since the introduction of the school-based HPV vaccine program might illustrate the population impact of the BC provincial school-based HPV vaccination program.

KEYWORDS
cervical intraepithelial neoplasia, immunization programs, papillomavirus vaccines, prevention

1 | INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection, with a lifetime risk of approximately 80%.[1] Globally, approximately 5% of all cancers can be attributed to HPV.[2] Since licensure of prophylactic vaccines against multiple HPV genotypes, many countries and jurisdictions have implemented HPV vaccination in their routine immunization programs.[3,4] Three HPV vaccines have been used in public health programs so far: the bivalent HPV vaccine protects against HPV16/18, which are responsible for 70% of cervical cancers, the quadrivalent vaccine which also covers HPV6/11, responsible for 90% of anogenital warts and the nonavalent vaccine which covers five additional high-risk HPV types, HPV31/33/45/52/58, responsible for an approximate additional 20% of cervical cancers.[5] In addition, besides high efficacy against the types included in the vaccines, population-based studies have indicated that the bivalent HPV vaccine is effective in the prevention of HPV31/33/45 as well, which is called cross-protection.[6]

British Columbia (BC), Canada commenced HPV vaccination (quadrivalent vaccine) in the publicly funded, provincial school-based immunization program in September 2008.[7] A catch-up school-based program was offered to girls between September 2008 and June 2011 in Grade 9 (birth cohorts 1994-1996, 14-15 years of age), with uptake rates between 58% and 62%.[8,9] The routine program includes girls born in 1997 or later and is delivered in Grade 6 (11-12 years of age) with uptake rates for up-to-date complete vaccination series ranging from 60% to 69%. (Figure S1) Since October 2014, the program uses a two dose series, and since September 2016, the program uses the nonavalent HPV vaccine. In addition, as of September 2017, HPV vaccination has been offered to boys in Grade 6 through the program.[7] BC also conducted a onetime catch-up program starting 2012 for women born 1987 to 1993 using the bivalent HPV vaccine.

Comprehensive vaccine evaluation programs were established in many jurisdictions around the world to monitor the impact of the HPV vaccine. Impact of the vaccine on HPV prevalence, anogenital warts and cervical dysplasia rates on a population-level has become evident.[10-19] Using data from the BC Cervix Screening Program, our study aimed to evaluate the impact of the provincial HPV vaccine program on ecological trends for CIN2 and CIN3 in young women 16 to 28 years of age between 2004 and 2017.

What's new

HPV vaccines effectively prevent HPV infection and HPV-associated cancers. In this ecological analysis, the authors studied the impact of a province-wide, publicly funded, school-based HPV-vaccination program in Canada up to 9 years after vaccine introduction. Compared to pre-vaccine levels, significant reductions were observed in rates of cervical intraepithelial neoplasia grades 2 and 3 (CIN2 and CIN3) among women 16-23 years of age. No changes were observed in women ages 24-28 years of age, who were not eligible for the school-based vaccine program.

2 | METHODS

2.1 | Data collection

BC has a centralized cervix screening program since the early 1960s[20] for the early detection and treatment of cervical abnormalities. The structure and organization of the BC Cancer Cervix Screening Program has been described in detail previously.[7] All screening results from the province are captured in one central database at BC Cancer. Conventional Pap smears for cytology testing are currently the standard of care for screening within the program. During the period of follow-up (2004-2017), screening recommendations changed in 2010 and 2016 (Table 1).[20-22] Up to 2010, women were recommended to commence screening when sexually active annually for 3 years and every 2 years thereafter, as of 2010 screening was recommended to start at 21 years or 3 years after sexual debut, again annually for 3 years and every 2 years thereafter. As of 2016, women are recommended to screen from 25 years onward every 3 years.

Data were abstracted from the BC Cancer Cervix Screening Program database for every cervical cytology and histopathological result in women 16 to 28 years of age (birth cohorts 1976-2001) from January 1, 2004 to December 31, 2017. An overview of the birth cohorts and their age per calendar year of screening is shown in Figure 1. The first birth cohorts that were eligible for vaccination in the routine and catch-up school-based immunization program were 1994 and 1997, birth cohort 1994 turned 16 in 2010, therefore possible effects of the school-based immunization program might become visible in our population as of 2010. Data for screening years 2004 to 2012 has been reported previously, but included

European Journal of Paediatric Neurology 31 (2021) 38–45

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Melatonin for neuroprotection in neonatal encephalopathy: A systematic review & meta-analysis of clinical trials

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ARTICLE INFO

Article history:
Received 18 August 2020
Received in revised form
11 January 2021
Accepted 4 February 2021

Keywords:
Hypoxic-ischemic encephalopathy (HIE)
Neonatal encephalopathy (NE)
Newborn
Neuroprotection
Melatonin
Therapeutic hypothermia (HT)
Certainty of evidence (COE)

ABSTRACT

Objective: Melatonin has shown neuroprotective properties in pre-clinical studies of perinatal asphyxia through antioxidant, anti-apoptotic and anti-inflammatory actions. Studies have also demonstrated its safety and efficacy in neonatal encephalopathy (NE). However, its role in the current era of therapeutic hypothermia (HT) is unclear. The review aims to describe the currently available clinical evidence for Melatonin as a potential therapy for NE.

Methods: **Data Sources:** We searched Medline, EMBASE, CINAHL, LILACS, and Cochrane central databases, published journals, and conference proceedings from inception to May 31, 2020. **Study Selection:** Randomized controlled trials (RCTs) of Melatonin for NE in term or late preterm infants reporting neurodevelopmental outcomes, death, or both. The evidence quality was evaluated using the GRADE system, while the recommendations were taken according to the quality.

Results: We included five RCTs involving 215 neonates. Long-term development outcome data is lacking in all except in one small study, reporting significantly higher composite cognition scores at 18 months. One study reported intermediate 6-month favorable development on follow-up. Meta-analysis of mortality in combined HT + Melatonin group vs HT alone (Studies = 2, participants = 54) demonstrated no significant reduction with relative risk (RR) 0.42; 95%CI, 0.99–1.12). The overall GRADE evidence quality was very low for a very small sample size. We did not meta-analyze the data for Melatonin alone therapy without HT, as the included studies were of very low quality.

Conclusions: Despite strong experimental data supporting the role of Melatonin as a neuroprotective agent in NE (both alone and as an adjunct with therapeutic hypothermia), the clinical data supporting the neuroprotective effects in neonates is limited. Larger well designed, adequately powered multicentre clinical trials are urgently needed to define the neuroprotective role of Melatonin in optimizing outcomes of NE.

Contents

Abbreviations: aEEG, Amplitude integrated electroencephalography; HIE, Hypoxic-ischemic encephalopathy; HI, Hypoxia and ischemia; HT, therapeutic hypothermia; LOE, level of evidence; NE, Neonatal encephalopathy; MRI, Magnitude Resonance Imaging.

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https://doi.org/10.1016/j.ejpn.2021.02.003
1090-3798/

Asian Journal of Psychiatry 58 (2021) 102601

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Reducing the stigma of mental health disorders with a focus on low- and middle-income countries

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ARTICLE INFO

Keywords:
Culture
Depression
Low- and middle-income countries
Mental health
Mental health disorders
Stigma

ABSTRACT

Mental health disorders are a burgeoning global public health challenge, and disproportionately affect the poor. Low- and middle-income countries (LMICs) bear 80 % of the mental health disease burden. Stigma associated with mental health results in delayed help seeking, reduced access to health services, suboptimal treatment, poor outcomes and an increased risk of individuals' human rights violations. Moreover, widespread co-occurrence of physical comorbidities such as noncommunicable diseases with mental health disorders makes the treatment of both conditions challenging and worsens prognosis. This paper explores various aspects of stigma towards mental health with a focus on LMICs and assesses measures to increase help-seeking and access to and uptake of mental health services. Stigma impacts persons living with mental illness, their families and caregivers and healthcare professionals (mental health professionals, non-psychiatric specialists and general practitioners) imparting mental health care. Cultural, socio-economic and religious factors determine various aspects of mental health in LMICs, ranging from perceptions of health and illness, health seeking behavior, attitudes of the individuals and health practitioners and mental health systems. Addressing stigma requires comprehensive and inclusive mental health policies and legislations; sustainable and culturally-adapted awareness programs; capacity building of mental health workforce through task-shifting and interprofessional approaches; and improved access to mental health services by integration with primary healthcare and utilizing existing pathways of care. Future strategies targeting stigma reduction must consider the enormous physical comorbidity burden associated with mental health, prioritize workplace interventions and importantly, address the deterioration of population mental health from the COVID-19 pandemic.

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https://doi.org/10.1016/j.ajp.2021.102601
Received 29 December 2020; Accepted 7 February 2021
Available online 13 February 2021

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-021-04185-7

BRIEF REPORT

Molecular characterization of clinical carbapenem-resistant *Enterobacterales* from Qatar

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Received: 26 November 2020 / Accepted: 3 February 2021

Abstract

One hundred forty-nine carbapenem-resistant *Enterobacterales* from clinical samples obtained between April 2014 and November 2017 were subjected to whole genome sequencing and multi-locus sequence typing. *Klebsiella pneumoniae* (81, 54.4%) and *Escherichia coli* (38, 25.5%) were the most common species. Genes encoding metallo-β-lactamases were detected in 68 (45.8%) isolates, and OXA-48-like enzymes in 60 (40.3%). $bla_{\text{NDM-1}}$ (45; 30.2%) and $bla_{\text{OXA-48}}$ (29; 19.5%) were the most frequent. KPC-encoding genes were identified in 5 (3.6%) isolates. Most common sequence types were *E. coli* ST410 (8; 21.1%) and ST38 (7; 18.4%), and *K. pneumoniae* ST147 (13; 16%) and ST231 (7; 8.6%).

Keywords CRE · Carbapenemase · KPC · NDM · VIM · OXA · Enterobacterales · Qatar · Middle East

Introduction

Considerable variations exist in the epidemiology of carbapenemases in *Enterobacterales* from different parts of the world [1]. Awareness of the locally prevalent carbapenemases is relevant to the appropriate selection of antimicrobial therapy for carbapenem-resistant *Enterobacterales* (CRE) infections [2]. Moreover, the molecular epidemiology of CRE could help guide control efforts. The aim of this study was to identify the predominant carbapenemases in CRE from Qatar and to elucidate their molecular epidemiology.

Methods

All carbapenem-resistant *Enterobacterales* isolates from clinical specimens received at Hamad Medical Corporation Microbiology Department during the period between April 2014 and November 2017 were included. The department provides diagnostic microbiology services for all public hospitals in Qatar. Laboratory methods for bacterial identification, antimicrobial susceptibility testing, whole genome sequencing and analysis are described in the supplementary data file.

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Published online: 22 February 2021

Contemporary Clinical Trials 103 (2021) 106321

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Randomized clinical trial of Fibromyalgia Integrative Training (FIT teens) for adolescents with juvenile fibromyalgia – Study design and protocol

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ARTICLE INFO

Keywords:
Juvenile fibromyalgia
RCT- randomized clinical trial
Pediatric chronic pain
Cognitive behavioral therapy
Neuromuscular training

ABSTRACT

Objective: Juvenile-onset fibromyalgia (JFM) is a chronic debilitating pain condition that negatively impacts physical, social and academic functioning. Cognitive-behavioral therapy (CBT) is beneficial in reducing functional disability among adolescents with JFM but has only a modest impact on pain reduction and does not improve physical exercise participation. This randomized controlled trial (RCT) aims to test whether a novel intervention that combines CBT with specialized neuromuscular exercise training (the Fibromyalgia Integrative Training program for Teens "FIT Teens") is superior to CBT alone or a graded aerobic exercise (GAE) program. *Design/Methods:* This 3-arm multi-site RCT will examine the efficacy of the FIT Teens intervention in reducing functional disability (primary outcome) and pain intensity (secondary outcome), relative to CBT or GAE. All interventions are 8-weeks (16 sessions) in duration and are delivered in small groups of 4–6 adolescents with JFM. A total of 420 participants are anticipated to be enrolled across seven sites with approximately equal allocation to each treatment arm. Functional disability and average pain intensity in the past week will be assessed at baseline, post-treatment and at 3-, 6-, 9- and 12-month follow-up. The 3-month follow-up is the primary endpoint to evaluate treatment efficacy; longitudinal assessments will determine maintenance of treatment gains. Changes in coping, fear of movement, biomechanical changes and physical fitness will also be evaluated.

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https://doi.org/10.1016/j.cct.2021.106321
Received 20 July 2020; Received in revised form 27 January 2021; Accepted 9 February 2021
Available online 20 February 2021

Case Reports > BMJ Case Rep. 2021 Feb 26;14(2):e238283. doi: 10.1136/bcr-2020-238283.

Staged penile reconstruction with pedicled groin flap for penile shaft necrosis following circumcision

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Affiliations + expand

PMID: 33637492 PMCID: PMC7919566 (available on 2023-02-26) DOI: 10.1136/bcr-2020-238283

Abstract

A 10-year-old boy was referred by urologist to plastic surgery department with penile shaft necrosis after debridement of necrotic tissue and dry eschar that extends from the glans to the penile root and was started to separate. Also, they managed to insert urethral catheter. He had traditional circumcision 2 weeks earlier performed at home by a traditional health practitioner, resulting in full-thickness tissue loss involving skin and corpora cavernosa with sparing of the glans which was attached by stalk of scared tissue enveloping the spongiosum. After assessment and analysis of the defect was done, two-stage pedicled groin flap reconstruction was performed with satisfactory results. In this report, we are demonstrating procedure steps and outcome.

Keywords: circumcision; paediatric surgery; plastic and reconstructive surgery; urological surgery.

Conflict of interest statement

Competing interests: None declared.

frontiers in Immunology

OPINION
published: 18 February 2021
doi: 10.3389/fimmu.2020.625753

Primary Immunodeficiencies: A Decade of Progress and a Promising Future

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OPEN ACCESS

Edited by:
Silvia Danielian, Garrahan Hospital, Argentina

Reviewed by:
Anders Fasth, University of Gothenburg, Sweden
Stephanie Boisson-Dupuis, The Rockefeller University, United States

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Specialty section:
This article was submitted to Primary Immunodeficiencies, a section of the journal Frontiers in Immunology

Received: *03 November 2020*
Accepted: *29 December 2020*
Published: *18 February 2021*

Citation:
Meyts I, Bousfiha A, Duff C, Singh S, Lau YL, Condino-Neto A, Bezrodnik L, Ali A, Adeli M and Drabwell J (2021) Primary Immunodeficiencies: A Decade of Progress and a Promising Future. Front. Immunol. 11:625753. doi: 10.3389/fimmu.2020.625753

Keywords: primary immunodeficiencies, awareness, immune system, immune deficiency, genetics, COVID-19

INTRODUCTION

Around the world, over 6 million people are affected by primary immunodeficiencies, among which 70 to 90% remain undiagnosed (1). More than 430 different primary immunodeficiencies or primary immunodeficiency diseases (PIDs) have been described, caused by inherited defects in one or more component of the immune system. This leaves people living with PIDs more prone than other to infections but also to severe autoinflammation, autoimmunity, allergy, and malignancy (2, 3).

The ever-growing understanding of PIDs is crucial for future research and treatments, so that patients can enjoy an improved quality of life. The past decade has seen major advances in the field. However, many challenges still persist, some of which have been amplified by the COVID-19 crisis and need to be addressed in a collaborative way to allow another decade of progress.

OVERVIEW OF PIDS

PIDs are classified as rare diseases and cause a vulnerability to germs such as bacteria, viruses, fungi, and protozoa; infections that can turn chronic and generate long lasting healthcare issues

Journal of Pediatric Urology (2021) 17, 316–325

Review Article

Urethral plate quality assessment and its impact on hypospadias repair outcomes: A systematic review and quality assessment

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Keywords
Hypospadias; Urethral plate; Quality; Urethroplasty; Outcome

Received 21 December 2020
Revised 2 February 2021
Accepted 16 February 2021
Available online 23 February 2021

Summary

Background
The variability of the urethral plate (UP) characteristics is one of the factors that influence technical choices for hypospadias correction. However, it is difficult to objectively evaluate the UP, leading to controversies in this subject, and vague terms utilized in the literature to describe its characteristics.

Objective
We aim to analyze the previously described methods used to characterize and evaluate UP quality, emphasizing the pros and cons of each system, and highlighting its possible influence on different postoperative outcomes.

Methods
We searched the databases PubMed, Embase, and Cochrane Library CENTRAL from January 1, 2000 to August 20, 2020. The following concepts were searched: urethra reconstruction/urethra replacement/urethroplasty AND hypospadias/hypospadias, AND children AND "plate" with the gray literature search. Subgroup analyses were also carried out. The quality of the involved studies was reviewed operating a modified version of the Newcastle–Ottawa Scale (NOS).

Results
996 citations perceived as relevant to screening were retrieved. Thirteen studies were included comprising a total of 1552 cases. The number of patients in each study varied between 42 and 442, and the average post-surgical follow-up duration ranged between 6 months and twenty-six months. All studies used postoperative urethral stents of variable sizes and types. The impact of UP was most frequently assessed for cases treated with the tubularized incised plate (TIP) repair.

Conclusion
The UP quality seems to play a role as an independent factor influencing postoperative outcomes of hypospadias repair. Currently used strategies for the appraisal of UP quality are highly subjective with a low index of generalizability. Various attempts to overcome these limitations exist but none was consistently accepted, leaving a wide space for creative investigation in order to obtain an objective, reproducible, precise, and well-validated tool.

Introduction

The goal of the surgical reconstruction of hypospadias is to achieve "normal" functional and esthetic penile features [1,2]. Optimal surgical outcomes include a slit-like urethral opening at the vertex of the penile glans, a straight penis during erection, a conical-shaped glans, typical scrotal configuration and adequate urinary flow. The achievement of such remarkable results remains a great challenge. A significant number of post hypospadias repair complications still exist, reaching about 10% for distal and 40% for proximal hypospadias, despite the contemporary procedures providing more favorable results [3,4]. Several anatomical features play a role during the selection process among the different surgical approaches, including glans size, UP width, meatal position, and the degree of penile curvature. However, a limited number of studies have looked in detail the impact of such variables on the postoperative outcomes [5,6]. Preservation of the UP has been considered the landmark for the majority of techniques for distal hypospadias repairs, especially for the tubularized incised plate (TIP) and Thiersch Duplay's urethroplasty, the most frequently utilized procedures [1,7].

Holland and Smith first appraised the influence of the UP width on the surgical results [6]. They concluded that the presence of deep groove in the UP with $>$ 8 mm width decreases

https://doi.org/10.1016/j.jpurol.2021.02.017

Received: 7 September 2020 | Revised: 20 December 2020 | Accepted: 21 December 2020

DOI: 10.1002/osp4.480

ORIGINAL ARTICLE

Obesity Science and Practice Open Access WILEY

Core outcomes in gestational diabetes for treatment trials: The Gestational Metabolic Group treatment set

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Funding information

Qatar National Research Fund, Grant/Award Number: NPRP 10-0129-170274

Abstract

Aims: With the rising number of outcomes being reported following gestational diabetes (GDM), the outcomes in existing studies vary widely making it challenging to compare and contrast the effectiveness of different interventions for GDM. The purpose of this study was to develop a core outcome and measurement set (COS) for GDM treatment trials.

Materials & Methods: A Delphi study with structured consultation with stakeholders and discussion within a specialist Gestational Metabolic Group (GEM) were combined with a comprehensive systematic search across different databases (PubMed, Cochrane Library, and Embase). Several Delphi rounds over 2 years were conducted culminating in this report.

Results: The process resulted in a targeted set of outcomes constituting a "GEM treatment set" aligned with expert opinion. The final COS also included a measurement set for the 11 important clinical outcomes from three major domains: maternal metabolic, fetal, and pregnancy related.

Conclusions: Based on the results of this study, it is recommended that future clinical trials on GDM report outcomes uniformly keeping to the recommended COS outcomes.

KEYWORDS

core measurement set, core outcome set, gestational diabetes, treatment trials

1 | INTRODUCTION

Pre-pregnancy obesity and gestational weight gain (GWG) during pregnancy are key risk factors for the development of gestational diabetes and mellitus (GDM).[1,2] This consequence of maternal obesity and GWG are defined as the occurrence of glucose intolerance during pregnancy which commonly resolves after birth.[3] The prevalence of GDM is rising worldwide, ranging between 1% and 17%, depending on the detection methods and the diagnostic criteria.[4,5] Pre-gestational and GWG, both strongly associated with GDM, are recognized as a major contributor to short and long-term metabolic complications for mother[6] and offspring[7] resulting in an adverse health and economic

Mohammed Bashir and Asma Syed contributed equally.

Pediatric Neurology 119 (2021) 15–21

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Amelioration of Levetiracetam-Induced Behavioral Side Effects by Pyridoxine. A Randomized Double Blind Controlled Study

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ARTICLE INFO

Article history:
Received 10 November 2020
Accepted 28 February 2021
Available online 8 March 2021

Keywords:
Side effects
Levetiracetam
Pyridoxine
Behavior

ABSTRACT

Background: Levetiracetam is a relatively new-generation antiseizure drug approved for the treatment of focal and generalized seizures. Despite its favorable side effect profile and minimal drug-drug interactions, neuropsychiatric side effects are reported in up to 13% of children. A few case series have suggested that supplementation of pyridoxine may mitigate these side effects, but controlled trials are lacking. To address this issue, a randomized interventional study was carried out in a pediatric tertiary hospital to qualify and quantify the potential beneficial effect of pyridoxine in attenuating the neuropsychiatric side effects of levetiracetam in children.

Methods: A total of 105 children with epilepsy who were taking levetiracetam (as a monotherapy or an adjunct) who showed behavioral symptoms coinciding with the start of levetiracetam, were included. Patients randomly and blindly received either a therapeutic (pyridoxine group, 46 of 105, 44%) or a homeopathic dose of pyridoxine (placebo, 59 of 105, 56%). A 30-item behavioral checklist was used to qualify and quantify the behavioral side effects at baseline and at different time points following initiation of treatment.

Results: Both placebo and pyridoxine groups experienced a statistical reduction in behavioral scores when compared with baseline. Our study indicated that although there was a placebo effect, the improvement in neuropsychiatric symptoms was more prominent in children who received therapeutic doses of pyridoxine.

Conclusions: These data provide clinicians with pertinent evidence-based information that suggests that a trial of pyridoxine in patients who experience behavioral side effects due to the use of levetiracetam may avoid unnecessary change of antiseizure medications.

Introduction

Epilepsy is one of the most common neurological entities in the pediatric population, with a prevalence of 3.5 to 5.5 of 1000.[1] Antiseizure drugs remain the mainstay of seizure management, and attainment of complete seizure remission without adverse drug events remains the ultimate goal of epilepsy treatment.[2] However, in reality, finding a good balance between seizure control and drug side effects remains an important challenge in epilepsy management—a challenge that has motivated the search for newer drugs with novel mechanisms of action that are more efficacious and possess a more tolerable side effect profile.

Over the past two decades, there has been an exponential increase in the number of antiseizure drugs available on the market. Among these is levetiracetam, a renally excreted drug that stands out from other antiepileptic drugs due to its unique biochemical structure and its novel mechanism of action (blocks presynaptic release of neurotransmitters via blocking synaptic vesicle 2A).[3] Levetiracetam is efficacious for a variety of seizure types in both

Disclosure of Conflicts of Interest and funds: None of the authors have any conflict of interest. The study was funded by KFMC, Riyadh, Kingdom of Saudi Arabia (IRF No: 018-016).

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https://doi.org/10.1016/j.pediatrneurol.2021.02.010
0887-8994/

nutrients

MDPI

Article

Akkermansia, a Possible Microbial Marker for Poor Glycemic Control in Qataris Children Consuming Arabic Diet—A Pilot Study on Pediatric T1DM in Qatar

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Abstract: In Qatar, Type 1 Diabetes mellitus (T1DM) is one of the most prevalent disorders. This study aimed to explore the gut microbiome's relation to the continuous subcutaneous insulin infusion (CSII) therapy, dietary habits, and the HbA1c level in the pediatric T1DM subjects in Qatar. We recruited 28 T1DM subjects with an average age of 10.5 ± 3.53 years. The stool sample was used to measure microbial composition by 16s rDNA sequencing method. The results have revealed that the subjects who had undergone CSII therapy had increased microbial diversity and genus *Akkermansia* was significantly enriched in the subjects without CSII therapy. Moreover, genus *Akkermansia* was higher in the subjects with poor glycemic control (HbA1c > 7.5%). When we classified the subjects based on dietary patterns and nationality, *Akkermansia* was significantly enriched in Qataris subjects without the CSII therapy consuming Arabic diet than expatriates living in Qatar and eating a Western/mixed diet. Thus, this pilot study showed that abundance of *Akkermansia* is dependent on the Arabic diet only in poorly controlled Qataris T1DM patients, opening new routes to personalized treatment for T1DM in Qataris pediatric subjects. Further comprehensive studies on the relation between the Arabic diet, ethnicity, and *Akkermansia* are warranted to confirm this preliminary finding.

Keywords: *Akkermansia*; T1DM; Arabic diet; ethnicity; HbA1c; CSII therapy

Citation: Lakshmanan, A.P.; Kohil, A.; El Assadi, F.; Al Zaidan, S.; Al Abduljabbar, S.; Bangarusamy, D.K.; Al Khalaf, F.; Petrovski, G.; Terranegra, A. *Akkermansia*, a Possible Microbial Marker for Poor Glycemic Control in Qataris Children Consuming Arabic Diet—A Pilot Study on Pediatric T1DM in Qatar. *Nutrients* **2021**, *13*, 836. https://doi.org/10.3390/nu13030836

Academic Editor: Lynnette Ferguson

Received: 10 February 2021
Accepted: 24 February 2021
Published: 4 March 2021

1. Introduction

Type 1 diabetes mellitus (T1DM) is a metabolic disorder, and it is caused by the autoimmune destruction of pancreatic beta cells resulting in insulin deficiency. T1DM affects all age groups irrespective of gender. Based on the International Diabetes Federation (IDF) Diabetes Atlas, the incidence of T1DM continues to increase worldwide, with approximately one million cases presented annually [1], and the diabetic prevalent rate in Qatar is around 17% [2]. T1DM is associated with various other complications, such as severe hypoglycemia, ketoacidosis, diabetic retinopathy, nephropathy, and cardiovascular complications [3]. Despite the severity and the incidence of the disease, the etiopathogenesis of T1DM is still not fully understood, involving a complex interaction between environmental and genetic factors [4].

In managing T1DM patients, the therapeutic goal is to manage glucose control, which is accomplished by different treatments, such as insulin therapy and medical nutrition therapy. Insulin therapy (basal-bolus regimen) is one of the recommended approaches in

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01004-8

ORIGINAL ARTICLE

Novel ORAI1 Mutation Disrupts Channel Trafficking Resulting in Combined Immunodeficiency

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Received: 30 November 2020 / Accepted: 19 February 2021

Abstract

Store-operated Ca^{2+} entry (SOCE) represents a predominant Ca^{2+} influx pathway in non-excitable cells. SOCE is required for immune cell activation and is mediated by the plasma membrane (PM) channel ORAI1 and the endoplasmic reticulum (ER) Ca^{2+} sensor STIM1. Mutations in the *Orai1* or *STIM1* genes abolish SOCE leading to combined immunodeficiency (CID), muscular hypotonia, and anhidrotic ectodermal dysplasia. Here, we identify a novel autosomal recessive mutation in ORAI1 in a child with CID. The patient is homozygous for p.C126R mutation in the second transmembrane domain (TM2) of ORAI1, a region with no previous loss-of-function mutations. SOCE is suppressed in the patient's lymphocytes, which is associated with impaired T cell proliferation and cytokine production. Functional analyses demonstrate that the p.C126R mutation does not alter protein expression but disrupts ORAI1 trafficking. Orai1-C126R does not insert properly into the bilayer resulting in ER retention. Insertion of an Arg on the opposite face of TM2 (L135R) also results in defective folding and trafficking. We conclude that positive side chains within ORAI1 TM2 are not tolerated and result in misfolding, defective bilayer insertion, and channel trafficking thus abolishing SOCE and resulting in CID.

Keywords Combined immunodeficiency · ORAI1 · store-operated Ca^{2+} entry · trafficking · integral membrane protein · channel · Ca^{2+} signaling · immune cell function · myotonia · anhidrosis

Introduction

Store-operated Ca^{2+} entry (SOCE) is ubiquitous Ca^{2+} influx pathway that regulates cellular signaling [1–4]. SOCE is triggered downstream of PLC-linked agonists that result in the production of IP_3 and Ca^{2+} release from stores. Intracellular Ca^{2+} stores depletion is sensed by the resident ER transmembrane protein STIM1, which clusters and migrates to ER-PM contact sites (ER-PM CS) that are in close apposition to the PM (within 25–30 nm) [1–3]. STIM1 recruits ORAI1 through diffusional trapping and gates it open to trigger Ca^{2+} influx [1–3].

Gain-of-function (GoF) and loss-of-function (LoF) mutations in either ORAI1 or STIM1 in humans lead to distinct pathologies [3, 5–7]. Autosomal dominant GoF mutations in ORAI1 that result in excessive Ca^{2+} influx including p.S97C, p.G98S, p.L138F, and p.P245L, develop TAM/Stormorken syndrome with no obvious immune phenotype [3, 8–10]. By contrast, recessive LoF mutations that abolish SOCE, including p.A88SfsX25, p.R91W, p.G98R, p.A103E/p.L194P (compound het.), p.H165PfsX1, p.V181SfsX8, and p.L194P, result in combined immunodeficiency (CID), anhidrotic ectodermal dysplasia (AED), and muscular hypotonia [3, 5–7, 11–15]. As the SOCE channel in lymphocytes is referred to as the Ca^{2+}-release activated Ca^{2+} channel

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Published online: 01 March 2021

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Resource Announcements

GENOME SEQUENCES

Draft Genome Sequences of Seven *Vibrio cholerae* Isolates from Adult Patients in Qatar

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ABSTRACT We report the draft genome sequences of seven *Vibrio cholerae* isolates from patients. Four isolates were profiled as multilocus sequence type 69, serogroup O1, a subset of seventh-pandemic El Tor clonal isolates. Presented here are genome assemblies and evidence for major pathogenicity islands, virulence factors, and antimicrobial resistance genes.

Cholera is an acute diarrheal disease and is transmitted via untreated water carrying the etiological agent *Vibrio cholerae*. Serogroups O1 and O139 are the causative agents of the ongoing pandemic, the seventh, and sporadic outbreaks globally (1). *V. cholerae* O1 isolates can be classified as the classical or El Tor biotype based on genotypic and phenotypic characteristics (2). Since the 19th century, seven cholera pandemics have been recorded, and *V. cholerae* O1 El Tor is the most common serogroup (1, 3). Although cholera is endemic across Africa and Asia, the disease causes a serious public health burden in many places. However, *V. cholerae* has not been reported in Qatar.

Here, we report draft genome assemblies of seven *V. cholerae* strains from adults with cholera-like symptoms at Hamad Medical Corporation, Doha, Qatar. Strain H08 was isolated from blood, and six isolates were from stool. Briefly, swabs were inoculated onto mSuperCARBA solid medium (CHROMagar, France) and incubated under aerobic conditions at 35 ± 2°C for 18 to 24 h, minimizing exposure to light. After incubation, blue colonies were confirmed using the matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) Biotyper system (Bruker, MA). Antimicrobial susceptibility was determined using the Phoenix system (Becton, Dickinson, NJ). MICs for antibiotics were determined according to the CLSI breakpoints for *Vibrio* spp. (4). All sequence type 69 (ST69) isolates showed some level of resistance to the commonly employed antibiotics (4). *Vibrio* cultures were maintained in Difco LB broth (Fisher Scientific, Hampton, NH) with aeration at 37°C.

Genomic DNA was extracted using a ZymoBIOMICS DNA miniprep kit (Zymo Research, CA), and the concentrations were determined using a Qubit 4.0 fluorometer (Thermo Fisher Scientific, Waltham, MA). DNA libraries were constructed using the IonXpress Plus fragment library kit; they were enriched and barcoded using the IonXpress barcode adapter kit (Thermo Fisher, MA). PCR products were purified using SPRIselect reagent (Beckman Coulter, Indianapolis, IN). Sequencing was performed

Citation Al Malki A, Brumfield KD, Tsui CKM, Anand A, Rashed SM, Ibrahim E, Al Shamari H, Huq A, Colwell RR, Fotedar R. 2021. Draft genome sequences of seven *Vibrio cholerae* isolates from adult patients in Qatar. Microbiol Resour Announc 10:e01489-20. https://doi.org/10.1128/MRA.01489-20.

Editor Catherine Putonti, Loyola University Chicago

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Received 5 January 2021
Accepted 11 February 2021
Published 4 March 2021

Current Microbiology (2021) 78:1551–1565
https://doi.org/10.1007/s00284-021-02427-7

Metagenomic Analysis of Microbial Community Affiliated with Termitarium Reveals High Lignocellulolytic Potential

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Received: 25 September 2020 / Accepted: 11 February 2021 / Published online: 6 March 2021

Abstract
Termitarium (nest of termites) is a rich source of microbial populations whose resources remain untapped to date. Using the metagenomic sequencing approach, we generated 38 GB sequences comprising 808,386 contigs (896 MB) with a maximum contig size of 470 kb. The taxonomic profile obtained by BLAST against the NCBI NR database and annotation by MEGAN showed that the termitarium microbial community was dominated by Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes. Functional annotation using the CAZY database revealed a huge diversity of glycosyl hydrolase genes from 104 families, some of which appeared to be part of polysaccharide utilization systems (PUL). Strikingly, Actinobacteria was the main contributor of the cellulolytic and hemicellulolytic GHs. Genes involving in lignin degradation were also abundantly identified in this metagenome. Comparative analysis of COG profiles of termitarium with those of other lignocellulolytic microbial communities showed a distant clustering pattern resulting from the dietary differences in carbohydrate compositions. Altogether, this study revealed that termitarium hosts a unique microbial community, which can efficiently degrade lignocelluloses.

Introduction

The growing concern over the cost and sustained availability of fossil fuels has massively increased the desire to establish renewable fuel resources with lignocellulosic biomass. There has been an extensive demand for cellulolytic enzymes to convert lignocellulosic materials to biofuels with the escalating price of petroleum. Naturally occurring microorganisms render a promising strategy for identifying biotechnologically potential novel enzymes. In particular, termite species well known for their symbiotic relationship with their gut microbiota are intensely studied for lignocellulose conversion [1].

Termitarium is the nest of termites that provides a distinct ecological niche for the microorganisms for its rich nutrient content compared to neighboring soil. Termites play a pivotal role in circulating nutrients from decayed plant materials in the soil ecosystem. They build nests in various shapes and sizes based on the termite species and the surrounding environment. These termites construct mounds from soil belonging to different strata, which impacts the physical and chemical characteristics of both the soil used for construction and the soil of the surrounding areas. Construction of mounds thus affects the nearby soil pH and microbial population which is higher than neighboring soil [2]. Degradation of lignocellulosic organic matter is characteristic of termites due to the presence of specific microbiota [3]. They are considered the best model systems for studying the symbiotic association between microorganisms and animals.

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Open Access

Original Article

Pakistan's First Child & Adolescent Psychiatry Inpatient Unit: Characteristics of admitted patients and response to treatment over a 7-year period

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ABSTRACT

Background & Objective: Child & adolescent mental health needs to be considered as an integral component of overall health, however significant gaps exist in service provision especially inpatient services in Pakistan. The paper presents the characteristics of admitted youths and response to treatment in Pakistan's first dedicated child & adolescent psychiatry inpatient unit in Lahore over a period of first seven years. The aim of this study was to better understand the various characteristics of children and youth admitted to this inpatient unit and response to treatment over a seven years' period since the inception of the unit.

Methods: Inpatient medical records of children & adolescents admitted to dedicated Child & Adolescent Inpatient Unit at King Edward Medical University, Lahore were reviewed. Data was extracted regarding referral patterns, sociodemographic factors and diagnosis for the first seven years, from 2012 to 2019. Patients' scores on Strengths and Difficulties Questionnaire and Clinical Global Impressions Scales administered during intake were also reviewed.

Results: Six hundred and thirty-four (634) patients, 56% (355) being females were admitted to the unit during seven years with mean age of 12.3±2.3. Mean duration of admission was 15.60±6.3 days. Most predominant ICD-10 Axis-I psychiatric diagnosis were neurotic, stress related and somatoform disorders (262); mood disorders (78); schizophrenia, schizotypal & delusional disorders (77) and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (44). One hundred and fifty-nine (25%) children had comorbid diagnosis of intellectual disability on Axis-III. Strengths and difficulties questionnaire scores were in abnormal range for significant proportion (>50 %) of patients. CGI mean scores showed marked improvement at discharge.

Conclusion: Neurotic, stress related and somatoform disorders are the most common diagnosis in youth needing inpatient treatment in Pakistani setup. Study results indicate that there is a clear need for specialized inpatient child and adolescent services such as ours in low- & middle-income countries.

KEYWORDS: Adolescent, Child, Inpatient, Psychiatry, Psychiatric services.

doi: https://doi.org/10.12669/pjms.37.2.2611

How to cite this:

Imran N, Bodla ZH, Asif A, Shoukat R, Azeem MW. Pakistan's First Child & Adolescent Psychiatry Inpatient Unit: Characteristics of admitted patients and response to treatment over a 7-year period. Pak J Med Sci. 2021;37(2):305-311. doi: https://doi.org/10.12669/pjms.37.2.2611

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* Received for Publication: April 6, 2020
* Revision Received: September 25, 2020
* Accepted for Publication: December 26, 2020

INTRODUCTION

Low income countries like Pakistan face a multitude of social adversities including poverty, malnutrition, rapid urbanization, educational deprivation, drug abuse, increased crime, terrorism etc. thus increasing the risk of mental health problems in youth. Despite high prevalence

RESEARCH PAPER

Outcomes of Neonates Born to Mothers With Coronavirus Disease 2019 (COVID-19) – National Neonatology Forum (NNF) India COVID-19 Registry

National Neonatology Forum (NNF) COVID-19 Registry Group*

**List of group members provided as Annexure*

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Received: January 27, 2021; Initial review: February 25, 2021; Accepted: March 13, 2021.

Background: Limited evidence exists on perinatal transmission and outcomes of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in neonates.

Objective: To describe clinical outcomes and risk factors for transmission in neonates born to mothers with perinatal SARS-CoV-2 infection.

Design: Prospective cohort of suspected and confirmed SARS-CoV-2 infected neonates entered in National Neonatology Forum (NNF) of India registry.

Subjects: Neonates born to women with SARS-CoV-2 infection within two weeks before or two days after birth and neonates with SARS-CoV-2 infection.

Outcomes: Incidence and risk factors of perinatal transmission.

Results: Among 1713 neonates, SARS-CoV-2 infection status was available for 1330 intramural and 104 extramural neonates. SARS-CoV-2 positivity was reported in 144 intramural and 39 extramural neonates. Perinatal transmission occurred in 106 (8%) and horizontal transmission in 21 (1.5%) intramural neonates. Neonates roomed-in with mother had higher transmission risk (RR1.16, 95% CI 1.1 to 2.4; *P*=0.01). No association was noted with the mode of delivery or type of feeding. The majority of neonates positive for SARS-CoV2 were asymptomatic. Intramural SARS-CoV-2 positive neonates were more likely to be symptomatic (RR 5, 95%CI 3.3 to 7.7; *P*<0.0001) and need resuscitation (RR 2, 95%CI 1.0 to 3.9; *P*=0.05) compared to SARS-CoV-2 negative neonates. Amongst symptomatic neonates, most morbidities were related to prematurity and perinatal events.

Conclusion: Data from a large cohort suggests perinatal transmission of SARS-CoV-2 infection and increased morbidity in infected infants.

Keywords: *Horizontal transmission*, *Outcome*, *Perinatal transmission, Risk*.

Published online: March 20, 2021;***PII:*** S097475591600300

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 15 million individuals in India [1]. The SARS-CoV-2 infects both children and adults but has higher fatality in the elderly and individuals with co-morbidities [2]. SARS-CoV-2 infects pregnant women as much as other reproductive-age women [3]. The knowledge about the epidemiology, clinical characteri-stics, prevention, and treatment of SARS-CoV-2 infection is continually evolving. Currently available data on the consequences of SARS-CoV-2 infection in pregnancy, fetus, and the neonate is mostly from case reports, small case series, retrospective cohort or cross-sectional studies, compiled in a recent systematic review [4]. There is limited data on perinatal SARS-CoV-2 infection from the developing world. We report analysis from a large neonatal coronavirus disease 2019 (COVID-19) registry under the National Neonatology Forum (NNF) of India, on the incidence of perinatal transmission and the factors associated with it, and the clinical features of SARS-CoV-2 positive neonates.

METHODS

In this prospective cohort study, data were collected from various hospitals voluntarily enrolled in the NNF COVID-19 registry, which was initiated in April, 2020. Neonates born to women with SARS-CoV-2 infection within two weeks prior to or two days after delivery and neonates with confirmed SARS-CoV-2 infection within 28 days of life were eligible for enrolment in the study. COVID status of mothers and neonates was assessed by nasopharyngeal RT-PCR in all participating hospitals.

SARS-CoV-2 infected neonates were defined as those with a positive SARS-CoV-2 quantitative RT-PCR test in nasopharyngeal swab within 28 days of birth [5]. SARS-CoV-2 infected mothers were defined as those with a positive SARS-CoV-2 quantitative RT-PCR test in the

Intraoperative Management of a Child Undergoing Cardiac Surgery With Congenital Methemoglobinemia Detected in the Operating Room: A Case Report

Pradeep Bhaskar, MD,*† Saif Rehman, MD,*† Reyaz A. Lone, MS, Mch,†‡ Jiju John, MD,*† and Aslam Faris A. Sahabudheen, MD*†

Congenital methemoglobinemia is a rare disease that is easily overlooked in its mild form. It can lead to tissue hypoxia as methemoglobin does not possess oxygen-carrying capacity. Its management approach depends on the severity of the symptoms, methemoglobin level, and associated medical conditions. The perioperative management of congenital methemoglobinemia is well described in the literature; however, its management in children with congenital heart disease and undergoing cardiac surgery using cardiopulmonary bypass has not been reported. We present a case and its management where congenital methemoglobinemia was detected in the operating room in a child scheduled for cardiac surgery. (A&A Practice. 2021;15:e01395.)

GLOSSARY

ABG = arterial blood gas; **ASA** = American Society of Anesthesiologists; **CPB** = cardiopulmonary bypass; **Cyb5R** = cytochrome b5 reductase; **Fio_2** = fraction of inspired oxygen; **G6PD** = glucose-6-phosphate dehydrogenase; **Hb** = hemoglobin; **ICU** = intensive care unit; **MetHb** = methemoglobin; **NICU** = neonatal intensive care unit; **RVOT** = right ventricular outflow tract; **Sao_2** = oxygen saturation; **VBG** = venous blood gas

Methemoglobin is a form of hemoglobin (Hb) that results from oxidation of its heme molecule. The resulting ferric heme does not have the ability to carry oxygen. At the same time, the oxygen affinity for the remaining ferrous form increases, leading to the leftward shift of the oxyhemoglobin dissociation curve. Hence, the increased methemoglobin level can cause hypoxia at the cellular level. Normal levels of methemoglobin are maintained <2% by a balance of oxidation and reduction of the ferrous and ferric forms of iron in Hb. The majority of the patients with congenital methemoglobinemia are deficient in the enzyme cytochrome b5 reductase (Cyb5R) that is vital for the major reducing pathway of methemoglobin. Less commonly, it occurs from hemoglobin M disease where mutation happens in the globin chain resulting in an inability to carry oxygen.

The literature provides few citations on the perioperative management of both acquired and congenital methemoglobinemia.[1,2] The management approach in these reports varies from no intervention to administration of methylene blue and ascorbic acid in selected patients depending on the invasiveness of procedure, symptoms, and methemoglobin level. Although intervention resulted in a significant reduction of methemoglobin levels, there are no outcome data available to support its regular use. There is no report regarding anesthetic management of methemoglobinemia in children with congenital heart disease undergoing cardiac surgery using cardiopulmonary bypass (CPB). Here, we discuss the management of congenital methemoglobinemia, detected in the operating room in a child undergoing a redo-cardiac surgery. This report was approved by the institutional review board with a waiver of consent.

CASE DESCRIPTION

A 2-year-old boy, weighing 11.8 kg, with a history of Tetralogy of Fallot s/p complete surgical correction at 7 months of age was scheduled for an elective repair of increasing right ventricular outflow tract (RVOT) obstruction. The child was asymptomatic, and vital signs were normal during preoperative evaluation except the low-oxygen saturation on pulse oximeter (93%) on room air. The preoperative echocardiogram showed no residual shunts, right ventricular hypertrophy, and a peak RVOT gradient of 80 mm Hg. Intraoperatively, standard American Society of Anesthesiologists (ASA) monitors were applied, and anesthesia was induced with intravenous ketamine, fentanyl, and cisatracurium. The endotracheal tube was placed under direct laryngoscopy, and its position was confirmed with end-tidal carbon dioxide and equal bilateral breath sounds. Anesthesia was maintained with sevoflurane, fentanyl, and cisatracurium.

Fraction of inspired oxygen (Fio_2) was kept at 30% on mechanical ventilation. The vital signs remained stable except the pulse oximeter saturation of 90%–93%, which did not change by increasing Fio_2. An arterial line was inserted on the left radial artery, and a blood sample was drawn for an arterial blood gas (ABG) analysis. By visual inspection, the blood sample looked unusually dark (chocolate color). The ABG showed Po_2 of 250 mm Hg, oxygen

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Accepted for publication December 23, 2020.

Funding: None.

The authors declare no conflicts of interest.

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DOI: 10.1213/XAA.0000000000001395

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SUSCEPTIBILITY

Potency of Olorofim (F901318) Compared to Contemporary Antifungal Agents against Clinical *Aspergillus fumigatus* Isolates and Review of Azole Resistance Phenotype and Genotype Epidemiology in China

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ABSTRACT Triazole resistance in *Aspergillus fumigatus* is an increasing worldwide problem that causes major challenges in the management of aspergillosis. New antifungal drugs are needed, with novel targets, that are effective in triazole-resistant infection. In this study, we retrospectively evaluated the potency of the novel drug olorofim compared to contemporary antifungal agents against 111 clinical *A. fumigatus* isolates collected from Huashan Hospital, Shanghai, China, using EUCAST methodology, and we reviewed the literature on triazole-resistant *A. fumigatus* (TRAF) published between 1966 and 2020 in China. Olorofim was active *in vitro* against all tested *A. fumigatus* isolates, with a MIC_{90} of 0.031 mg/liter (range, 0.008 to 0.062 mg/liter). For 4 triazole-resistant *A. fumigatus* isolates, the olorofim MIC ranged between 0.016 and 0.062 mg/liter. The reported rates of TRAF in China are 2.5 to 5.56% for clinical isolates and 0 to 1.4% for environmental isolates. TR_{34}/L98H/S297T/F495I is the predominant resistance mechanism, followed by TR_{34}/L98H. Non-TR-mediated TRAF isolates, mostly harboring a *cyp51A* single point mutation, showed greater genetic diversity than TR-mediated resistant isolates. Resistance due to TR_{34}/L98H and TR_{34}/L98H/S297T/F495I mutations among TRAF isolates might have evolved from separate local isolates in China. Continuous isolation of TRAF in China underscores the need for systematic resistance surveillance as well as the need for novel drug targets, such as olorofim.

KEYWORDS olorofim, *Aspergillus fumigatus*, antifungal susceptibility, azole resistance, genetic diversity, China

Invasive aspergillosis (IA) in immunocompromised patients results in substantial morbidity and mortality (1). More than 40 *Aspergillus* species have been reported as causative agents of IA. *Aspergillus fumigatus* is the most common etiological agent of invasive and chronic pulmonary aspergillosis (1). Two classes of antifungal agents are licensed for the primary therapy of IA, namely, the triazoles and the polyene

Citation Su H, Zhu M, Tsui CK-M, van der Lee H, Tehupeiory-Kooreman M, Zoll J, Engel T, Li L, Zhu J, Lu Z, Zhang Q, Verweij PE, Deng S. 2021. Potency of olorofim (F901318) compared to contemporary antifungal agents against clinical *Aspergillus fumigatus* isolates and review of azole resistance phenotype and genotype epidemiology in China. Antimicrob Agents Chemother 65:e02546-20. https://doi.org/10.1128/AAC.02546-20.

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Received 8 December 2020
Returned for modification 7 January 2021
Accepted 2 March 2021
Accepted manuscript posted online 8 March 2021
Published 19 April 2021

scientific reports

Check for updates

OPEN

Screening pregnant women in a high-risk population with WHO-2013 or NICE diagnostic criteria does not affect the prevalence of gestational diabetes

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There are currently several diagnostic criteria for gestational diabetes (GDM). Both the WHO -2013 and NICE diagnose GDM based on a single step 75 g OGT; however; each uses different glucose thresholds. Previous studies have shown that the prevalence of GDM using the NICE criteria (GDM-N) is lower than that using the WHO-2013 criteria (GDM-W). Qatar has national diabetes in pregnancy program in which all pregnant women undergo OGTT screening using the WHO-2013 criteria. This study aims to define the prevalence of GDM using both criteria in a high-risk population. This retrospective study included 2000 women who underwent a 75 g (OGTT) between Jan 2016 and Apr 2016 and excluded patients with known pre-conception diabetes, multiple pregnancy, and those who did not complete the OGTT. We then classified the women into GDM-W positive, GDM-N positive but GDM-W negative, and normal glucose tolerance (NGT) population. A total of 1481 women (74%) had NGT using the NICE or the WHO-2013 criteria. The number of patients who met both criteria was 279 subjects (14%) with a good agreement (Kappa coefficient 0.67, p < 0.001). The NICE and the WHO-2013 criteria were discordant in 240 subjects (12% of the cohort); 6.7% met the WHO -2013 criteria only and only 5.3% met the NICE criteria. The frequency of pre-eclampsia, pre-term delivery, Caesarean-section, LGA and neonatal ICU admissions were significantly increased in the GDM-W group. However, the GDM-N positive but GDM-W negative had no increased risk of maternal or fetal complications apart from pregnancy-induced hypertension. The WHO-2013 and the NICE criteria classified a similar proportion of pregnant women, 21.5% and 20.1%, respectively, as having GDM; however, they were concordant in only 14% of the cases. Women who are GDM-N positive but GDM-W negative are not at increased risk of maternal and fetal pregnancy complications, except for pregnancy-induced hypertension. As the NICE criteria are more specific to the UK population, we would recommend the use of the WHO-2013 criteria to diagnose GDM in the MENA region and possibly other regions that do not have the same set-up as the UK.

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia first detected during pregnancy that is neither type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)[1]. Few areas of diabetes care have generated as much debate, controversy, and lack of consensus as GDM. Discussions cover the diagnostic criteria, classification, timing of screening, and method of screening (universal versus selective screening)[1–6]. The HAPO trial (Hyperglycaemia and Adverse Pregnancy Outcomes) followed 25,505 pregnancies from different ethnicities; who underwent 75 g OGTT (Oral Glucose Tolerance Test) between 24- 32 weeks' gestation[7]. This study showed

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Received: 3 January 2021 | Revised: 8 February 2021 | Accepted: 22 February 2021

DOI: 10.1002/ppul.25345

REVIEW

PEDIATRIC PULMONOLOGY WILEY

Frequency of ventilator circuit changes to prevent ventilator-associated pneumonia in neonates and children—A systematic review and meta-analysis

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Abstract

Objective: To assess the effect of different frequencies of ventilator circuit changes in neonates and children through a systematic review and meta-analysis.

Interventions: (1) "No routine change of ventilator circuit (unless visibly soiled)" versus "routine change at any fixed interval"; (2) routine change of circuit at "less frequent" versus "more frequent" intervals.

Outcomes: Primary outcomes were VAP rate (number of VAP episodes per 1000 ventilator-days) and all-cause mortality before discharge.

Methods: MEDLINE, CENTRAL, EMBASE, and CINAHL were systematically searched from inception till November 3, 2020. Two authors assessed trial eligibility and risk of bias, and independently extracted data. Data were synthesized using fixed effects model. GRADE was used to assess certainty of evidence (CoE).

Results: We identified six studies enrolling 768 participants evaluating circuit changes at two fixed intervals. Meta-analysis of studies on circuit changes "once in less than 7 days" versus "once weekly" showed no difference in VAP rate (risk ratio: 0.83 [0.38–1.81]; one randomized controlled trial (RCT) and 0.94 [0.49–1.81]; two before-after studies) or mortality before discharge (0.67 [0.34–1.3]; one RCT and 1.01 [0.63–1.64]; two before-after studies). CoE was very low. Less frequent circuit changes reduced health-care costs. No study evaluating "circuit changes only when visibly soiled" versus "circuit changes at a fixed interval" was identified.

Conclusion: There is no evidence to suggest that ventilator circuits can be safely left unchanged until visibly soiled in neonates and children. Extending circuit changes interval to "once weekly" may not increase VAP rate (CoE—very low) and reduces healthcare costs.

KEYWORDS

children, circuit change, neonate, ventilator-associated pneumonia

Received: 25 June 2020 | Revised: 12 February 2021 | Accepted: 5 March 2021

DOI: 10.1111/pedi.13200

PSYCHOLOGICAL ASPECTS OF DIABETES

Outpatient clinic-wide psychological screening for children and adolescents with type 1 diabetes in Qatar: An initiative for integrative healthcare in the Gulf region

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Funding information
Internal Hospital Grant (Sidra Internal Research Fund 2018 – SDR 20029)

Abstract

Objective: To identify culturally appropriate psychological screening measures for children and adolescents with type 1 diabetes in Qatar, determine rates of depressive and anxiety symptoms in a clinical sample, and examine associations between screening measures, demographic variables, medical characteristics, and diabetes treatment outcomes, specifically HbA1c.

Methods: A total of 150 participants with type 1 diabetes aged 10–17 were recruited. Participants were Arabic or English speaking and of Qatari and non-Qatari nationality. Participants completed the Mood and Feelings Questionnaire (child and parent proxy form), the Spence Children's Anxiety Scale, and the Pediatric Quality of Life, Diabetes version (child and parent proxy form). Glycosylated hemoglobin (HbA1c) on the date of the testing was recorded.

Results: Approximately ten percent (10.2%) of children and adolescents scored above the cutoff score of 27 indicating clinically significant depressive symptoms, and 12.8% of parents rated their child above the respective cutoff score of 21 for the parent proxy form. Further, 36% of the sample reported clinically significant anxiety symptoms, scoring above the cutoff score of 50. Parent report on their child's quality of life predicted HbA1c ($F[6, 140] = 5.42$, $p = 0.000$); $B = -0.05$, $p = 0.002$).

Conclusions: Rates of depressive and anxiety symptoms are comparable to those observed in western countries. Thus, systematic screening for depression and anxiety in children and adolescents with type 1 diabetes should be implemented in Qatar. This will help inform decisions to refer to mental health services and thus provide more integrated care, possibly improving treatment outcomes.

KEYWORDS

anxiety, depression, Middle East, psychological screening measures, quality of life, type 1 diabetes

Case Reports > J Nucl Med Technol. 2021 Sep;49(3):281-283. doi: 10.2967/jnmt.120.258343. Epub 2021 Mar 15.

Imaging Biomarkers in Lung Cancer with ^{68}Ga-DOTATATE, ^{18}F-Fluoride, and ^{18}F-FDG PET/CT Scans and the Theranostics Paradigm

Mehdi Djekidel [1], Ghulam Syed [2], Aladdin Kanbour [3]

Affiliations + expand

PMID: 33722922 DOI: 10.2967/jnmt.120.258343

Abstract

Lung cancer is the number 1 cause of cancer deaths in the United States. The prognosis is quite grim with the exception of stage 1. When faced with several failed therapeutic regimens and rapid progression of the disease, considering alternative therapies such as radiopharmaceutical therapies may be an option. We describe the case of a 36-y-old man with lung adenocarcinoma who had imaging molecular characterization of his disease with ^{18}F-FDG, ^{68}Ga-DOTATATE, and ^{18}F-fluoride PET/CT scans that were able to shed some light on molecular characterization of his disease and serve as a guide to potential targeted or personalized radiopharmaceutical therapeutic options.

Keywords: 18F-FDG; 18F-fluoride; 68Ga-DOTATATE; lung adenocarcinoma; lung cancer; theranostics.

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Mid-Term Outcomes Following Percutaneous Pulmonary Valve Implantation Using the "Folded Melody Valve" Technique

Zakaria Jalal, MD, PhD; Estíbaliz Valdeolmillos, MD; Sophie Malekzadeh-Milani, MD; Andreas Eicken, MD, PhD; Stanimir Georgiev, MD; Michael Hofbeck, MD; Ludger Sieverding, MD; Marc Gewillig, MD, PhD; Caroline Ovaert, MD, PhD; Helene Bouvaist, MD; Xavier Pillois, PhD; Jean-Benoit Thambo, MD, PhD*; Younes Boudjemline, MD, PhD*

BACKGROUND: The folded valve is a manual shortening of the Melody device, which has been validated as a valuable therapeutic option for the management of dysfunctional right ventricular outflow tracts needing a short valved stent. In this article, we aimed to evaluate, in a multicenter cohort, the mid-term outcomes of patients in whom a percutaneous pulmonary valve implantation was performed using the folded valve technique.

METHODS: A 2012 to 2018 retrospective multicenter study was performed in 7 European institutions. All patients who benefit from percutaneous pulmonary valve implantation with a folded Melody valve were included.

RESULTS: A total of 49 patients (median age, 19 years [range 4–56], 63% male) were included. The primary percutaneous pulmonary valve implantation indication was right ventricular outflow tract stenosis (n=19; 39%), patched native right ventricular outflow tracts were the most common substrate (n=15; 31%). The folded technique was mostly used in short right ventricular outflow tracts (n=28; 57%). Procedural success was 100%. After a median follow-up of 28 months (range, 4–80), folded Melody valve function was comparable to the immediate postimplantation period (mean transvalvular peak velocity=2.6±0.6 versus 2.4±0.6 m/s, $P>0.1$; only 2 patients had mild pulmonary regurgitation). Incidence rate of valve-related reinterventions was 2.1% per person per year (95% CI, 0.1%–3.9%). The probability of survival without valve-related reinterventions at 36 months was 90% (95% CI, 76%–100%).

CONCLUSIONS: The folded Melody valve is a safe technique with favorable mid-term outcomes up to 6.5 years after implantation, comparable with the usual Melody valve implantation procedure. Complications and reinterventions rates were low, making this technique relevant in selected patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: incidence ■ probability ■ pulmonary valve ■ retrospective ■ stent

Percutaneous pulmonary valve implantation (PPVI) has emerged in the last 2 decades as an effective and less invasive alternative to surgical valve replacement for the treatment of dysfunctional right ventricular outflow tracts (RVOTs).[1,2] Currently, 2 dedicated devices are used on a larger scale, including the Melody valve (Medtronic, Minneapolis, MN) and the Sapien XT valve (Edwards Lifescience, Irvine, CA). The Melody device consists of a bovine jugular venous valve, sutured within a bare-metal platinum-iridium stent (CP stent, NuMED,

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For Sources of Funding and Disclosures, see page 379.

frontiers in Pediatrics

CASE REPORT
published: 04 March 2021
doi: 10.3389/fped.2021.632915

Case Report: Recurring Peritonitis and Dialysis Failure in a Toddler on Peritoneal Dialysis

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We report a case of a 2-year-old-boy with end stage renal disease (ESRD) secondary to posterior urethral valves (PUV) on peritoneal dialysis (PD). Our patient developed multiple episodes of peritonitis, refractory anemia and feeding intolerance over a 12-month-period. He was treated with multiple courses of intraperitoneal antibiotics. Despite being on high-calorie formula, he was slowly thriving. The feeding intolerance was attributed to past history of prematurity, gastro-esophageal reflux disease and ESRD co-morbidities. He had anemia resistant to erythrocyte stimulating agents and iron supplementation. His family received re-training and mastered the PD techniques. They reported no breach of the aseptic techniques. His workup which included multiple AP abdominal XR-plain films were read as unremarkable and showed the gastrostomy tube (GT) and the PD catheter in good position. He completed his antibiotic courses as prescribed after each peritonitis episode, peritoneal fluid cultures repeated after each treatment completion showed no growth. During the last peritonitis episode, our patient developed ultrafiltration failure. A cross-table abdominal XR was obtained to evaluate the peritoneal catheter position and showed an intra-abdominal foreign body. During surgery, a needle was laparoscopically removed from the ileum and the PD catheter was replaced. Subsequently, our patient's feeding intolerance and resistant anemia resolved. Finally PD was successfully resumed.

Keywords: pediatric, peritoneal dialysis, end stage renal disease, peritonitis, foreign body

OPEN ACCESS

Edited by:
Rupesh Raina,
Akron Children's Hospital,
United States

Reviewed by:
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Specialty section:
This article was submitted to Pediatric Nephrology, a section of the journal Frontiers in Pediatrics

Received: *24 November 2020*
Accepted: *02 February 2021*
Published: *04 March 2021*

Citation:
Mohammed EH, Chandy S, Kadhi AE and Shatat IF (2021) Case Report: Recurring Peritonitis and Dialysis Failure in a Toddler on Peritoneal Dialysis. Front. Pediatr. 9:632915. doi: 10.3389/fped.2021.632915

INTRODUCTION

Every year, 1,500 children develop end stage renal disease (ESRD) in the USA (1), of whom one-third start on peritoneal dialysis (PD) and two-third start hemodialysis (HD) (2). PD is the predominant modality of renal replacement therapy (RRT) in infants and young children (2, 3) contributing to 96% of RRT in the 1st year of life (4).

PD provides multiple advantages compared to HD, to list some of which; PD is associated with better preservation of residual renal function and vascular access by avoidance of central venous access placement and its complications. PD when performed via cycler therapy at home and during the nighttime -as in most of the pediatric chronic PD therapies- minimizes interruption of daily activities, schooling and is arguably more physiological compared to HD, however requires substantial investment from the caregivers (5). On the other hand, children on PD are more likely to have hypoproteinemia and hypogammaglobulinemia as a result of peritoneal protein losses (3), increased dietary requirements, caregiver exhaustion and stress (5) and most importantly are more

European Journal of Pediatrics
https://doi.org/10.1007/s00431-021-04051-w

ORIGINAL ARTICLE

Clinical and genetic characteristics of patients with congenital hyperinsulinism in 21 non-consanguineous families from Serbia

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Received: 14 December 2020 / Revised: 7 February 2021 / Accepted: 21 March 2021

Abstract

Persistent hypoglycaemia in newborns and infants is most commonly caused by congenital hyperinsulinism (CHI). Most CHI studies report outcomes in children from both consanguineous and non-consanguineous families which can affect the phenotype-genotype analysis. The aim of this study was to analyze characteristics of patients with CHI in 21 non-consanguineous families from Serbia. This retrospective cohort study included a total of 21 patients with CHI treated in the Mother and Child Healthcare Institute of Serbia during the past 20 years. The prevalence of macrosomia at birth was very low in our cohort (4.8%). Median age at presentation was 6 days, with seizures as the presenting symptom in 76% of patients. Only four patients (19%) were diazoxide unresponsive, and eventually underwent pancreatectomy. Genetic testing was performed in 15 patients and genetic diagnosis was confirmed in 60%, with all patients being heterozygous for detected mutations. The *ABCC8* gene mutations were detected in 55.6%, *GLUD1* in three patients (33.3%) with HIHA syndrome and one patient had *HNF4A* gene mutation and unusual prolonged hyperglycaemia lasting 6 days after diazoxide cessation. Neurodevelopmental deficits persisted in 33% of patients.

Conclusion: This is the first study regarding CHI patients in Serbia. It suggests that in countries with low consanguinity rate, majority of CHI patients are diazoxide responsive. The most common mutations were heterozygous *ABCC8*, followed by *GLUD1* and *HNF4A* mutations, suggesting the potential benefit of population-tailored genetic analysis approach, targeting the mutations causing CHI via dominant inheritance model in regions with low consanguinity rates.

What is Known:

- *Persistent hypoglycaemia during infancy and early childhood is most commonly caused by congenital hyperinsulinism (CHI).*
- *Consanguinity is a very important factor regarding the genetics and phenotype of CHI, increasing the risk of autosomal recessive genetic disorders, including the severe, diazoxide-unresponsive forms caused by recessive inactivating mutations in ABCC8 and KCNJ11.*

What is New:

- *Results of the present study which included CHI patients from 21 non-consanguineous families suggest that in countries with low consanguinity rates, majority of CHI patients can be diazoxide responsive, with most common mutations being heterozygous ABCC8, followed by GLUD1 and HNF4A mutations.*

Keywords Congenital hyperinsulinism · CHI · Hypoglycaemia · Consanguinity · Treatment · Outcome

Communicated by Peter de Winter

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Published online: 26 March 2021

QMJ
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QATAR MEDICAL JOURNAL

RESEARCH ARTICLE

Impact of attention deficit hyperactivity disorder and gender differences on academic and social difficulties among adolescents in Qatari Schools

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http://dx.doi.org/10.5339/qmj.2021.11
Submitted: 26 June 2020
Accepted: 20 September 2020

Cite this article as: Kamal M, Al-Shibli S, Shahbal S, Yadav SK. Impact of attention deficit hyperactivity disorder and gender differences on academic and social difficulties among adolescents in Qatari Schools, Qatar Medical Journal 2021:11 http://dx.doi.org/10.5339/qmj.2021.11

كيوساينس
QSCIENCE
دار جامعة حمد بن خليفة للنشر
HAMAD BIN KHALIFA UNIVERSITY PRESS

ABSTRACT

Background: To evaluate the social and academic impact of adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and gender differences compared with their non-ADHD peers.

Methods: A cross-sectional descriptive study using a standardized rating scale of teacher observations was conducted in the schools of Qatar from 7th to 12th grades. Teachers completed Swanson, Nolan, and Pelham (SNAP-IV) rating scale questionnaires for the ADHD core symptoms together with nine questions to evaluate the academic and social difficulties in all participants.

Results: A total of 1775 students (mean age: 15±1.5 years; boys/girls: 717/1058) were included in this study. Based on the SNAP-IV rating scale, 150 students were showing core symptoms of ADHD and classified as having ADHD (8.5%; boys/girls; 93/57) and 1625 students as non-ADHD peers (91.5%; boys/girls; 624/1001). Prevalence of ADHD among adolescent students is 8.5%, and it varied significantly between genders with 13% of boys and 5.4% of girls affected by this disorder. Adolescents with ADHD had more academic and social difficulties than their non-ADHD peers, the boys more so than the girls. Boys with inattentive subtype of ADHD had more academic difficulties than girls, while girls had more social difficulties than boys.

Conclusion: The results of this study revealed that ADHD among adolescents is substantially associated with academic and social difficulties in the school environment. Gender differences among students with ADHD should be considered in the school and clinical environment.

Keywords: ADHD, adolescents, academic performance, social difficulties, inattentive subtype

Sohail *et al. Gut Pathog* (2021) 13:21
https://doi.org/10.1186/s13099-021-00411-x

Gut Pathogens

SHORT REPORT Open Access

Microbiome profiling of rotavirus infected children suffering from acute gastroenteritis

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Abstract

Background: Rotavirus (RV) is a leading cause of pediatric diarrhea and mortality worldwide. The virus causes acute gastroenteritis characterized by moderate to severe vomiting, diarrhea, dehydration, and fever. Microbial dysbiosis caused by RV infection may significantly influence disease prognosis and the development of other chronic diseases. The gut microbiome plays a vital role in enteric immune response for rotavirus vaccine (RVV) that requires further elucidations. The current study evaluates the gut microbiome of RV positive children and compares gastroenteritis manifestation in children admitted to the Pediatric Emergency Centre, Hamad Medical Cooperation, Doha, Qatar. Stool samples were collected from thirty-nine RV positive and eight healthy control children. 16S rRNA sequence was performed using the Illumina MiSeq platform.

Results: The data demonstrated a significant increase in microbiome diversity denoted by higher relative abundances of phylum Proteobacteria ($p = 0.031$), Fusobacteria ($p = 0.044$) and genus *Streptococcus* ($p \leq 0.001$) in the infected group relative to the control. Similarly, district clustering pattern (PERMANOVA $p = 0.01$) and higher species richness (Shannon entropy $p = 0.018$) were observed in the children who received two RVV doses compared with the non-vaccinated or single-dose groups. These microbiome changes were represented by over-abundance of phylum Bacteroidetes ($p = 0.003$) and Verrucomicrobia ($p \leq 0.001$), and lower expression of family *Enterobacteriaceae* in two RVV doses group. However, microbiome composition was not associated with diarrhea, vomiting, and other parameters of gastroenteritis.

Conclusions: The observations assert significant microbial signatures of RVV, which is dose-dependent, and suggest manipulating these microbes as a novel approach for improving RVV efficacy. Further studies are warranted to investigate the immune status of these patients and mechanistic investigation to enhance RVV seroconversion.

Keywords: Rotavirus, Rotavirus vaccine, Acute gastroenteritis, Microbiome, Proteobacteria

Background

Diarrhea is the second leading cause of mortality in children after pneumonia, causing one out of nine child deaths worldwide [1]. The Global Burden of Disease Study 2016 estimated that rotavirus (RV) caused 128,500 deaths in children and was responsible for an estimated 258 million infectious diarrhea cases worldwide [1]. Despite the availability of the rotavirus vaccine (RVV), the virus is the leading cause of diarrhea-related mortalities in children under five years of age [2]. Literature shows that vaccine efficacy is region-specific and depicts poor seroconversion, particularly in low-and middle-income countries [2]. Human clinical trial data suggest a possible link between the gut microbiome and the enteric immune system's response for low RVV efficacy [2–4].

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Melatonin for non-operating room sedation in paediatric population: a systematic review and meta-analysis

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2020-320592).

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Received 31 August 2020
Revised 24 January 2021
Accepted 28 February 2021
Published Online First 30 March 2021

To cite: Ahmed J, Patel W, Pullattayil AK, *et al*. *Arch Dis Child* 2022;**107**:78–85.

ABSTRACT

Context The literature on melatonin as a sedative agent in children is limited.

Objective To conduct a systematic review of studies assessing the efficacy and safety of melatonin for non-operating room sedation in children.

Methods Medline, Embase, Cochrane Library and Cumulative Index to Nursing and Allied Health were searched until 9 April 2020 for studies using melatonin and reporting one of the prespecified outcomes of this review. Two authors independently assessed the eligibility, risk of bias and extracted the data. Studies with a similar study design, comparator and procedure were pooled using the fixed-effect model.

Results 25 studies (clinical trials=3, observational studies=9, descriptive studies=13) were included. Melatonin was used for electroencephalogram (EEG) (n=12), brainstem evoked response audiometry (n=8) and magnetic resonance imaging (MRI) (n=5). No significant differences were noted on meta-analysis of EEG studies comparing melatonin with sleep deprivation (SD) (relative risk (RR) 1.06 (95% CI 0.99 to 1.12)), melatonin with chloral hydrate (RR 0.97 (95% CI 0.89 to 1.05)) and melatonin alone with melatonin and SD combined (RR 1.03 (95% CI 0.97 to 1.10)) for successful procedure completion. However, significantly higher sedation failure was noted in melatonin alone compared with melatonin and SD combined (RR 1.55 (95% CI 1.02 to 2.33)) for EEG. Additionally, meta-analysis showed lower sleep latency for melatonin compared with SD (mean difference −10.21 (95% CI −11.53 to −8.89) for EEG. No major adverse events were reported with melatonin.

Conclusion Although several studies were identified, and no serious safety concerns were noted, the evidence was not of high quality to establish melatonin's efficacy for non-operating room sedation in children.

What is already known on this topic?

- Melatonin, a natural sleep hormone secreted by the pineal gland, has sedative properties and is being used for non-operating room sedation in children.
- The literature on melatonin as a sedative agent in children is limited.

What this study adds?

- The review summarises the current evidence on melatonin's use for non-operating room sedation in children.
- The review finds no serious adverse events using melatonin as a sedative in children from a limited number of studies.
- Despite melatonin's popularity, the review did not identify high-quality evidence to justify its efficacy for non-operating room sedation in children.
- Despite melatonin's popularity, the review did not identify high-quality evidence to justify its efficacy for non-operating room sedation in children.

INTRODUCTION

Non-operating room (non-OR) sedation refers to the administration of sedation outside the operating room to patients undergoing uncomfortable or painful procedures.[1 2] It is often required in children undergoing non-invasive diagnostic procedures, such as electroencephalogram (EEG), brainstem evoked response audiometry (BERA) and magnetic resonance imaging (MRI).[2 3] Adequate sedation is required to improve the diagnostic yield of the procedure by avoiding motion artefacts, particularly in children who are either anxious or with developmental disabilities or behavioural problems.[4 5] Studies report that inadequate sedation fails to achieve adequate imaging, causes a delay in diagnosis and increases healthcare costs.[6] However, sedation in children is not completely risk-free, and it can cause serious adverse events, such as hypoxaemia, respiratory compromise and cardiovascular instability.[7] Although uncommon, these risks are significantly higher in premature infants, neonates and children with comorbidities and developmental disabilities.[7–9] Several measures like sleep deprivation, swaddling, behavioural therapy, distraction, have been tried with varying success, but many children eventually require sedation for completion of the procedure.[3 10]

The National Institute for Clinical Excellence and American College of Emergency Physicians suggest various sedative medications, including chloral hydrate for various painless procedure in children. Chloral hydrate has good efficacy, but its onset is slow, unpredictable and the duration of action is longer.[10 11] The reported side effects of chloral hydrate range from 1.7% to 20% with a major concern for respiratory depression, paradoxical excitement, laryngeal spasm, low therapeutic index

viruses

MDPI

Article

Prevalence and Phylogenetic Analysis of Parvovirus (B19V) among Blood Donors with Different Nationalities Residing in Qatar

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Abstract: Human parvovirus (B19V) is the causative agent of erythema infectiosum in children and is linked to a wide range of clinical manifestations. Studies related to B19V prevalence in the Middle East and North Africa (MENA) region and other parts of Asia are very scarce. The objectives of this study were to estimate the seroprevalence (anti-B19V IgM and IgG), the viremia rate (B19V DNA), and the circulating genotypes of B19V among blood donors in Qatar. Methods: Donors' blood samples (n = 5026) from different nationalities, mainly from the MENA region and South East Asia, were collected from 2014–2016. Samples were tested for the B19V DNA using RT-PCR. Furthermore, 1000 selected samples were tested to determine the seroprevalence of B19V antibodies using enzyme-linked immunosorbent assay (ELISA). Genotyping was performed on 65 DNA positive samples by sequencing of nested PCR fragments (NS1-VP1u region, 927 nt). Results: Only 1.4% (70/5026) of the samples had detectible B19V DNA in their blood. B19V DNA prevalence statistically decreased with age (p = 0.03). Anti-B19V IgG was detected in 60.3% (561/930) of the tested samples, while only 2.1% (20/930) were IgM-positive and 1.2% (11/930) were both IgM- and IgG-positive. B19V genotyping showed a predominance of Genotype 1 (100%). Sequence analysis of the NS1-VP1u region revealed 139 mutation sites, some of which were amino acid substitutions. Conclusion: Our results indicated a relatively high seroprevalence of B19V in Qatar. Most importantly, B19 DNA was detected among Qatari and non-Qatari blood donors. Therefore, blood banks in Qatar might need to consider screening for B19V, especially when transfusion is intended for high-risk populations, including immunocompromised patients.

Keywords: B19V; seroprevalence; blood donors; viremia; transfusion

Citation: Abdelrahman, D.; Al-Sadeq, D.W.; Smatti, M.K.; Taleb, S.A.; AbuOdeh, R.O; Al-Absi, E.S.; Al-Thani, A.A.; Coyle, P..V.; Al-Dewik, N.; Qahtani, A.A.A.; et al. Prevalence and Phylogenetic Analysis of Parvovirus (B19V) among Blood Donors with Different Nationalities Residing in Qatar. *Viruses* **2021**, *13*, 540. https://doi.org/10.3390/v13040540

Academic Editor: Luciana Barros de Arruda

Received: 20 February 2021
Accepted: 14 March 2021
Published: 24 March 2021

Journal of Fungi

MDPI

Article

Genomic Epidemiology of *Candida auris* in Qatar Reveals Hospital Transmission Dynamics and a South Asian Origin

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Abstract: *Candida auris* is an emerging, multidrug-resistant fungal pathogen that has become a public health threat with an increasing incidence of infections worldwide. *Candida auris* spreads easily among patients within and between hospitals. Infections and outbreaks caused by *C. auris* have been reported in the Middle East region including Oman, Kuwait, Saudi Arabia, and Qatar; however, the origin of these isolates is largely unknown. Pathogen whole genome sequencing (WGS) was used to determine the epidemiology and drug resistance mutations of *C. auris* in Qatar. Forty-four samples isolated from patients in three hospitals and the hospital environment were sequenced by Illumina NextSeq. Core genome single nucleotide polymorphisms (SNPs) revealed that all isolates belonged to the South Asian lineage with genetic heterogeneity that suggests previous acquisition from foreign healthcare. The genetic variability among the outbreak isolates in the two hospitals (A and B) was low. Four environmental isolates clustered with the related clinical isolates, and epidemiologically linked isolates clustered together, suggesting that the ongoing transmission of *C. auris* could be linked to infected/colonized patients and the hospital environment. Prominent mutations Y132F and K143R in *ERG11* linked to increased fluconazole resistance were detected.

Keywords: candidiasis; candidemia; emerging infectious disease; Middle East; nosocomial outbreak

Citation: Salah, H.; Sundararaju, S.; Dalil, L.; Salameh, S.; Al-Wali, W.; Tang, P.; Ben Abid, F.; Tsui, C.K.M. Genomic Epidemiology of *Candida auris* in Qatar Reveals Hospital Transmission Dynamics and a South Asian Origin. *J. Fungi* **2021**, *7*, 240. https://doi.org/10.3390/jof7030240

Academic Editors: Jacques F. Meis and Anuradha Chowdhary

Received: 1 March 2021
Accepted: 19 March 2021
Published: 23 March 2021

1. Introduction

Invasive candidiasis is of major public health importance because it is associated with increased mortality, higher healthcare costs, and longer hospital stays compared with other healthcare-associated infections [1]. This problem is compounded by the progressive increase in antifungal resistance among clinically relevant *Candida* spp. such as *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. auris*, and *C. tropicalis* driven by the widespread use of antifungal drugs in human healthcare [1,2].

Candida auris has become an emerging opportunistic pathogen, which was first reported in 2009 as an isolate from the external ear of an inpatient at a hospital in Japan [3]. It has since been identified as a cause of nosocomial bloodstream infections (BSI) in numerous countries in East Asia, the Middle East, Africa, the United States, and Europe [4–9]. Since *C. auris* is resistant to multiple classes of antifungal agents, able to tolerate temperatures up to 42 °C, and capable of person-to-person transmission and persistence in the hospital

Journal of Asthma and Allergy

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ORIGINAL RESEARCH

Sensitization to Common Allergens Among Children with Asthma and Allergic Rhinitis in Qatar

This article was published in the following Dove Press journal:
Journal of Asthma and Allergy

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Background: Childhood asthma (A) and allergic rhinitis (AR) are common in Qatar. Aeroallergens sensitization is integral in disease pathogenesis and clinical presentation. Determining sensitization patterns assists clinicians in tailoring an efficient medical management.

Objective: To determine the aeroallergen sensitization pattern and relationship to clinical parameters.

Methods: A retrospective review of children (2–14-years) files with i) Pediatric Allergist/or Pulmonologist confirmed-diagnosis of A, and AR, and ii) positive skin prick test (SPT).

Results: Among 473 patients (69.1% males; 30.9% females), aged 7.6 years, family history was positive in 66.3%: 59.4% in A, 64.2% AR, and 78.2% A-AR. The number of allergens/patients was 2.1±1.7. Median eosinophil count was 400 cells/ul and IgE 287 KU/L. Rates of A, AR, and A-AR varied significantly in children ≤5 years compared to >10 years: A was 43.2% vs 17.8%, and AR 34.5% vs 16.4%. Two hundred and four children (43.1%) were mono-sensitized, 215 (45.5%) oligosensitized (2–3 allergens), and 54 (11.4%) polysensitized (≥4 allergens). A-AR ranked the top number of positive allergens. The commonest aeroallergen was Der p1 (38.1%), followed by Der f (29.0%), cat (22.6%), alternaria (18.8%), American cockroach (18.4%), and dog (14.0%). House dust mite (HDM) and American cockroach were commoner in ≤5 years than older >10-year children (52.5%, 24.1%), while cat and dog allergens were commoner in older ones (37.1%, 21.6%).

Conclusion: Family history is quite positive in patients with A and AR. Common aeroallergens include HDM, cats, and alternaria in the young children, while animal allergens were commoner in the older children.

Keywords: asthma, allergic rhinitis, skin prick test, children

Introduction

The prevalence of respiratory allergic disorders has increased in the last few decades and has become a major medical concern, and the impact of these diseases is huge on patients, families, and societies.[1,2]

Despite decades of research, little is known about which factors are the main determinants of the high and of the large global variation in asthma and other respiratory allergic disease prevalence.[3] By the time children reach middle school (10–13 years of age), asthma is very strongly associated with common inhalant allergens.[4] At this age, the odds ratio for wheezing among sensitized compared to non-sensitized individuals is often 6 folds or higher[5,6].

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DovePress
http://doi.org/10.2147/JAA.S295228

Cureus

Open Access Case Report

DOI: 10.7759/cureus.13928

Incidental Malignant Colonic Polyp Detected in a Resected Ischaemic Large Bowel: A Case Report and Literature Review

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Abstract

Most patients with bowel cancer are symptomatic at the time of the diagnosis. They may present with a change in bowel habit, bleeding per rectum, abdominal pain, anaemia, weight loss or bowel obstruction. Colonic carcinoma can also be diagnosed incidentally during screening programs. Moreover, it may be incidentally detected in CT scans being performed for other indications or encountered during surgery for other causes. Some patients with colonic bowel ischaemia have associated large bowel cancer, where the ischaemic segment is usually proximal to the tumour and not necessarily associated with bowel obstruction. We are presenting a rare case of incidental malignant colonic polyp detected in a resected ischaemic large bowel in an 88-year-old gentleman. This was a very small tumour that was not visible macroscopically or detectable by imaging. Pathological examination of non-tumour colorectal resection specimens, as in this case, should include careful macroscopic examination and sequential block selection along the length of the colon, and where there is diffuse mucosal abnormality, block selection at 100mm interval is also advised. Attention to and block selection from any suspicious-looking area is warranted in all cases of non-tumour colorectal resections if such microscopic-sized malignancies of the type seen in our patient are to be picked up.

Categories: Pathology, Radiology, General Surgery
Keywords: malignant colonic polyp, colonic cancer, colorectal cancer, adenocarcinoma, laparotomy, lynch syndrome

Review began 02/24/2021
Review ended 03/15/2021
Published 03/16/2021

Introduction

Colonic malignancy occupies fourth place among the most common cancers in the UK and is regarded as the second most frequent cause of cancer-related mortality. Every year, more than 42,000 new cases are diagnosed, and currently around 268,000 people are living with colonic cancer in the UK. The diagnosis of colonic cancer is usually made by histological examination of a biopsy that is gotten during colonoscopy or from a surgical specimen, with the vast majority of tumours of the colon being carcinomas. Of the carcinomas, more than 90% are adenocarcinomas [1]. Incidental colorectal carcinoma is defined as a clinically inapparent carcinoma of the large intestine diagnosed or discovered unexpectedly. It can be detected in imaging for other reasons [2], during colonoscopy bowel cancer screening [3], during surgical intervention for unrelated causes, as well as in autopsy. In this case, it was discovered during pathologic examination of a subtotal colectomy specimen removed for ischaemic colitis. The prevalence of incidentally discovered colon carcinoma, as well as the molecular patterns of these incidental tumours in the UK, is underreported, and as such its importance in the evaluation of the incidence and future trends of colon cancers is currently unknown.

Case Presentation

An 88-year-old male presented with a recent history of acute abdominal pain and vomiting. His past medical history included ischaemic heart disease, cerebrovascular accident and an open repair of abdominal aortic aneurysm 10 years earlier, in addition to an unoperated incisional hernia. On examination, the patient was septic and in cardiogenic shock. Urgent CT abdomen and pelvis showed free intra-abdominal air (Figure *1*), thickened descending and proximal sigmoid colon with locules of transmural air, as well as locules of extra-luminal gas around it, and this was thought to be the site of the perforation. Because of the presence of aortobiiliac stent within the abdominal aortic aneurysm, origin of the inferior mesenteric artery could not be delineated. However normally opacified tributaries of inferior mesenteric artery supplying the sigmoid and descending colon via collaterals were demonstrated (Figures *2*, *3*, *4*). The patient had undergone an emergency laparotomy, adhesiolysis and subtotal colectomy with an end ileostomy. Intra-operative findings included friable large bowel from mid-sigmoid to caecum with a widespread ischaemic appearance and

How to cite this article
Idaewor P, Lesi O, Elremeli M, et al. (March 16, 2021) Incidental Malignant Colonic Polyp Detected in a Resected Ischaemic Large Bowel: A Case Report and Literature Review. Cureus 13(3): e13928. DOI 10.7759/cureus.13928

RESEARCH ARTICLE

Outcome of first relapse of Hodgkin lymphoma: single institution experience

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Abstract

Objective: To determine outcome of first relapse of Hodgkin lymphoma with standard dose chemotherapy, and to identify the prognostic factors predicting survival outcome in paediatric patients.

Method: The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of Hodgkin lymphoma patients who relapsed at least 3 months after the completion of initial treatment from January 2001 to December 2010. Probabilities of overall survival, event-free survival and cumulative incidence were calculated. Data was analysed using SPSS 21.

Results: Of the 43 patients, 31(72%) were males and 12(29%) were females. Mean age at relapse was 11±3.3 years (range: 4-17 years). In 31(72%) patients, early post-operative intraperitoneal chemotherapy was employed. Median follow-up of the cohort was 62 months (interquartile range: 4-187 months). Overall survival and event-free survival at 10 years was 23(54%) and 15(35%) respectively. On univariate analysis, initial disease stage (p=0.021), stage at relapse (p=0.003), treatment protocol (p=0.005), treatment responsiveness at initial two cycles of salvage chemotherapy (p=0.002) and at the end of treatment assessment (p=0.0009) were statistically significant factors. Multivariate cox regression analysis revealed disease stage at relapse (p=0.004), chemotherapy regimen (p=0.025) and end-of-treatment disease evaluation (p=0.005) as the significant variables.

Conclusion: Improved outcome with early post-operative intraperitoneal chemotherapy regimen was noted for Hodgkin lymphoma patients who had disease-free interval >2 years.

Keywords: B symptoms, Chemo-sensitivity, Mediastinal mass, Stage 4, Relapse Hodgkin lymphoma. (JPMA 71: 883; 2021)

DOI: https://doi.org/10.47391/JPMA.1114

Introduction

Children with Hodgkin lymphoma (HL) have excellent outcome with 5 years survival rates between 80-90% by virtue of combined modality treatment. However, 10% patients with localised disease and 25% of those with advanced disease suffer relapse after first-line treatment.[1-4] Children with relapsed HL (rHL) have a substantial chance of cure depending on prognostic factors at the time of relapse. The backbone of salvage regimens is based on non-cross resistant drugs in combination with and without radiation.[5-7] Since the introduction of high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT), remission rate for relapsed HL patients has improved with reported overall survival (OS) and disease-free survival (DFS) of 65% and 60% respectively in the high-risk group.[8-10] In adults, shorter time to relapse, anaemia and higher stage at the time of relapse are considered poor predictors of outcome.[11] In paediatric series, previously identified predictors of poor survival included time to frontline treatment failure, presence of B-symptoms, mediastinal bulk, extra-nodal disease, advanced stage, anaemia at the time of treatment failure and chemo-sensitivity to salvage regimen. However, there is no uniform model for risk stratification and treatment assignment based on prognostic factors at the time of relapse.[7,12-14]

The current study was planned to examine outcome for first relapse of HL treatment with standard dose chemotherapy with and without radiation, but without HDCT and ASCT, and to identify prognostic factors that predicted survival outcome in paediatric rHL.

Materials and Methods

The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of HL patients who relapsed at least 3 months after the completion of initial treatment from January 2001 to December 2010. The data was retrieved after approval from the institutional ethics review board`. Relapsed HL was defined as diagnosis of HL at least 3 months after the completion of initial treatment where end-of-therapy evaluation had confirmed complete response (CR) on the basis of conventional imaging criteria. Data of patients with primary progressive/refractory disease was excluded.

Data was collected by reviewing electronic medical records (EMR) from the time of initial diagnosis and after the time of first relapse. In addition, records of multidisciplinary

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Received: 17 December 2020 | Revised: 17 March 2021 | Accepted: 22 March 2021

DOI: 10.1002/mgg3.1674

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Founder mutation in the PMM2 promotor causes hyperinsulinemic hypoglycaemia/polycystic kidney disease (HIPKD)

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Funding information
Wellcome Trust; Medical Research Council, Grant/Award Number: 98144; Royal Society, Grant/Award Number: 105636/Z/14/Z; Kids Kidney Research, Grant/Award Number: 105636/Z/14/Z; Juan Rodes, Grant/Award Number: 105636/Z/14/Z; Great Ormond Street Hospital Charity, Grant/Award Number: 105636/Z/14/Z; St Peter's Trust for Kidney Bladder & Prostate Research, Grant/Award Number: 105636/Z/14/Z; European Commission, Grant/Award Number: 2012-305608; David and Elaine Potter Foundation; Instituto de Salud Carlos III, Grant/Award Number: CP11/00263

Abstract

Background: Polycystic kidney disease with hyperinsulinaemic hypoglycaemia (HIPKD) is a recently described disease caused by a single nucleotide variant, c.-167G>T, in the promoter region of *PMM2* (encoding phosphomannomutase 2), either in homozygosity or compound heterozygosity with a pathogenic coding variant in *trans*. All patients identified so far are of European descent, suggesting a possible founder effect.

Methods: We generated high density genotyping data from 11 patients from seven unrelated families, and used this information to identify a common haplotype that included the promoter variant. We estimated the age of the promoter mutation with *DMLE+* software, using demographic parameters corresponding to the European population.

Results: All patients shared a 0.312 Mb haplotype which was absent in 503 European controls available in the 1000 Genomes Project. The age of this mutation was estimated as 105–110 generations, indicating its occurrence around 600 BC, a time of intense migration, which might explain the presence of the same mutations in Europeans around the globe.

Conclusion: The shared unique haplotype among seemingly unrelated patients is consistent with a founder effect in Europeans.

KEYWORDS
founder effect, hyperinsulinism, hypoglycaemia, *PMM2* gene, polycystic kidney disease, promoter

Horia Stanescu and Daniela Iancu contributed equally.

Review > J Nucl Med Technol. 2021 Sep;49(3):265-268. doi: 10.2967/jnmt.120.258939. Epub 2021 Apr 5.

^{68}Ga–DOTATATE PET/CT for Neuroblastoma Staging: Utility for Clinical Use

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PMID: 33820858 DOI: 10.2967/jnmt.120.258939

Abstract

Metaiodobenzylguanidine (MIBG) imaging has been the standard for neuroblastoma staging for many decades. Novel agents such as ^{18}F-DOPA and ^{68}Ga-DOTATATE are being used nowadays in academic centers. During the coronavirus disease 2019 (COVID-19) pandemic, procurement of ^{123}I-MIBG has proved particularly challenging, necessitating the use of ^{68}Ga-DOTATATE PET. ^{68}Ga-DOTATATE is Food and Drug Administration-approved for imaging of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. **Methods:** ^{68}Ga-DOTATATE PET/CT imaging was performed for staging of 3 pediatric patients with neuroblastoma at our institution. A review of the literature was also completed. **Results:** ^{68}Ga-DOTATATE PET/CT scans were successfully performed on all patients. All patients showed ^{68}Ga-DOTATATE-avid disease. PET scans showed an excellent spatial resolution and demonstrated high accuracy in concordance with current European Association of Nuclear Medicine guidelines. **Conclusion:** We have presented ^{68}Ga-DOTATATE PET/CT imaging for staging of neuroblastoma and believe it can reliably be used as an alternative to ^{123}I-MIBG. It has technical, clinical, and practical advantages making it an attractive option. Further multicenter studies are required before it can be recommended for standard clinical use.

Keywords: 68Ga-DOTATATE; COVID-19; MIBG; neuroblastoma imaging.

Pediatric Radiology
https://doi.org/10.1007/s00247-021-04997-x

ORIGINAL ARTICLE

Non-radiologist-performed abdominal point-of-care ultrasonography in paediatrics — a scoping review

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Received: 18 May 2020 / Revised: 6 October 2020 / Accepted: 3 February 2021

Abstract

Background Historically, US in the paediatric setting has mostly been the domain of radiologists. However, in the last decade, there has been an uptake of non-radiologist point-of-care US.

Objective To gain an overview of abdominal non-radiologist point-of-care US in paediatrics.

Materials and methods We conducted a scoping review regarding the uses of abdominal non-radiologist point-of-care US, quality of examinations and training, patient perspective, financial costs and legal consequences following the use of non-radiologist point-of-care US. We conducted an advanced search of the following databases: Medline, Embase and Web of Science Conference Proceedings. We included published original research studies describing abdominal non-radiologist point-of-care US in children. We limited studies to English-language articles from Western countries.

Results We found a total of 5,092 publications and selected 106 publications for inclusion: 39 studies and 51 case reports or case series on the state-of-art of abdominal non-radiologist point-of-care US, 14 on training of non-radiologists, and 1 each on possible harms following non-radiologist point-of-care US and patient satisfaction. According to included studies, non-radiologist point-of-care US is increasingly used, but no standardised training guidelines exist. We found no studies regarding the financial consequences of non-radiologist point-of-care US.

Conclusion This scoping review supports the further development of non-radiologist point-of-care US and underlines the need for consensus on who can do which examination after which level of training among US performers. More research is needed on training non-radiologists and on the costs-to-benefits of non-radiologist point-of-care US.

Keywords Abdomen · Children · Non-radiologist · Point-of-care · Scoping review · Training · Ultrasound

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Published online: 10 April 2021

European Radiology
https://doi.org/10.1007/s00330-021-07906-w

RADIOLOGICAL EDUCATION

Referral guidelines for medical imaging in children: an ESR-EuroSafe Imaging survey on availability, awareness and use in clinical practice among European radiologists

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Received: 22 June 2020 / Revised: 9 February 2021 / Accepted: 16 March 2021

Abstract

Objectives Justification of medical exposures from medical imaging is fundamental to radiation protection. Referral guidelines are intended to help physicians decide when an imaging study is justified. For two decades, referral guidelines have been a legally binding requirement for European Union member states. Recently, the European Society of Radiology (ESR) developed iGuide tool, which provides evidence-based referral guidance for imaging inclusive of children. The aim of this survey was to assess the availability, use and familiarity of referral guidelines for medical imaging in children and knowledge about the availability of ESR iGuide among ESR member radiologists.

Methods Over a 2-month period (15 September–15 November 2019), 33,257 ESR member radiologists were invited to respond to an anonymised web-based questionnaire, which consisted of 12 multiple-choice questions.

Results In total, 2067/33,257 responses (6.3%) were received from 52 countries. A total of 1068 out of 2067 (51.7%) respondents were aware that imaging referral guidelines are a legal requirement. One thousand five (48.6%) of all respondents did not know whether dedicated guidelines for imaging in children were available, and only 653 (31.2%) were aware of the mainstays of the available guidelines. Similarly, just 746 (36.1%) of all respondents were aware of ESR iGuide availability and features.

Conclusions The information gathered confirms that effective and widespread adoption of imaging referral guidelines is lacking, especially in children. Further work is required to improve uptake and awareness.

Lay summary Referral guidelines are based on evidence and should guide referring physicians and radiologists in justifying radiological studies in order to minimise radiation exposure and at the same time optimise diagnostic performances.

These guidelines have to be implemented in Europe by EU directive and exist both for paediatric and adult patients. Following the referral guidelines is of utmost importance for children as the effects of radiation doses are more critical at a young age.

The European Society of Radiology has developed evidence-based referral guidelines specifically for children and developed at the same time a web-based tool to optimise referral, the ESR iGuide.

The present publication reports on a survey carried out among ESR members to assess the availability, use of and familiarity with the referral guidelines and their knowledge about the availability of the ESR iGuide.

With 2067 respondents from 52 countries in Europe and beyond, the survey gives food for thought. Just half of the respondents were aware that the availability of referral guidelines is a legal requirement, which also means that they are likely not using them. The same holds true for the referral guidelines for children, as about half of the respondents are unaware of their availability.

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Published online: 15 April 2021

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COVID-19 vaccine hesitancy in perinatal women: a cross sectional survey

https://doi.org/10.1515/jpm-2021-0069
Received February 6, 2021; accepted April 14, 2021;
published online April 27, 2021

Abstract

Objectives: To explore attitudes to COVID-19 vaccination among perinatal women.
Methods: A nationwide online, cross-sectional survey was conducted in Qatar from 15th October 2020 to 15th November 2020 with voluntary participation open to all adult residents. Of the respondents, the population group for this study comprised the 341 pregnant and breastfeeding participants. The survey utilized a composite questionnaire incorporating a validated instrument to measure vaccine attitudes. The responses were recorded and analysed with statistical analysis being performed with SPSS software. Outcome measures included intentions towards vaccination and potential factors influencing vaccine hesitancy (contextual factors, vaccine specific concerns and group/individual influences).
Results: Perinatal women exhibited a vaccine hesitancy rate of 25% towards COVID-19 immunisation. The main concerns of the group were of infection risks and main factor determining vaccine hesitancy was of vaccine specific safety concerns. Previous vaccine "acceptors" showed vaccine hesitancy to COVID-19 immunisation. A third of the group cited non availability of the vaccine as a concern.
Conclusions: COVID-19 vaccine trials amongst pregnant and lactating women have lagged behind those for general populations and this has compounded concerns around safety in this special group. Perinatal women constitute a vulnerable group and play an important role in vaccination of wider family members. This study highlights the need for trials and data for COVID-19 vaccine in this group to be able to achieve appreciable numbers needed for herd immunity and ultimately control of the pandemic.

Keywords: attitudes; breastfeeding; COVID-19; immunization; perinatal; pregnancy; vaccine hesitancy.

Introduction

The past year has witnessed the world being engulfed by a health crisis of unprecedented proportions. The Coronavirus disease 2019 (COVID-19) pandemic has spread to 215 countries and led to over 1.9 million lives being lost [1]. It has negatively impacted world economies, caused loss of livelihood, overwhelmed health infrastructure and led to restriction of personal liberty on a large scale [2–4].

With the pandemic showing no signs of abating, governments are now focused on using vaccination as a viable strategy to control the pandemic and restore normalcy. By 14th of January 2021, the coronavirus vaccine tracker reported 91 coronavirus vaccines under trial with two approved for use [5]. Historically, immunization has been a public health success story which has promoted human health and longevity through the prevention of infectious diseases [6]. However, recent years have witnessed a growing number of people who are declining immunization due to perceived safety concerns [7, 8]. This evolving problem of vaccine hesitancy and the challenge it could pose to global health has been declared as one of the top 10 global health threats by the WHO [9]. The WHO has responded by establishing the SAGE group (Strategic Advisory Group of Experts) to study vaccine hesitancy and refusal [10].

In the context of COVID-19, the development and trial of vaccines has been expedited and has taken place under intense media scrutiny. In this situation, reports in the media about vaccine reactions under trial as well as a public perception that the vaccine development was rushed has led to a growing number of individuals who are dubious about the vaccine and would refuse immunization

Suruchi Mohan and Shuja Reagu share first authorship.

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frontiers in Pediatrics

ORIGINAL RESEARCH
published: 12 April 2021
doi: 10.3389/fped.2021.646517

Hydronephrosis Classifications: Has UTD Overtaken APD and SFU? A Worldwide Survey

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OPEN ACCESS

Edited by:
Venkata R. Jayanthi, Nationwide Children's Hospital, United States

Reviewed by:
Onur Telli, Istanbul Kartal Dr. Lutfi Kirdar Education and Research Hospital, Turkey
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Specialty section:
This article was submitted to Pediatric Urology, a section of the journal Frontiers in Pediatrics

Received: *27 December 2020*
Accepted: *23 February 2021*
Published: *12 April 2021*

Citation:
Vallasciani S, Bujons Tur A, Gatti J, Machado M, Cooper CS, Farrugia MK, Zhou H, El Anbari M and Lopez P-J (2021) Hydronephrosis Classifications: Has UTD Overtaken APD and SFU? A Worldwide Survey. Front. Pediatr. 9:646517. doi: 10.3389/fped.2021.646517

Objective: To collect baseline information on the ultrasonographic reporting preferences.

Method: A 13-multiple choice questionnaire was designed and distributed worldwide among pediatric urologists, pediatric surgeons, and urologists. The statistical analysis of the survey data consisted of 3 steps: a univariate analysis, a bivariate and a multivariate analysis.

Results: Three hundred eighty participants responded from all the continents. The bivariate analysis showed the significant differences in the geographical area, the years of experience and the volume of cases. Most of the physicians prefer the SFU and APD systems because of familiarity and simplicity (37 and 34%, respectively). Respondents noted that their imaging providers most often report findings utilizing the mild-moderate-severe system or the APD measurements (28 and 39%, respectively) except for North America (SFU in 50%). Multivariate analysis did not provide significant differences.

Conclusion: Our study evaluates the opinions regarding the various pediatric hydronephrosis classification systems from a large number of specialists and demonstrates that there is no single preferred grading system. The greatest reported shortcoming of all the systems was the lack of universal utilization. The observations taken from this study may serve as basis for the construction of a common worldwide system. As APD and SFU are the preferred systems and the UTD a newer combination of both, it is possible that with time, UTD may become the universal language for reporting hydronephrosis. This time, based on the result of this survey, seems not arrived yet.

Keywords: hydronephrosis, classification, survey, pediatric urology, ultrasound, pediatric radiology

Corneal confocal microscopy identifies a reduction in corneal keratocyte density and sub-basal nerves in children with type 1 diabetes mellitus

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Received 11 February 2021
Revised 10 April 2021
Accepted 20 April 2021

To cite: Gad H, Al-Jarrah B, Saraswathi S, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2021-319057

ABSTRACT

Purpose To assess whether alterations in stromal keratocyte density are related to loss of corneal nerve fibres in children with type 1 diabetes mellitus (T1DM).

Methods Twenty participants with T1DM and 20 age-matched healthy controls underwent corneal confocal microscopy. Corneal sub-basal nerve morphology and corneal keratocyte density (KD) were quantified.

Results Corneal nerve fibre density (CNFD) (p<0.001), corneal nerve branch density (p<0.001), corneal nerve fibre length (CNFL) (p<0.001) and inferior whorl length (IWL) (p<0.001) were lower in children with T1DM compared with healthy controls. Anterior (p<0.03) and mid (p=0.03) stromal KDs were lower with no difference in posterior KD (PKD) in children with T1DM compared with controls. Age, duration of diabetes, height, weight and body mass index did not correlate with anterior (AKD), mid (MKD) or PKD. Inverse correlations were found between glycated haemoglobin and PKD (r=−0.539, p=0.026), bilirubin with MKD (r=−0.540, p=0.025) and PKD (r=−0.531, p=0.028) and 25-hydroxycholecalciferol with MKD (r=−0.583, p=0.018). CNFD, CNFL and IWL did not correlate with AKD, MKD or PKD.

Conclusion This study demonstrates a reduction in corneal nerves and anterior and mid stromal KD in children with T1DM, but no correlation between corneal nerve and keratocyte cell loss.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) affects over half a million children worldwide.[1 2] Diabetic neuropathy is a major complication in adults with T1DM resulting in neuropathic pain and foot ulceration.[3 4] Although, clinical neuropathy is rare, there are reports of neuropathy in children with T1DM.[5–8] We have previously used corneal confocal microscopy (CCM) to identify significant corneal nerve loss in adults[9] and adolescents[10–12] with T1DM, even those without diabetic retinopathy[13] or microalbuminuria.[14] In adults, corneal nerve loss is associated with painful diabetic neuropathy,[15] has good diagnostic utility for diabetic neuropathy[9 16] and predicts incident diabetic neuropathy.[17 18] The mechanisms underlying corneal nerve loss are complex, however in adults with diabetes, corneal nerve loss has been associated with age, glycated haemoglobin (HbA1c), body mass index (BMI), blood pressure, low-density lipoprotein cholesterol and triglycerides.[19–21] Our previous studies in children have shown no association between corneal nerve loss and the duration of diabetes, HbA1c or lipids.[12 13] This suggests that other factors may be important in the development of early corneal nerve damage.

Corneal keratocytes are fibroblast-like cells within the stroma that maintain the integrity and mechanical stability of the cornea.[22–24] Stromal keratocytes and activated fibroblasts have recently been shown to produce multiple pro-inflammatory and neurotrophic factors which have a dose-dependent effect on neurite outgrowth.[25] We have previously used CCM to quantify alterations in the epithelium, stromal keratocytes and endothelium in adults[26] and adolescents[13] with diabetes. A reduction in anterior mid and posterior keratocyte density has been correlated with corneal nerve loss in adults with type 1 and type 2 diabetes.[23] However, corneal nerve loss was found with preserved keratocyte density in adults without diabetic retinopathy with a reduction in keratocyte density only occurring in patients with diabetic retinopathy.[26] Recently we have shown reduced corneal nerve and keratocyte densities in obese patients with and without diabetes with a correlation between corneal nerve fibre length and anterior keratocyte density and an improvement in both nerve and keratocyte densities and triglycerides and BMI, after bariatric surgery.[27]

In children with T1DM we and others have shown loss of corneal nerves,[11 14] but with normal[13] or increased[11] keratocyte densities. In the present study, we have assessed whether clinical and metabolic alterations are associated with a change in anterior, mid and posterior stromal keratocyte density and corneal nerve fibre morphology in children with T1DM and healthy controls.

MATERIALS AND METHODS

Study subjects

Twenty participants with T1DM (age 14±2 years, diabetes duration 4.08±2.91 years, HbA1c 9.3%±2.1%) and 20 age-matched healthy controls were recruited from outpatient clinics in Sidra Medicine and underwent CCM. Patients with a history of any other cause of neuropathy,

European Journal of Obstetrics & Gynecology and Reproductive Biology 261 (2021) 98–102

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Obstetric violence: Comparing medical student perceptions in India and the UK

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ARTICLE INFO

Article history:
Received 16 February 2021
Accepted 11 April 2021

Keywords:
Obstetric violence
Medical education
Standards of care
Intrapartum care

ABSTRACT

Objective(s): Obstetric Violence refers to professional deficiencies in maternity care, which can occur in both low and high resource settings. Examples include non-dignified care, lack of respect when giving care, discrimination and abandonment of care. The objective of this study was to assess knowledge and attitudes towards obstetric violence in a cohort of medical students in India and the UK.
Study design: An online survey was sent to 240 UK and 280 Indian medical students. This incorporated a video showing a dramatized scenario of obstetric violence. The survey assessed participant's demographics and prior knowledge of obstetric violence. Participants scored their perceptions of eight behaviours in the video on visual analogue scales. Participants were asked to reflect on their own practice and score this. Comparisons of survey responses between UK and Indian participants were made using chi squared/Student's *t*-test.
Results: 62 Indian medical students and 58 UK medical students completed the survey. Indian medical students were significantly more likely to be male ($p < 0.001$). 26 % of UK participants had previously heard the term obstetric violence, compared to 34 % of Indian participants ($p = 0.15$). Both were able to correctly define obstetric violence at similar rates (32 % versus 34 %). Indian medical students were significantly less critical ($p < 0.001$) of all eight scored behaviours in the video of obstetric violence compared to their UK counterparts. UK medical students were significantly less likely to agree that the video had changed their perception on how teams should behave and act in this context ($p < 0.001$).
90 % of UK participants and 38 % of Indian participants had received training in professional behaviours. 14 % of UK participants had seen examples of obstetric violence in clinical practice compared to 49 % of Indian participants.
Conclusions: UK and Indian medical students were able to identify behaviours associated with obstetric violence, although the majority were previously unaware of the term. Indian medical students in this study were less critical of obstetric violence in the video, which may be because of cultural reasons, greater numbers of male students, greater exposure to obstetric violence or less training on professional behaviours. Standardised training to prevent obstetric violence should be part of undergraduate medical training internationally.

Introduction

The expectation of respectful and dignified healthcare provision during pregnancy and childbirth is a fundamental right for every pregnant woman. However, the standard of care provided to women in this context varies across the globe, including in different settings and economic scenarios. There are many examples of non-dignified and sometimes even abusive patterns of care being provided to pregnant women and reporting on the scale of these professional deficiencies in maternity care is increasing [1,2]. These types of behaviour are not restricted to low socio-economic countries having also been found in high income settings [3–5]. There is clear evidence that exposure to a

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https://doi.org/10.1016/j.ejogrb.2021.04.013
0301-2115/

Cumulative Application of Creatinine and Urine Output Staging Optimizes the Kidney Disease: Improving Global Outcomes Definition and Identifies Increased Mortality Risk in Hospitalized Patients With Acute Kidney Injury

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OBJECTIVES: Acute kidney injury is diagnosed according to creatinine and urine output criteria. Traditionally, both are applied, and a severity stage (1–3) is conferred based upon the more severe of the two; information from the other criteria is discarded. Physiologically, however, rising creatinine and oliguria represent two distinct types of renal dysfunction. We hypothesized that using the information from both criteria would more accurately characterize acute kidney injury severity and outcomes.

DESIGN: Prospective cohort study.

SETTING: Multicenter, international collaborative of ICUs.

PATIENTS: Three thousand four hundred twenty-nine children and young adults admitted consecutively to ICUs as part of the Assessment of the Worldwide Acute Kidney Injury, Renal Angina and Epidemiology Study.

MEASUREMENTS AND MAIN RESULTS: The Kidney Disease: Improving Global Outcomes creatinine and urine output acute kidney injury criteria were applied sequentially, and the two stages were summed, generating an Acute Kidney Injury (AKI) Score ranging from 1 to 6. The primary outcome was 28-day mortality; secondary outcomes were time until ICU discharge and nonrecovery from acute kidney injury. Models considered associations with AKI Score, assessing the relationship unadjusted and adjusted for covariates. Twenty-eight–day mortality and nonrecovery from acute kidney injury were modeled using logistic regression. For 28-day ICU discharge, competing risks analysis was performed. Although AKI Scores 1–3 had similar mortality to no Acute Kidney Injury, AKI Scores 4–6 were associated with increased mortality. Relative to No Acute Kidney Injury, AKI Scores 1–6 were less likely to be discharged from the ICU within 28 days. Relative to AKI Score 1, AKI Scores 2–6 were associated with higher risk of nonrecovery. Within the traditional Kidney Disease: Improving Global Outcomes Stage 3 acute kidney injury cohort, when compared with AKI Score 3, AKI Scores 4–6 had increased mortality, AKI Scores 5–6 had prolonged time to ICU discharge, and AKI Score 6 experienced higher nonrecovery rates.

CONCLUSIONS: Cumulative application of the creatinine and urine output criteria characterizes renal excretory and fluid homeostatic dysfunction simultaneously. This Acute Kidney Injury score more comprehensively describes the outcome implications of severe acute kidney injury than traditional staging methods.

KEY WORDS: acute kidney injury; epidemiology; Kidney Disease: Improving Global Outcomes

DOI: 10.1097/CCM.0000000000005073

European Journal of Obstetrics & Gynecology and Reproductive Biology 261 (2021) 205–210

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Dengue in pregnancy: Review article

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ARTICLE INFO

Article history:
Received 6 November 2020
Received in revised form 16 April 2021
Accepted 23 April 2021

Keywords:
Dengue
Pregnancy
Perinatal outcome

ABSTRACT

Dengue is the most common viral mosquito- borne disease. It is a major public health problem, especially in tropical and sub-tropical areas worldwide. According to the World Health Organization (WHO), approximately 40% of the world's population (over 2.5 billion people) live in areas with high risk of contracting dengue infection. Adults of childbearing age and pregnant women are travelling more frequently to tropical areas. Therefore exposing themselves to specific arboviral infections such as dengue, which may impact ongoing and future pregnancies. Clinical manifestations of dengue are wide ranging from asymptomatic to needing intensive care in cases of hemorrhagic dengue fever. The effects of dengue during and on pregnancy are unclear, moreover there is a lack of a cohesive reference to inform women of reproductive age who live in or travel to endemic areas and are at risk of contracting dengue. Here we present review of literature specifically looking at etiology, pathogenesis, clinical manifestations, management of dengue in pregnancy as well as its effect on maternal health and fetal outcomes. There is clear evidence to suggest adverse maternal outcomes in women with symptomatic dengue in low resource countries. A high index of clinical suspicion and early referral to tertiary center will prevent maternal –fetal serious adverse events in endemic areas.

This review will help Clinicians in advising as well as managing women who travel during pregnancy to endemic areas as well as clinicians based in endemic areas who are managing women with dengue in pregnancy.

Introduction

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of World in recent years. According to its incidence and mortality rate, dengue ranked as the second most serious vector-borne disease worldwide, following malaria [1]. Dengue virus (DENV) is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*. These mosquitoes are also vectors of chikungunya, yellow fever and Zika viruses. Dengue is caused by a virus of the Flaviviridae family and there are four distinct, but closely related, serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV-3 and DENV-4).

The incidence of dengue fever (DF) globally has grown dramatically in recent decades. Dengue is endemic in more than 100 countries in Southeast Asia, the Americas, the western Pacific, Africa and the eastern Mediterranean regions, and its incidence has increased 30-fold in the past 50 years [1]. Asia represents around 70% of the global burden of disease. Recent estimates made in 2013 cite that 390 million people have dengue virus infections with 96 million cases annually worldwide, more than three times WHO's 2012 estimate. However, the true disease burden is not well known, especially in India, Indonesia, Brazil, China, and Africa [2]. (Dengue exacts a high economic burden on both governments and individuals. Dengue illness in the Americas costs US$2·1 billion per year on average, excluding vector control, exceeding costs of other viral illnesses. In Southeast Asia, 2·9 million dengue episodes and 5906 deaths were estimated annually, with an annual economic burden of $950 million [3]. Its rapid global emergence is related to demographic and societal changes of the past 50–60 years, including unprecedented population growth, increasing movement of people (and consequently viruses), urbanization and breakdown of public health infrastructure and vector control [4].

The number of cases, including explosive outbreaks, are increasing in the regions above. Disease spread has been reported in Europe in recent years. Local transmission was reported for the first time in France and Croatia in 2010 and imported cases were detected in 3 other European countries [5]. Travelers' play an important role in global dengue epidemiology, carrying viruses from one region to another [6].

A vast majority of cases are asymptomatic or mild and can be self-managed as well as being misdiagnosed as other febrile

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https://doi.org/10.1016/j.ejogrb.2021.04.035
0301-2115/

frontiers in Pediatrics

REVIEW
published: 26 April 2021
doi: 10.3389/fped.2021.635631

Impact of Acute Kidney Injury on Critically Ill Children and Neonates

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Acute kidney injury (AKI) is a clinical syndrome that manifests as an abrupt impairment of kidney function. AKI is common in critically ill pediatric patients admitted to the pediatric intensive care units. AKI is a deleterious complication in critically ill children as it is associated with increased morbidity and mortality. This review provides an overview of the incidence, morbidity, and mortality of AKI in critically ill children in general and specific cohorts such as post-cardiac surgeries, sepsis, critically ill neonates, and post stem cell transplantation.

Keywords: acute kidney injure, volume overload, critically ill children, neonatal intensive care unit, COVID-19

OPEN ACCESS

Edited by:
Danielle Elise Soranno, University of Colorado, United States

Reviewed by:
David Joseph Askenazi, University of Alabama at Birmingham, United States
Tennille N. Webb, University of Alabama at Birmingham, United States

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Specialty section:
This article was submitted to Pediatric Nephrology, a section of the journal Frontiers in Pediatrics

Received: *30 November 2020*
Accepted: *16 March 2021*
Published: *26 April 2021*

Citation:
Leghrouz B and Kaddourah A (2021) Impact of Acute Kidney Injury on Critically Ill Children and Neonates. Front. Pediatr. 9:635631. doi: 10.3389/fped.2021.635631

INTRODUCTION

Acute kidney injury (AKI) refers to a clinical syndrome manifested as abrupt impairment of kidney function. Although the first systematic terminology and classification of AKI were not developed till 2002 by the Acute Dialysis Quality Initiative (ADQI) group, the clinical manifestations and the deleterious impacts of this syndrome were reported in ancient medical scripts. In his Aphorisms written sometime in 400 *BCE,* Hippocrates described oliguric kidney failure complicating a febrile illness and described the generalized edema as "leucophlegmatia," which means an overabundance of white phlegm as an attempt to interpret the cause of the white skin color seen in such edematous patients (1). Throughout history, researchers and clinicians gave this syndrome different terms, such as "ischuria renalis" in the 1800s, acute Bright's disease in the early 1900s, and "war nephritis" during the First World War (2, 3). However, the description of this syndrome was not based on a systematic approach till the "Risk, Injury, Failure, Loss, and End-Stage (RIFLE)" criteria were developed by the ADQI working group in 2004 in adults (4). Since then, the RILFE criteria were modified and refined to include more precise criteria and different terminology. In 2007, "pediatric" RIFLE criteria were adopted for children (5) and the acute kidney injury network (AKIN) working group added further criteria and modified the staging of AKI severity (6). Finally, a comprehensive definition and staging that take into consideration the previously described criteria were introduced by the Kidney Disease Improving Global Outcomes (KDIGO) in 2012 (3) as shown in **Table 1**.

This chapter provides an overview of AKI epidemiology in critically ill pediatric patients and its associated morbidity and mortality. Additionally, we looked into the epidemiology and outcomes of AKI in specific populations of critically ill children.

INCIDENCE OF AKI IN HOSPITALIZED CHILDREN

AKI is common in hospitalized pediatric patients with variably reported incidences ranging from 0.34% up to 5% in different studies (7, 8). It is more common in critically ill children than other hospitalized children, with a reported incidence of 30–50% (9, 10). This high incidence rate sets AKI as the commonest medical complication in critically ill pediatric patients admitted to pediatric intensive care units (ICU) (7).

Available online at www.sciencedirect.com

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journal homepage: www.journals.elsevier.com/resuscitation-plus

Experimental paper

Chest compression by two-thumb encircling method generates higher carotid artery blood flow in swine infant model of cardiac arrest

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Abstract

Objective: Two-Thumb(TT) technique provides superior quality chest compressions compared with Two-Finger(TF) in an instrumented infant manikin. Whether this translates to differences in blood flow, such as carotid arterial blood flow(CABF), has not been evaluated. We hypothesized that TT-CPR generates higher CABF and Coronary Perfusion Pressure(CPP) compared with TF-CPR in a neonatal swine cardiac arrest model.

Methods: Twelve anesthetized & ventilated piglets were randomized after 3 min of untreated VF to receive either TT-CPR or TF-CPR by PALS certified rescuers delivering a compression rate of 100/min. The primary outcome, CABF, was measured using an ultrasound transonic flow probe placed on the left carotid artery. CPP was calculated and end-tidal CO_2($ETCO_2$) was measured during CPR. Data(mean $\pm$ SD) were analyzed and p-value $\leq$0.05 was considered statistically significant.

Results: Carotid artery blood flow (% of baseline) was higher in TT-CPR (66.2 $\pm$ 35.4%) than in the TF-CPR (27.5 $\pm$ 10.6%) group, p = 0.013. Mean CPP (mm Hg) during three minutes of chest compression for TT-CPR was 12.5 $\pm$ 15.8 vs. 6.5 $\pm$ 6.7 in TF-CPR, p = 0.41 and $ETCO_2$ (mm Hg) was 29.0 $\pm$ 7.4 in TT-CPR vs. 20.7 $\pm$ 5.8 in TF-CPR group, p = 0.055.

Conclusion: TT-CPR achieved more than twice the CABF compared with TF-CPR in a piglet cardiac arrest model. Although CPP and $ETCO_2$ were higher during TT-CPR, these parameters did not reach statistical significance. This study provides direct evidence of increased blood flow in infant swine using TT-CPR and further supports that TT chest compression is the preferred method for CPR in infants.

Keywords: Cardiopulmonary resuscitation, Two-thumb CPR, Two-finger CPR, Swine cardiac arrest, Carotid artery blood flow

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http://dx.doi.org/10.1016/j.resplu.2021.100118
Received 22 December 2020; Received in revised form 25 February 2021; Accepted 22 March 2021
Available online xxx

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Article type : Review

Title:

DATASET FOR THE REPORTING OF NEPHRECTOMY SPECIMENS FOR WILMS' TUMOUR TREATED WITH PREOPERATIVE CHEMOTHERAPY: RECOMMENDATIONS FROM THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY RENAL TUMOUR STUDY GROUP

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Short running title:

SIOP-RTSG Wilms' tumour dataset

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/HIS.14394

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Conflict of Interest statement:

The authors declare no conflicts of interest.

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Word count: 3207 words

Abstract: 244 words

Abstract

Datasets for histopathological reporting of many cancer types are developed by the International Collaboration on Cancer Reporting (ICCR) and are used in order to ensure standardised and uniformly accepted reporting as one of the essential requirements for comparison across patient populations in evaluating and validating pathological prognostic and predictive factors. Wilms' tumours are rare and international reporting guidelines have not been published by the ICCR yet. The assessment of Wilms' tumours is different, depending on the treatment approach. The Children's Oncology Group, followed mainly in North America, advocate primary surgery, and the International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG), followed in most countries around the world, use preoperative chemotherapy as a first step, resulting in different subclassifications, staging criteria and histopathological prognostic factors. This dataset is developed for the countries and institutions following the SIOP-RTSG approach, and it contains core (required) and non-core (recommended) elements, based on the results of the previous SIOP-RTSG studies which are incorporated in the latest SIOP-RTSG UMBRELLA 2016 Study protocol. The core elements include clinical information, additional specimen submitted, macroscopic tumour site and appearance, tumour focality, tumour dimensions, macroscopic extent of invasion, block identification key, histological tumour type, histological tumour grade and risk group assessment, microscopic extent of invasion, lymphovascular invasion, resection margin status, regional lymph node status, histologically confirmed distant metastases, and pathological staging (SIOP staging system). The dataset should improve communication for patient care and prognostic determination of the old and new histopathological features.

Key words: dataset, Wilms' tumour, nephroblastoma, structured report, checklist

Jis Thomas*, Tawa Olayemi Olukade, Aliya Naz, Husam Salama, Mai Al-Qubaisi, Hilal Al Rifai and Sawsan Al-Obaidly

The neonatal respiratory morbidity associated with early term caesarean section – an emerging pandemic

https://doi.org/10.1515/jpm-2020-0402
Received August 21, 2020; accepted April 22, 2021;
published online May 7, 2021

Abstract

Objectives: To examine the impact of early term caesarean section (CS) on respiratory morbidity and early neonatal outcomes when elective caesarean section was carried out before 39 completed weeks gestation in our population.

Methods: A one-year population-based retrospective cohort analysis using routinely collected hospital data. Livebirths from women who had elective lower segment cesarean section (ELSCS) for uncomplicated singleton pregnancies at early term (ET) 37+0 to 38+6 weeks were compared to full term (FT)≥39+0 weeks gestation. Exclusion criteria included diabetes, antenatal corticosteroid use, stillbirths, immediate neonatal deaths, normal vaginal deliveries and emergency caesareans sections. The outcomes were combined respiratory morbidity (tachypnea [TTN] and respiratory distress syndrome [RDS]), Apgar <7 at 5 min of age, respiratory support, duration of respiratory support and NICU admission.

Results: Out of a total of 1,466 elective CS with term livebirths, the timing of CS was early term (ET) n=758 (52%) and full term (FT) n=708 (48%). There was a higher incidence of respiratory morbidities and neonatal outcomes in the ET in comparison to FT newborns. In the univariable analysis, significant risks for outcomes were: the need for oxygen support OR 2.42 (95% C.I. 1.38–4.22), respiratory distress syndrome and/or transient tachypnea of newborn (RDSF/TTN) OR 2.44 (95% C.I. 1.33–4.47) and neonatal intensive care unit (NICU) admission OR 1.91 (95% C.I. 1.22–2.98). Only the need for oxygen support remained (OR 1.81, 95% C.I. 1.0–3.26) in the multivariable analysis. These results were observed within the context of a significantly higher proportion of older, multiparous, and higher number of previous caesarean sections in the early term CS group.

Conclusions: There is a significant risk of respiratory morbidities in infants born by elective cesarean section prior to full term gestation. Obstetricians should aim towards reducing the high rate of women with previous multiple cesarean sections including balancing the obstetric indication of early delivery among such women with the evident risk of neonatal respiratory morbidity.

Keywords: early term caesarean section; elective lower segment caesarean section; full term caesarean section; neonatal respiratory morbidity; NICU admission.

Introduction

There is an alarming and consistent global rise in the rates of cesarean sections accounting for almost 21 percent of the total global birth [1, 2]. Despite being a lifesaving procedure in medically indicated cases, the unprecedented rise in caesarean rates is disturbing as is associated with significant short term and long term maternal and neonatal morbidities [3]. Published literature reports that when compared with vaginal birth, elective caesarean birth is associated with a two to almost seven fold increase in the risk of respiratory morbidities (in terms of transient tachypnea of newborn [TTN], respiratory distress syndrome [RDS], persistent pulmonary hypertension and neonatal intensive care unit [NICU] admission) in the near term neonate [4, 5]. There is consistent evidence from prospective large multicenter studies that the magnitude of

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Neuroscience meets nurture: challenges of prematurity and the critical role of family-centred and developmental care as a key part of the neuroprotection care bundle

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Received 3 October 2020
Revised 1 April 2021
Accepted 13 April 2021
Published Online First 10 May 2021

To cite: Soni R, Tscherning Wel-Wel C, Robertson NJ. *Arch Dis Child Fetal Neonatal Ed* 2022;**107**:F242–F249.

ABSTRACT

Advances in neonatal–perinatal medicine have resulted in increased survival at lower gestations. Although the incidence of germinal matrix haemorrhage-intraventricular haemorrhage and cystic periventricular leucomalacia is reducing, a new phenotype of preterm brain injury has emerged consisting of a combination of destructive and dysmaturational effects. Consequently, severe neurological disability is reported at a lower rate than previously, but the overall morbidity associated with premature birth continues to present a large global burden and contributes significantly to increased financial costs to health systems and families. In this review, we examine the developmental milestones of fetal brain development and how preterm birth can disrupt this trajectory. We review common morbidities associated with premature birth today. Although drug-based and cell-based neuroprotective therapies for the preterm brain are under intense study, we outline basic, sustainable and effective non-medical, family-centred and developmental care strategies which have the potential to improve neurodevelopmental outcomes for this population and need to be considered part of the future neuroprotection care bundle.

INTRODUCTION

Despite advances in medical knowledge and techniques, prematurity and its sequelae continue to present a significant global challenge. Here we review the burden of prematurity, preterm brain development and injury, commonly associated neurodevelopmental morbidities, and focus on the evidence in support of developmental and family-centred care practices to enhance preterm brain development and neurodevelopmental outcomes.

PRETERM BIRTH AND SURVIVAL

Nearly 15 million babies are born preterm every year (WHO definition <37 completed weeks' gestation). The 10 countries with the highest rates of prematurity (mainly sub-Saharan Africa and South Asia) account for 60% of all preterm births worldwide. Although rates are highest on average for low-income countries (11.8%), followed by lower middle-income countries (11.3%) and lowest for upper middle-income and high-income countries (9.4% and 9.3%), relatively high preterm birth rates are seen in many individual high-income countries where they contribute substantially to neonatal mortality and morbidity[1] (figure 1).

For infants born at 22+0–25+6 weeks in the UK, survival to discharge has continued to improve over the decades from 40% in 1995, to 66% in 2014.[2] Several international studies have similarly indicated an incremental improvement in survival for the most premature babies over the last one to two decades.[3–5] The largest changes in outcome are at the lowest gestational ages (GAs). At 22 weeks' GA, recent cohort studies from the USA, UK, Sweden and Germany indicate that approximately 30% of live-born babies who receive active treatment survive to discharge.[5]

PRETERM BRAIN DEVELOPMENT

The human central nervous system (CNS) develops with a pattern similar to all mammals, beginning as a simple neural tube and gradually developing features through hugely complex and strictly regulated processes. The growth rate in the human CNS is higher than any other organ from the 4th postconceptional week (PCW) to the 3rd postnatal year.[6] The association areas of the cerebral neocortex develop more slowly, and the gestation period and childhood are much longer compared with other mammals. This period of dependency and the prolonged developmental course allows, more than any other species, the environment to shape the development of cognition, social and emotional factors. In addition, the developing human brain has larger proliferative areas and diverse subtypes of neural and progenitor cells that lead to increased brain expansion, especially of the neocortex.[6]

Fetal development is the most important period for neurogenetic events, with regard to number of neurons (proliferation), their molecular diversity (molecular specification), allocation in the cortex (migration), phenotype differentiation (dendritogenesis), and is a time for the growth of axons (axonogenesis) and functional contacts (synaptogenesis).[7] The subplate zone of the telencephalon plays a pivotal role in the development of the human brain and is the most prominent transient compartment of the fetal cortex. It is the major site of synaptogenesis and neuron maturation and is a site for increasing the number of associative and thalamocortical pathways in the human neocortex.[7] Most developmental processes extend into the postnatal period, especially processes associated

Pediatric Radiology
https://doi.org/10.1007/s00247-021-05034-7

ESPR

Practical approach for the diagnosis of biliary atresia on imaging, part 2: magnetic resonance cholecystopancreatography, hepatobiliary scintigraphy, percutaneous cholecysto-cholangiography, endoscopic retrograde cholangiopancreatography, percutaneous liver biopsy, risk scores and decisional flowchart

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Received: 10 October 2020 / Revised: 23 November 2020 / Accepted: 21 February 2021

Abstract

We aim to present a practical approach to imaging in suspected biliary atresia, an inflammatory cholangiopathy of infancy resulting in progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts. Left untreated or with failure of the Kasai procedure, biliary atresia progresses to biliary cirrhosis, end-stage liver failure and death within the first years of life. Differentiating biliary atresia from other nonsurgical causes of neonatal cholestasis is difficult as there is no single method for diagnosing biliary atresia and clinical, laboratory and imaging features of this disease overlap with those of other causes of neonatal cholestasis. In this second part, we discuss the roles of magnetic resonance (MR) cholecystopancreatography, hepatobiliary scintigraphy, percutaneous biopsy and percutaneous cholecysto-cholangiography. Among imaging techniques, ultrasound (US) signs have a high specificity, although a normal US examination does not rule out biliary atresia. Other imaging techniques with direct opacification of the biliary tree combined with percutaneous liver biopsy have roles in equivocal cases. MR cholecystopancreatography and hepatobiliary scintigraphy are not useful for the diagnosis of biliary atresia. We propose a decisional flowchart for biliary atresia diagnosis based on US signs, including elastography, percutaneous cholecysto-cholangiography or endoscopic retrograde cholangiopancreatography and liver biopsy.

Keywords Bile duct · Biliary atresia · Endoscopic retrograde cholangiopancreatography · Hepatobiliary scintigraphy · Infants · Liver · Magnetic resonance imaging · Percutaneous cholecysto-cholangiography · Percutaneous liver biopsy

Introduction

Biliary atresia is an important cause of obstructive jaundice in infants causing progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts and resulting in biliary cirrhosis in the absence of early surgery. Jaundice with pale stools and dark urine is present within the first days or weeks of life. The prevalence of biliary atresia ranges from 1 in 5,000 to 1 in 20,000 worldwide depending on the geographic area, with the highest prevalence in Taiwan [1–3]. The aetiology of biliary atresia is unknown and different causes have been proposed including viral infections, genetic factors or toxins [4].

There are two forms of biliary atresia: the non-syndromic form, which accounts for about 80% of cases, and the syndromic form, also called biliary atresia splenic malformation syndrome, which accounts for about 20% of cases [3]. The syndromic form is associated with polysplenia (asplenia), intestinal malrotation, preduodenal portal vein, interrupted

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Published online: 11 May 2021

Journal of Ultrasound
https://doi.org/10.1007/s40477-021-00590-y

Pulmonary hypertension in late onset neonatal sepsis using functional echocardiography: a prospective study

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Received: 18 January 2021 / Accepted: 27 April 2021

Abstract

Purpose Pulmonary hypertension (PH) in the newborn period is associated with significant morbidity and mortality. Sepsis has been identified as an independent risk factor for PH in newborns. Data on the proportion and severity of PH in association with neonatal sepsis are scarce. This study was aimed to measure the pulmonary artery systolic pressure (PASP) in neonates with late onset sepsis (LOS) and to estimate the proportion of PH in neonatal sepsis using functional echocardiography (FnECHO).

Methods This prospective observational study was conducted at a tertiary neonatal intensive care unit (NICU). All neonates admitted in the NICU with suspected LOS underwent FnECHO within 6 hours of onset of clinical signs and PASP was recorded. Pulmonary hypertension was defined as PASP of > 35 mmHg. PASP of neonates with positive culture results (proven LOS) was compared with that of gestational age-matched stable controls without sepsis.

Results Thirty three neonates with proven LOS were analysed (study group). Sixteen neonates (49%) in the study group had PH. Mean PASP of the study group was significantly higher than that of the control group (35.3 ± 10.13 mmHg and 12.58 ± 3.92 mmHg, respectively; $P < 0.0001$). None of the neonates in the control group had PH.

Conclusion Pulmonary artery pressure was higher in neonates with late onset neonatal sepsis as compared to that of stable babies without sepsis. Pulmonary hypertension was seen in nearly half of term as well as preterm neonates with late onset sepsis.

Keywords Functional echocardiography · Neonatal sepsis · Pulmonary hypertension

Introduction

Persistent elevation of pulmonary vascular resistance (PVR) after birth delays normal transition, leading to persistent pulmonary hypertension of the newborn (PPHN) [1]. Pulmonary hypertension (PH) in the neonatal period may be primary or secondary to conditions such as meconium aspiration syndrome, respiratory distress syndrome (RDS), congenital diaphragmatic hernia, pulmonary hypoplasia, pneumonia, sepsis, perinatal asphyxia or cardiac disorders [2]. Persistent pulmonary hypertension of the newborn is associated with substantial morbidity, mortality, and neurodevelopmental delay in developing as well as developed countries [3, 4].

Sepsis has been identified and reported as an independent cause of PH in newborns in animal and human studies [5, 6]. Sepsis complicated by PH can lead to severe hypoxemia and worsen the outcome and course of affected patients. There are several case reports of neonatal sepsis in which development of PH has led to significant morbidity as well as mortality [7–9]. On the other hand, early detection of PH in neonates with sepsis has led to specific interventions directed at management of PH with a favorable outcome [10, 11].

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Published online: 15 May 2021

JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2021.1926327

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Can virus–virus interactions impact the dynamics of the covid-19 pandemic?

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Communicated by Ramaswamy H. Sarma

ABSTRACT

Viral respiratory infections can occur in pandemics and can spread rapidly within communities resulting in health concerns globally. Several respiratory viruses co-circulate at one specific time. However, interface between different viruses has not been clearly established. This interaction is crucial to delineate, especially during pandemics, including the one relate to covid-19. This commentary will provide a brief description of how respiratory viruses interact and the outcome of this interaction on a pandemic.

ARTICLE HISTORY
Received 26 March 2021
Accepted 2 May 2021

KEYWORDS
Covid-19; virus interaction

1. Introduction

Viral respiratory infections are very common and enact health concerns globally (Wylie et al., 2017). Recently, the world population has been preoccupied with the covid-19 pandemic that has claimed many lives (Hendaus, 2020; Hendaus & Jomha, 2020a, 2020b). Coronaviruses (CoVs) are enveloped, positive single-stranded RNA of the family *Coronaviridae* viruses and are known for their typical spherical morphology with core case and glycoprotein. CoVs consist of the following 4 genera: α, β, γ and δ coronavirus genus. The β coronavirus group includes the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), and Covid-19 (Hendaus, 2020; Hendaus & Jomha, 2020a, 2020b, 2021).

The nature of acquired immune responses after natural infection of COVID-19 is not very clear yet. Studies have shown that detectable antibody levels against COVID-19 infection decrease in only few months after infection (Saad-Roy et al., 2020).

This dreaded COVID-19 situation has triggered international scientists to develop new approaches to combat the pandemic. Vaccines and anti-virial agents such as remdesivir have emerged as potential candidates to fight the virus (Hendaus, 2020, Hendaus & Jomha 2021). Recently, non-structural protein 15 (Nsp15) has appeared as a promising candidate that can target specific vital components of the viral genome, and hence infection (Sharma et al., 2021). Another candidate target is the main protease (Mpro) because of its vital role in managing of the polyproteins which are required for viral replication. A study published by Bhardwaj et al. (2020) has shown that bioactive molecules found in tea plant can act as an inhibitor for the Mpro of COVID-19. In a different study, Bhardwaj et al. (2021) concluded that acridinedione showed a substantial interaction with Mpro of COVID-19.

Health precautions, including social distancing, proper hand washing and masking during the covid-19 pandemic, might have highly contributed in the decreased transmission of common seasonal viruses such as influenza (Chu et al., 2020). However, interference among viruses might play a role in denying those common seasonal viruses to emerge (Zheng et al., 2017).

Viral interference has been interpreted as an occurrence where one virus can alter the immunity of the host, leading to transient protection against infection with another virus or viruses (Schultz-Cherry, 2015). This concept has been dated back to the year 1929 when McKinney (1929) studied mosaic diseases in the Canary Islands, suggesting that animal and plant viruses interfere. The same concept was also described in 1945, when Delbruck (1945) explained the mutual exclusion and the depressor effects. The investigators concluded that when a single bacterium is infected by many viruses, only one virus survive. The function of innate immunity in viral interference has also been demonstrated in further old manuscripts (Dianzani, 1975; Isaacs & Burke, 1959). In this context, further studies have proved the unidirectional growth inhibition and enhanced viral replication (Goto et al., 2016; Shinjoh et al., 2000). Moreover, in the recent years, clinical data as well as contemporary mathematical simulations have shown that viral interference is real and can disrupt seasonal infections, even pandemics (Nickbakhsh et al., 2019; Wu et al., 2020).

Covid-19 illness is considered as relatively novice and certain details regarding its infection are missing. The development of efficient therapeutics depend on the advances of cellular and molecular means of COVID-19 infections. This development should focus on the importance of

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JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2021.1927847

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

COVID-19 vector-based vaccine causing thrombosis

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Communicated by Ramaswamy H. Sarma

ABSTRACT

The number of people affected by COVID-19 is staggering and countries are rushing and competing to vaccinate their populations. However, there has been a concern about the association between COVID-19 vector-based vaccines and thrombosis. The proposed mechanism by which a COVID-19 vector-based vaccine can cause thrombosis is called vaccine-induced immune thrombotic thrombocytopenia (VITT). This commentary will provide an easy sketch of VITT as well as presentation of thrombosis after COVID-19 vaccines and proposed treatment.

ARTICLE HISTORY
Received 25 April 2021
Accepted 1 May 2021

KEYWORDS
COVID-19; thrombosis; vaccines

1. Introduction

Coronavirus disease 2019 (COVID-19) has been linked to significant morbidity and mortality (Hendaus 2020; Hendaus & Jomha 2020a, 2021b), and the ultimate objective of vaccine development is to provide efficacious protection to humans against COVID-19 (Hodgson et al., 2021).

The world health organization (WHO) has published on its dynamic dashboard that as of April 19, 2021, 142,238,073 individuals have been infected with COVID-19 (including 3,032,124 deaths), and 843,158,196 have received the vaccine so far (WHO, 2021).

Recently, there has been a concern about the association between a COVID-19 vector-based vaccine and thrombosis. This concern has led to a halt in the use of vaccines made by Johnson & Johnson (J&J) and the Oxford–AstraZeneca vaccine by some authorities (COVID vaccines 2021). Current literature (Greinacher et al., 2021; Muir et al., 2021; Schultz et al., 2021) has suggested that this type of thrombosis resembles a phenomenon called heparin induced thrombocytopenia (HIT), a condition that can occur after the use of the anti-coagulant heparin (despite the fact that the vaccine recipients did not receive heparin). HIT is a severe reaction to heparin, where the latter forms a complex with platelet factor 4 (PF4), leading to anti-PF4/heparin IgG antibodies. These antibodies can activate platelets, resulting in a prothrombotic syndrome (Greinacher 2015). The laboratory diagnosis of HIT is confirmed with anti-PF4/heparin antibodies (Cuker et al., 2012).

However, until now, it is not known which component of the vaccine is causing this type of vaccine-induced immune thrombotic thrombocytopenia, although a study conducted in 2013 by Jaax et al. (2013) concluded that complex formation with nucleic acids and aptamers changes the antigenic properties of platelet factor 4.

2. Components of vector COVID-19 vaccines

The most common vector vaccines currently available are Johnson & Johnson (J&J) and the Oxford–AstraZeneca vaccine.

COVID-19 viral vector-based vaccines use a modified virus (the vector) to transport spike proteins found on the surface of the virus, into human cells. These materials eventually instruct human cells to produce large amounts of antigen, which then result in the induction of an immune response (CDC, 2021).

The J&J COVID-19 vaccine comprise of a recombinant, replication-incompetent adenovirus type 26 expressing the SARS-CoV-2 spike protein, trisodium citrate dihydrate, ethanol, citric acid monohydrate, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate-80, and sodium chloride (Emergency Use Authorization 2021).

On the other hand, the comprise of a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS CoV-2 Spike (S) glycoprotein, L-Histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, L-Histidine, ethanol, sucrose, sodium chloride, and disodium edetate dihydrate (Information for Healthcare Professionals on COVID-19 2021).

3. Studies

Several studies have investigated the thrombotic thrombocytopenia phenomenon after COVID-19 vector vaccination.

Greinacher et al (Greinacher et al., 2021) evaluated the clinical and laboratory features of 11 patients [median age of 36 years (range, 22–49)] in Austria and Germany in who developed thrombosis or thrombocytopenia following vaccination with ChAdOx1 nCov-19 (AstraZeneca). Investigators utilized a standard enzyme-linked immunosorbent assay to identify platelet factor 4 (PF4)–heparin antibodies and a

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Received: 18 January 2021 | Revised: 25 March 2021 | Accepted: 24 April 2021

DOI: 10.1002/ajmg.a.62254

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

De novo variants in *TCF7L2* are associated with a syndromic neurodevelopmental disorder

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Abstract

TCF7L2 encodes transcription factor 7-like 2 (OMIM 602228), a key mediator of the evolutionary conserved canonical Wnt signaling pathway. Although several

Funding information
Duke University Health System; European Union and Région Normandie; National Human Genome Research Institute grant, Grant/Award Number: HG009141; National Human Genome Research Institute, the National Eye Institute, and the National Heart, Lung and Blood Institute, Grant/Award Number: UM1 HG008900; National Institute of Mental Health (Translational Post-doctoral Training in Neurodevelopment), Grant/Award Number: T32MH112510; NINDS, Grant/Award Number: NS035129; PROGETTO GENE, (GENE - Genomic analysis Evaluation NEtwork) founded by PROGETTI DI INNOVAZIONE IN AMBITO SANITARIO E SOCIO SANITARIO (BANDO EX DECRETO N. 2713 DEL 28/02/2018); Qatar National Research Fund, Grant/Award Number: NPRP 5-175-3-051

large-scale sequencing studies have implicated *TCF7L2* in intellectual disability and autism, both the genetic mechanism and clinical phenotype have remained incompletely characterized. We present here a comprehensive genetic and phenotypic description of 11 individuals who have been identified to carry de novo variants in *TCF7L2*, both truncating and missense. Missense variation is clustered in or near a high mobility group box domain, involving this region in these variants' pathogenicity. All affected individuals present with developmental delays in childhood, but most ultimately achieved normal intelligence or had only mild intellectual disability. Myopia was present in approximately half of the individuals, and some individuals also possessed dysmorphic craniofacial features, orthopedic abnormalities, or neuropsychiatric comorbidities including autism and attention-deficit/hyperactivity disorder (ADHD). We thus present an initial clinical and genotypic spectrum associated with variation in *TCF7L2*, which will be important in informing both medical management and future research.

KEYWORDS
autism, intellectual disability, myopia, neurodevelopmental disorder, *TCF7L2*

1 | INTRODUCTION

TCF7L2 encodes a high mobility group (HMG) box-containing transcription factor and is located on chromosome 10q25.2-q25.3. Although it was initially identified and referred to as *TCF4* (Castrop et al., 1992; Clevers, 2006), it should not be confused with the currently designated *TCF4* (ITF2/SEF2-1B/SEF2/E2-2, MIM 602272), which is located on Chromosome 18 and associated with Pitt–Hopkins syndrome. *TCF7L2* mediates canonical Wnt signaling. Signaling by secreted Wnt proteins through this pathway leads to release of the protein beta-catenin (CTNNB1) from a repressive degradation complex in the cytoplasm, allowing it to accumulate and translocate to the nucleus, where it acts with DNA-binding factors including TCF7L2 to turn on Wnt-responsive target genes. TCF7L2 thus acts with beta-catenin as an on/off switch for transcriptional regulation. Through mostly genome-wide association studies, *TCF7L2* has been involved in a variety of human disease, including Type 2 diabetes mellitus, colon cancer, and schizophrenia (Alkelai et al., 2012; Folsom et al., 2008; Grant et al., 2006). *TCF7L2* is also known to be critical in central nervous system development (Chodelkova et al., 2018; Lee et al., 2017; Nagalski et al., 2013). It has been directly involved in processes as diverse as neurogenesis and thalamic development to mediating the effects of neuropsychiatric pharmacological agents including lithium and nicotine (Chodelkova et al., 2018; Duncan et al., 2019; Lee et al., 2017; Misztal et al., 2017; Nagalski et al., 2013). Large-scale sequencing studies have also identified a handful of isolated patients with de novo variants in *TCF7L2* in association with neurodevelopmental disorders, but clinical details are lacking (Iossifov et al., 2014; De Rubeis et al., 2014; Lelieveld et al., 2016; Jeremy F McRae et al., 2017 (Deciphering Developmental Disorders [DDD] Study), 2017; Guo et al., 2018; Liu et al., 2018; Satterstrom et al., 2020; Wang et al., 2020).

TCF7L2 encodes multiple alternatively spliced transcripts, and alternative splicing has been demonstrated to play an important role in the function and specificity of the transcriptional repertoire of TCF7L2 in a variety of tissues and contexts, including the brain (Nagalski et al., 2013; Prokunina-Olsson et al., 2009; Weise et al., 2009). *TCF7L2* is significantly intolerant to loss-of-function (LOF) variation, with significantly fewer observed LOF variants as compared to predicted, as indicated in the probability of being loss-of-function intolerant (pLI) score of 0.99–1 reported in the gnomAD and ExAC databases. There is also a region of missense constraint encompassing the HMG box domain indicating additional intolerance to missense variation (Samocha et al., 2017).

We describe here the genotypic and clinical phenotypic spectrum of 11 individuals with de novo, heterozygous variants in *TCF7L2* presenting with a neurodevelopmental disorder.

2 | MATERIALS AND METHODS

Patients were ascertained from GeneMatcher through the Matchmaker Exchange Network between May 2019 and December 2020 (Philippakis et al., 2015; Sobreira et al., 2015). *TCF7L2* variants were detected on exome sequencing in 10 individuals, and on a trio autism/intellectual disability gene panel at a commercial lab in one individual. No additional plausible candidate gene variants were identified (Supplementary Table 1). One additional patient was excluded from the cohort because the phenotype was confounded by perinatal hypoxic–ischemic injury; the data for this individual (S1) are included in Supplementary Table 1. Institutional review board approval was obtained.

JAMA Pediatrics | Original Investigation

Delivery Room Interventions for Hypothermia in Preterm Neonates
A Systematic Review and Network Meta-analysis

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IMPORTANCE Prevention of hypothermia in the delivery room is a cost-effective, high-impact intervention to reduce neonatal mortality, especially in preterm neonates. Several interventions for preventing hypothermia in the delivery room exist, of which the most beneficial is currently unknown.

OBJECTIVE To identify the delivery room thermal care intervention that can best reduce neonatal hypothermia and improve clinical outcomes for preterm neonates born at 36 weeks' gestation or less.

DATA SOURCES MEDLINE, the Cochrane Central Register of Controlled Trials, Embase, and CINAHL databases were searched from inception to November 5, 2020.

STUDY SELECTION Randomized and quasi-randomized clinical trials of thermal care interventions in the delivery room for preterm neonates were included. Peer-reviewed abstracts and studies published in non–English language were also included.

DATA EXTRACTION AND SYNTHESIS Data from the included trials were extracted in duplicate using a structured proforma. A network meta-analysis with bayesian random-effects model was used for data synthesis.

MAIN OUTCOMES AND MEASURES Primary outcomes were core body temperature and incidence of moderate to severe hypothermia on admission or within the first 2 hours of life. Secondary outcomes were incidence of hyperthermia, major brain injury, and mortality before discharge. The 9 thermal interventions evaluated were (1) plastic bag or plastic wrap covering the torso and limbs with the head uncovered or covered with a cloth cap; (2) plastic cap covering the head; (3) skin-to-skin contact; (4) thermal mattress; (5) plastic bag or plastic wrap with a plastic cap; (6) plastic bag or plastic wrap along with use of a thermal mattress; (7) plastic bag or plastic wrap along with heated humidified gas for resuscitation or for initiating respiratory support in the delivery room; (8) plastic bag or plastic wrap along with an incubator for transporting from the delivery room; and (9) routine care, including drying and covering the body with warm blankets, with or without a cloth cap.

RESULTS Of the 6154 titles and abstracts screened, 34 studies that enrolled 3688 neonates were analyzed. Compared with routine care alone, plastic bag or wrap with a thermal mattress (mean difference [MD], 0.98 °C; 95% credible interval [CrI], 0.60-1.36 °C), plastic cap (MD, 0.83 °C; 95% CrI, 0.28-1.38 °C), plastic bag or wrap with heated humidified respiratory gas (MD, 0.76 °C; 95% CrI, 0.38-1.15 °C), plastic bag or wrap with a plastic cap (MD, 0.62 °C; 95% CrI, 0.37-0.88 °C), thermal mattress (MD, 0.62 °C; 95% CrI, 0.33-0.93 °C), and plastic bag or wrap (MD, 0.56 °C; 95% CrI, 0.44-0.69 °C) were associated with greater core body temperature. Certainty of evidence was moderate for 5 interventions and low for plastic bag or wrap with a thermal mattress. When compared with routine care alone, a plastic bag or wrap with heated humidified respiratory gas was associated with less risk of major brain injury (risk ratio, 0.23; 95% CrI, 0.03-0.67; moderate certainty of evidence) and a plastic bag or wrap with a plastic cap was associated with decreased risk of mortality (risk ratio, 0.19; 95% CrI, 0.02-0.66; low certainty of evidence).

CONCLUSIONS AND RELEVANCE Results of this study indicate that most thermal care interventions in the delivery room for preterm neonates were associated with improved core body temperature (with moderate certainty of evidence). Specifically, use of a plastic bag or wrap with a plastic cap or with heated humidified gas was associated with lower risk of major brain injury and mortality (with low to moderate certainty of evidence).

JAMA Pediatr. 2021;175(9):e210775. doi:10.1001/jamapediatrics.2021.0775
Published online May 24, 2021.

Supplemental content

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Journal Pre-proof

Low-level amikacin resistance induced by AAC(6′)-Ib and AAC(6′)-Ib-cr in ESBL-producing Enterobacterales isolated from urine in children

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PII: S2213-7165(21)00126-0
DOI: https://doi.org/10.1016/j.jgar.2021.04.026
Reference: JGAR 1577

To appear in: *Journal of Global Antimicrobial Resistance*

Received date: 10 November 2020
Revised date: 13 April 2021
Accepted date: 22 April 2021

Please cite this article as: Hassan Al Mana , Sathyavathi Sundararaju , Nahla O. Eltai , Sara H. Al-Hadidi , Mohammad Rubayet Hasan , Patrick Tang , Andrés Pérez-López , Low-level amikacin resistance induced by AAC(6′)-Ib and AAC(6′)-Ib-cr in ESBL-producing Enterobacterales isolated from urine in children, *Journal of Global Antimicrobial Resistance* (2021), doi: https://doi.org/10.1016/j.jgar.2021.04.026

Highlights

1. There is an increasing trend towards using amikacin monotherapy to treat urinary tract infections in children caused by ESBL producers given the low resistance rates to this agent among ESBL-producing Enterobacterales worldwide.

2. The incidence of ESBL-producing Enterobacterales co-producing AAC(6')-Ib-cr is increasing worldwide driven by the global dominance of CTX-M-15 enzyme.

3. We found that ESBL-producing amikacin-susceptible isolates harbouring aac(6')-Ib and aac(6')-Ib-cr genes often had increased MICs for amikacin, which theoretically could hamper to achieve Cmax/MIC ratio >8.

4. Well-designed clinical trials considering PK-PD parameters are needed to determine whether amikacin is a reliable carbapenem-sparing option to treat urinary tract infections in children caused by ESBL producers with MIC of 4-16 mg/L due to the production of AAC(6')-Ib and its cr variant.

Biomedicine & Pharmacotherapy 140 (2021) 111736

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Original article

Bifidobacterium reduction is associated with high blood pressure in children with type 1 diabetes mellitus

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ARTICLE INFO

Keywords:
Microbiota
Pediatric
Diabetes
Hypertension
Blood pressure
Dysbiosis

ABSTRACT

Children with Type 1 diabetes mellitus (T1DM) have an elevated risk of abnormal blood pressure (BP) measurements and patterns. Both hypertension and T1DM are well-known risk factors for cardiovascular disease and kidney failure. The human microbiome has been linked to both diabetes and hypertension, but the relationship between the gut microbiome and BP in children with T1DM is not well-understood. In this cross-sectional study, we examined the relationship between resting office BP and gut microbiota composition, diversity, and richness in children with T1DM and healthy controls. We recruited 29 pediatric subjects and divided them into three groups: healthy controls (HC, n = 5), T1DM with normal BP (T1DM-Normo, n = 17), and T1DM with elevated BP (T1DM-HBP, n = 7). We measured the BP, dietary and clinical parameters for each subject. We collected fecal samples to perform the 16s rDNA sequencing and to measure the short-chain fatty acids (SCFAs) level. The microbiome downstream analysis included the relative abundance of microbiota, alpha and beta diversity, microbial markers using Linear Discriminant effect size analysis (LEfSe), potential gut microbial metabolic pathways using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) and metabolic pathways validation using Statistical Inference of Associations between Microbial Communities And host phenotype (SIAMCAT) machine learning toolbox. Our study results showed that T1DM-HBP group had distinct gut microbial composition (at multiple taxonomic levels) and reduced diversity (richness and abundance) compared with T1DM-Normo and HC groups. Children with T1DM-HBP showed a significant reduction of *Bifidobacterium* levels (especially *B. adolescentis*, *B. bifidum*, and *B. longum*) compared to the T1DM-Normo group. We also observed unique gut-microbial metabolic pathways, such as elevated lipopolysaccharide synthesis and glutathione metabolism in children with T1DM-HBP compared to T1DM-Normo children. We can conclude that the reduction in the abundance of genus *Bifidobacterium* could play a significant role in elevating the BP in pediatric T1DM subjects. More studies are needed to corroborate our findings and further explore the potential contributing mechanisms we describe.

Abbreviations: BMI, Body mass index; BP, Blood pressure; CSII, continuous subcutaneous insulin infusion; DBP, Diastolic blood pressure; DBPI, Diastolic blood pressure index; GPR41, G-protein coupled receptor 41; GPR43, G-protein coupled receptor 43; GPR109a, G-protein coupled receptor 109a; GSH, Glutathione; g_UC, genus_unclassified; g/day, gram/day; HbA1c, Glycated Hemoglobin A1c; HC, Healthy control; HDL, High-density lipoprotein; HTN, Hypertension; iNOS, Inducible nitric oxide; IQR, Interquartile range; IR, Inflammatory response; Kcal/day, Kilocalorie/day; LEfSe, Linear discriminant analysis effect size; LDL, Low-density lipoprotein; LPS, Lipopolysaccharide; mg/day, milligram/day; μg/day, microgram/day; mmHg, millimeter mercury; MUFA, monounsaturated fatty acid; NO, Nitric oxide; Olfr78, Olfactory receptor 78; OTUs, Operational taxonomic units; OW/OB, Overweight/Obese; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; PUFA, Polyunsaturated fatty acid; QIIME, Quantitative Insights Into Microbial Ecology; SBP, Systolic blood pressure; SBPI, Systolic blood pressure index; SEM, Standard error of the mean; SCFAs, Short-chain fatty acids; SIAMCAT, Statistical Inference of Associations between Microbial Communities And host phenoType; T1DM, Type 1 diabetes mellitus; T1DM-HBP, Type 1 diabetes mellitus-high blood pressure; T1DM-Normo, Type 1 diabetes mellitus-normal blood pressure; T2DM, Type 2 diabetes mellitus; TG, Triglyceride.

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https://doi.org/10.1016/j.biopha.2021.111736
Received 11 March 2021; Received in revised form 4 May 2021; Accepted 11 May 2021
Available online 23 May 2021

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01053-z

ORIGINAL ARTICLE

Consensus Middle East and North Africa Registry on Inborn Errors of Immunity

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Received: 23 March 2021 / Accepted: 26 April 2021

Abstract

Background Inborn errors of immunity (IEIs) are a heterogeneous group of genetic defects of immunity, which cause high rates of morbidity and mortality mainly among children due to infectious and non-infectious complications. The IEI burden has been critically underestimated in countries from middle- and low-income regions and the majority of patients with IEI in these regions lack a molecular diagnosis.

Methods We analyzed the clinical, immunologic, and genetic data of IEI patients from 22 countries in the Middle East and North Africa (MENA) region. The data was collected from national registries and diverse databases such as the Asian Pacific Society for Immunodeficiencies (APSID) registry, African Society for Immunodeficiencies (ASID) registry, Jeffrey Modell Foundation (JMF) registry, J Project centers, and International Consortium on Immune Deficiency (ICID) centers.

Results We identified 17,120 patients with IEI, among which females represented 39.4%. Parental consanguinity was present in 60.5% of cases and 27.3% of the patients were from families with a confirmed previous family history of IEI. The median age of patients at the onset of disease was 36 months and the median delay in diagnosis was 41 months. The rate of registered IEI patients ranges between 0.02 and 7.58 per 100,000 population, and the lowest rates were in countries with the highest rates of disability-adjusted life years (DALY) and death rates for children. Predominantly antibody deficiencies were the most frequent IEI entities diagnosed in 41.2% of the cohort. Among 5871 patients genetically evaluated, the diagnostic yield was 83% with the majority (65.2%) having autosomal recessive defects. The mortality rate was the highest in patients with non-syndromic combined immunodeficiency (51.7%, median age: 3.5 years) and particularly in patients with mutations in specific genes associated with this phenotype (*RFXANK*, *RAG1*, and *IL2RG*).

Conclusions This comprehensive registry highlights the importance of a detailed investigation of IEI patients in the MENA region. The high yield of genetic diagnosis of IEI in this region has important implications for prevention, prognosis, treatment, and resource allocation.

Keywords Inborn errors of immunity · Primary immunodeficiency · Epidemiology · Burden of disease · Molecular diagnosis

Introduction

Inborn errors of immunity (IEIs), formerly known as primary immunodeficiency disorders (PIDs), are a heterogeneous group of diseases that affect the development and/or function of the immune system [1]. More than

Article Summary Line This study presents the most extensive registry of patients from the MENA region with a strikingly high yield of molecular diagnosis with vital implications for the targeted treatment and management of these diseases.

Extended author information available on the last page of the article

Published online: 29 May 2021

Received: 17 January 2021 | Revised: 28 April 2021 | Accepted: 7 May 2021

DOI: 10.1002/pbc.29143

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

ONCOLOGY: RESEARCH ARTICLE

Comparative analysis of the clinical characteristics and outcomes of patients with Wilms tumor in the United Kingdom and Japan

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Selected preliminary results were displayed on a poster at the 50th congress of the International Society of Paediatric Oncology and the 61st Annual Meeting of the Japanese Society of Pediatric Hematology/Oncology. The abstracts of these communications were published in Pediatric Blood and Cancer, Volume 65, Issue S2 (https://doi.org/10.1002/pbc.27455), and Volume 66, Issue S5 (https://doi.org/10.1002/pbc.28049).

Abstract

Background: Wilms tumor (WT) demonstrates epidemiological differences by world region and ethnicity. To enhance understanding of these differences, we retrospectively analyzed clinical trial data sets from the UK and Japan over a 20-year period.

Procedure: We used data from three consecutive clinical trials in the UK and a single study in Japan that enrolled patients diagnosed during 1996-2015, to compare clinical characteristics and outcomes between countries.

Results: During 1996-2015, 1395 patients in the UK and 537 in Japan were included. Japanese patients have a significantly younger median age at diagnosis than those in the UK (28 months vs 39 months). The proportion of patients with stage IV, large tumors, and anaplastic histology appears to be higher in the UK than in Japan (18% vs 11%, 62% vs 49%, 8% vs 3%, respectively). During 2005-2015, 77 hospitals treated WT in Japan compared with only 20 hospitals in the UK. Five-year overall survival of patients with WT was over 90% in both countries, but five-year event-free survival of

Abbreviations: BWS, Beckwith-Wiedemann syndrome; CI, confidence interval; CT, computed tomography; EFS, event-free survival; GU, genitourinary; HH, hemihypertrophy; HR, hazard ratio; IMPORT, Improving Population Outcomes of Renal Tumours of childhood; JSPS, Japanese Society of Pediatric Surgeons; JWiTS, Japanese Wilms Tumour Study; LOI, loss of imprinting; NWTS, National Wilms Tumor Study; OS, overall survival; SIOP-RTSG, The Renal Tumour Study Group of the International Society of Paediatric Oncology; WAGR syndrome, syndrome characterized by Wilms tumor, aniridia, and genitourinary abnormalities as well as intellectual disability (formerly referred to as mental retardation); WT, Wilms tumor

European Journal of Obstetrics & Gynecology and Reproductive Biology 262 (2021) 188–197

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Ultrasound diagnosis of infections in pregnancy

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ARTICLE INFO

Article history:
Received 20 February 2021
Received in revised form 5 May 2021
Accepted 12 May 2021

Keywords:
Fetal infections
Ultrasound sound
Congenital malformations
Cytomegalovirus
Rubella
Toxoplasmosis
Zika
Syphilis
Varicella zoster

ABSTRACT

Pregnancy is a unique period in which several changes occur in the mother, to ensure that the semiallograft fetus is not rejected. Some of these changes decrease the immunity of the mother to infections. As such, some infections in pregnancy which may not ordinarily cause severe symptoms can be more severe in the mother and importantly some of these infections pose a danger to the fetus either directly or indirectly. In dealing with infections in pregnancy, attention should focus on both the consequences of the infection on the mother as well as in the fetus. Over the last decade, some of these infections have significantly influenced clinical practice. This series on Infections in Pregnancy in this journal provides a comprehensive cover of this topic. Here we focus on the fetal impact of infections in pregnancy and how ultrasound scan can help in identifying some of these infections and more importantly map out pathways for managing the pregnancies including counselling and additional invasive procedures.

Introduction

Infections in pregnancy may either be symptomatic or asymptomatic, making it difficult to estimate just how common these are. Most have no effects but some have varying consequences on both the mother and the fetus, influenced no doubt by the impact of pregnancy on the immune status of the woman [1]. Infections that may affect the fetus can be viral, bacterial, protozoal or fungal.

Amongst the viral infections are rubella, cytomegalovirus, herpes simplex, hepatitis, varicella zoster, zika, parvovirus B19, human immunodeficiency virus, Coronavirus and *Coxsackie virus*. Bacterial infections include *Treponema pallidum*, *Listeria monocytogenes*, *Chlamydia trachomatis*, *Neisseria gonorrhoea, Mycobacterium tuberculi* and *Bordetella pertussis* while protozoan infections include *Toxoplasma gondii* and fungi include *Candida albicans*.

When pregnant women present with specific symptoms/signs of infections, appropriate serological investigations are often instituted to help make a diagnosis. However, with regards to fetal infections, ultrasound is an essential tool in identifying definite cases of intrauterine infections and those with suspected intrauterine infections requiring further investigations.

Frequently, it is the initial abnormal ultrasound findings that triggers maternal serological testing for congenital infections. In some cases, the diagnosis of infections from routine screening tests performed in pregnancy or based on the mother's symptomatology triggers targeted ultrasound scans with the aim of detecting fetal sequelae.

Once a congenital infection is diagnosed, ultrasound can be used to help gauge fetal prognosis and guide further investigations and management. In this review which complements the articles on various infections in pregnancy in this special issue, we highlight the typical ultrasound features associated with specific infections and the role of ultrasound in diagnosis and management especially of complications of congenital infections such as fetal anaemia.

Viral infections

Cytomegalovirus (CMV)

CMV is the most common viral infection in pregnancy as well as the most common viral cause of congenital infections. Congenital CMV affects 0.2–2.5 % of all live births, is the leading non-genetic cause of sensorineural hearing loss and a major cause of

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https://doi.org/10.1016/j.ejogrb.2021.05.027
0301-2115/

Cureus

Open Access Original Article

DOI: 10.7759/cureus.15192

Tracheal Bronchus and Associated Anomaly Prevalence Among Children

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Abstract

Background and objectives

Tracheal bronchus (TB) is a rare congenital airway anomaly originating from the trachea, with a reported prevalence of 0.9%-3% in children. Although TB was studied in the literature, this anomaly was not evaluated in Qatar. Our study aimed to identify the prevalence and congenital anomalies associated with TB in children in Qatar.

Design

In this descriptive study, we identified patients who underwent flexible bronchoscopy (FB) at two large tertiary centers in Qatar from July 2007 to November 2020. The patients' demographic, bronchoscopic, and radiologic data were collected. The prevalence of TB and associated congenital anomalies were determined.

Results

Of 1786 patients who underwent FB, 20 (1.12%) were diagnosed with TB. The median age at the time of diagnosis was 31 months (range, 2-154 months). The associated congenital anomalies were identified in 16 cases (80%; p = 0.007). Cardiac defects represent the most common associated anomaly (8/20, 40%).

Conclusion

This study revealed that TB is an uncommon airway anomaly and emphasizes its significant association with other congenital malformations. Our findings should alert physicians to other associated TB anomalies and provide timely management when needed.

Categories: Pediatrics, Pediatric Surgery, Pulmonology
Keywords: tracheal bronchus, trachea, airway anomalies, bronchoscopy, chromosomal abnormalities

Review began 05/11/2021
Review ended 05/18/2021
Published 05/23/2021

Introduction

Tracheal bronchus (TB) is a rare congenital tracheal anomaly, which is defined as the presence of an ectopic bronchus arising from the lateral wall of the trachea and supplies the right upper lobe [1]. In the literature, the prevalence of TB is between 0.9% and 3% [2-4]. The majority of TB cases are asymptomatic and diagnosed incidentally by advanced chest imaging or bronchoscopy [4,5].TB may present with recurrent pneumonia, cough, stridor, wheezing, bronchiectasis, or atelectasis of the affected lobe [1,6,7]. Most often, TB is associated with other congenital anomalies, such as congenital heart disease, pulmonary vasculature abnormalities, airway anomalies, or chromosomal anomalies [4,6,8].

A TB is classified as either displaced (if the right upper lobe bronchus has posterior and anterior bifurcation only) or supernumerary (if the ectopic bronchus coexists with the normal right upper lobe bronchus trifurcation); the displaced is more frequent than the supernumerary type [9]. The term pig bronchus or bronchus suis (a normal anatomy present in pigs) is often used when it supplies the entire right upper lobe (usually the right side) [1,10].

Arbitrarily, Conacher classified TB based on its origin from the trachea as follows: Type I is the TB originating at the junction of the middle and lower one-third of the trachea, type II is the TB ascending at the lower third of the trachea, and type III is the TB arising from the lower trachea, near the carina forming the carina trifurcation appearance [11].

Although TB was studied in the literature, this anomaly was not evaluated in Qatar. Therefore, our study aimed to determine the prevalence of TB and associated congenital anomalies in children who underwent flexible bronchoscopy (FB) for respiratory symptoms in Qatar. This recognition is essential to define the burden of this anomaly in our population and understand its implications.

How to cite this article
Al-Naimi A, Hamad S, Abushahin A (May 23, 2021) Tracheal Bronchus and Associated Anomaly Prevalence Among Children . Cureus 13(5): e15192. DOI 10.7759/cureus.15192

INTERNATIONAL JOURNAL OF ENVIRONMENTAL HEALTH RESEARCH
https://doi.org/10.1080/09603123.2021.1931050

Monitoring the effect of environmental conditions on safety of fresh produce sold in Qatar's wholesale market

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ABSTRACT

Fresh produce imported by Qatar are mostly sold at the wholesale produce market (WPM) located in open-air and near major animal markets and slaughterhouses. This study was the first in Qatar to monitor the effect of environmental conditions on the microbial quality and safety of fresh produce sold at the WPM over 1 year. The monitoring involved the collection of 540 produce samples along with samples of air, soil, and surface swabs. Samples were analyzed for total aerobic bacteria (TAB); generic *Listeria* spp., *Staphylococcus* spp., *Salmonella* spp.; total coliforms and total fungi. Bacterial and fungal isolates were identified using 16S rRNA/ITS rRNA markers. Environmental/sanitary factors significantly impacted the prevalence of microorganisms in all samples tested. Produce quality was rated 'poor' during the months of November–February or May–August, with TAB and coliform counts exceeding 6 and 4 $\log_{10}$ CFU/g, respectively. *Bacillus subtilus, Enterobacter cloacae, E. faecium, P. expansium, P. aurantiocandidum*, and *A. niger* were the most abundant species with prevalence rate of 11–30%. The high microbial load of environmental samples indicates that the location of the WPM near livestock markets is likely impacting the microbial quality of fresh produce. Therefore, effective control measures need to be implemented at WPM to improve produce safety yearlong.

ARTICLE HISTORY
Received 27 November 2020
Accepted 12 May 2021

KEYWORDS
Fresh produce; environmental conditions; microbial quality; qatar

Introduction

The state of Qatar is a small arid country located in the Arabian Gulf. More than 90% of the fresh produce sold in Qatar are imported from overseas. The import of fresh produce has more than doubled between 2010 and 2019 with a value increase from 50 USD million to 119 USD million, respectively (Trading Economics 2020, https://tradingeconomics.com/qatar/imports/vegetable - fruit-nut-food-preparations). Once the produce reaches the country, the distribution takes place in the large Wholesale Produce Market (WPM) located in a vast open area with major sources of potential contamination nearby, namely a fish market, livestock market, poultry market, slaughterhouses, and sprawling industrial area.

Several studies reported how the environmental and meteorological factors could influence the prevalence of various pathogens on fresh produce before, during or after harvesting (Haley et al. 2009; Ivanek et al. 2009; Gorski et al. 2011; Faour-Klingbeil et al. 2016; Abatcha et al. 2018; Li et al. 2018; Roth et al. 2018; Fadiji et al. 2019; Oyedele et al. 2020; Yi et al. 2020). Produce contamination

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Analytic comparison between three high-throughput commercial SARS-CoV-2 antibody assays reveals minor discrepancies in a high-incidence population

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Performance of three automated commercial serological IgG-based assays was investigated for assessing SARS-CoV-2 "ever" (past or current) infection in a population-based sample in a high exposure setting. PCR and serological testing was performed on 394 individuals. SARS-CoV-2-IgG seroprevalence was 42.9% (95% CI 38.1–47.8%), 40.6% (95% CI 35.9–45.5%), and 42.4% (95% CI 37.6–47.3%) using the CL-900i, VidasIII, and Elecsys assays, respectively. Between the three assays, overall, positive, and negative percent agreements ranged between 93.2–95.7%, 89.3–92.8%, and 93.8–97.8%, respectively; Cohen's kappa statistic ranged from 0.86 to 0.91; and 35 specimens (8.9%) showed discordant results. Among all individuals, 12.5% (95% CI 9.6–16.1%) had current infection, as assessed by PCR. Of these, only 34.7% (95% CI 22.9–48.7%) were seropositive by at least one assay. A total of 216 individuals (54.8%; 95% CI 49.9–59.7%) had evidence of ever infection using antibody testing and/or PCR during or prior to this study. Of these, only 78.2%, 74.1%, and 77.3% were seropositive in the CL-900i, VidasIII, and Elecsys assays, respectively. All three assays had comparable performance and excellent agreement, but missed at least 20% of individuals with past or current infection. Commercial antibody assays can substantially underestimate ever infection, more so when infection rates are high.

Coronavirus disease 2019 (COVID-19), due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a global health challenge. As of November 22, 2020, the COVID-19 burden included 57.6 million confirmed cases and 1.3 million deaths worldwide[1]. Meanwhile, the true extent of exposure to the SARS-CoV-2 infection and how far different national populations are from herd immunity remain poorly understood. Commercial serological assays are increasingly being used to address this gap in evidence. The extent to which such assays can capture ever infection (defined as past or prior infection) in a population remains to be elucidated. Understanding who has been exposed and potentially acquired immunity against this virus may help

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Yadav et al. *Translational Psychiatry* (2021)11:349
https://doi.org/10.1038/s41398-021-01473-w

Translational Psychiatry

REVIEW ARTICLE Open Access

Genetic variations influence brain changes in patients with attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a neurological and neurodevelopmental childhood-onset disorder characterized by a persistent pattern of inattentiveness, impulsiveness, restlessness, and hyperactivity. These symptoms may continue in 55–66% of cases from childhood into adulthood. Even though the precise etiology of ADHD is not fully understood, it is considered as a multifactorial and heterogeneous disorder with several contributing factors such as heritability, auxiliary to neurodevelopmental issues, severe brain injuries, neuroinflammation, consanguineous marriages, premature birth, and exposure to environmental toxins. Neuroimaging and neurodevelopmental assessments may help to explore the possible role of genetic variations on ADHD neuropsychobiology. Multiple genetic studies have observed a strong genetic association with various aspects of neuropsychobiological functions, including neural abnormalities and delayed neurodevelopment in ADHD. The advancement in neuroimaging and molecular genomics offers the opportunity to analyze the impact of genetic variations alongside its dysregulated pathways on structural and functional derived brain imaging phenotypes in various neurological and psychiatric disorders, including ADHD. Recently, neuroimaging genomic studies observed a significant association of brain imaging phenotypes with genetic susceptibility in ADHD. Integrating the neuroimaging-derived phenotypes with genomics deciphers various neurobiological pathways that can be leveraged for the development of novel clinical biomarkers, new treatment modalities as well as therapeutic interventions for ADHD patients. In this review, we discuss the neurobiology of ADHD with particular emphasis on structural and functional changes in the ADHD brain and their interactions with complex genomic variations utilizing imaging genetics methodologies. We also highlight the genetic variants supposedly allied with the development of ADHD and how these, in turn, may affect the brain circuit function and related behaviors. In addition to reviewing imaging genetic studies, we also examine the need for complementary approaches at various levels of biological complexity and emphasize the importance of combining and integrating results to explore biological pathways involved in ADHD disorder. These approaches include animal models, computational biology, bioinformatics analyses, and multimodal imaging genetics studies.

Background

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous neurobiological disorder of inattention, impulsivity, and hyperactivity, affecting 5–7% of children worldwide[1–4]. Severity status and symptoms of ADHD vary throughout a person's lifespan; however,

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Journal of Medical Radiation Sciences

Open Access

TECHNICAL EVALUATION

Technical evaluation of a clinical, bi-planar, digital, upright X-ray imaging unit

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Keywords
data collection, phantoms, imaging, quality control, radiation protection, technology, radiologic

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Received: 18 October 2020; Revised: 4 May 2021; Accepted: 22 May 2021

J Med Radiat Sci **00** (2021) 1–7

doi: 10.1002/jmrs.519

Abstract

We describe the technical evaluation of the commercially available, clinical, bi-planar, low dose, digital X-ray system (EOS System, EOS imaging, France). The unit is used for upright, weight-bearing musculoskeletal pathologies, in particular, in the spine and lower limbs. The evaluation incorporated tests on the X-ray generator performance, radiation/imaging field alignment, dose area product accuracy and image quality. The assessment methodology was based on objective parameters and required equipment readily available for technical evaluation of other radiological equipment. Results demonstrated that the system performs well within acceptable performance criteria with regard to X-ray generator performance, radiation/imaging field alignment and dose area product accuracy. In addition, results from the image-quality assessment were aligned with previously published work. The work presented in this article can be used for the technical evaluation of the EOS System at other clinical sites.

Introduction

Technical evaluation of radiological equipment installed in clinical sites is an integral part of the radiology quality assurance framework and a legislative requirement, ensuring the safe and optimised use of radiation for clinical imaging. Professional bodies have published guidelines on technical evaluation and commissioning methodologies for radiological equipment, for example, the European Commission has summarised a number of these tests and the proposed performance acceptability criteria in an extensive report.[1] However, these recommendations and guidelines cannot be applied in a straightforward manner for specialised radiological units such as the EOS System (EOS imaging, France), on account of its unique design.

The EOS System has found broad use in hospitals and orthopaedic specialty clinical centres for spinal and lower limb examinations. Previous work has shown that the EOS System has a strong potential for dose saving in patient studies compared to conventional digital radiography imaging, which can be even further reduced in its microdose function.[2,3] The unique technical characteristics and functionality of the system allow for significant dose reduction, which is an important consideration in particular for paediatric orthopaedic examinations which may require frequent follow-ups.[4, 5, 6]

The purpose of the work presented in this article is to demonstrate the methodology adopted by our team to perform the technical evaluation and commissioning for clinical use of the EOS System, and to present baseline values that can be applied as performance acceptability criteria.

Material and Methods

EOS system

The EOS System is shown in Figure 1 and its geometry depicted in Figure 2. Each X-ray tube/detector combination moves vertically at different lengths, as adjusted for each study by the operator, to obtain frontal/anteroposterior (AP) and lateral (LAT) images simultaneously. The distance by which the tube travels vertically during image acquisition for each study will henceforth be referred to as study length.

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Article type : Original Article

Original article

The Epidemiology, Genetic Landscape and Classification of Childhood Diabetes Mellitus in the State of Qatar

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Short title- Childhood Diabetes Mellitus in Qatar

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDI.13610

Word count- 3930

Abstract

Aims- To study the epidemiology, genetic landscape and causes of childhood diabetes mellitus (DM) in the State of Qatar.

Materials and methods- All patients (0-18 years) with DM underwent biochemical, immunological and genetic testing. ADA guidelines were used to classify types of DM. The incidence and prevalence of all the different types of DM were calculated.

Results- Total number of children with DM was 1325 (Type 1 (n=1096, ≥1 antibody), Type 2 (n=104), Type 1B (n=53), MODY (n=20), monogenic autoimmune (n=4), Neonatal Diabetes Mellitus (NDM) (n=10), syndromic DM (n=23) and double DM (n=15)). The incidence and prevalence of type 1 diabetes were 38.05 and 249.73 per 100,000 respectively and for type 2 were 2.51 and 23.7 per 100,000 respectively. Incidence of NDM was 34.4 per 1,000,000 live births and in indigenous Qataris incidence was 43.6. The prevalence of *type 1 diabetes* and *type 2 diabetes* in Qatari children was double to other nationalities. The prevalence of MODY in Qatar was 4.56 per 100,000.

Conclusions- This is the first prospective and comprehensive study to document the epidemiology and genetic landscape of childhood DM in this region. Qatar has the 4th highest incidence of type 1 DM with the incidence and prevalence being higher in Qatari compared to non-Qatari. The prevalence of type 2 DM is also higher in Qatar than the western countries. The incidence of NDM is the second highest in the world. *GCK* is the most common form of MODY and a large number of patients have type1B DM.

Key words- Epidemiology,Paediatric diabetes, type 1 diabetes, type 2 diabetes.

Introduction

Diabetes Mellitus (DM) is a chronic metabolic condition with hyperglycaemia resulting from inadequate production of insulin or resistance to insulin action. The chronic hyperglycaemia leads to macro and microvascular complications (1). The global burden of DM is rapidly increasing with an estimated average increase of 3-4% in

Hasan *et al. BMC Pediatrics* (2021) 21:267
https://doi.org/10.1186/s12887-021-02743-8

BMC Pediatrics

RESEARCH Open Access

COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a case series from a tertiary care pediatric hospital in Qatar

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Abstract

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe complication of coronavirus disease 2019 (COVID-19) in children, which is increasingly being reported worldwide. Here we report the first case series of 7 children diagnosed with MIS-C in Qatar.

Methods: Clinical features and outcomes of COVID-19 positive patients admitted to Sidra Medicine, Qatar from June to October 2020, who met the WHO case definition for MIS-C were reviewed.

Results: The mean age in our case series was 5.6 years, of which 71.4% were males. All patients were previously healthy but had a history of COVID-19 infection. Fever, rash, vomiting and abdominal pain were the most common symptoms (70–100%). The average hospitalization was 12.9 days with no case fatalities. Laboratory findings included lymphopenia and thrombocytopenia in most patients, as well as evidence of coagulopathy and elevated inflammatory markers such as C-reactive protein, ferritin and procalcitonin. Many patients (71.4%) required inotropic support in intensive care, while only one required respiratory support. Although all patients had elevated cardiac biomarkers, cardiovascular involvement was observed in 42.9% of patients with one patient developing a giant coronary aneurysm. All patients received intravenous immunoglobulin (IVIG) and 86% of patients received corticosteroids, with two patients requiring treatment with IL-1 inhibitors.

Conclusions: Our report is one of the first reports on MIS-C from Asia. Although clinical features and outcomes are not significantly different from those reported elsewhere, lack of case fatalities in our cohort may indicate that early recognition and prompt medical attention is necessary for a favorable outcome in MIS-C.

Keywords: COVID-19, SARS-CoV-2, Multisystem inflammatory syndrome (MIS-C), Kawasaki disease

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Title:

PROGNOSTIC SIGNIFICANCE OF HISTOPATHOLOGICAL RESPONSE TO PREOPERATIVE CHEMOTHERAPY IN UNILATERAL WILMS TUMOR: AN ANALYSIS OF 899 PATIENTS TREATED ON THE SIOP WT 2001 PROTOCOL IN THE UK CCLG AND GPOH STUDIES

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.33707

ABSTRACT

In the SIOP Wilms tumor (WT) studies preoperative chemotherapy is used as primary treatment, and tumors are classified thereafter by pathologists. Completely necrotic WTs (CN-WTs) are classified as low-risk tumors. The aim of the study was to evaluate whether a subset of regressive type WTs (RT-WTs)(67-99% chemotherapy-induced changes - CIC) showing an exceptionally good response to preoperative chemotherapy had comparably excellent survivals as CN-WTs, and to establish a cut-off point of CIC that could define this subset. The study included 2,117 patients with unilateral, nonanaplastic WTs from the UK-CCLG and GPOH-WT studies (2001-2020) treated according to the SIOP-WT-2001 protocol. There were 126 patients with CN-WTs and 773 with RT-WTs, stages I-IV. RT-WTs were subdivided into subtotally necrotic WTs (>95% CIC) (STN-WT96-99) (124 patients) and the remaining of RT-WT (RR-WT67-95)(649 patients). The 5-year EFS and OS for CN-WTs were 95.3% (±2.1%SE) and 97.3% (±1.5%SE), and for RT-WTs 85.7% (±1.14%SE, $P < 0.01$) and 95.2% (±0.01%SE, $P = 0.59$), respectively. CN-WT and STN-WT96-99 groups showed significantly better EFS than RR-WT67-95 ($P = 0.003$ and $P = 0.02$, respectively), which remained significantly superior when adjusted for age, local stage, and metastasis at diagnosis, in multivariate analysis, whereas OS were superimposable (97.3±1.5%SE for CN-WT; 97.8±1.5%SE for STN-WT96-99; 94.7±1.0%SE for RR-WT67-95). Patients with STN-WT96-99 share the same excellent EFS and OS as patients with CN-WTs, and although this was achieved by more treatment for patients with STN-WT96-99 than for patients with CN-WT, reduction in postoperative treatment of these patients may be justified.

Key words: Wilms tumor, preoperative chemotherapy, response, prognosis

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Cite this as: *BMJ* 2021;373:n1409
http://dx.doi.org/10.1136/bmj.n1409
Published: 11 June 2021

RATIONAL TESTING

Role of C reactive protein and procalcitonin in the diagnosis of lower respiratory tract infection in children in the outpatient setting

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What you need to know

- The difficulty of discriminating between viral and bacterial lower respiratory tract infection (LRTI) in children using clinical features alone often leads to overprescription of antibiotics
- Biomarkers such as C reactive protein (CRP) and procalcitonin (PCT) have a limited capacity to rule in bacterial pneumonia in children in ambulatory settings where the prevalence of bacterial pneumonia is low. (CRP and PCT have limited diagnostic value in severely ill children who meet criteria for pneumonia or sepsis and who are candidates for broad spectrum antibiotic therapy)
- There is growing evidence that antibiotic therapy can be safely withheld in children who are not severely ill with equivocal clinical presentation and low CRP (<20 mg/L) and PCT (<0.5 µg/L) levels

A previously healthy and fully vaccinated (including 13-valent pneumococcal conjugate vaccine) 22 month old boy is brought to the emergency department because of a 12 hour history of high fever (up to 40°C). He had had low grade fever, runny nose, cough, and decreased oral intake for the past two days. On examination, he did not look severely ill but was febrile (38.3°C). His respiratory rate was 45 breaths/minute (normal range 25-40 breaths/min at 18-24 months old), heart rate was 140 beats/minute (normal range 98-135 beats/min at 18-24 months), and blood oxygen level was 95%. Although breath sounds were not decreased, some bibasilar crackles were noted on chest auscultation. A chest x ray was interpreted as having bilateral peribronchial infiltrates and haziness in the right lower lobe. To aide their decision whether to initiate antibiotic therapy, clinicians requested blood tests, which revealed a white blood cell count of 22.5×10^9/L (60.0% neutrophils), a CRP of 30 mg/L (normal <5 mg/L), and a PCT of 0.25 µg/L (normal <0.5 µg/L).

Lower respiratory tract infections (LRTIs) in childhood are commonly of viral aetiology. Distinguishing viral from bacterial LRTI in children—and thus appropriately prescribing antibiotics—solely based on a medical history and physical examination can be challenging.[1] In these circumstances, an accurate marker for bacterial pneumonia would be useful in order to prevent return to medical care (if bacterial infection was not treated) and to avoid antibiotic use and adverse effects (when the underlying cause is viral). The National Institute for Health and Care Excellence (NICE) recommends point-of-care testing of C reactive protein (CRP) to guide antibiotic therapy for adults with symptoms of LRTI and diagnostic uncertainty after a clinical assessment (antibiotic treatment should be offered to patients with CRP levels >100 mg/L and avoided for CRP levels <20 mg/L).[2] Although CRP and procalcitonin lack sufficient sensitivity and specificity to rule in bacterial pneumonia in children in ambulatory care,[3,4] data generated over the past few years suggest that both biomarkers could help clinicians to reduce diagnostic uncertainty and unnecessary antibiotic prescriptions in a subset of children with LRTI and equivocal clinical features.

What are C reactive protein and procalcitonin?

C reactive protein (CRP) and peripheral white blood cell count are the most common biomarkers for infection in clinical practice worldwide. CRP, which is primarily produced by the liver in response to inflammation, plays a major role in inducing complement activation and facilitating phagocytosis by macrophages.[5,6] Procalcitonin (PCT) is a precursor peptide of the hormone calcitonin, which is secreted by a wide range of parenchymal cells in response to systemic inflammation. Although both biomarkers have a good negative predictive value to rule out serious bacterial infections, PCT is increasingly used to identify severe bacterial infections in children such as urinary tract infection and meningitis and to determine the risk of serious bacterial infection in infants with fever of unknown source and oncology patients with neutropenic fever, since it shows a more specific increase in response to bacterial infection, becomes elevated faster, and decreases earlier in response to appropriate antibiotic therapy than CRP (table 1).[5,7,8] PCT testing is mostly performed in emergency care settings in middle-high income settings because of its higher cost and longer turnaround time than CRP testing; CRP is widely used in primary care, including in some low income countries, because of its affordability and fast turnaround time (table 1).[5-8]

Level of Maternal Respiratory Syncytial Virus (RSV) F Antibodies in Hospitalized Children and Correlates of Protection

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Highlights

- Only 14% of maternal antibodies were present in infants at hospitalization.
- An average log2 EP titer of 10.2 directed to both F-protein conformations.
- Neutralizing activity in infants was greater than that of binding antibodies.
- A third of infants had a relatively high NAb titers, yet, they were hospitalized.

ABSTRACT:

Background: RSV is a major cause of lower respiratory infections among children, where no vaccine is available. The stabilized form of the fusion (F) protein, pre-F, is a leading vaccine candidate targeting different populations, including pregnant women. This study aimed to determine the magnitude and nature of RSV-directed maternal antibodies (matAbs) in hospitalized children with RSV infection. **Methods:** 65 paired blood samples were collected

from RSV-infected children below six months of age, and their corresponding mothers. All pairs were screened for pre-F and post-F antibodies levels using ELISA. The neutralizing antibodies (NAbs) in both groups were measured *in-vitro* against mKate RSV-A2 using H28 cells. **Results:** Only 14% of matAbs (log_2 12.8) were present in infants at hospitalization, with an average log_2 EP titer of 10.2 directed to both F-protein conformations. Additionally, 61.4% of maternal NAbs (log_2 EC_{50} = 9.4) were detected in infants (log_2 EC_{50} = 8.7), which were mostly pre-F exclusive (81%). Pre-F antibodies in children showed a positive correlation with matAbs titers and negative correlations with infants' age and bronchiolitis score. **Conclusions:** The maintenance of neutralizing activity in infants relative to maternal titers was greater than the maintenance of antibody binding based on ELISA, suggesting that higher potency antibodies may have a longer half-life than weakly neutralizing antibodies.

Keywords: RSV; F-protein; neonates; antibodies; protection; vaccine

Topic: pre-F protein; vaccines; pregnant women; young infants; RSV infection; immunity; NAbs

Issue Section: Major Article

INTRODUCTION:

RSV is a major cause of lower respiratory tract infections and hospitalization of pediatric patients in their first five years of life [1, 2]. The virus accounts for up to 60% of pneumonia and bronchiolitis, [3] and about 7.0% of deaths in infants between one month and one year of age [1]. In adults, RSV reinfection is frequent since exposure to the virus does not provide a long term

Received: 17 May 2021 | Revised: 26 May 2021 | Accepted: 1 June 2021

DOI: 10.1002/jcla.23876

RESEARCH ARTICLE

WILEY

Evaluation of automated molecular tests for the detection of SARS-CoV-2 in pooled nasopharyngeal and saliva specimens

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Abstract

Background: Pooling of samples for SARS-CoV-2 testing in low-prevalence settings has been used as an effective strategy to expand testing capacity and mitigate challenges with the shortage of supplies. We evaluated two automated molecular test systems for the detection of SARS-CoV-2 RNA in pooled specimens.

Methods: Pooled nasopharyngeal and saliva specimens were tested by Qiagen QIAstat-Dx Respiratory SARS-CoV-2 Panel (QIAstat) or Cepheid Xpert Xpress SARS-CoV-2 (Xpert), and the results were compared to that of standard RT-qPCR tests without pooling.

Results: In nasopharyngeal specimens, the sensitivity/specificity of the pool testing approach, with 5 and 10 specimens per pool, were 77%/100% (n = 105) and 74.1%/100% (n = 260) by QIAstat, and 97.1%/100% (n = 250) and 100%/99.5% (n = 200) by Xpert, respectively. Pool testing of saliva (10 specimens per pool; n = 150) by Xpert resulted in 87.5% sensitivity and 99.3% specificity compared to individual tests. Pool size of 5 or 10 specimens did not significantly affect the difference of RT-qPCR cycle threshold (C_T) from standard testing. RT-qPCR C_T values obtained with pool testing by both QIAstat and Xpert were positively correlated with that of individual testing (Pearson's correlation coefficient r = 0.85 to 0.99, $p < 0.05$). However, the C_T values from Xpert were significantly stronger ($p < 0.01$, paired t test) than that of QIAstat in a subset of SARS-CoV-2 positive specimens, with mean differences of −4.3 ± 2.43 and −4.6 ± 2 for individual and pooled tests, respectively.

Conclusion: Our results suggest that Xpert SARS-CoV-2 can be utilized for pooled sample testing for COVID-19 screening in low-prevalence settings providing significant cost savings and improving throughput without affecting test quality.

KEYWORDS
COVID-19, QIAstat-Dx Respiratory SARS-CoV-2 Panel, sample pooling, SARS-CoV-2, Xpert Xpress SARS-CoV-2

PLOS ONE

RESEARCH ARTICLE

Potent PDE4 inhibitor activates AMPK and Sirt1 to induce mitochondrial biogenesis

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Citation: Park S-J, Ahmad F, Bahde RJ, Philp A, Kim J, Huang T, et al. (2021) Potent PDE4 inhibitor activates AMPK and Sirt1 to induce mitochondrial biogenesis. PLoS ONE 16(6): e0253269. https://doi.org/10.1371/journal.pone.0253269

Editor: Ping Song, Georgia State University, UNITED STATES

Received: March 22, 2021

Accepted: June 1, 2021

Published: June 17, 2021

Data Availability Statement: All relevant data are within the manuscript and its Supporting information files.

Funding: JC HL006119 National Institutes of Health (NIH).

Competing interests: The authors have declared that no competing interests exist.

Abstract

AMP-activated protein kinase (AMPK) is an evolutionarily conserved energy sensor. Activation of AMPK leads to a number of metabolic benefits, including improved mitochondrial function in skeletal muscle and lowering of serum glucose levels in type-2 diabetes models. However, direct activation of AMPK leads to cardiac enlargement, and an alternative strategy that activates AMPK without affecting the heart is needed. Inhibition of phosphodiesterase 4 (PDE4), which is poorly expressed in the human heart, activates AMPK in other tissues. In a screen to identify novel PDE4 inhibitors, we discovered compound CBU91, which is 5–10 fold more potent than rolipram, the best characterized PDE4 inhibitor. CBU91, like rolipram, is able to activate AMPK and Sirt1 and increase mitochondrial function in myotubes. These findings suggest that activation of AMPK in myotubes is a general property of PDE4 inhibition and that PDE4 inhibition may activate AMPK in metabolically relevant tissues without affecting the heart.

Introduction

Intracellular cyclic adenosine monophosphate (cAMP) levels are tightly controlled by adenylate cyclases (ACs), which catalyze the cyclization of adenosine triphosphate (ATP) to cAMP, and phosphodiesterases (PDEs), which degrade cAMP by hydrolyzing the phosphodiester bond of cAMP to generate AMP [1]. The PDE family is composed of eleven members: PDEs 4, 7 and 8 selectively hydrolyze cAMP; PDEs 1, 2, 3, 10, and 11 hydrolyze both cAMP and cGMP; PDEs 5, 6 and 9 hydrolyze cGMP. PDE4, the largest member of the mammalian PDE family, is encoded by four genes, PDE4 A to D, which together produce more than 25 splice variants.

Seminars in Fetal and Neonatal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Therapies for neonatal encephalopathy: Targeting the latent, secondary and tertiary phases of evolving brain injury

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ARTICLE INFO

Keywords:
Neonatal encephalopathy
Neuroprotection
Neurorestoration
Therapeutic hypothermia

ABSTRACT

In term and near-term neonates with neonatal encephalopathy, therapeutic hypothermia protocols are well established. The current focus is on how to improve outcomes further and the challenge is to find safe and complementary therapies that confer additional protection, regeneration or repair in addition to cooling. Following hypoxia-ischemia, brain injury evolves over three main phases (latent, secondary and tertiary), each with a different brain energy, perfusion, neurochemical and inflammatory milieu. While therapeutic hypothermia has targeted the latent and secondary phase, we now need therapies that cover the continuum of brain injury that spans hours, days, weeks and months after the initial event. Most agents have several therapeutic actions but can be broadly classified under a predominant action (e.g., free radical scavenging, anti-apoptotic, anti-inflammatory, neuroregeneration, and vascular effects). Promising early/secondary phase therapies include Allopurinol, Azithromycin, Exendin-4, Magnesium, Melatonin, Noble gases and Sildenafil. Tertiary phase agents include Erythropoietin, Stem cells and others. We review a selection of promising therapeutic agents on the translational pipeline and suggest a framework for neuroprotection and neurorestoration that targets the evolving injury.

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[2] Dr. Robertson has a patent PCT/EP2018/056423 issued.

[3] Dr. Cotten has a patent cord tissue derived MSC for HIE pending.

https://doi.org/10.1016/j.siny.2021.101256

Available online 12 June 2021
1744-165X/

Please cite this article as: N, *Seminars in Fetal and Neonatal Medicine*, https://doi.org/10.1016/j.siny.2021.101256

Endocrinology, Diabetes & Metabolism CASE REPORTS

V S Nadhamuni and others | MEN1, GHRH and gigantism

ID: 20-0208; June 2021
DOI: 10.1530/EDM-20-0208

GHRH secretion from a pancreatic neuroendocrine tumor causing gigantism in a patient with MEN1

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Summary

A male patient with a germline mutation in MEN1 presented at the age of 18 with classical features of gigantism. Previously, he had undergone resection of an insulin-secreting pancreatic neuroendocrine tumour (pNET) at the age of 10 years and had subtotal parathyroidectomy due to primary hyperparathyroidism at the age of 15 years. He was found to have significantly elevated serum IGF-1, GH, GHRH and calcitonin levels. Pituitary MRI showed an overall bulky gland with a 3 mm hypoechoic area. Abdominal MRI showed a 27 mm mass in the head of the pancreas and a 6 mm lesion in the tail. Lanreotide-Autogel 120 mg/month reduced GHRH by 45% and IGF-1 by 20%. Following pancreaticoduodenectomy, four NETs were identified with positive GHRH and calcitonin staining and Ki-67 index of 2% in the largest lesion. The pancreas tail lesion was not removed. Post-operatively, GHRH and calcitonin levels were undetectable, IGF-1 levels normalised and GH suppressed normally on glucose challenge. Post-operative fasting glucose and HbA1c levels have remained normal at the last check-up. While adolescent-onset cases of GHRH-secreting pNETs have been described, to the best of our knowledge, this is the first reported case of ectopic GHRH in a paediatric setting leading to gigantism in a patient with MEN1. Our case highlights the importance of distinguishing between pituitary and ectopic causes of gigantism, especially in the setting of MEN1, where paediatric somatotroph adenomas causing gigantism are extremely rare.

Learning points

- It is important to diagnose gigantism and its underlying cause (pituitary vs ectopic) early in order to prevent further growth and avoid unnecessary pituitary surgery. The most common primary tumour sites in ectopic acromegaly include the lung (53%) and the pancreas (34%) (1): 76% of patients with a pNET secreting GHRH showed a *MEN1* mutation (1).
- Plasma GHRH testing is readily available in international laboratories and can be a useful diagnostic tool in distinguishing between pituitary acromegaly mediated by GH and ectopic acromegaly mediated by GHRH. Positive GHRH immunostaining in the NET tissue confirms the diagnosis.
- Distinguishing between pituitary (somatotroph) hyperplasia secondary to ectopic GHRH and pituitary adenoma is difficult and requires specialist neuroradiology input and consideration, especially in the MEN1 setting. It is important to note that the vast majority of GHRH-secreting tumours (lung, pancreas, phaeochromocytoma) are expected to be visible on cross-sectional imaging (median diameter 55 mm) (1). Therefore, we suggest that a chest X-ray and an abdominal ultrasound checking the adrenal glands and the pancreas should be included in the routine work-up of newly diagnosed acromegaly patients.

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Reducing neonatal phlebotomy blood losses through the accurate calculation of minimum test volume requirements

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Running Title: Reducing neonatal phlebotomy blood losses

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Declaration of competing interests: none
Funding: N/A
Ethical approval: Exempted by Sidra Medicine IRB (IRB00009930)
Guarantor: Eric Kilpatrick
Contributorship**:** ESK and EG conceived the idea, collected and analysed the data. The tool was developed by ESK with assistance from EG and BL. BL helped develop the idea and obtained ethical exemption. ESK wrote the paper draft and EG and BL amended and approved the final version.

Abstract word count: 250
Article word count: 2,611

Abstract

Background: Repeated phlebotomy for laboratory diagnostic testing is a known cause of iatrogenic anaemia and in critically ill neonates often leads to blood transfusion being required. This study has developed a spreadsheet clinical decision support (CDS) tool to allow neonatal staff to determine the true minimum blood volume (MBV) required to analyse groups of blood tests and modelled its potential benefit compared to the existing system in use.

Methods: The tool calculates the MBV accounting for novel factors including the current patient haematocrit for plasma/serum samples, instrument minimum test and dead volumes (including those where shared) and sharing of samples within/between laboratory departments.

A year of neonatal unit laboratory requests were examined comparing the volumes and containers of blood recommended by the hospital information system (HIS) with both the amount actually collected by staff and that recommended by the tool.

Results: 463 patients had 8,481 blood draws for 23,899 tests or test profiles over the year. The HIS recommended collecting 11,222mL of blood into 18,509 containers, while 17,734 containers were actually received (10,717mL if fully filled). The tool recommended collecting 4,915mL of blood into 15,549 containers.

Conclusions: This tool allows NICU staff to objectively determine the MBV required for a combination of tests and is generalisable between laboratory instruments. Compared to the HIS, use of the MBV-CDS tool could maximally reduce the volume of blood collected from this neonatal unit by more than a half. NICU staff had apparently already gone some way to determining their own minimum volumes required.

Keywords: clinical decision support, NICU, anaemia, phlebotomy, laboratory, informatics

Carter et al. BMC Cancer (2021) 21:740
https://doi.org/10.1186/s12885-021-08432-0

BMC Cancer

RESEARCH ARTICLE Open Access

Incidence of NUT carcinoma in Western Australia from 1989 to 2014: a review of pediatric and adolescent cases from Perth Children's Hospital

Tina Carter[1,2,3], Maxine Crook[1,2], Ashleigh Murch[2], Alex H. Beesley[3], Nick de Klerk[3], Adrian Charles[1,2,4] and Ursula R. Kees[3*]

Abstract

Background: NUT carcinoma (NC), previously known as NUT midline carcinoma, is a rare and very aggressive cancer that occurs in both children and adults. NC is largely chemoresistant, with an overall survival of less than 7 months. Because the carcinoma is not restricted to a particular organ, diagnosis is often a challenge. In the absence of a clearly determined incidence for NC, we sought to study the diagnosis of patients in a well-defined population.

Methods: We systematically reviewed records of all patients that presented to the Oncology Department of the Princess Margaret Hospital for Children from 1989 to 2014. This institution in the geographically isolated state of Western Australia has a catchment population of around 2 million. We then identified all high grade undifferentiated sarcomas or carcinomas in the 0–16 year age group.

Results: Over 26 years, we found 14 patients of 16 years or younger with undifferentiated malignant tumors. Of these, five tumors were positive by immunohistochemistry for the NUT/NUTM1 (Nuclear Protein in Testis) protein and/or the translocation t(15;19). Three patients presented with thoracic tumors, one with a para-spinal tumor, and one had an upper airway nasopharyngeal carcinoma. In all five cases, there was an initial response to therapy and then progression. This 26-year survey was conducted in a geographically isolated state with a well-defined population, and we determined an estimated incidence of NC of around 0.41 per million child years (0–16 yrs. of age) at risk. From three patients it was feasible to derive cell lines for further genetic analyses and drug screening.

Conclusions: For the first time, the incidence of NC could be determined in a well-defined geographic area. The calculated rate of NC incidence is consistent with a history of under-recognition for this malignancy. These findings indicate that improved diagnostic detection of NC would enable better management and counselling of patients. Our findings emphasize the heterogeneity of NC, and they highlight the need to develop personalised therapy options, and to consider a diagnosis of NC in undifferentiated malignant tumors.

Keywords: NC incidence, Carcinoma, Undifferentiated malignancy, NUTM1, Heterogeneity, Diagnosis, Rare, Aggressive

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Management of children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both: a national clinical practice consensus guideline

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Lancet Child Adolesc Health 2021; 5: 662–76

Published Online June 29, 2021 https://doi.org/10.1016/S2352-4642(21)00088-2

This online publication has been corrected. The corrected version first appeared at www.thelancet.com/child-adolescent on July 9, 2021

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Unexplained or idiopathic pituitary stalk thickening or central diabetes insipidus not only harbours rare occult malignancies in 40% of cases but can also reflect benign congenital defects. Between 2014 and 2019, a multidisciplinary, expert national guideline development group in the UK systematically developed a management flowchart and clinical practice guideline to inform specialist care and improve outcomes in children and young people (aged <19 years) with idiopathic pituitary stalk thickening, central diabetes insipidus, or both. All such cases of idiopathic pituitary stalk thickening and central diabetes insipidus require dynamic pituitary function testing, specialist pituitary imaging, measurement of serum β-human chorionic gonadotropin and alpha-fetoprotein concentrations, chest x-ray, abdominal ultrasonography, optometry, and skeletal survey for occult disease. Stalk thickening of 4 mm or more at the optic chiasm, 3 mm or more at pituitary insertion, or both, is potentially pathological, particularly if an endocrinopathy or visual impairment coexists. In this guideline, we define the role of surveillance, cerebrospinal fluid tumour markers, whole-body imaging, indications, timing and risks of stalk biopsy, and criteria for discharge. We encourage a registry of outcomes to validate the systematic approach described in this guideline and research to establish typical paediatric stalk sizes and the possible role of novel biomarkers, imaging techniques, or both, in diagnosis.

Introduction

Pituitary stalk thickening (PST) and central diabetes insipidus (CDI) are rare conditions (2–4 cases per 100 000 people for CDI)[1] that occur independently, synchronously, or metachronously. Children and young people (aged <19 years) with PST or CDI of indeterminate cause represent a diagnostic conundrum to differentiate the occult harmful, yet treatable, oncological, inflammatory, and infectious causes from benign congenital conditions.

Diagnostic criteria for defining PST are controversial, complicated by incidental findings, imprecise for stalk measurement at differing levels of the stalk, and do not have age-appropriate norms. There are few published clinical experiences, especially for children and young people. There are widely different prevalences of underlying causes in children and young people compared with adults,[2] and a paucity of high-quality studies or randomised trials in both age groups. This paucity in data, the rarity of the conditions, and their presentation to diverse specialties cause unacceptable inequalities in care. Under the auspice of the paediatric oncology society, Children's Cancer and Leukaemia Group (CCLG), and the paediatric endocrine society, British Society for Paediatric Endocrinology and Diabetes (BSPED), we aimed to develop a nationally endorsed clinical practice guideline for the investigation, management, and follow-up of children and young people with idiopathic PST, CDI, or both, to standardise service provision and to improve outcomes.

Methods

A national guideline development group comprising clinical experts across the UK in adult and paediatric endocrinology, oncology, neuroradiology, neuropathology, and neurosurgery was convened in 2014. The guideline was developed with AGREE II methodology,[3] and its objectives were summarised in 64 population, intervention, comparison, and outcome clinical questions,[4] and reviewed by UK stakeholders before a systematic literature search was done (figure 1).

On Oct 8, 2014, we systematically searched Ovid MEDLINE, PubMed, EMBASE, and Cochrane Library databases, using the terms "thickened pituitary stalk", "pituitary stalk thickening", "pituitary stalk lesion", "central diabetes insipidus", "neurogenic diabetes insipidus", or "idiopathic diabetes insipidus", for papers published in English between Jan 1, 1990, and Oct 7, 2014. On July 14, 2019, we updated our search to include publications from Oct 8, 2014, to July 13, 2019 (figure 1). We included studies reporting on the epidemiology, clinical presentation, diagnosis, investigation, treatment, or follow-up of idiopathic PST, CDI, or both, in children and young people, and excluded animal studies and those reporting PST or CDI that was syndromic or associated with trauma, hypoxia, prematurity, pregnancy, or post partum. Selected papers were appraised with the Grading of Recommendations, Assessment, Development and Evaluation criteria.[5] High-quality evidence was scarce. Where there was little or no evidence in paediatric populations, the guideline development group considered adult studies, and downgraded the evidence level accordingly.

First, the guideline development group reviewed the likelihood of different occult causes underlying idiopathic PST or CDI in children and young people, and found that it differed considerably from adults.[2] After an average of 6 years (range 2–10) of surveillance across 11 studies,[6–16]

European Journal of Obstetrics & Gynecology and Reproductive Biology 263 (2021) 171–175

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/euro

Full length article

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in pregnancy – An overview

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ARTICLE INFO

Article history:
Received 7 April 2021
Revised 8 June 2021
Accepted 14 June 2021

Keywords:
Coronaviruses
Respiratory syndrome
Pregnancy
Viral infection

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections, like most other viruses that affect the respiratory tract can cause severe maternal illness and adverse pregnancy outcomes. They are not only highly transmissible (acquired through droplets), but Host reservoirs such as dromedary camels for MERS-CoV and masked palm civet for SARS-CoV-1 are critical links in the onset of outbreaks. Clinically they present with flu-like symptoms and therefore a high index of suspicion is required to ensure timely diagnosis and tailored management. Although there are not many reported series on these infections in pregnancy they seem to be associated with an increased risk of preterm delivery and maternal mortality. Diagnosis is made by PCR from nasopharyngeal swabs. There are currently no effective anti-viral agents for these viruses but following infections various agents have been administered to patients. The most important aspect of management should be early identification of deterioration and intensive support and prevention of transmission. Our understanding of the evidence of the impact of both infections on pregnancies suggests the potential for future repeat outbreaks, hence the importance of maintaining vigilance across healthcare systems.

Introduction

The last published case reports, case series and epidemiological studies on SARS-CoV-1 and MERS were in 2004 and 2018 respectively. As SARS-CoV-1 and MERS belong to the same family as the etiological agent of the current pandemic (COVID-19), this review is a reminder of the differences and similarity between them.

Coronaviruses are single stranded RNA viruses from the subfamily *Coronavirinae* in the *Coronaviridae* family with significant propensity for genetic variation because of their large RNA genome [1–3]. The name 'coronavirus' derives from their crown-like morphology. They have been associated with infections in animals, human and birds. Four genera of coronaviruses are described: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus*. Animals and humans are infected by *Alpha* and *Beta* coronaviruses whilst birds are infected by *Delta* and *Gamma* coronaviruses [4].

Human coronaviruses such as HCoV-NL63, HCoV-HKU1, HCoV-229E and HCoV-043 have been previously associated with upper respiratory tract infections in immunocompromised subjects, children and the elderly [5]. Coronaviruses have been brought into the wider public health prominence due to the evidence of interspecies transmission of zoonotic coronaviruses which has led to outbreaks of a distinct type of human infection characterized by severe respiratory compromise. The novel coronaviruses that have been associated with severe respiratory disease in humans in recent times include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This review highlights the salient clinical diagnostic and epidemiologic features of MERS-CoV and SARS-Co-V-1 infections as seen during pregnancy.

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https://doi.org/10.1016/j.ejogrb.2021.06.020
2215-1532/

Cureus

Open Access Original Article

DOI: 10.7759/cureus.15948

Sputum and Plasma Neutrophil Elastase in Stable Adult Patients With Cystic Fibrosis in Relation to Chronic Pseudomonas Aeruginosa Colonization

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Abstract

Background and purpose

Neutrophil elastase (NE) has been implicated in the pathogenesis of airway inflammation in cystic fibrosis (CF) patients and it impairs defenses against *Pseudomonas aeruginosa* (PA) infection or colonization. Sputum NE may act as a biomarker of neutrophilic inflammation in CF patients. This study aimed to determine sputum and plasma total NE levels in clinically stable adult CF patients and control subjects, and their correlation to PA colonization and lung functions.

Methods

This is a cross-sectional study. Total NE was measured on spontaneously expectorated sputum and plasma obtained from 21 CF patients, aged 18-40 years, during routine visits to the adult CF clinic. This was compared to plasma obtained from 22 matching healthy controls. The levels of NE were measured by the magnetic bead-based multiplex assay.

Results

Sputum and plasma NE levels had a significant positive correlation (Pearson r=0.533, P=0.013) with PA colonization. Sixteen CF patients (76.2%) were chronically colonized with PA. Both median sputum and plasma NE were found to be higher in CF patients with PA as compared with non-PA patients, even though this difference was statistically insignificant. Sputum and plasma NE levels did not correlate with the percentage predicted forced expiratory volume in one second (FEV1), the forced vital capacity (FVC), and FEV1/FVC and no association with PA.

Conclusion

The findings suggest that clinically stable adult CF patients colonized with PA may have higher NE levels in both plasma and sputum as compared to non-PA CF patients and probably total NE does not influence lung functions.

Review began 05/31/2021
Review ended 06/15/2021
Published 06/26/2021

Categories: Internal Medicine, Infectious Disease, Pulmonology
Keywords: cystic fibrosis, neutrophil elastase, inflammation, adults, pseudomonas aeruginosa

Introduction

Cystic fibrosis (CF) is one of the most prevalent, life-shortening genetic diseases in the Caucasian population [1]. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7, which encodes an epithelial anion channel that impacts multiple organ systems [2]. In CF airways, CFTR dysfunction or absence instigates the accumulation of abnormally thick, sticky mucus in the respiratory tract, which impairs bacterial mucociliary clearance and allows the colonization of the airways by microbial pathogens with *Pseudomonas aeruginosa* (PA) as the most relevant pathogen in the CF lung disease [3]. A systematic review reported that PA infection and pancreatic insufficiency were most commonly associated with lower baseline and more rapid declines in lung function [4].

Airway neutrophilia is a common feature of CF lung disease and is associated with disease progression, often regardless of the initiating cause. Neutrophils and their products are thought to be key mediators of the inflammatory changes in the airways of patients with CF [5].

How to cite this article
Abdulwahab A, Allangawi M, Thomas M, et al. (June 26, 2021) Sputum and Plasma Neutrophil Elastase in Stable Adult Patients With Cystic Fibrosis in Relation to Chronic Pseudomonas Aeruginosa Colonization. Cureus 13(6): e15948. DOI 10.7759/cureus.15948

frontiers in Medicine

ORIGINAL RESEARCH
published: 16 June 2021
doi: 10.3389/fmed.2021.663694

Epidemiology Profile of Viral Meningitis Infections Among Patients in Qatar (2015–2018)

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OPEN ACCESS

Edited by:
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Lebanese University, Lebanon

Reviewed by:
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Specialty section:
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

Received: *03 February 2021*
Accepted: *10 May 2021*
Published: *16 June 2021*

Citation:
Mathew S, Al Khatib HA, Al Ansari K, Nader J, Nasrallah GK, Younes NN, Coyle PV, Al Thani AA, Al Maslamani MA and Yassine HM (2021) Epidemiology Profile of Viral Meningitis Infections Among Patients in Qatar (2015–2018). Front. Med. 8:663694. doi: 10.3389/fmed.2021.663694

Background: Little is known about the etiology of meningitis in the MENA region, including Qatar. Viral agents are considered the major cause for meningitis worldwide. Here, we present primary data about the etiology and clinical and demographic characteristics of viral meningitis (VM) in Qatar between 2015 and 2018.

Methods: We retrospectively collected data from Hamad Medical Corporation (HMC), which provides about 80% of healthcare services in Qatar. Data were collected for the period between 2015 and 2018. During this time period, 6,705 specimens were collected from patients with suspected meningitis attending HMC and primary healthcare centers. These specimens were tested for a panel of viruses using the "FTD Viral meningitis" multiplex real-time PCR kit that detects Adenovirus (ADV), Human herpesvirus 1&2 (HSV1 and HSV2), Epstein–Barr virus (EBV), Enteroviruses (EV), Cytomegalovirus (CMV), Varicella zoster virus (VZV), and Parechovirus (PV).

Results: Only 10.9% (732/6,705) of all suspected meningitis cases were caused by viral agents. 60.9% of the reported cases were males, compared to 39.1% in females. Most of the infections (73.9%) were reported in children younger than 10 years of age. EV were identified as the main causative agent (68.7%), followed by EBV (7.5%) and ADV (6.8%). Other viral agents including VZV, PV, HSV-1, and HSV-2 were also detected with a lower frequency. Confirmed VM were more prevalent among Qatari subjects compared to other nationalities. We observed no specific seasonality of viral agents, but a slight rise was recorded during the spring seasons (March to June). Fever (59.4%, 435/732) and acute central nervous system (CNS) infection (15.6%, 114/732) were initial symptoms of most cases.

Conclusion: This is the first report about the molecular epidemiology of VM in Qatar. In line with the international records, our data showed that EV is responsible for 68.7% of Qatar's VM cases. Further studies are needed to genotype and serotype the identified viruses.

Keywords: viral meningitis, epidemiology, enterovirus, genotyping, clinical outcome

Am J Nucl Med Mol Imaging 2021;11(3):188-195
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0128458

Original Article

^{18}F-FDOPA and ^{68}Ga-dotatate PET imaging in congenital hyperinsulinism

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Received December 17, 2020; Accepted May 7, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Congenital hyperinsulinism (CHI) occurs most commonly in infants but may also be discovered in older children. It presents with recurrent episodes of hypoglycemia due to high endogenous insulin levels. There is a focal and diffuse form of the disease depending on the extent of pancreatic involvement. Hyperplasia of the islet cells results in hyperfunctioning pancreatic β cells and the ensuing clinical disease. Medical treatment fails in several patients and surgery has been shown to be very effective in improving prognosis and even resolution of disease in the focal form. Several genetic mutations have been uncovered and these may also be predictive of prognosis. Anatomical imaging alone including ultrasound, CT and MRI are rarely able to detect any abnormality in the pancreas. PET plays a major role in the distinction between the focal and diffuse forms of the disease. It also guides surgical intervention by providing information on the location of the focal hyperfunctioning islet cells. Imaging children and infants in this disease is quite challenging. We propose to show the benefit of using two PET tracers in this disease. ^{18}F-FDOPA has been used quite successfully in the evaluation of CHI. ^{68}Ga-DOTATATE has also been described to be helpful although inferior to ^{18}F-FDOPA. We illustrate imaging of CHI patients in 3 different scans and briefly review the literature. ^{18}F-FDOPA as described in the literature is superior but when unavailable ^{68}Ga-DOTATATE may be a reasonable alternative.

Keywords: CHI, congenital hyperinsulinism, DOTATATE, FDOPA, hyperinsulinism, nesidioblastosis, PHI, PHH, persistent hyperinsulinemic hypoglycemia

Introduction

Congenital hyperinsulinism (CHI) previously known as nesidioblastosis or persistent hyperinsulinemic hypoglycemia of infancy occurs most commonly in infants but may also be discovered in older children. It is a congenital disorder due to over-secretion of insulin and does not include acquired conditions of persistent hypoglycemia [1]. Hyperplasia of the islet cells results in hyperfunctioning pancreatic β cells and the ensuing clinical disease. The goal is early diagnosis and treatment in order to prevent any neurological sequelae (i.e developmental delay, seizures) and try to prevent the development of postsurgical diabetes. In some cases, CHI can be transient and will self-resolve by 3-4 months of age. However, in the persistent form of CHI optimal control of blood sugar levels is important in order to avoid any sequelae. A variety of nutritional and medication-based interventions are used to maintain euglycemia and avoid any neurological sequelae. When the latter fails surgical interventions are performed. Long term development in the diffuse form of CHI of glucose intolerance and insulin-dependent diabetes mellitus has been described to occur by 14 years of age in 100% and 91% respectively of 58 patients who underwent subtotal pancreatectomy [2]. Arya et al also reported similar findings [3]. Hence medical treatment fails in several patients and surgery has been shown to be very effective in improving prognosis and even resolution of disease more so in the focal form. Prognosis is therefore excellent in the focal form of CHI when successful surgical resection of the focal lesion is performed. Several genetic mutations have been uncovered and these may also be predictive of prognosis [4-7]. PET plays a major

COVID-19 versus SARS: A Comparative Review

Short running title: COVID-19 versus SARS.

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Abstract: The two genetically similar severe acute respiratory syndrome coronaviruses, SARS-CoV-1 and SARS-CoV-2, have each been responsible for global epidemics of vastly different scales. Although both viruses arose from similar origins, they quickly diverged due to differences in their transmission dynamics and spectrum of clinical presentations. The potential involvement of multiple organs systems, including the respiratory, cardiac, gastrointestinal and neurological, during infection necessitates a comprehensive understanding of the clinical pathogenesis of each virus. The management of COVID-19, initially modelled after SARS and other respiratory illnesses, has continued to evolve as we accumulate more knowledge and experience during the pandemic, as well as develop new therapeutics and vaccines. The impact of these two coronaviruses has been profound for our health care and public health systems, and we hope that the lessons learned will not only bring the current pandemic under control, but also prevent and reduce the impact of future pandemics.

Keywords: COVID-19; SARS; Coronavirus: Infectious Disease; Public Health

Stem Cell Research 54 (2021) 102433

Contents lists available at ScienceDirect

Stem Cell Research

journal homepage: www.elsevier.com/locate/scr

Lab Resource: Single Cell Line

An induced pluripotent stem cell line derived from a patient with neonatal diabetes and Fanconi-Bickel syndrome caused by a homozygous mutation in the *SLC2A2* gene

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A B S T R A C T

Recessive mutations in the glucose transporter gene *SLC2A2 (GLUT2)* lead to permanent neonatal diabetes (PNDM) and Fanconi Bickel Syndrome (FBS). Here, we generated an induced pluripotent stem cell (iPSC) line, QBRIi012-A, from a 24-month-old boy with FBS and PNDM due to homozygous nonsense mutation in the *SLC2A2* gene (c.901C > T). The QBRIi012-A was fully characterized using different approaches. The cell line showed normal karyotype and was able to differentiate into the three germ layers *in vitro*. This iPSC line provides a novel human cell model to understand the pathophysiology of FBS and diabetes associated with *SLC2A2* defects.

Resource Table

Unique stem cell line identifier	QBRIi012-A
Alternative name(s) of stem cell line	*GLUT2*-exo-mut iPSCs
Institution	Qatar Biomedical research institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar
Contact information of distributor	Essam M. Abdelalim (emohamed@hbku.edu.qa)
Type of cell line	iPSC
Origin	Human
Additional origin info	Age: 24 months Sex: Male Ethnicity: Palestinian
Cell Source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector contains OCT3/4, SOX2, c-MYC, and KLF4
Genetic Modification	YES
Type of Modification	Hereditary
Associated disease	Fanconi-Bickel syndrome (FBS) and permanent neonatal diabetes (PNDM)
Gene/locus	Gene: *SLC2A2* Locus: 3q26.2 Mutation: c.901 C>T in exon 6
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	*Date cell line archived or deposited in repository*
Cell line repository/bank	N/A
Ethical approval	The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018-002).

1. Resource utility

We established an iPSC line from a patient with a homozygous nonsense mutation in the *SLC2A2* gene. This iPSC line provides a novel human model for investigating the role of GLUT2 in the development of Fanconi-Bickel syndrome (FBS) and diabetes.

2. Resource details

The glucose transporter 2 (GLUT2) facilitates the glucose uptake and

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https://doi.org/10.1016/j.scr.2021.102433
Received 19 May 2021; Received in revised form 11 June 2021; Accepted 13 June 2021
Available online 21 June 2021

Human AGR2 Deficiency Causes Mucus Barrier Dysfunction and Infantile Inflammatory Bowel Disease

Short Title: AGR2 deficiency causes infantile IBD

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Synopsis:

This report describes the discovery of a human AGR2 deficiency causing monogenic infantile inflammatory bowel disease due to goblet cell depletion and mucus barrier defect.

Abstract

BACKGROUNDS AND AIM: The gastrointestinal epithelium plays a crucial role in maintaining homeostasis with the gut microbiome. Mucins are essential for intestinal barrier function and serve as a scaffold for antimicrobial factors. MUC2 is the major intestinal gel-forming mucin produced predominantly by goblet cells. Goblet cells express AGR2, a protein disulfide isomerase (PDI) that is crucial for proper processing of gel-forming mucins. Here, we investigated two siblings who presented with severe infantile onset inflammatory bowel disease. **METHODS:** We performed whole genome sequencing to identify candidate variants. We quantified goblet cell numbers using H&E histology and investigated the expression of gel-forming mucins, stress markers, and goblet cell markers using immunohistochemistry. AGR2-MUC2 binding was evaluated using co-immunoprecipitation. Endoplasmic reticulum (ER) stress regulatory function of mutant AGR2 was examined by expression studies in HEK293T using tunicamycin to induce ER stress. **RESULTS:** Both affected siblings were homozygous for a missense variant in *AGR2*. Patient biopsies showed reduced goblet cells, depletion of MUC2, MUC5AC, and MUC6, upregulation of AGR2, and elevated ER stress. The mutant AGR2 showed reduced capacity to bind MUC2 and alleviate tunicamycin-induced ER stress. **CONCLUSIONS:** Phenotype-genotype segregation, functional experiments, and the striking similarity of the human phenotype to the *AGR2*$^{-/-}$ mouse models suggest that the AGR2 missense variant is pathogenic. The Mendelian deficiency of AGR2, termed “Enteropathy caused by AGR2 deficiency, Goblet cell Loss, and ER Stress” (EAGLES), results in a mucus barrier defect, the inability to mitigate ER stress, and causes infantile onset IBD.

Key words: **AGR2; MUC2; ER stress; intestinal metaplasia; Goblet cells,**

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In vitro Interleukin-7 treatment partially rescues MAIT cell dysfunction caused by SARS-CoV-2 infection

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MAIT cells have been shown to be activated upon several viral infections in a TCR-independent manner by responding to inflammatory cytokines secreted by antigen-presenting cells. Recently, a few studies have shown a similar activation of MAIT cells in response to severe acute respiratory coronavirus 2 (SARS-CoV-2) infection. In this study, we investigate the effect of SARS-CoV-2 infection on the frequency and phenotype of MAIT cells by flow cytometry, and we test in vitro stimulation conditions on the capacity to enhance or rescue the antiviral function of MAIT cells from patients with coronavirus disease 2019 (COVID-19). Our study, in agreement with recently published studies, confirmed the decline in MAIT cell frequency of hospitalized donors in comparison to healthy donors. MAIT cells of COVID-19 patients also had lower expression levels of TNF-alpha, perforin and granzyme B upon stimulation with IL-12 + IL-18. 24 h' incubation with IL-7 successfully restored perforin expression levels in COVID-19 patients. Combined, our findings support the growing evidence that SARS-CoV-2 is dysregulating MAIT cells and that IL-7 treatment might improve their function, rendering them more effective in protecting the body against the virus.

Mucosal-associated invariant T (MAIT) cells are a sub-population of innate T lymphocytes with effector-like properties[1]. They are mainly found in the blood, lung, liver, and mucosa serving as sentinels against microbial and fungal infection[1,2]. Upon activation, they secrete pro-inflammatory cytokines and can kill bacteria or viral-infected cells by secretion of the cytolytic molecules granzyme B and perforin[3]. MAIT cells have been shown to be activated during human viral infections such as dengue virus, hepatitis C virus, and influenza virus[4]. MAIT cell activation correlates with disease severity in acute dengue infection[5], and the reconstitution of MAIT cell levels in peripheral blood was suggested to have a positive outcome in HIV patients[6]. MAIT cells can be activated in viral infections in response to IL-12 or IL-15 together with IL-18[7,8], and IL-7 is known to enhance the production of cytolytic molecules by these cells[8]. One study showed that the use of IL-7 alongside anti-retroviral therapy increased the number and frequency of MAIT cells in the peripheral blood of patients chronically infected with HIV[9].

The effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the immune system has been investigated in several studies; the most significant findings included a correlation between the severity

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nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01446-y

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mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar

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The SARS-CoV-2 pandemic continues to be a global health concern. The mRNA-1273 (Moderna) vaccine was reported to have an efficacy of 94.1% at preventing symptomatic COVID-19 due to infection with 'wild-type' variants in a randomized clinical trial. Here, we assess the real-world effectiveness of this vaccine against SARS-CoV-2 variants of concern, specifically B.1.1.7 (Alpha) and B.1.351 (Beta), in Qatar, a population that comprises mainly working-age adults, using a matched test-negative, case-control study design. We show that vaccine effectiveness was negligible for 2 weeks after the first dose, but increased rapidly in the third and fourth weeks immediately before administration of a second dose. Effectiveness against B.1.1.7 infection was 88.1% (95% confidence interval (CI): 83.7–91.5%) ≥14 days after the first dose but before the second dose, and was 100% (95% CI: 91.8–100.0%) ≥14 days after the second dose. Analogous effectiveness against B.1.351 infection was 61.3% after the first dose (95% CI: 56.5–65.5%) and 96.4% after the second dose (95% CI: 91.9–98.7%). Effectiveness against any severe, critical or fatal COVID-19 disease due to any SARS-CoV-2 infection (predominantly B.1.1.7 and B.1.351) was 81.6% (95% CI: 71.0–88.8%) and 95.7% (95% CI: 73.4–99.9%) after the first and second dose, respectively. The mRNA-1273 vaccine is highly effective against B.1.1.7 and B.1.351 infections, whether symptomatic or asymptomatic, and against any COVID-19 hospitalization and death, even after a single dose.

In a randomized clinical trial, the mRNA-1273 (Moderna) vaccine had a reported efficacy of 94.1% in preventing symptomatic coronavirus disease 2019 (COVID-19) due to infection with wild-type variants[1]. The first immunization using this vaccine in Qatar was recorded on 28 December 2020, but mass vaccination did not start until late February 2021 with the accelerated arrival of vaccine shipments. As the vaccination campaign was scaled up, the country experienced two back-to-back severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) waves that were triggered by the introduction and expansion of the B.1.1.7 (Alpha[2]) and B.1.351 (Beta[2]) variants[3]. This created a unique epidemiological opportunity to assess the real-world effectiveness of this vaccine against infection with these variants of concern, as well as against severe forms of COVID-19 disease.

Results

Study population. Between 28 December 2020 and 10 May 2021, 256,037 individuals in Qatar received at least one dose of the mRNA-1273 vaccine and 181,304 completed the two-dose regimen. Among those with a vaccination record, the median dates at first and second dose were 5 and 29 April 2021, respectively. The median time elapsing between the first and second doses was 28 days (interquartile range (IQR): 28–29 days), with 94.6% of individuals receiving their second dose ≤30 days after the first dose.

Flowcharts describing the population selection process for investigation and estimation of vaccine effectiveness are presented in Extended Data Figs. 1–3, and the demographic characteristics of the sample for each outcome of vaccine effectiveness are presented in Table 1. Median age in the study sample for estimation of vaccine effectiveness against infection with B.1.1.7 was 31 years (IQR: 19–38), against infection with B.1.351 was 32 years (IQR: 25–39) and against severe, critical or fatal disease was 43 years (IQR: 37–51). Of note is that Qatar has a young and diverse demographic, where only 9% of its resident population are >50 years of age and 89% are expatriates from >150 countries[4,5].

Weekly rounds of viral genome sequencing from 8 March to 10 May 2021 identified B.1.351 (n = 369; 64.4%), B.1.1.7 (n = 58;

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Journal of Adolescent Health 69 (2021) 1032–1040

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Using Mobile Health to Improve Asthma Self-Management in Early Adolescence: A Pilot Randomized Controlled Trial

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Article history: Received February 17, 2021; Accepted June 7, 2021
Keywords: Asthma; Self-management; Apps; mHealth; Applications

A B S T R A C T

Purpose: Early adolescence is an important developmental period where youth take primary responsibility for asthma self-management. Helpful caregiver support during this time is pivotal in determining whether early adolescents successfully develop asthma self-management behaviors. AIM2ACT is a dyadic mobile health intervention designed to increase helpful caregiver support as early adolescents engage in asthma self-management behaviors. We conducted a pilot randomized controlled trial to determine the feasibility and acceptability of AIM2ACT and conduct preliminary tests of efficacy.
Methods: We randomized adolescents (12–15 years old) and a caregiver to receive AIM2ACT (n = 17) or a self-guided attention control condition (n = 16) for 20 weeks. We conducted assessment visits at baseline, postintervention, and 4-month follow-up. Outcomes included family asthma management (primary outcome), adolescent asthma control, lung function (forced expiratory volume in 1 second), asthma-related quality of life, asthma management self-efficacy, and family communication.
Results: We randomized 33 dyads and had 100% retention in the trial among AIM2ACT participants. Dyads frequently engaged with AIM2ACT (M = 21 days for adolescents, 32.65 days for caregivers) and reported very high satisfaction with content, functionality, and helpfulness. Participants randomized to AIM2ACT had significant improvements in asthma control scores ($p = .04$) compared to control that surpassed the minimally clinically important difference threshold. Although not statistically significant, the magnitude of improvements in family asthma management, asthma-related quality of life, and family communication was larger in the AIM2ACT group.
Conclusions: AIM2ACT is a feasible and acceptable dyadic mobile health asthma self-management intervention that improves asthma control.

IMPLICATIONS AND CONTRIBUTION

Early adolescents commonly report asthma self-management difficulties. Helpful caregiver support is pivotal in determining whether adolescents master asthma self-management behaviors, making this a key intervention target. AIM2ACT, a dyadic mobile health intervention designed to increase helpful caregiver support of early adolescents' asthma self-management, is feasible, acceptable, and improves asthma control.

Asthma affects >6 million youth in the U.S. [1] and is a leading cause of morbidity [2]. Optimal asthma self-management entails self-monitoring symptoms, avoiding triggers, and, for those with persistent subtypes, consistently taking inhaled corticosteroids [3]. National asthma guidelines indicate that developing and

Conflicts of interest: The authors have no conflicts of interest to disclose.
Clinical Trial Registration: NCT02302040.

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1054-139X/
https://doi.org/10.1016/j.jadohealth.2021.06.011

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Gene therapy for spinal muscular atrophy: the Qatari experience

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by hypotonia, progressive muscle weakness, and wasting. Onasemnogene abeparvovec (Zolgensma®) is a novel gene therapy medicine, FDA-approved in May 2019 for the treatment of SMA. This study aimed to describe Qatari experience with onasemnogene abeparvovec by reviewing the clinical outcomes of 9 SMA children (7 SMA type 1 and 2 with SMA type 2) aged 4–23 months treated between November 2019 and July 2020. Children <2 years with 5q SMA with a bi-allelic mutation in the *SMN1* gene were eligible for gene therapy. Liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin), platelet count, coagulation profile, troponin-I levels, and motor scores (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND]), were regularly monitored following gene therapy. All patients experienced elevated AST or ALT, two experienced high prothrombin time, and one experienced elevated bilirubin; all of these patients were asymptomatic. Furthermore, one event of vomiting after infusion was reported in one patient. Significant improvements in CHOP INTEND scores were observed following therapy. This study describes the short-term outcomes and safety of onasemnogene abeparvovec, which is well tolerated and shows promise for early efficacy.

Gene Therapy; https://doi.org/10.1038/s41434-021-00273-7

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder and the most common fatal inherited disease of infancy resulting from a genetic mutation in the *SMN1* gene located on chromosome 5q13 [1]. Patients with SMA experience progressive muscle weakness and wasting resulting from loss of motor neurons in the spinal cord anterior horn cells [2]. The incidence of SMA is ~1 in 6000–10,000 live births, with the majority (60%) being SMA type 1 [3]. In the Middle East, incidence of SMA has been reported to range from 10 to 193 per 100,000 births [4–7]. SMA incidence of up to 40-fold higher than the Western world [4] is potentially a result of the increased rate of consanguineous marriages in the region. Consanguinity was reported in 45.5% of SMA patients in Egypt [8]. Globally, carrier frequency has been estimated to range between 1 in 45 and 1 in 100 people [3]. The carrier frequency in the region, however, is thought to be much higher, with 1 in 20 normal individuals unrelated to SMA patients being carriers [9].

Nusinersen (Spinraza®), the first drug approved for the treatment of SMA, is an antisense oligonucleotide, which increases the amount of functional SMN protein in the central nervous system by alternative splicing of the *SMN2* gene [10]. Nusinersen has been shown to improve motor function in SMA type 1 and 2 patients, as well as increase survival in SMA type 1 patients [10]. Onasemnogene abeparvovec (Zolgensma®) is a novel gene therapy for treatment of SMA, which uses the adeno-associated virus vector to deliver the functional *SMN1* gene to the motor neurons [11]. Onasemnogene abeparvovec, approved by the US Food and Drug Administration (FDA) in May 2019, has been shown to improve motor function in infants with severe SMA type 1 [12]. Such treatments are able to slow disease progression or prevent disease development if used prior to symptoms development; nevertheless, multidisciplinary management and support is required to treat the complications of the disease [2].

Studies describing the use of onasemnogene abeparvovec for the treatment of SMA are limited: clinical trials have been undertaken in the USA [11–13]. Furthermore, two retrospective cohort studies in the USA and Germany have also been conducted [14, 15]. Whilst these studies have assessed the safety and efficacy of onasemnogene abeparvovec, there is the need for greater evidence worldwide including data from the Middle East where the incidence of SMA is greater.

The aim of this case series paper is to describe the first Qatari experience with the use of onasemnogene abeparvovec in children with SMA. In this paper, an overview of the treatment pathway, screening for the likely adverse events by assessing

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Received: 8 December 2020 Revised: 2 June 2021 Accepted: 16 June 2021
Published online: 19 July 2021

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[Intervention Review]

Interventions for the management of abdominal pain in ulcerative colitis

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Editorial group: Cochrane Gut Group.
Publication status and date: New, published in Issue 7, 2021.

Citation: Sinopoulou V, Gordon M, Dovey TM., Akobeng AK. Interventions for the management of abdominal pain in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No.: CD013589. DOI: 10.1002/14651858.CD013589.pub2.

ABSTRACT

Background

Ulcerative colitis (UC) is a chronic inflammation of the colon characterised by periods of relapse and remission. It starts in the rectum and can extend throughout the colon. UC and Crohn's disease (CD) are the most common inflammatory bowel diseases (IBDs). However, UC tends to be more common than CD. It has no known cure but can be managed with medication and surgery. However, studies have shown that abdominal pain persists in up to one-third of people with UC in remission. Abdominal pain could be a symptom of relapse of the disease due to adverse effects of medication, surgical complications and strictures or adhesions secondary to UC.

Objectives

To assess the efficacy and safety of interventions for managing abdominal pain in people with ulcerative colitis.

Search methods

We searched CENTRAL, MEDLINE and five other databases and clinical trials registries on 28 April 2021. We contacted authors of relevant studies and ongoing or unpublished trials that may be relevant to the review. We also searched references of trials and systematic reviews for any additional trials.

Selection criteria

All published, unpublished and ongoing randomised trials that compared interventions for the management of abdominal pain with other active interventions or standard therapy, placebo or no therapy were included. People with both active and inactive disease were included. We excluded studies that did not report on any abdominal pain outcomes.

Data collection and analysis

Two review authors independently conducted data extraction and 'Risk of bias' assessments. We analysed data using Review Manager 5. We expressed dichotomous and continuous outcomes as risk ratios (RRs) and mean differences (MDs), respectively, with 95% confidence intervals. We assessed the certainty of the evidence using the GRADE methodology.

Main results

We included five studies (360 randomised participants). Studies considered mainly participants in an inactive state of the disease.

No conclusions could be drawn about the efficacy of any of the interventions on pain frequency, pain intensity, and treatment success. The certainty of the evidence was very low for all comparisons because of imprecision due to sparse data, and risk of bias.

One study compared a low FODMAPs diet (n=13) to a sham diet (n=13). The evidence is very uncertain about the effect of this treatment on pain frequency (MD -4.00, 95% CI -20.61 to 12.61) and intensity (MD -9.00, 95% CI -20.07 to 2.07). Treatment success was not reported.

Original research

Delineating the genotypic and phenotypic spectrum of *HECW2*-related neurodevelopmental disorders

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2021-107871).

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Received 1 April 2021
Accepted 6 July 2021
Published Online First 28 July 2021

To cite: Acharya A, Kavus H, Dunn P, *et al*. *J Med Genet* 2022;**59**:669–677.

ABSTRACT

Background Variants in *HECW2* have recently been reported to cause a neurodevelopmental disorder with hypotonia, seizures and impaired language; however, only six variants have been reported and the clinical characteristics have only broadly been defined.

Methods Molecular and clinical data were collected from clinical and research cohorts. Massive parallel sequencing was performed and identified individuals with a *HECW2*-related neurodevelopmental disorder.

Results We identified 13 novel missense variants in *HECW2* in 22 unpublished cases, of which 18 were confirmed to have a de novo variant. In addition, we reviewed the genotypes and phenotypes of previously reported and new cases with *HECW2* variants (n=35 cases). All variants identified are missense, and the majority of likely pathogenic and pathogenic variants are located in or near the C-terminal HECT domain (88.2%). We identified several clustered variants and four recurrent variants (p.(Arg1191Gln);p.(Asn1199Lys);p.(Phe1327Ser);p.(Arg1330Trp)). Two variants, (p.(Arg1191Gln);p.(Arg1330Trp)), accounted for 22.9% and 20% of cases, respectively. Clinical characterisation suggests complete penetrance for hypotonia with or without spasticity (100%), developmental delay/intellectual disability (100%) and developmental language disorder (100%). Other common features are behavioural problems (88.9%), vision problems (83.9%), motor coordination/movement (75%) and gastrointestinal issues (70%). Seizures were present in 61.3% of individuals. Genotype-phenotype analysis shows that HECT domain variants are more frequently associated with cortical visual impairment and gastrointestinal issues. Seizures were only observed in individuals with variants in or near the HECT domain.

Conclusion We provide a comprehensive review and expansion of the genotypic and phenotypic spectrum of *HECW2* disorders, aiding future molecular and clinical diagnosis and management.

INTRODUCTION

Neurodevelopmental disorders (NDDs) affect >3% of children worldwide and can often pose a significant burden on both the individual and their family. NDDs with intellectual disability (ID) are characterised by cognitive impairment and challenges with adaptive behaviour.[1] Genetic factors have been shown to play an important role in the aetiology of NDDs, especially in more severe NDDs.[2 3] Family based sequencing approaches have demonstrated that undiagnosed cases of ID are largely caused by de novo variants in genes and/or pathways which genetically overlap with other NDDs.[4–7]

HECW2, also known as NEDL2, is a member of the Nedd4 family of mammalian E3 ubiquitin ligases involved in regulation of p73 stability.[8 9] Several members of Nedd4 are involved in cell signalling pathways that directly affect proliferation, migration and differentiation through glial cell line-derived neurotrophic factor (GDNF)/Ret signalling.[8 10] HECW2 combines directly with p73, a member of the p53 family that is predominantly expressed in adult brain, heart and lungs and plays a significant role in both adult and embryonal neurogenesis.[8 9 11] Additionally, p73 knockout mice show developmental defects of the central nervous system, embryonal and adult neurogenesis and display a reduction in cortical thickness due to the loss of mature cortical neurons.[11] Animal models of HECW2 show severe abnormalities in early development. Hecw2 null mice die within 2 weeks after birth with progressive bowel motility defect and a decreased number of enteric neurons.[10] Knockdown of *hecw2a* in zebrafish led to early morphological abnormalities of the brain, spinal cord, eyes, the body trunk and tail.[12]

Recently, independent studies have identified 6 de novo heterozygous likely pathogenic and pathogenic missense variants in *HECW2* in 13 families with ID/developmental delay, hypotonia, seizures and other variable features.[12–18] In this study, we include 22 new cases and expand the

Pediatric Cardiology
https://doi.org/10.1007/s00246-021-02671-5

REVIEW ARTICLE

Congenital Aorto-Cardiac Connections (CACC) Revisited: Introduction of a Novel Anatomic-therapeutic Classification

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Received: 5 April 2021 / Accepted: 23 June 2021

Abstract
Abnormal congenital aorto-cardiac communications (CACC) are a heterogeneous constellation of anomalies that provide an abnormal connection between the aorta and other cardiac chambers or structures, including the atria, ventricles, the main pulmonary artery, and the coronary sinus. The current terminology of CACC has significant errors and shortcomings including inconsistent and interchangeable use of terms of fistula and tunnel and lack of an inclusive classification with practical information on therapeutic management. The aims of this study were threefold: firstly, to perform a concise narrative review of congenital pathologic connections between the aortic root and cardiac chambers which include rupture of congenital sinus of Valsalva aneurysm, aorto-left ventricular and less commonly right ventricular tunnels, coronary cameral fistulas, and aorto-atrial communications; secondly, to investigate the differentiating features of the so-called aorta right atrial tunnel (ARAT), with and without coronary artery take-off from the tunnel, and coronary cameral fistula (CCF) by applying a differential diagnostic assistance toolbox to two groups of patients with ARAT and CCF; and lastly, to propose a practical and inclusive anatomic-therapeutic classification for CACCs. The two main cornerstones of the proposed classification are the type of the connector between the aorta and cardiac chamber (hole versus passage) and the nature of the connecting passage (anatomic versus extra-anatomic). We classified CACCs into three types. Depending on the intramural versus extramural course of the extra-anatomic connecting passage, type 3 is further subdivided into type 3A and type 3B.

Keywords Congenital aorto-cardiac communications · Aorto-ventricular tunnel · Aorta right atrial tunnel · Coronary cameral fistula · Rupture of congenital sinus of Valsalva aneurysm

Introduction

Abnormal congenital aorto-cardiac communications (CACC) are a heterogeneous constellation of anomalies that provide an abnormal connection between the aorta and other cardiac chambers or structures, including the atria, ventricles, the main pulmonary artery and the coronary sinus. Excluding anomalous vessels originating from the descending aorta, we are reviewing the congenital pathologic connections between the aortic root and cardiac chambers, which include rupture of congenital aneurysm of sinus of Valsalva, aorto-left ventricular and less commonly right ventricular tunnels, coronary cameral fistulas, and aorto-atrial communications [1, 2]. The current terminology found in the literature has significant errors and shortcomings. First and foremost, the main terms of fistula and tunnel are frequently used inconsistently and interchangeably for quite different anatomical pathologies. Either the same pathologic anatomies are called differently

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Published online: 29 July 2021

Cormier-Daire *et al. Orphanet J Rare Dis* (2021) 16:333
https://doi.org/10.1186/s13023-021-01971-6

Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

The first European consensus on principles of management for achondroplasia

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Abstract

Achondroplasia is the most common type of skeletal dysplasia, caused by a recurrent pathogenic variant in the fibroblast growth factor receptor 3 (*FGFR3)*. The management of achondroplasia is multifaceted, requiring the involvement of multiple specialties across the life course. There are significant unmet needs associated with achondroplasia and substantial differences in different countries with regard to delivery of care. To address these challenges the European Achondroplasia Forum (EAF), a network of senior clinicians and orthopaedic surgeons from Europe and the Middle East representative of the achondroplasia clinical community, came together with the overall aim of improving patient outcomes. The EAF developed a consensus on guiding principles of management of achondroplasia to provide a basis for developing optimal care in Europe. All members of the EAF were invited to submit suggestions for guiding principles of management, which were consolidated and then discussed during a meeting in December 2020. The group voted anonymously on the inclusion of each principle, with the requirement of a 75% majority at the first vote to pass the principle. A vote on the level of agreement was then held. A total of six guiding principles were developed, which cover management over the lifetime of a person with achondroplasia. The principles centre on the lifelong management of achondroplasia by an experienced multidisciplinary team to anticipate and manage complications, support independence, and improve quality of life. There is focus on timely referral to a physician experienced in the management of achondroplasia on suspicion of the condition, shared decision making, the goals of management, access to adaptive measures to enable those with achondroplasia to access their environment, and the importance of ongoing monitoring throughout adolescence and adulthood. All principles achieved the 75% majority required for acceptance at the first vote (range 91–100%) and a high level of agreement (range 8.5–9.6). The guiding principles of management for achondroplasia provide all healthcare professionals, patient advocacy groups and policy makers involved in the management of achondroplasia with overarching considerations when developing health systems to support the management of achondroplasia.

Keywords: Achondroplasia, Guiding principles, European Achondroplasia Forum

Background

Achondroplasia is the most common form of skeletal dysplasia, with an estimated prevalence of 3.72–4.6 per 100,000 births [1, 2]. It is caused by a recurrent pathogenic variant in the fibroblast growth factor receptor 3 (*FGFR3*) and is characterised by disproportionate short stature, macrocephaly, frontal bossing, mid-face hypoplasia and trident-shaped hands [3, 4]. Complications of

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Original Research

Can commercial automated immunoassays be utilized to predict neutralizing antibodies after SARS-CoV-2 infection? A comparative study between three different assays

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1. Abstract

Background: High-throughput assays that can infer neutralizing activity against SARS-CoV-2 are of great importance for assessing the immunity induced by natural infection and COVID-19 vaccines. We aimed to evaluate the performance and degree of correlation of three fully automated anti-SARS-CoV-2 immunoassays with neutralization activity using a surrogate virus-neutralizing test (sVNT) from GenScript, targeting the receptor-binding domain. **Methods**: 110 sera collected from PCR-confirmed asymptomatic COVID-19 individuals were tested for neutralizing antibodies (nAbs) using the sVNT. Positive samples were tested on three automated immunoassays targeting different viral antigens: Mindray CL-900i®, Abbott Architect, and Ortho VITROS®. The diagnostic sensitivity, specificity, agreement, and correlation with the sVNT were assessed. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal thresholds for predicting the presence of neutralizing activity by each assay. **Results**: All three assays showed 100% specificities.

Submitted: 19 April 2021 Revised: 22 May 2021 Accepted: 4 June 2021 Published: 30 July 2021

frontiers in Genetics

REVIEW
published: 23 July 2021
doi: 10.3389/fgene.2021.721556

Metabolomics in the Diagnosis and Prognosis of COVID-19

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Coronavirus disease 2019 (COVID-19) pandemic triggered an unprecedented global effort in developing rapid and inexpensive diagnostic and prognostic tools. Since the genome of SARS-CoV-2 was uncovered, detection of viral RNA by RT-qPCR has played the most significant role in preventing the spread of the virus through early detection and tracing of suspected COVID-19 cases and through screening of at-risk population. However, a large number of alternative test methods based on SARS-CoV-2 RNA or proteins or host factors associated with SARS-CoV-2 infection have been developed and evaluated. The application of metabolomics in infectious disease diagnostics is an evolving area of science that was boosted by the urgency of COVID-19 pandemic. Metabolomics approaches that rely on the analysis of volatile organic compounds exhaled by COVID-19 patients hold promise for applications in a large-scale screening of population in point-of-care (POC) setting. On the other hand, successful application of mass-spectrometry to detect specific spectral signatures associated with COVID-19 in nasopharyngeal swab specimens may significantly save the cost and turnaround time of COVID-19 testing in the diagnostic microbiology and virology laboratories. Active research is also ongoing on the discovery of potential metabolomics-based prognostic markers for the disease that can be applied to serum or plasma specimens. Several metabolic pathways related to amino acid, lipid and energy metabolism were found to be affected by severe disease with COVID-19. In particular, tryptophan metabolism via the kynurenine pathway were persistently dysregulated in several independent studies, suggesting the roles of several metabolites of this pathway such as tryptophan, kynurenine and 3-hydroxykynurenine as potential prognostic markers of the disease. However, standardization of the test methods and large-scale clinical validation are necessary before these tests can be applied in a clinical setting. With rapidly expanding data on the metabolic profiles of COVID-19 patients with varying degrees of severity, it is likely that metabolomics will play an important role in near future in predicting the outcome of the disease with a greater degree of certainty.

Keywords: COVID-19, SARS-CoV-2, metabolomics, diagnosis, prognosis, volatile organic compounds, mass-spectrometry, nuclear magnetic resonance

OPEN ACCESS

Edited by:
Puthen Veettil Jithesh,
Hamad Bin Khalifa University, Qatar

Reviewed by:
Liuyang Wang,
Duke University, United States
Ingrid Fricke-Galindo,
Instituto Nacional de Enfermedades Respiratorias (INER), Mexico

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Specialty section:
This article was submitted to Human and Medical Genomics, a section of the journal Frontiers in Genetics

Received: *07 June 2021*
Accepted: *05 July 2021*
Published: *23 July 2021*

Citation:
Hasan MR, Suleiman M and Pérez-López A (2021) Metabolomics in the Diagnosis and Prognosis of COVID-19. Front. Genet. 12:721556. doi: 10.3389/fgene.2021.721556

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has created massive disruptions and loss of human lives around the world. As of May 2021, the number of laboratory-confirmed cases exceeded 170 million and 3.6 million people succumbed to the disease (WHO, 2020a). The outbreak of COVID-19 emerged at the end of 2019 in Wuhan, China in the form of a series of

^{68}Ga-NODAGA-Exendin-4 PET/CT Improves the Detection of Focal Congenital Hyperinsulinism

Marti Boss*[1], Christof Rottenburger*[2,3], Winfried Brenner[3], Oliver Blankenstein[4], Vikas Prasad[3,5], Sonal Prasad[3,6], Paolo de Coppi[7], Peter Kühnen[4], Mijke Buitinga[1], Pirjo Nuutila[8,9], Timo Otonkoski[10,11], Khalid Hussain[12], Maarten Brom[1], Annemarie Eek[1], Jamshed Bomanji[2], Pratik Shah*[13,14], Martin Gotthardt[1]

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Surgery with curative intent can be offered to congenital hyperinsulinism (CHI) patients, provided that the lesion is focal. Radiolabeled exendin-4 specifically binds the glucagonlike peptide 1 receptor on pancreatic β-cells. In this study, we compared the performance of ^{18}F-DOPA PET/CT, the current standard imaging method for CHI, and PET/CT with the new tracer ^{68}Ga-NODAGA-exendin-4 in the preoperative detection of focal CHI. **Methods:** Nineteen CHI patients underwent both ^{18}F-DOPA PET/CT and ^{68}Ga-NODAGA-exendin-4 PET/CT before surgery. The images were evaluated in 3 settings: a standard clinical reading, a masked expert reading, and a joint reading. The target (lesion)-to-nontarget (normal pancreas) ratio was determined using SUV_{max}. Image quality was rated by pediatric surgeons in a questionnaire. **Results:** Fourteen of 19 patients having focal lesions underwent surgery. On the basis of clinical readings, the sensitivity of ^{68}Ga-NODAGA-exendin-4 PET/CT (100%; 95% CI, 77%–100%) was higher than that of ^{18}F-DOPA PET/CT (71%; 95% CI, 42%–92%). Interobserver agreement between readings was higher for ^{68}Ga-NODAGA-exendin-4 than for ^{18}F-DOPA PET/CT (Fleiss $\kappa = 0.91$ vs. 0.56). ^{68}Ga-NODAGA-exendin-4 PET/CT provided significantly ($P = 0.021$) higher target-to-nontarget ratios (2.02 ± 0.65) than did ^{18}F-DOPA PET/CT (1.40 ± 0.40). On a 5-point scale, pediatric surgeons rated ^{68}Ga-NODAGA-exendin-4 PET/CT as superior to ^{18}F-DOPA PET/CT. **Conclusion:** For the detection of focal CHI, ^{68}Ga-NODAGA-exendin-4 PET/CT has higher clinical sensitivity and better interobserver correlation than ^{18}F-DOPA PET/CT. Better contrast and image quality make ^{68}Ga-NODAGA-exendin-4 PET/CT superior to ^{18}F-DOPA PET/CT in surgeons' intraoperative quest for lesion localization.

Received Mar. 17, 2021; revision accepted May 5, 2021.
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Published online Jul. 2, 2021.

Key Words: congenital hyperinsulinism; focal CHI; diagnostic imaging; ^{68}Ga-NODAGA-exendin-4 PET/CT; ^{18}F-DOPA PET/CT

J Nucl Med 2022; 63:310–315
DOI: 10.2967/jnumed.121.262327

Congenital hyperinsulinism (CHI) is the most common cause of persistent and recurrent hypoglycemia in neonates. It occurs with an incidence of 1 in 35,000–40,000 births (*1*). CHI often presents in neonates as poor feeding, seizures, jitteriness, hypotonia, apnea, cyanosis, hypothermia, or a hypoglycemia-induced life-threatening event (*2*). CHI can also manifest in infancy or childhood and, in rare cases, even in adolescents or young adults (*3*). To avoid brain injury, early diagnosis and proper treatment of CHI are crucial. The diagnosis of CHI is based on clinical findings and hypoglycemic events, combined with inappropriately high insulin or C-peptide levels or low insulinlike growth factor–binding protein 1 levels (*4*,*5*). In diffuse CHI, which accounts for 60%–70% of all cases, there is diffuse involvement of the pancreatic β-cells, with enlarged hyperfunctioning cells that have abnormally large nuclei and abundant cytoplasm (*6*,*7*). This subform is caused by recessive or dominant mutations in the *ABCC8* or *KCNJ11* genes, encoding for the β-cell adenosine triphosphate–sensitive potassium channels. Diffuse CHI is treated primarily with medication, such as octreotide and diazoxide. However, many patients with recessive mutations in the *ABCC8* and *KCNJ11* genes are unresponsive to this therapy, and near-total pancreatectomy may then be the only option to avoid devastating hypoglycemia. Even after such an invasive procedure, some children present with recurring hypoglycemia, requiring further treatment with medication or even reoperation (*8*).

Focal CHI accounts for 30%–40% of all CHI cases associated with the adenosine triphosphate–sensitive potassium channel genes. This form is characterized by focal adenomatous islet cell

Journal of the Endocrine Society, 2021, Vol. 5, No. 10, 1–7
https://doi.org/10.1210/jendso/bvab131
Clinical Research Article

Clinical Research Article

The Epidemiology and Genetic Analysis of Children With Idiopathic Type 1 Diabetes in the State of Qatar

Tasneem Abdel-Karim,[1,*] Basma Haris,[1,*] Houda Afyouni,[1] Shayma Mohammed,[1] Amel Khalifa,[1] Maryam Al-Maadheed,[1] Mahmoud Zyoud,[1] Ahmed Elawwa,[1] Fawziya Al-Khalaf,[1] Goran Petrovski,[1] and Khalid Hussain[1]

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Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; DM, diabetes mellitus; GAD65, glutamic acid decarboxylase (65 kDa); HbA1c, glycated hemoglobin A1c; IA2, islet cell autoantibodies; IAA, insulin autoantibodies; MODY, maturity onset diabetes of the young; TPO, thyroid peroxidase; ZnT8, zinc transporter 8.

Received: 16 May 2021; Editorial Decision: 23 July 2021; First Published Online: 29 July 2021; Corrected and Typeset: 26 August 2021.

Abstract

Context: Idiopathic type 1 diabetes is characterized by the absence of autoantibodies and the underlying mechanisms are not clear.
Objective: We aimed to study the epidemiology, describe the clinical characteristics, and report results of genetic studies in pediatric patients with idiopathic type 1 diabetes.
Methods: This was a prospective study of type 1 diabetes patients attending Sidra Medicine from 2018 to 2020. Autoantibodies (GAD65, IAA, IA-2A, and ZnT8) were measured and genetic testing was undertaken in patients negative for autoantibodies to rule out monogenic diabetes. Demographic and clinical data of patients with idiopathic type 1 diabetes were compared with patients with autoimmune type 1 diabetes.
Results: Of 1157 patients with type 1 diabetes, 63 were antibody-negative. Upon genome sequencing, 4 had maturity onset diabetes of the young (MODY), 2 had Wolfram syndrome, 1 had H syndrome, and 3 had variants of uncertain significance in MODY genes; 53 patients had idiopathic type 1 diabetes. The most common age of diagnosis was 10 to 14 years. C-peptide level was low but detectable in 30 patients (56.6%) and normal in 23 patients (43.4%) The average body mass index was in the normal range and 33% of the patients had a history of diabetic ketoacidosis (DKA).
Conclusion: Four percent of the children had idiopathic type 1 diabetes. There were statistically significant differences in the C-peptide level and insulin requirement between the 2 groups. DKA was less common in the idiopathic group. Mutations in MODY genes suggest the importance of autoantibody testing and genetic screening for known causes

ISSN 2472-1972

Original Article

Parents attitudes toward the human papilloma virus (HPV) vaccine: A new concept in the State of Qatar

Mohamed A. Hendaus[1,2,3], Manasik Hassan[2,3], Moza Alsulaiti[4], Tasabeh Mohamed[4], Reem Mohamed[4], Dure Yasrab[4], Hadeel Mahjoob[4], Ahmed H. Alhammadi[1,2,3]

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Abstract

Background: Human papillomavirus (HPV) is one of the leading causes of cervical and genital cancer in both genders. **Purpose:** To delineate parental attitude regarding HPV in Qatar. **Methods:** A cross-sectional study using a questionnaire was conducted at Sidra Medicine, Qatar. **Results:** A total of 334 questioners were completed. More than 60% of the parents were not aware that HPV can cause cervical and genital cancer. When asked about the level of comfort in giving their children a vaccine that would prevent them from getting genital cancer, 77% of the participants answered "very comfortable." Interestingly, less than 4% of the parents stated that their children's primary care physicians ever mentioned that such a vaccine exists. When asked about the most preferable mode of receiving information regarding the HPV vaccine, 54% preferred the clinician's office, followed by 34% of whom preferred social media. In terms of the preferred age to receive the vaccine, 45% of the participants preferred to administer the vaccine to their children before they were mature enough to understand sexual relations, while 22% recommended vaccination right before marriage and 15% preferred to wait till they were grown up and decide for themselves. Furthermore, only 42% of the caregivers agreed that it is important to explain to their children that the vaccine can protect against some of the sexually transmitted infections. Finally, approximately 20% of the participants were not convinced about the HPV vaccine. **Conclusion:** A large proportion of parents residing in Qatar have a positive perception regarding the HPV vaccine. TheParents' attitudes and perceptions are considered indispensable targets for community health intervention. We will share the result of our study with the ministry of public health in Qatar with a goal to incorporate the HPV vaccine in the National Immunization Schedule.

Keywords: Children, HPV, pediatric, Qatar, vaccine

Introduction

Human papillomavirus (HPV) is transmitted mainly via sexual encounters. Two HPV types (16 and 18) cause 70% of cervical cancers and pre-cancerous cervical lesions. Moreover, HPV can cause cancers of the penis, vagina, anus, vulva, and oropharynx. Globally, the incidence of cervical cancer is around 5,70,000

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Received: 08-06-2020 **Revised:** 05-09-2020
Accepted: 08-09-2020 **Published:** 30-07-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1122_20

How to cite this article: Hendaus MA, Hassan M, Alsulaiti M, Mohamed T, Mohamed R, Yasrab D, *et al*. Parents attitudes toward the human papilloma virus (HPV) vaccine: A new concept in the State of Qatar. J Family Med Prim Care 2021;10:2488-93.

Original Article

Medication take-back programs in Qatar: Parental perceptions

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Abstract

Purpose: To identify parental perception of a take-back program for medications. **Materials and Methods:** A cross-sectional study using a questionnaire was conducted at Hamad Medical Corporation, the only tertiary pediatric hospital in the State of Qatar at the time of the study. Qatar is a rapidly developing country with limited national data on the awareness of medication misuse among adults living with children at home and on the safety practices regarding medication disposal. **Results:** 305 questionnaires were completed (response rate = 90%). More than 80% of parents were in between 20 and 39 years of age, 70% of them were females, and 80% were college graduates. Approximately 90% of participants have immediate relatives who were taking medications for chronic diseases. Almost 60% of parents stated that they keep unused medications at home, whereas 10% were not aware of the fate of the left over medications. Approximately 95% of the parents dispose the expired medications. In terms of the mode of disposing the medications, 66% of caregivers dispose the medication bottle or package in the trash can, whereas 14% remove the medications from the bottles or packages and throw them in the trash, and 15% put them through the drain. When asked if participants read disposal measures in the medication pamphlet, only 10% answered "always," whereas 26% answered "sometimes." Participants were asked if they have heard of any medications take-back programs, 75% answered no, whereas 14% were not sure. However, almost 60% of them will use the take-back program if available and 18% were not sure. **Conclusion:** Parents residing in the State of Qatar have deficiencies in knowledge about medication disposal. Parent's attitudes and perceptions are considered indispensable targets for community health intervention. Our next step is to share our data with the ministry of health to spread awareness about the proper disposal of medicines and take-back programs in Qatar.

Keywords: Children, disposal, medication, pediatric, Qatar, storage

Introduction

Unused medications consist of contaminated, expired, spilt sera, vaccines, and drugs that are no longer needed and need to be disposed of properly.[1] The fate of unused medications has been a concern globally. The reason could be the lack of proper programs to take back those medications. In many parts of the world, medication waste has been a burden on the healthcare system and the economy.[2]

Grandparents' medications comprise 10%–20% of accidental pediatric intoxications in the United States. Storing medication in child-resistant containers does not totally avert a child from gaining access to the drug.[3]

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Received: 10-06-2020 **Revised:** 23-08-2020
Accepted: 30-08-2020 **Published:** 30-07-2021

Access this article online
Quick Response Code:
Website: www.jfmpc.com
DOI: 10.4103/jfmpc.jfmpc_1141_20

How to cite this article: Hendaus MA, Darwish S, Saleh M, Mostafa O, Eltayeb A, Al-Amri M, *et al*. Medication take-back programs in Qatar: Parental perceptions. J Family Med Prim Care 2021;10:2697-702.

SYSTEMATIC REVIEW

Gastrointestinal manifestations of COVID-19 in children: a systematic review and meta-analysis

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Received 4 May 2020
Revised 7 July 2020
Accepted 6 August 2020

To cite: Akobeng AK, Grafton-Clarke C, Abdelgadir I, *et al*. *Frontline Gastroenterology* Epub ahead of print: [please include Day Month Year]. doi:10.1136/flgastro-2020-101529

ABSTRACT

Objectives To summarise the published evidence on the gastrointestinal manifestations of COVID-19 in children and to determine the prevalence of gastrointestinal symptoms.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, CINAHL and the WHO's database of publications on novel coronavirus. We included English language studies that had described original demographic and clinical characteristics of children diagnosed with COVID-19 and reported on the presence or absence of gastrointestinal symptoms. Meta-analysis was conducted using the random-effects model. The pooled prevalence of gastrointestinal symptoms was expressed as proportion and 95% CI.

Results The search identified 269 citations. Thirteen studies (nine case series and four case reports) comprising data for 284 patients were included. Overall, we rated four studies as having a low risk of bias, eight studies as moderate and one study as high risk of bias. In a meta-analysis of nine studies, comprising 280 patients, the pooled prevalence of all gastrointestinal symptoms was 22.8% (95% CI 13.1% to 35.2%; I^2=54%). Diarrhoea was the most commonly reported gastrointestinal symptom followed by vomiting and abdominal pain.

Conclusions Nearly a quarter of children with COVID-19 have gastrointestinal symptoms. It is important for clinicians to be aware of the gastrointestinal manifestation of COVID-19.

PROSPERO registration number CRD42020177569.

Significance of this study

What is already known on this topic

- COVID-19 has been declared as a pandemic by the WHO.
- The main features of COVID-19 are respiratory and include cough, sore throat, dyspnoea and pneumonia.

What this study adds

- Gastrointestinal symptoms are common in children with COVID-19.
- Nearly a quarter of children with COVID-19 have gastrointestinal symptoms.
- The most common gastrointestinal symptom is diarrhoea followed by vomiting and abdominal pain.

BACKGROUND

COVID-19 is a highly contagious disease that was first reported in Wuhan, Hubei Province, China in December 2019. Within weeks of the emergence of the disease, it had spread to several countries and the WHO declared the outbreak as a Public Health Emergency of International Concern in January 2020 and as a pandemic in March 2020.[1] According to the dashboard of the Center for Systems Science and Engineering at Johns Hopkins University, Baltimore, USA,[2] the disease has been reported in 187 countries, affected over 3 million people worldwide and caused over 230 000 deaths as at 30 April 2020.

COVID-19 is caused by SARS-CoV-2, previously known as the 2019 novel coronavirus (2019-nCoV). SARS-CoV-2 is a novel member of coronaviruses which are a large class of highly diverse, enveloped, positive-sense, single-stranded RNA viruses.[3] Most reported cases of the disease are adults, but the disease also affects children, including neonates.[4] The first reported paediatric case of COVID-19 was probably a 10-year-old boy from Shenzhen, China, who was diagnosed with the condition in January 2020.[5]

There have been a number of studies describing the clinical features of COVID-19 since the disease was first

PLOS ONE

RESEARCH ARTICLE

ELBW and ELGAN outcomes in developing nations–Systematic review and meta-analysis

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OPEN ACCESS

Citation: Ramaswamy VV, Abiramalatha T, Bandyopadhyay T, Shaik NB, Bandiya P, Nanda D, et al. (2021) ELBW and ELGAN outcomes in developing nations–Systematic review and meta-analysis. PLoS ONE 16(8): e0255352. https://doi.org/10.1371/journal.pone.0255352

Editor: Harald Ehrhardt, Center of Pediatrics, GERMANY

Received: February 24, 2021

Accepted: July 15, 2021

Published: August 5, 2021

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: BPD, Bronchopulmonary dysplasia; CoE, Certainty of evidence; ELBW, Extremely low birth weight; ELGANs, Extremely low gestational

Abstract

Context

Morbidity and mortality amongst extremely low birth weight (ELBW) and extremely low gestational age neonates (ELGANs) in developing nations has not been well studied.

Objectives

Evaluate survival until discharge, short- and long-term morbidities of ELBW and ELGANs in LMICs.

Data sources

CENTRAL, EMBASE, MEDLINE and Web of Science.

Study selection

Prospective and retrospective observational studies were included.

Data extraction and synthesis

Four authors extracted data independently. Random-effects meta-analysis of proportions was used to synthesize data, modified QUIPS scale to evaluate quality of studies and GRADE approach to ascertain the certainty of evidence (CoE).

Results

192 studies enrolling 22,278 ELBW and 18,338 ELGANs were included. Survival was 34% (95% CI: 31% - 37%) (CoE–low) for ELBW and 39% (34% - 44%) (CoE—moderate) for

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01086-4

ORIGINAL ARTICLE

Genetic Analysis of a Cohort of 275 Patients with Hyper-IgE Syndromes and/or Chronic Mucocutaneous Candidiasis

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Received: 11 August 2020 / Accepted: 5 June 2021

Abstract
Hyper-IgE syndromes and chronic mucocutaneous candidiasis constitute rare primary immunodeficiency syndromes with an overlapping clinical phenotype. In recent years, a growing number of underlying genetic defects have been identified. To characterize the underlying genetic defects in a large international cohort of 275 patients, of whom 211 had been clinically diagnosed with hyper-IgE syndrome and 64 with chronic mucocutaneous candidiasis, targeted panel sequencing was performed, relying on Agilent HaloPlex and Illumina MiSeq technologies. The targeted panel sequencing approach allowed us to identify 87 (32 novel and 55 previously described) mutations in 78 patients, which generated a diagnostic success rate of 28.4%. Specifically, mutations in *DOCK8* (26 patients), *STAT3* (21), *STAT1* (15), *CARD9* (6), *AIRE* (3), *IL17RA* (2), *SPINK5* (3), *ZNF341* (2), *CARMIL2/RLTPR* (1), *IL12RB1* (1), and *WAS* (1) have been detected. The most common clinical findings in this cohort were elevated IgE (81.5%), eczema (71.7%), and eosinophilia (62.9%). Regarding infections, 54.7% of patients had a history of radiologically proven pneumonia, and 28.3% have had other serious infections. History of fungal infection was noted in 53% of cases and skin abscesses in 52.9%. Skeletal or dental abnormalities were observed in 46.2% of patients with a characteristic face being the most commonly reported feature (23.1%), followed by retained primary teeth in 18.9% of patients. Targeted panel sequencing provides a cost-effective first-line genetic screening method which allows for the identification of mutations also in patients with atypical clinical presentations and should be routinely implemented in referral centers.

Keywords Primary immunodeficiency · Hyper-IgE syndrome · Chronic mucocutaneous candidiasis · Genetics · Targeted panel sequencing · Next-generation sequencing

Introduction

Hyper-IgE syndromes (HIES) and chronic mucocutaneous candidiasis (CMC) constitute rare primary immunodeficiency syndromes with overlapping phenotypes. HIES have traditionally been characterized by the clinical triad of recurrent pneumonias, recurrent skin abscesses, and markedly elevated serum IgE levels [1–3]. Eczema and eosinophilia represent further hallmarks. The most common underlying genetic defects are loss of function mutations of the transcription factor *STAT3* [4, 5], which, in addition to the triad already mentioned, are associated with dental, skeletal, and connective tissue abnormalities [4, 5]. In contrast, *DOCK8* deficiency is characterized by severe viral infections, e.g., with herpes viruses, papilloma viruses, and molluscum contagiosum virus as well as the increased

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Published online: 14 August 2021

Received: 28 July 2021 | Accepted: 28 July 2021
DOI: 10.1002/ccd.29898

SCAI THINK TANK PROCEEDING

WILEY

Hot topics in interventional cardiology: Proceedings from the society for cardiovascular angiography and interventions (SCAI) 2021 think tank

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Abstract

The Society for Cardiovascular Angiography and Interventions (SCAI) Think Tank is a collaborative venture that brings together interventional cardiologists, administrative partners, and select members of the cardiovascular industry community annually for high-level field-wide discussions. The 2021 Think Tank was organized into four parallel sessions reflective of the field of interventional cardiology: (a) coronary intervention, (b) endovascular medicine, (c) structural heart disease, and (d) congenital heart disease. Each session was moderated by a senior content expert and co-moderated by a member of SCAI's Emerging Leader Mentorship program. This document presents the proceedings to the wider cardiovascular community in order to enhance participation in this discussion, create additional dialog from a broader base, and thereby aid SCAI, the industry community and external stakeholders in developing specific action items to move these areas forward.

KEYWORDS
congenital heart disease, coronary artery disease, pediatrics, peripheral arterial disease, structural heart disease intervention

1 | INTRODUCTION

The annual Society for Cardiovascular Angiography and Interventions (SCAI) Think Tank brings together content experts, SCAI leaders, and key industry partners for a one-day session on timely topics within the four pillars of interventional cardiology—coronary, peripheral, structural, and congenital. The themes of this year centered on quality assurance of coronary and peripheral procedures, either at ambulatory surgical centers or in the hospital setting, the need to expand indications for minimally invasive structural procedures to meet the needs of an aging cardiovascular population, and the need to track implantable devices over time in our pediatric patients with congenital heart disease (CHD) who have now been able to achieve a longer life expectancy into young adulthood, middle age, and beyond. It is hoped that these discussions stimulate further initiatives within SCAI, our members, and our industry colleagues to meet these contemporary demands and help us achieve better outcomes for our cardiovascular patients.

2 | CORONARY: PERCUTANEOUS CORONARY PROCEDURES IN THE AMBULATORY SURGERY CENTER—WHAT DOES THIS MEAN TO THE PRACTICE, OVERSIGHT, VALUE, AND QUALITY OF PROCEDURAL AREAS?

Over the last 35 years, percutaneous coronary intervention (PCI) has evolved considerably in terms of device technology, pharmacologic options, and procedural techniques. In parallel with these scientific advancements by our members and industry partners, the rates of PCI-related complications have dropped precipitously despite the increasing anatomic and clinical complexity seen more routinely now in patients presenting with coronary artery disease.[1,2] Accordingly, same-day discharge after PCI has been increasingly adopted and PCI has been expanded to centers without cardiothoracic surgical back up.[3,4] With these developments in care processes and improved

Received: 14 April 2021 | Revised: 22 May 2021 | Accepted: 28 June 2021

DOI: 10.1002/ccr3.4591

CASE REPORT

Clinical Case Reports Open Access WILEY

Virtual training on advanced hybrid closed-loop system MiniMed 780G in a teenager with type 1 diabetes previously treated with multiple daily injections: A case report

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Funding information
No financial and material support was provided for this study

Abstract

Virtual pump training program for novel devices in people with type 1 diabetes on multiple daily injections can be an effective tool to initiate an advanced HCL system (MiniMed 780G) and to improve glycemic control in a safe manner without severe hypoglycemia and hyperglycemia.

KEYWORDS

advanced hybrid closed-loop system, multiple daily injections, type 1 diabetes, virtual training

1 | INTRODUCTION

A 12-year-old girl with type 1 diabetes on multiple daily injections commenced advanced hybrid closed loop (AHCL), Minimed 780G insulin pump using a virtual pump training. Training, initiation in Manual Mode of AHCL, initiation in Auto Mode of AHCL, and follow-up visits were performed using Zoom video conferencing platform. HbA1c decreased from 7.4% to 5.8%, 3 months after advanced AHCL initiation.

The current COVID-19 pandemic has rapidly moved the traditional (face to face) care delivery to new forms of consultations taking place through telehealth. The diabetes community has learned the valuable lessons about optimally supporting the most vulnerable people with diabetes, where remote technologies can ultimately improve diabetes care and outcomes for everyone.[1]

Type 1 diabetes (T1D) management takes a unique place in telehealth, where personal diabetes devices provide data sharing, such as Bluetooth-enabled glucometers, continuous glucose monitoring (CGM), insulin pumps, and smart insulin pens. The patient's personal glucose and insulin data can be automatically uploaded via the Internet to a cloud-specific databases, and health providers can use different applications to review the aggregated device data.

The use of telehealth in diabetes management has substantially increased during the COVID-19 pandemic, and several studies on remote initiation of insulin pumps in people with T1D [2-4] have shown that training and education for specific insulin pump, such as hybrid closed-loop (HCL) systems, can be virtually initiated using specific protocols.

Advanced HCL System, Minimed 780G (Medtronic) is a novel device,[5] commercially available in Europe (CE Mark) from October 2020 and approved for children above 7 years, adolescents, and adults with T1D. The device uses an algorithm that automatically adjusts the basal insulin delivery in addition with auto-bolus correction for high glucose levels, if

Kumar *et al. BMC Pregnancy and Childbirth* (2021) 21:570
https://doi.org/10.1186/s12884-021-04029-4

BMC Pregnancy and Childbirth

STUDY PROTOCOL Open Access

Omouma: a prospective mother and child cohort aiming to identify early biomarkers of pregnancy complications in women living in Qatar

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Abstract

Background: Pregnancy is governed by multiple molecular and cellular processes, which might influence pregnancy health and outcomes. Failure to predict and understand the cause of pregnancy complications, adverse pregnancy outcomes, infant's morbidity and mortality, have limited effective interventions. Integrative multi-omics technologies provide an unbiased platform to explore the complex molecular interactions with an unprecedented depth. The objective of the present protocol is to build a longitudinal mother-baby cohort and use multi-omics technologies to help identify predictive biomarkers of adverse pregnancy outcomes, early life determinants and their effect on child health.

Methods/design: : One thousand pregnant women with a viable pregnancy in the first trimester (6–14 weeks of gestation) will be recruited from Sidra Medicine hospital. All the study participants will be monitored every trimester, at delivery, and one-year post-partum. Serial high-frequency sampling, including blood, stool, urine, saliva, skin, and vaginal swabs (mother only) from the pregnant women and their babies, will be collected. Maternal and neonatal health, including mental health and perinatal growth, will be recorded using a combination of questionnaires, interviews, and medical records. Downstream sample processing including microbial profiling, vaginal immune response, blood transcriptomics, epigenomics, and metabolomics will be performed.

Discussion: It is expected that the present study will provide valuable insights into predicting pregnancy complications and neonatal health outcomes. Those include whether specific microbial and/or epigenomics signatures, immune profiles are associated with a healthy pregnancy and/or complicated pregnancy and poor neonatal health outcome. Moreover, this non-interventional cohort will also serve as a baseline dataset to understand how familial, socioeconomic, environmental and lifestyle factors interact with genetic determinants to influence health outcomes later in life. These findings will hold promise for the diagnosis and precision-medicine interventions.

Keywords: Birth cohort, Pregnancy, Multi-omics, Microbiome, Precision Medicine, Sidra Medicine, Qatar, Middle East

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Published in final edited form as:
Sci Immunol. 2021 August 19; 6(62): . doi:10.1126/sciimmunol.abl4348.

X-linked recessive TLR7 deficiency in 1% of men under 60 years with life-threatening COVID-19

A full list of authors and affiliations appears at the end of the article.

Abstract

Autosomal inborn errors of type I IFN immunity and autoantibodies against these cytokines underlie at least 10% of critical COVID-19 pneumonia cases. We report very rare, biochemically deleterious X-linked *TLR7* variants in 16 unrelated male individuals aged 7 to 71 years (mean: 36.7 years) from a cohort of 1,202 male patients aged 0.5 to 99 years (mean: 52.9 years) with unexplained critical COVID-19 pneumonia. None of the 331 asymptomatically or mildly infected male individuals aged 1.3 to 102 years (mean: 38.7 years) tested carry such *TLR7* variants ($p = 3.5 \times 10^{-5}$). The phenotypes of five hemizygous relatives of index cases infected with SARS-CoV-2 include asymptomatic or mild infection (n=2, 5 and 38 years), or moderate (n=1, 5 years), severe (n=1, 27 years), or critical (n=1, 29 years) pneumonia. Two boys (aged 7 and 12 years) from a cohort of 262 male patients with severe COVID-19 pneumonia (mean: 51.0 years) are hemizygous for a deleterious TLR7 variant. The cumulative allele frequency for deleterious *TLR7* variants in the male general population is $< 6.5\times10^{-4}$. We also show that blood B-cell lines and myeloid cell subsets from the patients do not respond to TLR7 stimulation, a phenotype rescued by wild-type *TLR7*. The patients' blood plasmacytoid dendritic cells (pDCs) produce low levels of type I IFNs in response to SARS-CoV-2. Overall, X-linked recessive TLR7 deficiency is a highly penetrant genetic etiology of critical COVID-19 pneumonia, in about 1.8% of male patients below the age of 60 years. Human TLR7 and pDCs are essential for protective type I IFN immunity against SARS-CoV-2 in the respiratory tract.

One Sentence Summary:

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Author contributions

A.K.-K., A.Am., A.C., A.G., A.-L.N., Be.Bo., E.J., F.A.A. F.O., J.R., L.M., M.A., M.M-V., M.M., M.O., MRL.MR., N.M., Pa.Ba., Q.P., Q.Z., S.J.P., Sa.Ko., S.M., T.A., T.K., T.Le V., V.B., V.S., P.Z. and Y.Z. performed or supervised experiments, generated and analyzed data, and contributed to the manuscript by providing figures and tables. A.C., A.B., Au.Pu., Be.Bi., Da.Mat., K.B., L.A., and Y.S. performed computational analyses of data. A.Ai., A.Ar., A.-C.N., A.M.N., A.N., A.N.S., A.S., Au.Pu., C.B., C.F., C.K., C.L.D., C.T., D.E.P., Da.Man., D.S., E.J., E.S., F.B., F.P., G.C., G.M., G.N., H.A., H.S., I.A.D., I.G.B., J.C.R.G., J.G.R., J.L.F., J.R., J.T., K.C., L.F.R., L.E.C., L.H., L.N., L.P-S., M.G., L.M.A., M.S., N.A.O., N.H., O.C., P.Be., P.Br., P.C., P.R-Q., P.S-P., Pa.Ba., Pa.Bo., Q.P.-H., Q.Z., R.C., R.N., R.P., S.A., S.B., S.T., Se.Ke.,, T.M.C., T.O., Y.T.B., and Y.T-L. evaluated and recruited patients to the COVID and/or control cohorts. Be.Bo., Q.Z., A.C., L.A. and J.-L.C. wrote the manuscript. All the authors edited the manuscript. J.-L.C. supervised the project.

Competing interests:

R.P.L a non-executive director of Roche. Because Roche is active in the diagnosis and treatment of SARS-CoV-2, this role could, in these contentious times, be construed as a conflict of interest, which I should disclose. V.S. has received speaker fees from GILEAD.

European Journal of Obstetrics & Gynecology and Reproductive Biology 265 (2021) 1–6

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/euro

Full length article

Vaccination in pregnancy – The when, what and how?

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ARTICLE INFO

Article history:
Received 7 May 2021
Revised 24 July 2021
Accepted 5 August 2021

Keywords:
Vaccination
Pregnancy
Mortality

ABSTRACT

Immunization is a fundamental component of preventive healthcare. This gain special significance in pregnancy. Maternal antigen-specific IgG, is actively transported across the placenta during pregnancy. This significantly, contributes to infant immunity in the first few months of life. Vaccination during pregnancy has the potential to indirectly protect the most vulnerable infants during the first few months of life, when vaccine responses are generally poor and it is difficult to achieve rapid protection through immunization. This is especially relevant when there is prior exposure to infection in woman or vaccine administration. A vaccine given during pregnancy in these women would result in a booster response and a relatively high level of IgG protecting their children in initial few months of life. Passive antibody transfer from mother to fetus can protect fetuses from infection until their own immunization schedule is initiated.

Lack of administration of appropriate vaccination to women during pregnancy lead to an increase in maternal and fetal morbidity and mortality from preventable infections like influenza, pertussis. Various preventable infections can lead to intensive care unit admission for mothers, preterm birth, and low birth weight babies.

Recent covid pandemic has brought issue of vaccine use in pregnancy at forefront of all expectant mothers.

Immunization with inactivated virus, bacterial vaccine and toxoids showed no evidence of adverse fetal effects.

As a rule, live attenuated vaccines are not recommended in pregnancy.

This paper gives snapshot of all vaccines, which can be used in pregnancy along with brief details regards various bacterial and viral infections , their common clinical features and effects on pregnancy outcome as well as fetus. This is will provide a useful guide for healthcare providers.

Introduction

Vaccination is the most successful and cost-effective tool in providing prevention from diseases. It has led to the eradication of diseases like small pox, and controlled diseases like whooping cough and polio in various countries. The antenatal period is an opportunity for physicians to obtain an immunization history, plan and discuss when best to administer vaccines. Vaccines can be categorized into live, killed and purified macromolecules that include inactivated toxins, conjugated unit and subunit vaccines.[1]

During pregnancy maternal immune response adapts to accommodate the fetus and placenta without compromising maternal immunity. Vaccination during the antepartum period provides passive immunity to fetus through placental transfer until the baby's immune system is mature to combat infections or the baby is due for vaccination. Only maternal IgG antibodies can be transferred through the placenta facilitated by Fc receptors on syncytiotrophoblast of placenta. Due to its highest affinity, IgG1 has the greatest transport efficiency. Infections like Human Immunodeficiency Virus and Malaria are associated with reduced placental transfer of antibodies.[2] Vaccines are mainly against bacterial and viral infections.

This article summarizes use of various vaccines used in women during pregnancy and immediate postpartum period. The vaccines are broadly classified as a. used against bacterial infections b. used against viral infections

We will first discuss vaccines used against bacterial infections with brief clinical details of each infection as well as pregnancy implications for the same.

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https://doi.org/10.1016/j.ejogrb.2021.08.009
2215-1532/

Primary Care Diabetes xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Unifying the diagnosis of gestational diabetes mellitus: Introducing the NPRP criteria

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ARTICLE INFO

Article history:
Received 20 July 2021
Received in revised form 8 August 2021
Accepted 9 August 2021
Available online xxx

Keywords:
Gestational diabetes
Diagnostic criteria
Glucose tolerance test
Pregnancy complications
Type 2 diabetes

ABSTRACT

Aims: Disagreement about the appropriate criteria for the diagnosis of gestational diabetes mellitus (GDM) persists. This study examines an alternative approach which combines information from all time-points on the glucose tolerance test (GTT) into a single index and expands the GDM spectrum into four categories using data from three geographically and ethnically distinct populations.
Methods: A retrospective observational study design was used. Data from Wisconsin, USA (723 women) was used in derivation of the criterion and data from Doha, Qatar (1284 women) and Cape Town, South Africa (220 women) for confirmation. Pregnant women without pre-existing diabetes with a GTT done between 23 and 30 weeks gestation were included. A novel index was derived from the GTT termed the weighted average glucose (wAG). This was categorized into four pre-defined groups (henceforth National Priorities Research Program (NPRP) criterion); i) normal gestational glycemia (NGG), ii) impaired gestational glycemia (IGG), iii) GDM and iv) high risk GDM (hGDM).
Results: In the Doha cohort, compared to the NGG group, the odds of large for gestational age babies increased 1.33 fold ($P = 0.432$), 2.86 fold ($P < 0.001$) and 3.35 fold ($P < 0.001$) in the IGG, GDM and hGDM groups respectively. The odds of pregnancy induced hypertension increased 2.10 fold ($P = 0.024$) in GDM & hGDM groups compared to the IGG and NGG groups. In the Cape Town cohort, a third of women in the GDM group and two-thirds in the hGDM group progressed to T2DM at 5 years.
Conclusions: The NPRP categorization identifies four distinct risk clusters of glycemia in pregnancy which may aid better decision making in routine management, avoid potential over-diagnosis of women at lower risk of complications and assist with diabetes prevention in women at high-risk after an index pregnancy with GDM.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia first detected during pregnancy that is neither type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) [1,2]. GDM is associated with an increased risk of maternal and fetal complications, increased medical cost [3] and can only be established through biochemical testing, typically between 24–28 weeks' gestation. Despite wide agreement that any form of hyperglycaemia should be managed during pregnancy, there is still a substantial disagreement on which diagnostic process should be used and which glucose threshold(s) merit a diagnosis of GDM [4]. The two widely used criteria for the diagnosis of GDM rely on individual time-point thresholds on a 2-h [5] or a 3-h [6] glucose tolerance test (GTT), and require elevated values at one or two time points respectively for the diagnosis. As such, the number of elevated time-point values required and different glycaemic thresholds will alter the

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https://doi.org/10.1016/j.pcd.2021.08.006
1751-9918/

animals

MDPI

Review

Quality of Reporting in Preclinical Urethral Tissue Engineering Studies: A Systematic Review to Assess Adherence to the ARRIVE Guidelines

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Simple Summary: We have conducted a systematic review to investigate the quality of reporting in preclinical experiments exploring tissue engineering approaches for urethral repair. This was performed based on the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines in a total of 28 articles from 2014 to 2020. Inadequate reporting of the essential points of research experiments was observed that could remarkably affect clarity, reproducibility, and translatability. A complete statement of the ethical review permission and guidelines followed was missing in 54% of the studies. Details to ensure reproducibility of the studies, such as animal housing, husbandry, and anesthetics, were infrequently reported. No paper stated the sample size estimation methodology. The quality of reporting improved marginally over the study period. We encourage the utilization of the ARRIVE checklist items when reporting preclinical studies to help the publication of manuscripts that would allow a precise judgment of their scientific merit.

Abstract: Preclinical research within the area of urethral tissue engineering has not yet been successfully translated into an efficient therapeutic option for patients. This gap could be attributed, in part, to inadequate design and reporting of the studies employing laboratory animals. In this study, a systematic review was conducted to investigate the quality of reporting in preclinical studies utilizing tissue engineering approaches for urethral repair. The scope was on studies performed in rabbits, published between January 2014 and March 2020. Quality assessment of the data was conducted according to the Animal Research: Reporting of in Vivo Experiments (ARRIVE) guidelines by the scoring of a 38-item checklist in different categories. A total of 28 articles that fulfilled the eligibility criteria were included in the study. The range of ARRIVE score was from 0 to 100, taking into consideration having reported the item in question or not. The mean checklist score was 53%. The items that attained the highest scores included the number of animals utilized, the size of control and experimental groups, and the definition of experimental outcomes. The least frequently reported items included the data regarding the experimental procedure, housing and husbandry, determination and justification of the number of animals, and reporting of adverse events. Surprisingly, full disclosure about ethical guidelines and animal protocol approval was missing in 54% of the studies. No paper stated the sample size estimation. Overall, our study found that a large number of studies display inadequate reporting of fundamental information and that the quality of reporting improved marginally over the study period. We encourage a comprehensive implementation of the ARRIVE guidelines in animal studies exploring tissue engineering for urethral repair, not only to facilitate effective translation of preclinical research findings into clinical therapies, but also to ensure compliance with ethical principles and to minimize unnecessary animal studies.

Keywords: urethral strictures; hypospadias; animal experiments; quality assessment; translational research

Citation: Abbas, T.O.; Elawad, A.; Pullattayil S., A.K.; Pennisi, C.P. Quality of Reporting in Preclinical Urethral Tissue Engineering Studies: A Systematic Review to Assess Adherence to the ARRIVE Guidelines. *Animals* **2021**, *11*, 2456. https://doi.org/10.3390/ani11082456

Academic Editors: Michael E. Davis and Emrah Yatkin

Received: 7 April 2021
Accepted: 17 August 2021
Published: 21 August 2021

antibiotics

MDPI

Article

Whole-Genome Sequencing for Molecular Characterization of Carbapenem-Resistant Enterobacteriaceae Causing Lower Urinary Tract Infection among Pediatric Patients

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Citation: Al Mana, H.; Sundararaju, S.; Tsui, C.K.M.; Perez-Lopez, A.; Yassine, H.; Al Thani, A.; Al-Ansari, K.; Eltai, N.O. Whole-Genome Sequencing for Molecular Characterization of Carbapenem-Resistant Enterobacteriaceae Causing Lower Urinary Tract Infection among Pediatric Patients. *Antibiotics* **2021**, *10*, 972. https://doi.org/10.3390/antibiotics10080972

Academic Editors: Francesca Andreoni and Gabriella Orlando

Received: 20 June 2021
Accepted: 5 August 2021
Published: 12 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Antibiotic resistance is a growing public health problem globally, incurring health and cost burdens. The occurrence of antibiotic-resistant bacterial infections has increased significantly over the years. Gram-negative bacteria display the broadest resistance range, with bacterial species expressing extended-spectrum β-lactamases (ESBLs), AmpC, and carbapenemases. All carbapenem-resistant *Enterobacteriaceae* (CRE) isolates from pediatric urinary tract infections (UTIs) between October 2015 and November 2019 ($n = 30$). All isolates underwent antimicrobial resistance phenotypic testing using the Phoenix NMIC/ID-5 panel, and carbapenemase production was confirmed using the NG-Test CARBA 5 assay. Whole-genome sequencing was performed on the CREs. The sequence type was identified using the Achtman multi-locus sequence typing scheme, and antimicrobial resistance markers were identified using ResFinder and the CARD database. The most common pathogens causing CRE UTIs were *E. coli* (63.3%) and *K. pneumoniae* (30%). The most common carbapenemases produced were OXA-48-like enzymes (46.6%) and NDM enzymes (40%). Additionally, one *E. coli* harbored IMP-26, and two *K. pneumoniae* possessed mutations in *ompK37* and/or *ompK36*. Lastly, one *E. coli* had a mutation in the *marA* porin and efflux pump regulator. The findings highlight the difference in CRE epidemiology in the pediatric population compared to Qatar's adult population, where NDM carbapenemases are more common.

Keywords: carbapenem-resistance; *Enterobacteriaceae*; Qatar; CRE; OXA-48

1. Introduction

Antibiotic resistance is a growing public health problem globally, incurring health and cost burdens. The occurrence of antibiotic-resistant bacterial infections has increased significantly over the years. In 2013, the Center for Disease Control and Prevention (CDC) issued an antibiotic resistance threats report estimating approximately two million infections annually in the United States [1]. By 2017, the number increased to approximately 2.8 million, and deaths increased from 23,000 to 35,900 [2]. Beta-lactams are the most used antibiotics worldwide and include the penicillins, cephalosporins, monobactams, and carbapenems; they all share a typical beta-lactam ring. Gram-negative bacteria display the broadest range of resistance, with bacterial species expressing extended-spectrum β-lactamases (ESBLs), AmpC, and carbapenemases [3]. Of these, carbapenem-resistant

Evolution, Medicine, and Public Health [2021] pp. 246–247 doi:10.1093/emph/eoab021

CLINICAL BRIEF

Emerging fungal pathogen: *Candida auris*

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Emerging fungal pathogen: *Candida auris*

Fungal infections cause over 1.5 million deaths per year, and a quarter million of these deaths are caused by the genus *Candida* [1]. The mortality rate of invasive candidiasis (infections by *Candida*) can be greater than 40% due to limited treatment options and increased antifungal resistance [1].

Since 2009, *Candida auris* emerged across six continents and evolved simultaneously as five distinct geographic clades [2, 3]. *Candida auris* has become a global threat as it can colonize the skin, medical devices and hospital environments, causing nosocomial outbreaks of blood and urinary tract infections worldwide (Fig. 1) [2].

Evolutionary perspectives

Most fungal pathogens of humans and other mammals are opportunistic pathogens. Mammals are endothermic and have a high basal body temperature relative to the surrounding environment that limits infections by the majority of environmental fungi. *Candida auris* is distinct from most environmental fungi in that it thrives at mammalian body temperatures, enabling its rapid adaptation to mammalian hosts [4, 5]. Rising global temperatures due to anthropogenic climate change may have selected for thermotolerant strains of *C. auris*, leading to its emergence as a pathogenic fungus in humans across a wide geographic range [4–6]. *Candida auris* was recently identified in a salt marsh and sandy beach, a plausible reservoir in which it may have adapted to a warm, high salinity environment [7]. Adaptation to such an environment may have enabled *C. auris* to persist on the skin due to its thermal and salt tolerance.

Candida auris can spread among patients in hospitals and is intrinsically resistant to one or more classes of antifungals, which makes it particularly difficult to treat in health care settings [8]. The acquisition of multi-drug resistance could be due to the mis/overuse of antifungal drugs [8]. Comparative genomics demonstrated that *C. auris* has expanded families of transporters and lipases as well as mutations and copy number variants in genes/enzymes linked to increased resistance and virulence [2]. Investigating the fitness trade-offs in traits that confer resistance and virulence in *C. auris* would be beneficial to understanding the evolutionary potential of pathogenic strains.

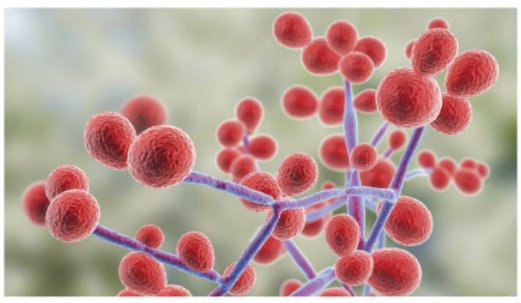

Figure 1. Illustration of yeast pathogen *Candida auris*

Future implications

Pathogenic fungi pose a great threat to immunocompromised individuals, such as people living with human immunodeficiency virus (HIV) and solid organ transplant recipients [7]. Clinical evidence suggests that patients receiving novel immunotherapies for cancer may also be particularly susceptible to fungal infections [9], and secondary

Pediatric Cardiology
https://doi.org/10.1007/s00246-021-02710-1

CASE REPORT

Topsy-Turvy Heart with Aortopulmonary Window and Severe Airway Malacia: Prenatal Diagnosis and Review of the Literature

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Received: 23 June 2021 / Accepted: 18 August 2021

Abstract
The topsy-turvy heart is a very rare cardiac malformation that involves a global 90° clockwise rotation of the heart along its long axis. This rotation results in the displacement of the great arteries and severe elongation and stretching of the brachiocephalic arteries and the bronchi. We present an unusual case of topsy-turvy heart diagnosed prenatally with a large aorto-pulmonary window and. This case gives an insight into the morphological details and clinical presentation of this rare malformation and its associated complications. We also present a review of the literature of this rare anomaly showing only 15 live cases that have been published with only three cases diagnosed prenatally.

Keywords Topsy-turvy heart · Superior–inferior ventricle · Aortopulmonary window · Vascular anomalies

Introduction

Topsy-turvy heart is a very rare cardiac malposition anomaly first described by Freedom et al. [1]. It involves a global 90° clockwise rotation of the entire heart with its great vessels around its long axis resulting in superior–inferior or upstairs–downstairs position of the ventricles. The right ventricle (RV) becomes more superior in relation to the left ventricle (LV), while the great arteries become displaced inferiorly and posteriorly into the mediastinum. This spatial derangement results in significant elongation of the brachiocephalic vessels and significant stretching of the trachea and bronchi leading to various degrees of airway anomalies and compression. Associated cardiac anomalies mainly include aorto-pulmonary (AP) window and atrial septal defects (ASDs). Its natural history and management are unclear due to the paucity of cases described in the literature to date.

We report a case of topsy-turvy heart prenatally diagnosed with AP window, suspected aortic coarctation, and lung deformities. We also summarize the cases reported in the literature of this rare anomaly, which include only fifteen living cases with only three cases diagnosed prenatally.

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Case Presentation

A 20-year-old mother gravida 1 para 0 (G1P0) with history of congenital lobar emphysema was referred for fetal cardiac evaluation at 22 weeks of gestation because of suspected fetal cardiac anomaly with ventricular septal defect. Parents were first cousins with a family history of congenital bronchiectasis in the mother's uncle and congenital cardiac abnormality (single ventricle physiology) in a paternal uncle. Fetal scan also revealed possible bronchial compression, single umbilical artery type 2 with persistent vitelline artery, and hypoplastic abdominal aorta. Fetal echocardiogram revealed superior–inferior ventricles with normal atrioventricular and ventriculoarterial relationships, a drop-out in the membranous ventricular septum suggestive of a defect, abnormally short ascending aorta, elongated subclavian artery, and a large AP window (Figs. 1, 2, 3). Pregnancy was smooth and the patient delivered at term by elective cesarean section (C/S) due to her pulmonary emphysema.

The baby was born with a birth weight of 2750 g, Apgar scores were 1, 6, and 8 at 1, 5, and 10 min, respectively. The baby was intubated right after delivery and was admitted to the neonatal intensive care unit (NICU). Post-natal

Published online: 27 August 2021

Sustained Inflation Versus Intermittent Positive Pressure Ventilation for Preterm Infants at Birth: Respiratory Function and Vital Sign Measurements

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Keywords: Preterm, sustained inflation, resuscitation
Supported by the National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): R03HD 086655-01A1 (to E.F.), K23HD084727-01A1 (to E.F.), and U01-HD072906-01A1 (to H.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.
.
Portions of this study were presented at the Pediatric Academic Societies annual meeting, April 24-May 1, 2019, Baltimore, Maryland.

Objective: To characterize respiratory function monitor (RFM) measurements of

sustained inflations and intermittent positive pressure ventilation (IPPV) delivered non-

Lung aeration is essential for successful newborn transition after birth,(1) and almost all extremely preterm infants require support to achieve this goal. Intermittent positive pressure ventilation (IPPV) is recommended to support lung aeration for apneic or bradycardic newborns.(2) Sustained inflation (SI), in which the inflation is maintained >5 seconds, is a proposed alternative.(3) A respiratory function monitor (RFM) uses an in-line flow sensor between the gas flow and respiratory interface to calculate data on delivered inflations during positive pressure ventilation. A direct comparison of SI and IPPV on respiratory function with simultaneous vital sign measurements after birth has not been described.

The Sustained Aeration of Infant Lungs (SAIL) trial (Clinicaltrials.gov Identifier NCT02139800) was designed to determine if SI is superior to IPPV to prevent bronchopulmonary dysplasia or death among extremely preterm infants.(4) In a subgroup of SAIL trial participants, RFM and vital sign measurements were recorded during the study intervention and subsequent resuscitation. The objective of the present study was to identify the effects of SI and IPPV on real-time objective measurements of respiratory function and vital signs.

Methods

This was an ancillary study to the multi-site international SAIL trial. (4) SAIL randomized eligible infants born between 23- 26 $^{6/7}$ weeks' gestation to receive up to 2 SIs for 15 seconds each with peak inspiratory pressures (PIPs) of 20-25 cm H_2O, or IPPV with an initial PIP of 20 cm H_2O that was then titrated. Subsequent interventions were based on local protocols. All participants with RFM data recorded from five SAIL

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The prevalence, immune profile, and clinical characteristics of children with celiac disease and type 1 diabetes mellitus in the state of Qatar

https://doi.org/10.1515/jpem-2021-0452
Received May 11, 2021; accepted August 16, 2021;
published online August 30, 2021

Abstract

Objectives: Children with antibody positive type 1 diabetes mellitus (type 1 diabetes) are at an increased risk of developing celiac disease (CD) which suggests a common autoimmune basis with both high-risk human lymphocyte antigen (HLA) and non-HLA factors playing a role in the pathophysiology. We aim to describe the prevalence, immune profile, and clinical characteristics of children with CD who have type 1 diabetes mellitus in Qatar.

Methods: All children (aged 0–18 years) attending a regional diabetes clinic with antibody positive type 1 diabetes were screened for CD. Measurement of tissue transglutaminase IgA and IgG as well as anti-endomysial antibody, was done, clinical details about the birth history, family history of diabetes and CD, age of onset, and ethnicity were collected.

Results: Out of the 1,325 children with antibody positive type 1 diabetes, 54 were identified to have CD on screening and then confirmed on small bowel biopsy. The prevalence of CD in the type 1 diabetes childhood population in Qatar is 4.07%. CD and type 1 diabetes were more prevalent in the Qatari children (n=32) as compared to non-Qatari (n=22) and occurred mostly in the age group 6–10 years. The most common type 1 diabetes antibodies in children with CD were glutamic acid decarboxylase and insulin autoantibody. Twelve subjects were asymptomatic for CD symptoms and picked up only on screening.

Conclusions: The prevalence of CD in children with type 1 diabetes in Qatar is comparable to reports from around the world. Many children were asymptomatic and thus routine screening is recommended.

Keywords: celiac disease; pediatric diabetes; type 1 diabetes.

Introduction

Celiac disease (CD) is a chronic autoimmune enteropathy that is due to a combination of genetic predisposition and exposure to gluten-containing food. The triggering agent for CD is gluten in the diet with gliadin peptides activating the recruitment of infiltrating T-lymphocytes producing Interferon-gamma (IFN-γ) and Interleukin-15 (IL-15) [1]. Among the genetic factors that increase the risk of CD disease include the major histocompatibility complex (MHC) class II, with human lymphocyte antigen (HLA) DQ2 and DQ8, conferring the highest risk of the disease [2]. Among the environmental factors, gastrointestinal microbiota seems to be associated with the onset of CD with an increased number of Proteobacteria and Bacteroidetes and a reduced number of Firmicutes, especially in the active phase of the disease [3]. The prevalence and presentation of CD vary among populations. Type 1 diabetes mellitus (type 1 diabetes) is an autoimmune disease characterized by T-cell mediated destruction of the insulin-producing pancreatic beta-cells of the pancreas. Patients with type 1 diabetes have serum auto-antibodies against beta-cell auto-antigens, including insulin autoantibody (IAA), glutamic acid decarboxylase (GAD65), protein tyrosine phosphatase (IA2 or ICA512), and zinc transporter (ZnT8). The risk of developing type 1 diabetes is increased in patients with MHC class II, with HLA DQ2 and DQ8 [4].

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frontiers in Pediatrics

SYSTEMATIC REVIEW
published: 09 August 2021
doi: 10.3389/fped.2021.718647

Preclinical Experiments for Hypospadias Surgery: Systematic Review and Quality Assessment

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Background: There is a steadily growing number of different reconstructive surgical procedures for hypospadias that were tested on animal models prior to their human application. However, the clinical translatability and reproducibility of the results encountered in preclinical urethral reconstruction experiments is considered poor, with significant factors contributing to the poor design and reporting of animal experiments. Our objective was to evaluate the quality of the design and reporting in published articles of urethral reconstructive preclinical studies.

Methods: Both PubMed and EMBASE databases were searched for animal urethral repair experiments between January 2014 and September 2019. Internal quality (bias) was evaluated through several signaling questions arising from the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE), while the quality of reporting was assessed by the Animal Research: Reporting of *In vivo* Experiments (ARRIVE) guidelines by scoring of a 20-item checklist.

Results: A total of 638 articles were initially screened after the literature search. Employing the inclusion and exclusion criteria, 30 studies were chosen for full-text screening and 21 studies were considered eligible for the quality assessment. The mean score of the checklist was 66%. The elements that accomplished the highest grades included the number of animals utilized, the number in each investigational and control group, and the delineation of investigational conclusions. The items that were least commonly stated comprised information about the experimental method, housing and husbandry, rationalization of the number of animals, and reporting of adverse events. No paper stated the sample size estimation.

Conclusion: We found that several critical experiment design principles were poorly reported, which hinders a rigorous appraisal of the scientific quality and reproducibility of the experiments. A comprehensive implementation of the ARRIVE guidelines in animal studies exploring urethral repair is necessary to facilitate the effective translation of preclinical research findings into clinical therapies.

Keywords: hypospadias, animal experiments, quality assessment, clinical translation challenge, translational research

OPEN ACCESS

Edited by:
Alexander Springer,
Medical University of Vienna, Austria

Reviewed by:
Einar Olafur Arnbjornsson,
Skåne University Hospital, Sweden
Alfredo Berrettini,
IRCCS Ca 'Granda Foundation
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Specialty section:
This article was submitted to Pediatric Urology, a section of the journal Frontiers in Pediatrics

Received: *01 June 2021*
Accepted: *05 July 2021*
Published: *09 August 2021*

Citation:
Abbas TO, Elawad A, Kareem A, Pullattayil S AK, Ali M and Alnaimi A (2021) Preclinical Experiments for Hypospadias Surgery: Systematic Review and Quality Assessment. Front. Pediatr. 9:718647. doi: 10.3389/fped.2021.718647

Received: 22 March 2021 | Revised: 8 July 2021 | Accepted: 30 July 2021

DOI: 10.1002/ccr3.4703

CASE REPORT

Clinical Case Reports Open Access WILEY

The effect of advanced hybrid closed loop system on glycated hemoglobin (HbA1c) in a young male with type 1 diabetes mellitus and growth hormone treatment: A case report

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Funding information
This report was funded by Sidra Medicine in Doha, Qatar.

Abstract

The advanced hybrid closed loop system MiniMed 780G can be an effective tool to improve glycemic control and decrease the health burden in a young male with type 1 diabetes and short stature.

KEYWORDS

advanced hybrid closed-loop system, growth hormone deficiency, growth hormone treatment, type 1 diabetes

1 | INTRODUCTION

A 16-year-old male patient with type 1 diabetes (T1D) and growth hormone (GH) treatment was commenced on the advanced hybrid closed loop (AHCL), MiniMed 780G. His HbA1c decreased from 8.6% to 6.7%, three months after AHCL initiation. AHCL improves glycemic control in T1D patients and is on GH treatment.

Type 1 diabetes (T1D) and growth hormone (GH) deficiency are relatively uncommon. The prevalence of GH deficiency ranges between 1:3500 and 1:8700 with an incidence of T1D below 15 years of age of 1:5000.[1] Combined GH treatment with insulin therapy is rarely prescribed in children and adolescents, and physicians can be reluctant prescribing GH due to deterioration in glycemic control. GH plays an important role in glucose, lipid, and protein metabolism, and its deficiency or excess can impact carbohydrate metabolism.

Initiation of GH treatment in patients with T1D is a challenge for both patients and healthcare providers. Patients need to monitor glucose levels more frequently and adjust insulin doses accordingly, especially at the beginning of GH treatment, while health providers must address specific guidelines for fine-tuning of both basal and bolus insulin.

Glycemic control during the GH treatment can be managed with adequate insulin adjustments, where HbA1c can either remain unchanged[2] or can increase.[3] Continuous subcutaneous insulin infusion (CSII), known as "open loop," can be a preferred method compared to multiple daily injections (MDI), allowing improved management of the nocturnal hyperglycemia caused by insulin resistance consequent to the GH administration.[2]

One of the recent technological advances in diabetes is the integration of CSII with continuous glucose monitoring (CGM) into a closed loop system, such as

IDCases 26 (2021) e01260

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

An enemy in shadows—Mycoplasma hominis septic arthritis and iliopsoas abscess: Case report and review of the literature

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ARTICLE INFO

Article history:
Received 4 July 2021
Received in revised form 19 August 2021
Accepted 21 August 2021
Available online xxxx

Keywords:
Mycoplasma hominis
septic arthritis
rituximab
PCR
doxycycline

ABSTRACT

Mycoplasma hominis (M. hominis) is fastidious and difficult to grow bacteria with the ability to colonize the genitourinary and respiratory tracts. Infrequently can cause a variety of genitourinary tract infections, pregnancy complications, and neonatal diseases. M. hominis rarely reported to cause extragenital infections and seldomly native joint septic arthritis particularly in immunocompromised hosts, raising diagnostic challenges and is often associated with delayed diagnosis and high morbidity and mortality. We report the case of a 30-year-old patient who developed M. hominis native left hip septic arthritis with iliopsoas abscess after receiving rituximab for newly diagnosed thrombotic thrombocytopenic purpura (TTP). The diagnosis of M. hominis hip septic arthritis with iliopsoas involvement was confirmed following repeated joint and abscess aspiration and identification of the organism with the aid of culture and specific Polymerase chain reaction (PCR). The patient was subsequently treated with a prolonged course of antibiotics targeting the organism with a favorable outcome. The clinical presentations, assessment, and management of this rare entity of M. hominis related extragenital infections are outlined. In addition, the literature on similar cases was reviewed to raise awareness and avoid devastating consequences.

Introduction

M. hominis belongs to the Mycoplasmataceae family within the Mollicutes class, the smallest and simplest self-replicating free-living bacteria. It constitutes one of the genital mycoplasma species capable of causing human infections which include Ureaplasma urealyticum, Ureaplasma parvum, and Mycoplasma genitalium [1]. M. hominis is part of the flora of the genitourinary tract of healthy individuals with colonization rates ranging between 21% and 53%. However, it is potentially pathogenic and can cause genitourinary, maternal, and neonatal infections [2].

Rarely, M. hominis can cause a wide variety of extragenital infections including native joint septic arthritis, particularly in immunocompromised hosts. Many immunocompromising conditions have been implicated as risk factors for the development of septic arthritis, but most importantly low IgG level seems to be a major determinant [3].

Characteristically slow-progressing infections with repeatedly negative cultures and subsequent joint destruction are frequently observed if not recognized and treated promptly.

The clinical presentation is usually undistinguished M. hominis septic arthritis from typical infective arthritis raising the need for highly sensitive and specific identification methods [4].

The slow and fastidious growth habits of M. hominis limit the timely diagnosis of acute infection by conventional culture methods and lack of cell wall hinder detection by gram staining from the affected joints. Many molecular methods have been developed to avoid delaying the diagnosis, including Real-time PCR and specific Mycoplasma homins 16Sr RNA [2].

Usually, a combination of prolonged antibiotic therapy targeting the organism in addition to appropriate surgical interventions such as arthroscopy, joint washout, or abscess drainage is the mainstay of management [4].

In the present report, we describe a case of Mycoplasma hominis native hip septic arthritis with iliopsoas abscess, which was

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https://doi.org/10.1016/j.idcr.2021.e01260
2214-2509/

JGH Open An open access journal of gastroenterology and hepatology Open Access

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12621

REVIEW ARTICLE

Understanding multiseptated gallbladder: A systematic analysis with a case report

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Key words
biliary pain, cholecystectomy, honeycomb gallbladder, multi-septated gallbladder.

Accepted for publication 14 July 2021.

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Declaration of conflict of interest: Authors have no conflict of interest to disclose.

Funding support: Qatar National Library

Abstract

Multiseptated gallbladder (MSG) (also known as "Honeycomb gallbladder") is a rare condition that was first described by Knetsch in 1952, and there are around 150 cases described over the world. MSG has been described as a congenital anomaly in most of the cases and as acquired in a few. Moreover, the phenomenon was described with a variety of different symptoms and management. The aim of this article is to have better understanding of this condition and management approach. We are reporting a 4-year-old girl, who presented to Sidra Medicine, Qatar with MSG. We have also included 97 cases for review and analysis. The median age of presentation of the condition was 27 years but may present in neonates and in the elderly, while gender was not a risk factor. Abdominal pain is the most common presenting symptom, but it can present without symptoms. Certain congenital anomalies were detected in the pancreaticobiliary system in few patients with MSG. Medical treatment was reported in eight symptomatic patients, four of whom failed therapy. Cholecystectomy was performed in 40 patients, which resulted in resolutions of symptoms in 13 of them. Based on the available literature, congenital MSG is probably due to in-pouching of gallbladder wall to its own cavity forming septa containing muscular fibers. MSG can be diagnosed solely via imaging, and ultrasound appears to be an effective and feasible mode of diagnosis. Medical treatment efficacy is not well-known, but cholecystectomy has resulted in complete resolution in symptomatic patients.

Introduction

Multiseptated gallbladder (MSG) (also called "Honeycomb gallbladder") is a rare condition that was initially described by Knetsch in 1952,[1] and there has been less than 150 reported worldwide.

The etiology of MSG is not very clear yet and multiple embryological hypotheses have been suggested. Many of the reported cases of MSG have been diagnosed incidentally and the rest presented with a variety of different symptoms.[2,3] We present a case of an MSG seen at Sidra Medicine, the only tertiary pediatric center in the State of Qatar.

Given the rarity of incidence and the wide variation of presentations and management, we are conducting an extensive literature review and analysis of available data to have better understanding of this condition and management approach. To the authors' knowledge, this manuscript is the latest and most comprehensive review of reported cases of MSG.

Case report

A 4-year-old girl presented to the pediatric outpatient clinic complaining of chronic constipation, associated with intermittent abdominal pain, initially described as nonspecific. There was no history of fever, vomiting, diarrhea, or urinary symptoms. Past medical history was remarkable for recurrent urinary tract infections. Family history was unremarkable. Her vital signs during her first clinic visit were within normal limits for her age. Her weight and body mass index (BMI) were on the 99th centile for age (z-score 2.38). On physical examination, her abdomen was soft, with no tenderness, no masses, and no organomegaly. The rest of the physical examination was normal.

On further follow up, her constipation improved with Polyethylene glycol; however, she continued to have recurrent abdominal pain, which was ill-localized, postprandial, and exacerbated by fatty meals.

Laboratory tests showed serum white blood cells of 8.1 $\times 10$ (9)/L, hemoglobin of 125 g/L, platelets of 383 $\times 10$(9)/L, albumin of 44 g/L, aspartate aminotransferase of 31 U/L, and alanine aminotransferase of 16 U/L, total bilirubin of 9 μmol/L, C-reactive protein of 3.1 mg/L, and erythrocyte sedimentation rate of 65 mm/h. Serum glucose, creatinine, blood urea nitrogen, calcium, sodium, chloride, and potassium were normal as well as urine analysis and culture.

Ultrasonography of the abdomen was done, revealing multiseptations in the gallbladder (Fig. 1a,b). No evidence of gallbladder wall thickening, pericholecystic fluid, or cholelithiasis were found.

Journal of Tropical Pediatrics, 2021, 67(4), 1–9
doi: 10.1093/tropej/fmab086
Original Paper

Less Invasive Surfactant Administration (LISA) vs. Intubation Surfactant Extubation (InSurE) in Preterm Infants with Respiratory Distress Syndrome: A Pilot Randomized Controlled Trial

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ABSTRACT

Objective: There has been an endeavor in recent years, to administer surfactant by minimally invasive techniques to neonates with surfactant deficiency. The objective of this study was to compare the need for intubation and mechanical ventilation after surfactant delivery, using Less Invasive Surfactant Administration (LISA) technique and Intubation SURfactant Extubation (InSurE), in preterm infants with respiratory distress syndrome (RDS).

Methods: We conducted a pilot randomized control trial (RCT) at a tertiary care center over a period of 18 months. Preterm neonates with RDS (gestational age 28–36 weeks) were randomized to receive surfactant within 6 h of birth by InSurE or LISA. The primary outcome was need for intubation and mechanical ventilation within 72 h of birth. Infants were followed until discharge for adverse events and complications.

Results: A total of 40 infants were analyzed (20 in each group). There was no difference in the need for intubation and mechanical ventilation within 72 h of birth between the two groups [InSurE, 6 (30%) and LISA, 6 (30%), relative risk 1.0, 95% confidence interval 0.51–1.97]. About 15% of infants in both groups had adverse events during the procedure. There was no statistically significant difference in the rates of major complications or duration of respiratory support, hospital stay and mortality.

Conclusion: We found LISA to be feasible and equally effective as InSurE for surfactant administration in the treatment of RDS in preterm infants. Future larger RCTs are required to compare the efficacy and long-term outcomes of LISA with the standard invasive methods of surfactant administration.

KEYWORDS: InSurE, less invasive surfactant administration, preterm, respiratory distress syndrome, surfactant

INTRODUCTION

Respiratory distress syndrome (RDS) is one of the important causes of morbidity and mortality in preterm neonates, characterized by a deficiency of pulmonary surfactant at birth, leading to respiratory distress and the need for respiratory support. For the more severe forms of RDS, exogenous intra-tracheal surfactant administered through an endotracheal tube (ET), followed by a short duration of mechanical ventilation (MV), has been the traditional modality of treatment of surfactant deficiency, and has been shown to reduce morbidity and mortality in RDS [1, 2]. Animal studies have suggested that, even a short period of positive pressure ventilation is harmful to the immature lungs, leading to complications, such as bronchopulmonary dysplasia (BPD) [3]. Various studies have shown that early use of non-invasive respiratory support in the form of nasal continuous positive airway pressure (nCPAP) after delivery reduced the need for MV, along with a trend toward decreased incidence of BPD [4, 5]. The InSurE technique was introduced by Verder, *et al.* [6] to reduce the duration of MV, which involves INtubation, administration of SURfactant, immediate Extubation followed by continuation of nCPAP for respiratory support. This method of exogenous surfactant delivery was thereafter adopted and used widely by many neonatal units across the world [7, 8]. However, the InSurE technique also involves intubation, which is an invasive procedure and positive pressure ventilation after surfactant administration.

Therefore, there has been an endeavor in recent years, to administer surfactant without the invasive procedure of intubation and positive pressure ventilation. These methods are known as Less Invasive Surfactant Administration (LISA) or Minimally Invasive Surfactant Therapy (MIST). In this method, surfactant is instilled into the trachea of a spontaneously breathing neonate on nCPAP, via a thin catheter placed in the trachea. The catheter is removed after administration of surfactant, and nCPAP therapy is continued. Other similar minimally invasive methods of delivering surfactant include instilling surfactant via a laryngeal mask [9] or through nebulization [10], or as an intra-pharyngeal instillation [11].

In recent years, studies have been carried out worldwide, demonstrating that LISA via thin catheter without intubation, in neonates diagnosed to have RDS, is feasible, and has similar efficacy in comparison with the conventional invasive method [12, 13]. Some randomized control trials (RCTs) found reduced need for MV, fewer days of respiratory support and lower rates of BPD in the LISA or MIST group, with no differences in mortality and serious adverse events as compared to standard therapy [14, 15].

Data from developing countries on LISA are limited. There are very few Indian RCTs published, that compare LISA with the invasive methods of surfactant administration. This study has been designed to assess the feasibility of LISA in preterm infants diagnosed to have RDS, and compare its efficacy and short-term effects with the InSurE technique.

MATERIAL AND METHODS

This open-label RCT was conducted in a tertiary neonatal intensive care unit (NICU) in a university hospital in Western India between January 2019 and June 2020.

The inclusion and exclusion criteria were as follows:

Inclusion criteria: spontaneously breathing preterm infants with RDS diagnosed within 24 h of life and meeting two or more criteria for surfactant therapy from ≥28 weeks 0 days to 36 weeks 6 days' gestational age.

Exclusion criteria: infants with anatomical abnormalities of upper airway; major congenital anomalies; congenital diaphragmatic hernia; trachea-esophageal

fistula; choanal atresia; cleft palate; and poor respiratory efforts. Also, infants requiring intubation and invasive ventilation due to hemodynamic instability or fraction of inspired oxygen (FiO_2) requirement $\geq$0.6 were excluded.

RDS was diagnosed based on clinical features (need for supplemental oxygen or respiratory support, tachypnea, grunting and intercostal retractions) and typical chest radiograph suggestive of RDS (bilateral reticulogranular pattern of the lung parenchyma, air bronchograms and low lung volume). Detailed antenatal history, such as use of antenatal steroids, diabetes, hypertension and chorioamnionitis was taken and clinical examination was done to rule out anatomical abnormalities of the upper airway.

Preterm infants with RDS were initially stabilized on non-invasive ventilation (NIV) in the form of nCPAP or nasal intermittent positive pressure ventilation (NIPPV). Surfactant was given if respiratory distress increased on NIV and two or more of the following criteria were met: Silverman–Andersen respiratory severity score (SAS) $\geq$4 [16], FiO_2 requirement >0.3 for <30 weeks and >0.4 for $\geq$30 weeks, chest X-Ray suggestive of Grade II or III RDS [17] and arterial/alveolar (a/A) oxygen ratio <0.2 on arterial blood gas analysis. Infants were randomly assigned to receive surfactant by LISA or InSurE using block randomization done by Research Randomizer online software.

For spontaneously breathing infants on NIV in the intervention group (LISA), a 5 Fr feeding tube was placed in the trachea 1–2 cm beyond vocal cords, directly visualizing the cords with a laryngoscope. Magill forceps were used if needed. The surfactant (100 mg/kg body weight) was instilled intratracheally via the catheter. The catheter was then removed, and non-invasive respiratory support was continued. The procedure was performed by neonatologists trained for delivery of surfactant by LISA. A second person observed the procedure to look for any adverse events, such as apnea or bradycardia. If apnea occurred during the procedure, physicians were instructed to apply manual breaths on NIV. Patients in the control group (InSurE) were intubated with an ET; a 5 Fr catheter was passed through ET tube and surfactant was administered, followed by positive pressure ventilation with T-piece resuscitator. ET was removed after surfactant instillation and non-invasive respiratory support was continued. No premedication was used during both procedures. Surfactant application was repeated after an interval of 6–12 h if FiO_2 requirement was $\geq$0.4 in either group. Infants in either group were intubated and mechanically ventilated if they had any of the following: severe respiratory distress with SAS $\geq$7, FiO_2 requirement $\geq$0.6 on NIV, pH <7.2, pCO_2 $\geq$60 mmHg or significant apnea. In both groups, all other treatments, including ventilator settings were as per unit protocols.

The primary outcome of the study was need for intubation and MV within 72 h of birth. The patients were followed until discharge from hospital for secondary outcomes, which included intraventricular hemorrhage (IVH), hemodynamically significant patent ductus arteriosus (hsPDA), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and BPD. Also, duration of MV, non-invasive respiratory support, need for repeat surfactant doses, length of hospital stay and adverse events during surfactant administration were recorded. To detect IVH, cranial ultrasound was performed on Days 3, 7 and 14 of birth. BPD was diagnosed on the basis of National Institutes of Child Health and Development diagnostic criteria [18]. Patient characteristics, antenatal history findings, clinical examination findings and outcomes of each intervention were documented on a pre-set proforma and excel sheet.

LISA is not currently being practiced in our unit. We planned this study as a pilot trial to assess the feasibility of this relatively newer method of surfactant administration, and compare its efficacy with the standard therapy (InSurE). This project was a part of a post-graduate thesis with a time limit of 18 months. From our NICU records of previous years, we estimated that we would be able to enroll at least 40 preterm infants of the planned gestational age group during this period. Approval from institutional ethical committee was obtained and written informed consent was taken from the parents of infants eligible for study. The trial is registered with Clinical Trials Registry-India (CTRI/2019/04/018701).

STATISTICAL ANALYSIS

Qualitative data were presented as frequencies and percentages. Quantitative data were expressed as mean (standard deviation) or median (interquartile range). Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. To compare numerical variables, independent samples *t*-test or Mann–Whitney U-test were used. *p*-value <0.05 was considered significant. Data analysis was performed using SPSS statistical software version 19.0 (IBM SPSS Statistics).

RESULTS

A total of 759 preterm infants between 28^{+0} and 36^{+6} weeks gestational age were admitted in our NICU during the study period. Only 92 infants were assessed for eligibility, of which 40 underwent randomization (Fig. 1), 20 were assigned to InSurE group and 20 to LISA group. All infants in both the arms received allocated treatment. All infants were followed till discharge or death. Baseline characteristics were comparable in both the groups and are depicted in Table 1.

Primary and secondary outcomes are shown in Table 2. There was no statistically significant difference in the need for intubation within 72 h of birth between the InSurE and LISA group [relative risk (RR) 1.0, 95% confidence interval (CI) 0.51–1.97).

Among the secondary outcomes, major complications like IVH, BPD, hsPDA, NEC and ROP were more in the LISA group, but the difference was not statistically significant. MV was required in 35% (7/20) infants in the InSurE group and 40% (8/20) in LISA group. Median (IQR) duration of MV was higher in the InSurE group, 5 (2–7) days as compared to LISA group, 3.5 (1–7) days, but the *p*-value (0.38) was not significant. The median (IQR) duration of non-invasive support was similar in both the groups.

Repeat doses of surfactant were required in four patients (20%) in InSurE group and three patients (15%) in LISA group. About 15% of infants in both groups had adverse events, such as apnea or bradycardia during the procedure of surfactant instillation. Median (IQR) length of hospital stay was higher in the InSurE group, 37 (18.5–50.5) days vs. 30.5 (15.5–53) days in LISA group. However, this difference was not statistically significant ($p = 0.78$). Three patients died in the LISA group and one in the InSurE group, the difference was not statistically significant.

DISCUSSION

In this pilot RCT, we compared a less invasive method of surfactant instillation (LISA) with the standard invasive method (InSurE), in spontaneously breathing preterm infants with RDS. We found that the less invasive method was feasible and there was no difference in the need for MV within 72 h of birth in the two groups. Similarly, there was no statistically significant difference in the duration of ventilation, major complications, length of hospital stay, adverse events and mortality between the two groups.

Surfactant administration in newborns with RDS traditionally involves intubation and stabilization on MV, instillation of surfactant and weaning of ventilator support until the infant can be extubated. The InSurE technique was later developed and involved immediate extubation after instillation of surfactant. Since the brief period of intubation and positive pressure ventilation involved in the InSurE technique can also cause lung injury, alternative less invasive methods (LISA or MIST) for surfactant administration were explored. After an initial pilot trial by Verder, *et al.* [19], further modifications were tried and published subsequently, using different types of catheters for intra-tracheal instillation of surfactant with or without Magill forceps [11–13]. Initial trials were conducted in Germany, but gradually LISA was increasingly used in other parts of the world for the management of RDS [14, 20]. There are very few published trials on LISA from India.

Similar to our study, several other studies found no significant difference in the need of intubation and MV within 72 h of birth between InSurE and LISA group. Bao, *et al.* [13] conducted a single center, RCT in China among 90 spontaneously breathing preterm infants from 28 to 32 weeks gestational age and found no significant differences in the rate of MV in first 72 h. Similar findings were seen in a multicenter RCT from Iran [12]. A recently published single center RCT by Gupta, *et al.* [21], comparing InSurE and MIST did not find any difference

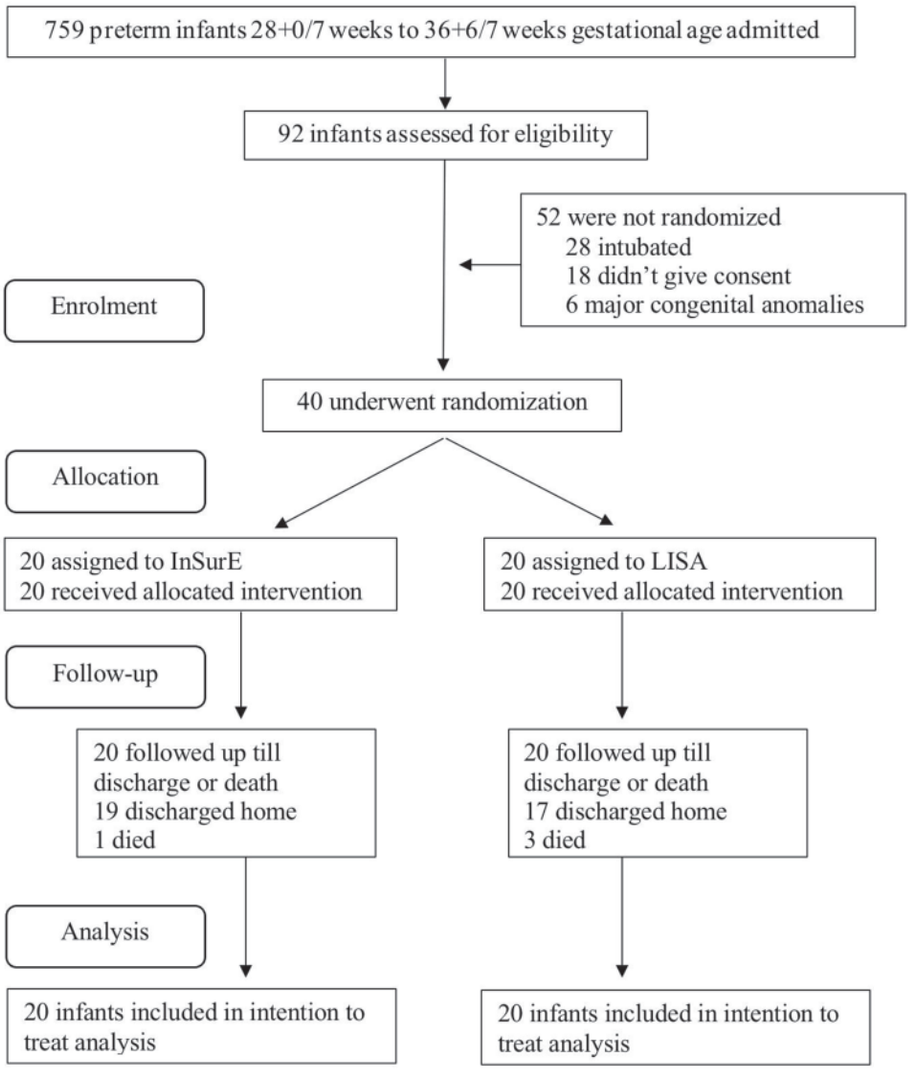

FIG. 1. Flow diagram for inclusion and analysis.

in the need of MV in first 72 h. However, some studies of similar design found significant reduction in the need of MV in the LISA group. A single center RCT of 200 preterm infants from Turkey compared thin catheter without intubation for surfactant administration ('Take Care') vs. InSurE and found significantly lower requirement of MV in first 72 h of life in the 'Take Care' group [14]. Various other studies in different parts of the world as well as meta-analyses also reported decreased need for invasive ventilation in the LISA group as compared to intubation for delivering surfactant [15, 22–24]. In our study, we used both NIPPV and nCPAP as primary respiratory support before instillation of surfactant. Majority of the studies, which found a significant difference in the need of MV in 72 h used nCPAP as their non-invasive mode of ventilation [14, 15, 25]. It is evident from the literature that NIPPV reduces the need of MV [26]. Also, NIPPV can facilitate pressure delivery to the alveoli by

TABLE 1. Comparison of baseline characteristics of the two groups

Characteristics	InSurE ($n = 20$)	LISA ($n = 20$)	*p*-value
Gender			
Male, *n* (%)	13 (65%)	11 (55%)	0.75*
Female, *n* (%)	7 (35%)	9 (45%)	
Birth weight, g, mean (±SD)	1500 (±500)	1460 (±580)	0.86**
Birth weight group			
ELBW (<1000 g)	2 (10%)	5 (25%)	0.66***
VLBW (1000–1499 g)	9 (45%)	7 (35%)	
LBW (1500–2499 g)	8 (40%)	7 (35%)	
≥2500 g	1 (5%)	1(5%)	
Gestational age (weeks), mean (±SD)	31.46 (±2.4)	31.36 (±2.48)	0.89**
Gestational age group			
28–31 weeks, *n* (%)	13 (65%)	13 (65%)	>0.99***
32–33 weeks, *n* (%)	4 (20%)	4 (20%)	
≥34 weeks, *n* (%)	3 (15%)	3 (15%)	
SGA *n* (%)	3 (15%)	3 (15%)	0.59***
AGA *n* (%)	17 (85%)	16 (80%)	
LGA *n* (%)	0 (0%)	1 (5%)	
APGAR score, median (IQR)			
1 min	7 (5–8)	7 (4–8)	0.317****
5 min	8 (8–8)	8 (7–8)	0.363****
Resuscitation requirement *n* (%)	6 (30%)	4 (20%)	0.71***
Mode of delivery			
Vaginal, *n* (%)	5 (25%)	4 (20%)	>0.99***
Caesarean, *n* (%)	15 (75%)	16 (80%)	
Antenatal steroids			
Complete course, *n* (%)	7 (35%)	4 (20%)	0.55***
Incomplete course, *n* (%)	11 (55%)	13 (65%)	
Not received, *n* (%)	2 (10%)	3 (15%)	
Antenatal complications			
Diabetes, *n* (%)	4 (20%)	2 (10%)	0.66***
Hypertensive disorder, *n* (%)	6 (30%)	5 (25%)	>0.99***
Chorioamnionitis, *n* (%)	3 (15%)	3 (15%)	>0.99***

InSurE, intubate-surfactant-extubate; LISA, less invasive surfactant administration; *n*, number; g, grams; SD, standard deviation; ELBW, extremely low birth weight; VLBW, very low birth weight; LBW, low birth weight; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; IQR, interquartile range.
*Chi-squared test.
**Unpaired *t*-test.
***Fisher's exact test.
****Mann–Whitney U-test.

overcoming tracheal obstruction and leaks during catheterization with a thin intra-tracheal catheter [27]. Both these factors may explain the lack of difference between LISA and InSurE groups in the primary outcome in our study. Another study that used NIPPV as their primary respiratory support also did not find any difference in the need of MV in 72 h [21]. The demographic profile of our study was

TABLE 2. Outcome parameters of infants with RDS after surfactant administration

Parameters	InSurE (n=20)	LISA (n=20)	RR (95% CI)	p-value
Primary outcome				
Intubation within 72 h of birth, n (%)	6 (30%)	6 (30%)	1.0 (0.51–1.97)	>0.99*
Secondary outcomes				
Major complications, n (%)				
IVH	2 (10%)	4 (20%)		0.66*
BPD	2 (10%)	5 (25%)		0.41*
hsPDA	2 (10%)	4 (20%)		0.66*
NEC	0	2 (10%)		0.49*
ROP	1 (5%)	4 (20%)		0.34*
Median (IQR) duration of MV (days)	5 (2–7) (n = 7)	3.5 (1–7) (n = 8)		0.38**
Median (IQR) duration of non-invasive respiratory support (days)	11 (5–29.5)	6 (5–22)		0.68**
Repeat dose of surfactant, n (%)	4 (20%)	3 (15%)		>0.99*
Median (IQR) length of hospital stay (days)	37 (18.5–50.5)	30.5 (15.5–53)		0.78**
Adverse events during surfactant administration (apnea/bradycardia), n (%)	3 (15%)	3 (15%)		>0.99*
Outcome				
Survived n (%)	19 (95%)	17 (85%)		0.60*
Died n (%)	1 (5%)	3 (15%)		

InSurE, intubate-surfactant-extubate; LISA, less invasive surfactant administration; RR, relative risk; 95% CI, 95% confidence interval; n, number; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; hsPDA, hemodynamically significant patent ductus arteriosus; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; d, days; IQR, interquartile range.
*Fisher's exact test.
**Mann–Whitney U-test.

slightly different from other studies, as we included preterm infants of a wider range of gestational age (28–36 weeks) with a mean gestational age of 31 weeks. The mean gestational age in studies conducted by Gopel, *et al.* [15] and Kanmaz, *et al.* [14] were 27 and 28 weeks, respectively. Most other

studies included preterm infants <34 weeks. Whether this difference in study population influenced the primary outcome is uncertain.

We found no significant difference in the duration of MV or non-invasive respiratory support between the two groups. Similar findings were reported by Bao, *et al.* [13] and Mohammadizadeh, *et al.* [12]. However, Kanmaz, *et al.* [14] and Jena, *et al.* [22] reported a lower duration of respiratory support in the LISA group as well as lesser rates of BPD. This likely reflects the lesser need of intubation after LISA in their studies. In our study, the need for repeat doses of surfactant was not statistically different in the two groups, similar to the findings of most studies of similar design [13, 14, 21].

Rate of adverse events during surfactant administration, such as bradycardia, desaturation and apnea were not high, and observed in 15% infants in both groups in our study. This was similar to the findings by Kanmaz, *et al.* [14] and Bao, *et al.* [13]. In contrast, Mohammadizadeh, *et al.* [12] observed a higher rate of bradycardia and desaturation events in both the groups and also a statistically significant difference in adverse events between the two groups (InSurE 63.2% vs. LISA 31.6%). This could be related to the premedication used before intubation in the InSurE group in their study or inadequate training for LISA. Quality assessment studies have demonstrated that the success rate of LISA technique correlates with the experience of the performer [28]. We conducted prior training of neonatologists to ensure their competence for delivering surfactant using the LISA technique. Also, our study included infants of higher gestation as well.

There was no difference in other major complications, such as IVH, hsPDA, NEC and ROP between the InSurE and LISA groups. Similar findings were reported by other studies [13, 21]. Length of hospital stay was also similar in InSurE and LISA group in our study, comparable to few other studies [25, 29]. However, Jena, *et al.* [22] reported lower duration of hospital stay in the LISA group. This might be related to the lesser rate of BPD in LISA group in their study. Only 1 out of 20 patients in our study died in the InSurE group, while 3 died in the LISA group. The difference was not statistically significant. This is consistent with the published literature [23].

This study is one of the few RCTs from India that has studied the feasibility and efficacy of LISA as a newer non-invasive method of surfactant delivery. We plan to conduct a larger RCT before we can incorporate LISA as a standard of care in our unit. This study has several limitations though. First, the sample size was small and therefore, there is a possibility of type II error. With a larger sample size in a future RCT, we would be able to stratify different gestational age groups and do subgroup analysis. Second, we did not include extremely preterm infants (gestation <28 weeks) in our study, so the findings cannot be extrapolated to this group. Third, since the procedures of both treatment arms were different from each other; the healthcare providers could not be blinded to the interventions. However, we ensured that the analysis of the study results was done by a statistician not involved in the study. Finally, we did not use premedication before intubation in the InSurE group to avoid respiratory depression. Pain can have short- and long- term neurological effects on the developing brain [30]. The risks of avoiding premedication must be weighed against that of adverse effects of sedation during LISA.

We conclude that delivery of surfactant by less invasive method (LISA) is feasible in the treatment of RDS in preterm infants of gestation 28–36 weeks. There was no difference in the need for intubation within 72 h of surfactant administration, adverse events or major complications between the LISA group and InSurE group. Future larger randomized controlled trials involving smaller gestational age groups as well are required to compare the efficacy and long-term outcomes of LISA with the standard invasive methods of surfactant administration currently employed.

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Original Article

Parental perception of medications safe storage in the State of Qatar

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Abstract

Purpose: The purpose of this study is to identify parental perception of household medication storage. **Methods:** A prospective cross-sectional study utilizing a questionnaire was carried out at Hamad Medical Corporation, the solely tertiary pediatric hospital in the State of Qatar at the time of the study. Qatar is a young developing country with limited data on the awareness of medication storage among adults with children at home and on the safety practices regarding medication storage. **Results:** Three hundred and five questionnaires were completed. The vast majority of parents were married, one-third of them were males, and more than three quarters were college graduates and younger than 40 years of age. Almost 80% of the parents had more than three children but less than seven. In addition, 23% of participants were health-care workers. Almost 90% of the participants stored medications in a place that is easy to reach. However, the same percentage stated that those medications were stored in a locked place and that children did not have access to them. Approximately 10% of caregivers store multiple medications in one bottle, and the same percentage of participants do not check the expiration date on the medication labels. In terms of the most common medications stored at home, antihypertensives were on top of the list. Our study has shown that parental education and being a health-care worker were each associated with the difficulty in reaching medications ($P = 0.006$ and $P = 0.011$, respectively). Moreover, the percentage of participants who shared medications was significantly higher among those who were not working in the health-care section compared to those who were ($P = 0.004$). In addition, being a female parent and a college graduate was associated with the possibility of keeping excess or leftover medications at home ($P = 0.025$). **Conclusion:** Parents residing in the State of Qatar have some deficiencies in knowledge about medication storage. Parent's attitudes and perceptions are deemed vital objectives for population's health intervention.

Keywords: Children, medication, pediatric, Qatar, storage

Introduction

Home accidents are grave public health issues in pediatrics. They account for a large proportion of morbidity and mortality in the pediatric population.[1] In the United States, 47% of calls received by poison control centers are concerned about children below 6 years of age.[2]

In the United States, there are more than 1.4 million poisonings in children and adolescents per year.[3] While in the State of Qatar, a cross-sectional study has shown that there were 1179 registered pre-school children poisoning cases in the main emergency department of the country in between 2009 and 2012.

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Received: 25-06-2020 **Revised:** 05-09-2020
Accepted: 07-09-2020 **Published:** 27-08-2021

Access this article online
Quick Response Code:
Website: www.jfmpc.com
DOI: 10.4103/jfmpc.jfmpc_1259_20

How to cite this article: Hendaus MA, Saleh M, Darwish S, Mostafa O, Eltayeb A, Al-Amri M, *et al*. Parental perception of medications safe storage in the State of Qatar. J Family Med Prim Care 2021;10:2969-73.

Original Article

Parenting style in a rapidly developing country: A report from the state of Qatar

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Abstract

Objective: To investigate the different styles of parenting in the State of Qatar, a country that is considered a cosmopolitan hub with rapid development. **Materials and Methods:** A cross-sectional study was conducted at Sidra Medicine, the only tertiary pediatric hospital in Qatar. Parents of children 3–14 years old were offered a questionnaire. **Results:** A total of 114 questionnaires were completed (response rate = 95%). Approximately 65% of parents were between 30 and 39 years of age. Almost 90% of parents state that they are confident of their parenting ability. More than 90% of the participating parents stated that they are responsive to their child's feeling and needs, give comfort and understanding when their child is upset, praise their child when well-behaved, give reasons why rules should be followed, help children understand the impact of their behavior, explain consequences of bad behavior, take into account their child's desire before asking him/her to do something, encourage their child to freely express him/herself when disagreeing with his/her parents, and show respect to their child's opinion. However, 60% of parents sometimes scold, yell, and criticize their child when he/she misbehaves but less than 50% of them use threats as a consequence with little or no justification. Furthermore, two-thirds of parents give consequences by putting their child off somewhere with little or no explanation. Moreover, one in four participants gives in to their child when he/she causes a commotion about something, threatens their child with consequences more often than actually giving them, and states consequences to their child and do not actually do them. **Conclusion:** Residents in Qatar have a mixed type of parental style (authoritative, authoritarian, and permissive). This study will guide us to raise the awareness about the types of parenting style in Qatar, in order to provide professional parenting counseling taking into consideration the cultural background.

Key words: Children, parenting, pediatric, Qatar, style

Introduction

During the crucial age of children's growth and development, the parents are the children's first tutors. Features of parental control, including supervising, discipline, autonomy conceding, in addition to emotional constituents of parent behaviors, including acceptance, warmth, and receptiveness, constantly rise as predictors of children's adjustment.[1] The degree to which parents exhibit behaviors in either control, emotion, or mixed grade their parenting style as permissive, authoritarian, or authoritative.[2] Caregivers who mainly exhibit control behaviors and less care are characterized as authoritarian,

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Received: 16-07-2020 **Revised:** 17-09-2020
Accepted: 26-05-2021 **Published:** 27-08-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1462_20

How to cite this article: Hendaus MA, Alozeib R, Saied L, Shehzad S, Abdulmajeed M, Arab K, *et al.* Parenting style in a rapidly developing country: A report from the state of Qatar. J Family Med Prim Care 2021;10:2947-51.

Acta Biomed 2021; Vol. 92, N. 4: e2021319 DOI: 10.23750/abm.v92i4.11572

Case report

A rare case of ovarian juvenile granulosa cell tumor in an infant with isosexual pseudo puberty and revision of literature

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Abstract. Juvenile ovarian granulosa cell tumors (JGCTs) are described infrequently in pediatrics, and their finding in infants is exceptional. We highlight the presenting symptoms, radiologic images, operative management, and histopathologic findings of a 9-month-old female with isosexual pseudo-puberty. An updated revision of literature in infants below the age of 12 months is also reported. (www.actabiomedica.it)

Key words: Precocious puberty, infant, ovary, granulosa cell tumor, estrogen.

Introduction

Ovarian neoplasms are infrequent in childhood, with an incidence of only 1–5% (1). They can be classified as epithelial, germ cell, or stromal. Within the stromal category, the most common tumor is the granulosa cell tumor (GCT). The juvenile subtype accounts for 5% of these cases. Juvenile granulosa cell tumours (JGCT) are defined as a variant form of adult granulosa cell tumors, as they have different clinical and pathologic features (2). In infants, less than 1-year JGCT is extremely rare, with very few reported cases in the literature (3). In this case report, we highlight the presenting symptoms, radiologic images, operative management, and histopathologic findings of a 9-month-old female with isosexual pseudo puberty.

Case presentation

A 9-month-old girl born at term presented with a day history of bloody vaginal secretions. The diaper was stained with streaks of blood mixed with mucus. The mother noticed, 2 months before, bilateral breast development and the presence of fine hair growth in the genital area. Parents were non-related, and they had no family history of endocrine disease or precocious puberty.

On physical examination, the child had no dysmorphic features. Her length and weight were in the normal range [75cm (1.66 SD) and 10.4 kg (1.85 SD), respectively]. She had no skin hyperpigmentation, no skeletal abnormalities, or dysmorphic features. The abdomen was soft with no organomegaly or palpable mass. Breast development corresponded to Tanner's stage 2 and fine pubic hair was evident. No neurological abnormalities were detected. The rest of the clinical examination was unrevealing.

Endocrine workup revealed elevated levels of estradiol (E2), anti-Mullerian hormone (AMH), inhibin A and B, and androstenedione. The luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were suppressed (Table 1).

Title: Real-Time SARS-CoV-2 Genotyping by High-Throughput Multiplex PCR Reveals the Epidemiology of the Variants of Concern in Qatar

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Abstract

Complementing whole genome sequencing strategies with high-throughput multiplex RT-qPCR genotyping allows for more comprehensive and real-time tracking of SARS-CoV-2 variants of concern. During the second and third waves of COVID-19 in Qatar, PCR genotyping, combined with Sanger sequencing of un-typeable samples, was employed to describe the epidemiology of the Alpha, Beta and Delta variants. A total of 9792 nasopharyngeal PCR-positive samples collected between April-June 2021 were successfully genotyped, revealing the importation and transmission dynamics of these three variants in Qatar.

Keywords: COVID-19, SARS-CoV-2, variants of concern (VOC), genotyping, epidemiology

Gao *et al. Microbiome* (2021) 9:187
https://doi.org/10.1186/s40168-021-01138-2

Microbiome

RESEARCH Open Access

Disease-induced changes in plant microbiome assembly and functional adaptation

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Abstract

Background: The plant microbiome is an integral part of the host and increasingly recognized as playing fundamental roles in plant growth and health. Increasing evidence indicates that plant rhizosphere recruits beneficial microbes to the plant to suppress soil-borne pathogens. However, the ecological processes that govern plant microbiome assembly and functions in the below- and aboveground compartments under pathogen invasion are not fully understood. Here, we studied the bacterial and fungal communities associated with 12 compartments (e.g., soils, roots, stems, and fruits) of chili pepper (*Capsicum annuum* L.) using amplicons (16S and ITS) and metagenomics approaches at the main pepper production sites in China and investigated how *Fusarium* wilt disease (FWD) affects the assembly, co-occurrence patterns, and ecological functions of plant-associated microbiomes.

Results: The amplicon data analyses revealed that FWD affected less on the microbiome of pepper reproductive organs (fruit) than vegetative organs (root and stem), with the strongest impact on the upper stem epidermis. Fungal intra-kingdom networks were less stable and their communities were more sensitive to FWD than the bacterial communities. The analysis of microbial interkingdom network further indicated that FWD destabilized the network and induced the ecological importance of fungal taxa. Although the diseased plants were more susceptible to colonization by other pathogenic fungi, their below- and aboveground compartments can also recruit potential beneficial bacteria. Some of the beneficial bacterial taxa enriched in the diseased plants were also identified as core taxa for plant microbiomes and hub taxa in networks. On the other hand, metagenomic analysis revealed significant enrichment of several functional genes involved in detoxification, biofilm formation, and plant-microbiome signaling pathways (i.e., chemotaxis) in the diseased plants.

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ARTICLE

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Bitot-like spots in children with normal vitamin A levels

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BACKGROUND/AIMS: A Bitot spot is a conjunctival lesion, classically associated with severe vitamin A deficiency. In this paediatric series, we describe conjunctival lesions indistinguishable from Bitot spots, seen in the presence of normal vitamin A levels.
METHODS: This descriptive case series was performed by retrospective review of case notes, including all patients with Bitot-like spots found to have normal serum vitamin A levels, seen at the Hospital for Sick Children, Toronto, between 2006 and 2016. Data collected included age at presentation, ophthalmic and systemic diagnoses, and the presence of recognised genetic mutations. Histopathology was reviewed in one case.
RESULTS: Ten patients with Bitot-like spots with laboratory-confirmed normal serum vitamin A levels were identified. The conjunctival lesions were indistinguishable clinically and histopathologically from classic Bitot spots and were noted to occur in a range of anterior segment pathologies, including aniridia, WAGR syndrome, Axenfeld–Rieger syndrome, and blepharokeratoconjunctivitis.
CONCLUSIONS: Bitot-like spots are found in children with a number of anterior segment pathologies in the absence of vitamin A deficiency.

Eye; https://doi.org/10.1038/s41433-021-01569-z

INTRODUCTION

A Bitot spot, first described by Pierre Bitot in 1863 [1, 2], is a conjunctival lesion classically associated with xerophthalmia, an umbrella term referring to the ocular manifestations of vitamin A deficiency [3]. Clinically, these lesions appear as well-defined, foamy white plaques on the bulbar conjunctiva. They are most commonly round or triangular in shape [2, 4], with a base abutting the temporal limbus and an apex projecting towards the lateral canthus. Extensive involvement of the bulbar conjunctiva is less common [2]. Appearance and incidence does not vary between adults and children [2].

The histopathology of a Bitot spot reveals metaplastic squamous epithelium together with keratin tangles and a loss of goblet cells. Gas-producing bacteria, *Corynebacterium xerosis* [5], dwell in the conjunctiva creating pockets of gas, giving the lesion its distinct foamy appearance [5, 6].

In the past, Bitot spots were considered to be pathognomic of vitamin A deficiency [5], allowing their presence to be used for screening patients for xerophthalmia, a preventable cause of blindness in the developing world. However, these lesions are also seen in other vitamin deficiencies, such as pellagra, a vitamin B deficiency state, as well as in the absence of any identifiable nutritional deficiency [2, 7]. The prevalence of cases reported from hot climates have led to the suggestion that exposure, drying, and actinic stimulation may play a role in their creation [7–10].

Here we present a paediatric case series of lesions clinically indistinguishable from the classic Bitot spot in the presence of normal vitamin A levels, almost all of which were associated with congenital or acquired anterior segment pathologies.

METHODS

This study was approved by the Hospital for Sick Children Research Ethics Board.

Ten consecutive cases were included with consent, all of whom were diagnosed with Bitot-like spots from April 2006 to November 2016, and in all of whom normal serum vitamin A levels were found on testing. Retrospective chart review was used to document date and age at diagnosis, visual acuities, other diagnosed ophthalmic and systemic conditions, and topical medication use, as well as any positive results from genetic panels.

All patients had clinical slit lamp photographs of their lesion, which were reviewed. The shape and size of the lesion, laterality, proximity to the limbus, orientation, and whether it had a foamy appearance were noted. In addition, a single patient underwent tissue biopsy of their lesion at the time of glaucoma seton surgery, which was sent for histopathological examination.

RESULTS

Ten children with a mean age at presentation of 7.9 years (range 3–11 years) were included and their findings are summarised in Table 1. Serum vitamin A levels ranged from 0.9 to 2.7 µmol/L, with 0.52 µmol/L being the lower limit of the normal range.

Four patients had single, unilateral lesions only, while six were bilaterally affected. Patients 2 and 7, both of whom had WAGR

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Received: 5 February 2020 Revised: 25 February 2021 Accepted: 20 April 2021
Published online: 16 September 2021

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Clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus among children in Qatar

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To describe the clinical features, epidemiology, autoantibody status, HLA haplotypes and genetic mechanisms of type 1 diabetes mellitus (T1DM). Patients (0–18 years) with diabetes were recruited. Clinical data was collected, autoantibodies and c-peptide were measured. Whole Genome Sequencing was performed. Genomic data analysis was compared with the known genes linked with T1DM and HLA alleles were studied. 1096 patients had one or more antibody positivity. The incidence of T1DM in 2020 was 38.05 per 100,000 children and prevalence was 249.73. GADA was the most common autoantibody followed by IAA. Variants in *GSTCD*, *SKAP2*, *SLC9B1*, *BANK1* were most prevalent. An association of HLA haplotypes DQA1*03:01:01G (OR = 2.46, *p* value = 0.011) and DQB1*03:02:01G (OR = 2.43, *p* value = 0.022) was identified. The incidence of T1DM in Qatar is the fourth highest in the world, IA2 autoantibody was the most specific with some patients only having ZnT8 or IA2 autoantibodies thus underlining the necessity of profiling all 4 autoantibodies. The genes associated with T1DM in the Arab population were different from those that are common in the Caucasian population. HLA-DQ was enriched in the Qatari patients suggesting that it can be considered a major risk factor at an early age.

Type 1 diabetes mellitus is the most common form of diabetes observed in children. It is a chronic multifactorial disease with a strong genetic component, which, through interactions with specific environmental factors, triggers disease onset. Type 1 diabetes mellitus usually presents itselft in early to mid childhood as a defect in insulin production through the autoimmune destruction of pancreatic beta-cells[1]. There are two forms of type 1 diabetes mellitus (1A autoimmune and 1B idiopathic). In the autoimmune type there is antibody mediated beta-cell destruction resulting in metabolic abnormalities which is manifested as impaired glucose tolerance first and then progresses to symptomatic hyperglycaemia. Approximately 50% of the familial clustering of genes, which increase the susceptibility risk of inheriting type 1 diabetes mellitus, are located within or in the Human Leucocyte Antigen (HLA) complex on chromosome 6[2].

The performance of high-density Genome Wide Association Studies (GWAS) enabled by the advent of high-throughput single nucleotide polymorphism (SNP) genotyping array technologies, many additional type 1 diabetes mellitus susceptibility loci and genes have now been discovered[3]. Recent meta-analyses of multiple datasets from independent investigators have brought the total of genes implicated in type 1 diabetes mellitus to nearly 60[4].

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Bayoumi *et al. BMC Pregnancy Childbirth* (2021) 21:651
https://doi.org/10.1186/s12884-021-04124-6

BMC Pregnancy and Childbirth

RESEARCH Open Access

Maternal and neonatal outcomes in mothers with diabetes mellitus in qatari population

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Abstract: Background: Diabetes Mellitus (DM) is a major cause of maternal, fetal, and neonatal morbidities. Our objective was to estimate the effect of both pre-pregnancy and gestational DM on the growth parameters of newborns in the Qatari population.

Methods: In this population-based cohort study, we compared the data of neonates born to Qatari women with both pre-pregnancy and gestational diabetes mellitus in 2017 with neonates of healthy non-diabetic Qatari women.

Results: Out of a total of 17020 live births in 2017, 5195 newborns were born to Qatari women. Of these, 1260 were born to women with GDM, 152 were born to women with pre-pregnancy DM and 3783 neonates were born to healthy non-diabetic (control) women. The prevalence of GDM in the Qatari population in 2017 was 24.25%. HbA1C% before delivery was significantly higher in women with pre-pregnancy DM (mean 6.19 ± 1.15) compared to those with GDM (mean 5.28 ± 0.43) (P <0.0001). The mean birth weight in grams was 3066.01 ± 603.42 in the control group compared to 3156.73 ± 577.88 in infants born to women with GDM and 3048.78 ± 677.98 in infants born to women with pre-pregnancy DM (P <0.0001). There was no statistically significant difference regarding the mean length (P= 0.080), head circumference (P= 0.514), and rate of major congenital malformations (P= 0.211). Macrosomia (Birth weight > 4000 gm) was observed in 2.7% of the control group compared to 4.8% in infants born to women with GDM, and 4.6% in infants born to women with pre-pregnancy DM (P= 0.001). Multivariate logistic regression analysis demonstrated that higher maternal age (adjusted OR 2.21, 95% CI 1.93, 2.52, P<0.0001), obesity before pregnancy (adjusted OR 1.71, 95% CI 1.30, 2.23, P<0.0001), type of delivery C-section (adjusted OR 1.25, 95% CI 1.09, 1.44, P=0.002), and body weight to gestational age LGA (adjusted OR 2.30, 95% CI 1.64, 2.34, P<0.0001) were significantly associated with increased risk of GDM.

Conclusion: Despite the multi-disciplinary antenatal diabetic care management, there is still an increased birth weight and an increased prevalence of macrosomia among the infants of diabetic mothers. More efforts should be addressed to improve the known modifiable factors such as women's adherence to the diabetic control program. Furthermore, pre-pregnancy BMI was found to be significantly associated with gestational DM, and this is a factor that can be addressed during pre-conceptional counseling.

Keywords: Gestational Diabetes Mellitus, Women, Newborn, Infant of Diabetic Mother, Qatari

Background

Gestational Diabetes Mellitus (GDM) occurs in 2-9% of pregnant women worldwide and is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" [1]. During pregnancy, the placenta secretes certain diabetogenic hormones including growth

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SURGICAL MANAGEMENT, STAGING, AND OUTCOMES OF WILMS TUMOURS WITH INTRAVASCULAR EXTENSION: RESULTS OF THE IMPORT STUDY

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ABSTRACT

Purpose: to review surgical management, tumour stage and clinical outcomes in children with intravascular extension of Wilms tumour (WT) registered in a national clinical study (2012-19).

Methods: WTs with presence/suspicion of tumour thrombus in the renal vein (RV) or beyond on radiology, surgery or pathology case report forms were identified. Only cases where thrombus was confirmed by surgeon and/or reference pathologist were included. Surgical management, disease stage, overall (OS) and event free survival (EFS) were investigated.

Results: 69/583 (11.8%) patients met the inclusion criteria. Forty-six (67%) had abdominal stage III due to thrombus-related reasons: 11 had macroscopically incomplete resection, including 8 cases where cavotomy was not performed; 20 had piecemeal complete resection of thrombus; 15 had microscopically positive resection margins at the RV. 66% of tumour thrombi contained viable tumour. There were eight relapses and five deaths. EFS, but not OS, was significantly associated with completeness of surgical resection (P<0.05). OS and EFS were also significantly associated with histological risk group (P<0.05) but not with viability of tumour thrombus (P=0.19; P=0.59).

Conclusions: WTs with intravascular extension have a high risk of local stage III due to thrombus-related reasons. Controlled complete removal of the thrombus should be the aim of surgery.

Keywords

Wilms tumor; Thrombus; Surgery; Local stage; Outcomes

Level of Evidence: Level II

List of Abbreviations

WT	Wilms tumour
cenRR	Central radiology review
cenPR	Central pathology review
CT	Computed tomography
CRF	Case report form
CCLG	Children's Cancer and Leukemia group

Received: 24 June 2021 | Revised: 29 July 2021 | Accepted: 23 August 2021

DOI: 10.1002/ajmg.a.62501

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Expanding on the phenotypic spectrum of Woodhouse-Sakati syndrome due to founder pathogenic variant in *DCAF17*: Report of 58 additional patients from Qatar and literature review

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Abstract

Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive neuroendocrine and ectodermal disorder caused by variants in the *DCAF17* gene. In Qatar, the c.436delC variant has been reported as a possible founder pathogenic variant with striking phenotypic heterogeneity. In this retrospective study, we report on the clinical and molecular characteristics of additional 58 additional Qatari patients with WSS and compare them to international counterparts' findings. A total of 58 patients with WSS from 32 consanguineous families were identified. Ectodermal and endocrine (primary hypogonadism) manifestations were the most common presentations (100%), followed by diabetes mellitus (46%) and hypothyroidism (36%). Neurological manifestations were overlapping among patients with intellectual disability (ID) being the most common (75%), followed by sensorineural hearing loss (43%) and both ID and aggressive behavior (10%). Distinctive facial features were noted in all patients and extrapyramidal manifestations were uncommon (8.6%). This study is the largest to date on Qatari patients with WSS and highlights the high incidence and clinical heterogeneity of WSS in Qatar due to a founder variant c.436delC in the *DCAF17* gene. Early suspicion of WSS among Qatari patients with hypogonadism and ID, even in the absence of other manifestations, would shorten the diagnostic odyssey, guide early and appropriate management, and avoid potential complications.

KEYWORDS
c.436delC, *DCAF17* gene, founder pathogenic variant, Qatar, variable clinical manifestations, Woodhouse-Sakati syndrome

Early Human Development 161 (2021) 105451

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Early discharge and hospital-assisted home care is associated with better neurodevelopmental outcome in preterm infants

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ARTICLE INFO

Keywords:
Home care
Preterm
Early discharge
Neurodevelopment
Breastmilk feeding

ABSTRACT

Aims: To compare hospital-assisted neonatal home care and standard hospital care for preterm newborns on neurodevelopment at 2 years corrected age, as well as duration of hospitalization, breastmilk rates, and readmissions before 1 year.

Methods: This observational study enrolled 415 inborn neonates $<34^{+6}$ weeks that received home care (2008 to 2015) in the French University Hospital of Toulouse and 3186 neonates from the national cohort of infants discharged in 2011 that received standard hospital neonatal care (EPIPAGE 2). Neurodevelopment at 2 years was assessed with the Ages and Stages Questionnaire-3 (ASQ-3).

Results: At two years corrected age, infants in home care had 61% less risk of overall low ASQ $\leq$220 (OR = 0.4 [0.3–0.5], $p < 0.001$) and 31–80% less risk of low scores in four out of five domains compared to standard care. Home care was associated with shorter hospital stays (− 9 days; $p < 0.001$), higher breastmilk rates at final discharge (OR = 3.6 [2.8–4.6], $p < 0.001$ for singletons and OR = 2.3 [1.6–3.1], $p < 0.001$ for multiples), and more breastmilk feeding for at least six months (OR = 1.8 [1.3–2.3], $p < 0.001$ for singletons, OR = 3.6 [2.1–6.3], $p < 0.001$ for multiples). Readmissions also occurred less frequently with home care than with standard care, except for twins (OR = 0.7 [0.6–0.8], $p < 0.001$).

Conclusion: Hospital-assisted neonatal home care for preterm infants was associated with better neurodevelopment at 2 years corrected age, shorter duration of hospitalization, and higher rates of breastmilk feeding at 6 months.

1. Introduction

Preterm birth is often associated with a long hospital stay. After initial care in the neonatal care unit (NCU), discharging home preterm infants depends on cardiorespiratory and thermal stability, parental capacity to care for these fragile neonates, and full oral feeding that will support appropriate growth [1–2]. The duration required for tube feeding depends on the neonatal history, the environment, and the neonatal units practices. In some cases, it can lead to prolonged hospitalization. A European study showed that the mean standard hospital stay for extremely preterm infants was 63.1 days, (range 54 to 70 days, depending on the region) [3]. The hospital stay was related to neonatal morbidity and to the diversity of current practices in different neonatal teams [4–6]. After discharge, preterm children are at higher risk of rehospitalisation in their first year of life, that occurred in 38% of very preterm children and 24% of moderately preterm children, in the French cohort EPIPAGE [7].

Hospital-assisted neonatal home care (HANHC) represents an alternative to standard hospital care for stable preterm infants who continue to need specialized care, like tube feeding. HANHC is common in Scandinavian countries, and its feasibility and safety have been documented [8–10]. Other studies have shown that similar programs were

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https://doi.org/10.1016/j.earlhumdev.2021.105451
Received 8 February 2021; Received in revised form 24 June 2021; Accepted 9 August 2021
Available online 21 August 2021

Received: 12 November 2020 | Revised: 14 August 2021 | Accepted: 20 September 2021

DOI: 10.1111/pan.14303

RESEARCH REPORT

Pediatric Anesthesia WILEY

Point-of-care ultrasound to confirm endotracheal tube cuff position in relationship to the cricoid in the pediatric population

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Funding information
This investigation was performed without funding.

Section Editor: Thomas Engelhardt

Abstract

Background: Anatomically, the subglottic area and the cricoid ring are the narrowest portions of the larynx. To limit the potential for damage related to mucosal pressure injuries from the presence of an endotracheal tube, the cuff should be placed below the cricoid in children. Previously, no clinical or imaging method has been used in real time to determine the exact location of the endotracheal tube cuff after endotracheal intubation. Point-of-care ultrasound may provide an option as a safe and rapid means of visualizing the endotracheal tube cuff and its relationship to the cricoid ring thereby achieving ideal endotracheal tube cuff positioning—below the cricoid.

Methods: In this prospective, nonrandomized trial, point-of-care ultrasound was used following endotracheal intubation in children to evaluate the position of the endotracheal tube cuff in relationship to the cricoid and tracheal rings. After anesthesia was induced and the trachea was intubated, the endotracheal tube cuff and its position in relation to the cricoid and tracheal rings were identified in the longitudinal plane using point-of-care ultrasound. With the patient's neck in a neutral position, the level of the proximal (cephalad) margin of the saline-filled cuff of the endotracheal tube was identified and recorded in relationship to the cricoid and tracheal rings. The ideal position is defined as the cephalad margin of the endotracheal tube cuff below the level of the cricoid.

Results: The study cohort included 80 patients, ranging in age from 1 to 78 months. In all patients, the cuff of the ETT, cricoid, and tracheal rings were identified. The cephalad end of the endotracheal tube cuff was found at the level of the cricoid in 16.3% of patients, at the first tracheal ring in 27.5% of patients, at the second tracheal ring in 23.8% of patients, at the third tracheal ring in 17.5% of patients, and at below the fourth tracheal ring in 15% of patients. Initial endotracheal tube cuff position had no significant association with age, height, weight, endotracheal tube size, and endotracheal tube type.

Conclusion: Point-of-care ultrasound provides a rapid and effective means of identifying the position of the endotracheal tube cuff in relationship to the cricoid ring. The technique may have applications in the perioperative arena, emergency departments, and intensive care units.

ORIGINAL ARTICLE

Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar

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ABSTRACT

BACKGROUND

Waning of vaccine protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (Covid-19) is a concern. The persistence of BNT162b2 (Pfizer–BioNTech) vaccine effectiveness against infection and disease in Qatar, where the B.1.351 (or beta) and B.1.617.2 (or delta) variants have dominated incidence and polymerase-chain-reaction testing is done on a mass scale, is unclear.

METHODS

We used a matched test-negative, case–control study design to estimate vaccine effectiveness against any SARS-CoV-2 infection and against any severe, critical, or fatal case of Covid-19, from January 1 to September 5, 2021.

RESULTS

Estimated BNT162b2 effectiveness against any SARS-CoV-2 infection was negligible in the first 2 weeks after the first dose. It increased to 36.8% (95% confidence interval [CI], 33.2 to 40.2) in the third week after the first dose and reached its peak at 77.5% (95% CI, 76.4 to 78.6) in the first month after the second dose. Effectiveness declined gradually thereafter, with the decline accelerating after the fourth month to reach approximately 20% in months 5 through 7 after the second dose. Effectiveness against symptomatic infection was higher than effectiveness against asymptomatic infection but waned similarly. Variant-specific effectiveness waned in the same pattern. Effectiveness against any severe, critical, or fatal case of Covid-19 increased rapidly to 66.1% (95% CI, 56.8 to 73.5) by the third week after the first dose and reached 96% or higher in the first 2 months after the second dose; effectiveness persisted at approximately this level for 6 months.

CONCLUSIONS

BNT162b2-induced protection against SARS-CoV-2 infection appeared to wane rapidly following its peak after the second dose, but protection against hospitalization and death persisted at a robust level for 6 months after the second dose. (Funded by Weill Cornell Medicine–Qatar and others.)

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This article was published on October 6, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2114114

PRIMER

Wilms tumour

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Abstract | Wilms tumour (WT) is a childhood embryonal tumour that is paradigmatic of the intersection between disrupted organogenesis and tumorigenesis. Many WT genes play a critical (non-redundant) role in early nephrogenesis. Improving patient outcomes requires advances in understanding and targeting of the multiple genes and cellular control pathways now identified as active in WT development. Decades of clinical and basic research have helped to gradually optimize clinical care. Curative therapy is achievable in 90% of affected children, even those with disseminated disease, yet survival disparities within and between countries exist and deserve commitment to change. Updated epidemiological studies have also provided novel insights into global incidence variations. Introduction of biology-driven approaches to risk stratification and new drug development has been slower in WT than in other childhood tumours. Current prognostic classification for children with WT is grounded in clinical and pathological findings and in dedicated protocols on molecular alterations. Treatment includes conventional cytotoxic chemotherapy and surgery, and radiation therapy in some cases. Advanced imaging to capture tumour composition, optimizing irradiation techniques to reduce target volumes, and evaluation of newer surgical procedures are key areas for future research.

Nephron-sparing surgery
An operation to remove a kidney tumour by removing only part of the surrounding normal renal parenchyma.

Wilms tumour (WT) is the most common renal tumour of infants and young children[1,2]. WT is intimately linked to early nephrogenesis, which it resembles morphologically[3] and transcriptionally[4,5]. WT may occur sporadically or in the context of bilateral tumours, multifocal disease and specified genetic predisposition syndromes that frequently include either genitourinary malformation or overgrowth[3]. Beyond genetic predisposition, external causative factors for WT are not yet defined. The molecular drivers frequently involve blockade of genetic pathways that guide normal embryogenesis of the genitourinary tract but are not restricted to these. Indeed, the cancer genes that underpin WT are diverse and surprisingly involve ~40 genes.

The implementation of international co-operative group trials and studies across North America, Australia, New Zealand, Europe and Brazil has contributed significantly to improving outcomes[6–8]. Two international multidisciplinary cooperative consortia — the Children's Oncology Group (COG) Renal Tumour Committee, previously known as the National Wilms Tumour Study Group (NWTSG), and the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (RTSG) — have conducted large multicentre studies since 1969 and 1971, respectively, which have defined the current diagnostic and therapeutic approach to patients with WT (FIG. 1). These groups continue research to optimize disease and patient risk classification and treatment strategies[9–11].

In the COG, WTs are treated with primary resection (if possible), followed by risk-adapted adjuvant therapy, whereas in the context of SIOP cooperation, neoadjuvant chemotherapy followed by resection and adjuvant therapy is the preferred treatment approach. Regardless of the initial approach, the overall survival of children with WT is remarkable with rates of >90%. Such satisfying survival rates have been achieved at the same time as fine-tuning treatment by adopting well-studied prognostic factors, leading to a two-drug regimen (vincristine and actinomycin D) prescribed in nearly two-thirds of affected children[7,10]. Notably, striking survival disparities still exist within countries[12] and between different parts of the world, which remain to be addressed[13,14]. However, 20% of patients relapse after first-line therapy and up to 25% of survivors report severe late morbidity of treatment[15,16]. Addressing the long-term effect of radical nephrectomy on renal function and cardiovascular function will probably drive more attention on expanding the role of nephron-sparing surgery (NSS)[17].

Molecular studies are expanding the landscape of cancer genes implicated in WT beyond exclusive roles in nephrogenesis[3]. The use of next-generation

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https://doi.org/10.1038/s41572-021-00308-8

Clinical Infectious Diseases

BRIEF REPORT

Severity, Criticality, and Fatality of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Beta Variant

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Beta (B.1.351)–variant coronavirus disease 2019 (COVID-19) disease was investigated in Qatar. Compared with the Alpha (B.1.1.7) variant, odds (95% confidence interval) of progressing to severe disease, critical disease, and COVID-19–related death were 1.24-fold (1.11–1.39), 1.49-fold (1.13–1.97), and 1.57-fold (1.03–2.43) higher, respectively, for the Beta variant.

Keywords. SARS-CoV-2; variant; infection; severe disease; epidemiology.

Commencing in mid-January 2021, Qatar experienced a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Alpha [1] (B.1.1.7)–variant wave that peaked in the first week of March [2–5], but was immediately followed by a Beta [1] (B.1.351)–variant wave that peaked in the first week of April [2–6]. This created a unique epidemiologic situation that allowed comparative assessment of the severity, criticality, and fatality of these 2 variants.

Received 1 August 2021; editorial decision 13 October 2021; published online 17 October 2021.

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Clinical Infectious Diseases® 2021;XX(XX):1–4

https://doi.org/10.1093/cid/ciab909

METHODS

We investigated severity (acute-care hospitalization) [7], criticality (intensive care unit [ICU] hospitalization) [7], and fatality [8] of both variants through 8 case-control studies applied to the complete national cohorts of SARS-CoV-2 infections, coronavirus disease 2019 (COVID-19) disease cases, and COVID-19–related deaths in Qatar, a country with diverse demographics where 89% of the population comprises expatriates from over 150 countries [9]. Data on polymerase chain reaction (PCR) testing and clinical characteristics were extracted from the national federated COVID-19 databases that have captured all SARS-CoV-2–related data since the start of the epidemic. These databases were retrieved from the integrated nationwide digital-health information platform (universal healthcare system), and include all records of PCR testing, antibody testing, vaccinations, COVID-19 hospitalizations, infection severity classification, and COVID-19–related deaths. Databases are complete at the national level with no missing information.

Records of PCR testing and clinical data for hospitalized patients with COVID-19 were examined. Details of the laboratory methods for PCR testing are found in Supplementary Text 1. Each person who had a PCR-positive test result and hospital admission was subject to an infection-severity assessment every 3 days until discharge or death. Individuals who progressed to COVID-19 disease between the time of the PCR-positive test result and the end of the study were classified based on their worst outcome, starting with death [8], followed by critical disease [7], and then severe disease [7].

Cases in the case-control studies were persons who progressed to COVID-19 severe disease, critical disease, or death. Controls were persons with asymptomatic or mild SARS-CoV-2 infections. Cases and controls were matched at a ratio of 1:3 by 10-year age group, sex, and biweekly interval of the PCR diagnosis date. Every case in Qatar that met the inclusion criteria and that could be matched to a control was included in the study. Classification of case severity, criticality, and fatality followed the World Health Organization guidelines [7, 8], and assessments were made by trained medical personnel through individual chart reviews. Details of the COVID-19 severity, criticality, and fatality classification are found in Supplementary Text 2.

From 18 January until 15 February 2021, the Alpha-variant wave expanded rapidly and weekly rounds of viral genome sequencing [2–5] of randomly collected samples confirmed the presence of this and other originally circulating "wild-type" variants, but documented only limited presence of the Beta variant and no other variants of concern [2–5]. This allowed a comparative assessment for the Alpha variant versus wild-type variants

Original Article

Endotracheal tube cuff position in relation to the cricoid in children: A retrospective computed tomography-based analysis

ABSTRACT

Background: The use of cuffed endotracheal tubes (ETT) has become the standard of care in pediatric practice. The rationale for the use of a cuffed ETT is to minimize pressure around the cricoid while providing an effective airway seal. However, safe care requires that the cuff lie distal to the cricoid ring following endotracheal intubation. The current study demonstrates the capability of computed tomography (CT) imaging in identifying the position of the cuff of the ETT in intubated patients.

Methods: In this retrospective study, the ETT cuff position was examined on the sagittal plane images of neck and chest CT scans of 44 children. The position of the proximal and the distal aspect of the ETT cuff inside the trachea was recorded in relation to the vertebral levels. The vertebral levels were used to estimate the location of the cricoid ring and its relationship to the cuff.

Results: The vertebrae were used as the primary landmarks to define the position of the cricoid and its relationship to the cuff of the ETT. Correlating vertebral levels with the cricoid for different age groups, the proximal (cephalad) edge of the ETT cuff was below the cricoid in 41 of 44 patients (93%). The ETT cuff was deep in 6 patients, below the 1st thoracic vertebra, with 2 ETTs in the right mainstem bronchus.

Conclusion: This is the first study demonstrating that the cuff of the ETT and its position in the trachea can be identified on CT imaging in children. The ETT cuff was below the level of the cricoid in the majority of patients irrespective of the patient's age as well as the size, make, and type of ETT.

Key words: Computed tomography imaging, cricoid ring, endotracheal intubation, endotracheal tube cuff, pediatric airway, trachea.

Introduction

The debate regarding the use of cuffed and uncuffed endotracheal tubes (ETTs) in infants and children has generally been settled in favor of the use of cuffed ETTs. The past 10 years have witnessed this change in clinical practice in both operating rooms and intensive care units (ICUs). Clinical studies have demonstrated several advantages of cuffed over

Access this article online	
Website: www.saudija.org	Quick Response Code
DOI: 10.4103/sja.sja_396_21	

How to cite this article: Wani TM, John J, Bahun V, AlGhamdi F, Tumin D, Tobias JD. Endotracheal tube cuff position in relation to the cricoid in children: A retrospective computed tomography-based analysis. Saudi J Anaesth 2021;15;403-8.

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Submitted: 27-May-2021, **Accepted:** 31-May-2021, **Published:** 02-Sep-2021

QMJ
A peer reviewed journal
QATAR MEDICAL JOURNAL

COMMENTARY

Delta variant of COVID-19: A simple explanation

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http://dx.doi.org/10.5339/qmj.2021.49
Submitted: 10 August 2021
Accepted: 19 September 2021

Cite this article as: Hendaus MA, Jomha FA. Delta variant of COVID-19: A simple explanation, Qatar Medical Journal 2021:49 http://dx.doi.org/10.5339/qmj.2021.49

كيوساينس
QSCIENCE
دار جامعة حمد بن خليفة للنشر
HAMAD BIN KHALIFA UNIVERSITY PRESS

ABSTRACT

Severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease (COVID-19), has undergone numerous mutations since its initial identification, leading to challenges in controlling the pandemic. Till date, several variants of concern have been identified. However, currently, the Delta variant (B.1.617.2) is the most dreaded one owing to its enhanced transmissibility and increased virulence. In addition, this variant can potentially facilitate fusion of the spike protein to cells or inhibit antibodies from binding to it. In this commentary, we have simplified the complexity of the nomenclature of variants related to COVID-19, concentrating on the Delta variant including its transmissibility, response to vaccines, and prevention.

INTRODUCTION

Coronavirus disease (COVID-19) has had a detrimental outcome on the global population and has caused millions of deaths worldwide. In addition, COVID-19 appears to the leading world health crisis since the influenza pandemic of 1918.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has undergone numerous mutations since its initial identification, leading to challenges in controlling the pandemic.[2]

So far, several variants have been of concern. The Alpha(B.1.1.7) variant was identified in United Kingdom in late December 2020, Beta(B.1.351) variant in South Africa in December 2020, and Gamma (P.1) variant in Brazil in early January 2021. The Delta(B.1.617.2) variant was first reported in India in December 2020 and is currently the most dreaded variant owing to its enhanced transmissibility and increased virulence.[3]

In this commentary, we simplify the complex nomenclature of COVID-19-causing viral variants.

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GENOME SEQUENCES

Draft Genome Sequence of *Rhodotorula mucilaginosa* from an Adult Patient in Qatar

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ABSTRACT *Rhodotorula mucilaginosa* is an opportunistic fungal pathogen of public health importance. We present the draft genome sequence of an isolate (Rhodo3571) cultured from an immunocompetent patient. The isolate is similar to other *R. mucilaginosa* genomes in the NCBI database. Presented here are the genome assembly and its comparison to other reference genomes.

Rhodotorula is a pigmented yeast, which is a normal environmental/commensal microorganism but it can cause opportunistic infections, such as those of the bloodstream, meningitis, and peritonitis (1, 2). *Rhodotorula mucilaginosa* has emerged as an opportunistic etiologic agent, particularly in immunocompromised patients, and infections have been reported in different parts of the world (3–6), including a recent *Rhodotorula* fungemia reported in Qatar (7). This article does not contain any studies with human participants or animals performed by any of the authors.

Here, we present a draft genome assembly of *R. mucilaginosa* (Rhodo3571) from an immunocompetent host, possibly associated with central venous catheter (CVC) infection at Hamad Medical Corporation (Doha, Qatar) (7). The yeast was isolated from blood; the blood culture aerobic vial that was flagged positive was subcultured on Sabouraud's dextrose agar (SDA; Difco, USA) and incubated under aerobic conditions at 35 ± 2°C for 18 to 24 h, minimizing exposure to light. After incubation, pink colonies were isolated on SDA, and the isolate was identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using the Bruker microflex system version 4 and the MALDI Biotyper (MBT) BDAL version 9.0 library (Bruker Daltonics, Germany). The identification was performed using the extended direct transfer method recommended by Bruker for identification of yeasts. In brief, a uniform thin layer of a yeast colony was smeared onto the MALDI target plate and overlaid with 1 μl 70% formic acid. It was allowed to dry at room temperature; then, 1 μl of HCCA matrix (Bruker Daltonics) was added to it. It was allowed to dry at room temperature again and then measured using the Bruker microflex system. The isolate was identified as *R. mucilaginosa* with a score of 2.08, which is considered reliable genus and species identification according to Bruker's cutoff score of ≥2.00. Antifungal susceptibility patterns were also characterized (7).

After growing the culture on SDA for 2 days, genomic DNA was extracted using the MasterPure yeast DNA purification kit (Lucigen Corporation, WI, USA). The DNA concentration was measured using the Qubit 2 fluorometer (Thermo Fisher), and DNA libraries were constructed using the Nextera XT DNA library preparation method (Illumina, Inc., CA, USA) and sequenced on the Illumina NextSeq 550 platform with 300 cycles (150-bp paired-end format) at Sidra Medicine. The adapter sequences were removed, and low-quality bases

Citation Sundararaju S, Salah H, Ibrahim EB, Perez-Lopez A, Abid FB, Tsui CKM. 2021. Draft genome sequence of *Rhodotorula mucilaginosa* from an adult patient in Qatar. Microbiol Resour Announc 10:e00725-21. https://doi.org/10.1128/MRA.00725-21.

Editor Jason E. Stajich, University of California, Riverside

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Received 22 July 2021
Accepted 24 September 2021
Published 21 October 2021

pathogens

MDPI

Article

Serum Cytokine Profile in Patients with Candidemia versus Bacteremia

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Abstract: Bloodstream *Candida* infections constitute a major threat for hospitalized patients in intensive care units and immunocompromised hosts. Certain serum cytokines play a decisive role in antimicrobial host defense. Cytokines may act as discriminatory biomarkers that can significantly increase in candidemia compared to bacteremia patients. The concentration of secreted cytokine/chemokines was determined using a multiplexed cytometric bead array run on a cell analyzer. The cytokines tested during the study were interleukin (IL)-1β, IL-6, IL-17A, IL-10, IFN-γ, IL-4, IL-2, IL-8, IL-12p70 and the tumor necrosis factor (TNF)-α. The cytokines of 51 candidemia patients were characterized and compared to the cytokine levels of 20 bacteremia patients. Levels were significantly elevated in patients with bloodstream infections compared to healthy controls. Cytokines comprising IL-2, IL-17A, IL-6 and IL-10 were significantly elevated in the patients with bloodstream *Candida* infection as compared to the patients having bloodstream bacterial infections. The levels were found to be promising as a potential diagnostic marker for bloodstream *Candida* infections.

Keywords: candidemia; bacteremia; risk factors; interleukins

Citation: Taj-Aldeen, S.J.; Mir, F.A.; Sivaraman, S.K.; AbdulWahab, A. Serum Cytokine Profile in Patients with Candidemia versus Bacteremia. *Pathogens* **2021**, *10*, 1349. https://doi.org/10.3390/pathogens10101349

Academic Editor: Dee Carter

Received: 22 July 2021
Accepted: 13 October 2021
Published: 19 October 2021

1. Introduction

The incidence of candidemia has increased dramatically, including the infections documented in intensive care units (ICUs). For example, 53% of documented candidemia in Hamad hospital, Qatar, was from the ICUs [1]. *Candida* spp. are the third most common microorganisms responsible for health-care-related bloodstream infections [2]. However, blood cultures for yeasts lack sensitivity and need prolonged incubation (> 48 h) to generate positive results. As a consequence, antifungal drugs are often prescribed either prophylactically, preemptively, or empirically in high-risk patients [3]. The resulting overuse of antifungal drugs may lead to the emergence of *Candida* species that are resistant to azoles and/or echinocandins [4,5].

The early diagnosis of fungal infection has become increasingly important in order to prevent invasive candidiasis. There are some reports suggesting that C-reactive protein (CRP) and procalcitonin (PCT) can be used to diagnose bacterial sepsis [6]; however, their role and other cytokines in diagnosis of fungal infections has not been clearly demonstrated. Host immunity is of clear importance for controlling *Candida* infections. Currently employed clinical characteristics do not differentiate between fungal and bacterial infections. Interleukins, promptly and transiently produced in response to infections and tissue injuries, contribute to host defense through the stimulation of acute phase responses, hematopoiesis and immune reactions [7,8]. This retrospective study aims to assess the risk factors associated with candidemia in ICUs and patients at high risk, to measure the serum

Priorities for child health research across the UK and Ireland

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-322636).

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Received 10 June 2021
Accepted 13 October 2021
Published Online First 29 October 2021

To cite: Cathie K, Sutcliffe AG, Bandi S, *et al*. *Arch Dis Child* 2022;**107**:474–478.

ABSTRACT

Background The General and Adolescent Paediatric Research Network in the UK and Ireland (GAPRUKI) was established in 2016. The aims of GAPRUKI are to unite general paediatricians around the UK and Ireland, to develop research ideas and protocols, and facilitate delivery of multicentre research.

Objectives To undertake a research prioritisation exercise among UK and Ireland general paediatricians.

Methods This was a four-phase study using a modified Delphi survey. The first phase asked for suggested research priorities. The second phase developed ideas and ranked them in priority. In the third phase, priorities were refined; and the final stage used the Hanlon Prioritisation Process to agree on the highest priorities.

Results In phase one, there were 250 questions submitted by 61 GAPRUKI members (66% of the whole membership). For phase two, 92 priorities were scored by 62 members and the mean Likert scale (1–7) scores ranged from 3.13 to 5.77. In a face-to-face meeting (phases three and four), 17 research questions were identified and ultimately 14 priorities were identified and ranked. The four priorities with the highest ranking focused on these three respiratory conditions: asthma, bronchiolitis and acute wheeze. Other priorities were in the diagnosis or management of constipation, urinary tract infection, fever, gastro-oesophageal reflux and also new models of care for scheduled general paediatric clinics.

Conclusion Research priorities for child health in the UK and Ireland have been identified using a robust methodology. The next steps are for studies to be designed and funded to address these priorities.

What is already known on this topic?

- ► Paediatric Emergency Research Network UK and Ireland and other international paediatric research networks have established research priorities of their members.
- ► There are no general paediatric research priorities for the UK.

What this study adds?

- ► General paediatric research priorities for UK and Ireland have been determined using a robust methodology.
- ► These results could be considered by research funders in the UK and Ireland when creating their research strategies.

INTRODUCTION

General paediatrics is an underfunded and underrepresented area of paediatric research.[1] Half of the medicines used for in general medical care of children and infants are given 'off label',[2 3] and most practice is not evidence based. Commissioned calls for research funding in general paediatrics are unusual and most funding opportunities are for research in paediatric subspecialty areas.[1]

The lack of available funding presents a challenge to converting research ideas into evidence-based practice.[4] The present situation means that 80% of consultant paediatricians have no time in their job plan for research.[3 4] Although 47% of newly appointed consultant would like to undertake more research work, only 23% expected to do so in 2017.[4]

The General and Adolescent Paediatric Research Network in the UK and Ireland (GAPRUKI) was established in 2016 to facilitate research in general paediatrics.[5] The GAPRUKI collaborators include general paediatric consultants, trainees, nurses and research personnel in the UK and Ireland who work in district general or tertiary paediatric hospitals. GAPRUKI will identify and develop research ideas and support multicentre studies. GAPRUKI works closely with established networks including the National Institute for Health Research (NIHR) Clinical Research Network (CRN) and General Paediatric Clinical Studies Group.

Other research networks have conducted prioritisation surveys to help plan the future direction of their research; for example, Paediatric Emergency Research Network in the UK and Ireland (PERUKI),[6] Paediatric Research in Emergency Departments International Collaborative Network in Australia and New Zealand (PREDICT),[7] and other research networks in North America, West Europe and Australia.[8 9] Here we report the GAPRUKI general paediatric research priority exercise.

METHODS

A four-phase study was conducted using a modified Delphi technique survey[10] and the Hanlon Prioritisation Process (HPP) (see figure 1).[11] Our survey was distributed using collaborative professional networks.

Hindawi
Case Reports in Pulmonology
Volume 2021, Article ID 1983864, 4 pages
https://doi.org/10.1155/2021/1983864

Case Report

Pleuropulmonary Blastoma (PPB) in Child with *DICER1* Mutation: The First Case Report in the State of Qatar

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Received 17 May 2021; Accepted 6 October 2021; Published 29 October 2021

Academic Editor: Akif Turna

Pleuropulmonary blastoma (PPB) is a rare intrathoracic malignancy, which arises from the lung parenchyma and/or pleura. PPB has strong genetic association with mutations in *DICER1* gene. Despite being rare, PPB is the most common lung tumor in children below 6 years of age. International registry of the disease has a total of 350 cases worldwide. We report the first case of PPB in the state of Qatar, which presented as a large cystic lung lesion. The patient was first thought to have benign congenital pulmonary airway malformation (CPAM) based on chest X-ray findings. The diagnosis of PPB was suspected based on chest CT scan findings and was confirmed after surgical resection of the cystic mass. The case highlights the need to consider PPB in the differential diagnosis of cystic lung lesions in children and the need for further radiological imaging (i.e., CT scan), genetic testing, and/or excisional biopsy to confirm the diagnosis.

1. Introduction

Congenital cystic lung lesions are a group of lung diseases which represent variable pathology ranging from benign congenital malformation to neoplasm. These lesions can present with an overlapping clinical and radiological features. Based on the type of the lesion, treatment approach can range from observation to surgical resection. Several classifications have been proposed based on the radiological and pathological features [1]. Pleuropulmonary blastoma (PPB) is an extremely rare and potentially serious subtype of neoplastic cystic lung lesions, which can be misdiagnosed as a benign congenial cystic lesion. Therefore, early diagnosis is essential.

PPB has strong genetic association with mutations in *DICER1* gene. The identification of such mutation in patients with cystic lung lesion can help with diagnosis and guide management. We report the clinical presentation and outcome of the first case of PPB in the state of Qatar with identified DICER1 gene.

2. Case Report

The patient is a 35-month-old boy, previously healthy who presented to emergency department with history of low-grade fever, rhinorrhea, and abdominal pain. There was no history of recurrent chest infections, bone pain, weight loss, or fatigue. Physical examination was significant for decreased breath sounds over posterior aspect of left lower chest zone. Chest X-ray showed large cystic lesion in left lower lobe (Figure 1). No previous chest X-rays were obtained for comparison.

Patient was referred to pediatric pulmonology clinic with a preliminary diagnosis of congenital pulmonary airway malformation (CPAM). Therefore, chest computed tomography (CT) was performed and showed multiseptated large cystic lesion within the left lower lobe with multiple solid nodules. Enlarged lymph nodes were also noted in the left paratracheal region; the largest lymph node measured 10 mm (Figure 2). The presence of solid nodules and the enlarged lymph nodes raised the possibility of pleuropulmonary blastoma.

JAMA | Original Investigation

Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar

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IMPORTANCE The effect of prior SARS-CoV-2 infection on vaccine protection remains poorly understood.

OBJECTIVE To assess protection from SARS-CoV-2 breakthrough infection after mRNA vaccination among persons with vs without prior SARS-CoV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS Matched-cohort studies in Qatar for the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines. A total of 1 531 736 individuals vaccinated with either vaccine between December 21, 2020, and September 19, 2021, were followed up beginning 14 days after receiving the second dose until September 19, 2021.

EXPOSURES Prior SARS-CoV-2 infection and COVID-19 vaccination.

MAIN OUTCOMES AND MEASURES Incident SARS-CoV-2 infection, defined as a polymerase chain reaction (PCR)–positive nasopharyngeal swab regardless of reason for PCR testing or presence of symptoms. Cumulative incidence was calculated using the Kaplan-Meier estimator method.

RESULTS The BNT162b2-vaccinated cohort comprised 99 226 individuals with and 290 432 matched individuals without prior PCR-confirmed infection (median age, 37 years; 68% male). The mRNA-1273–vaccinated cohort comprised 58 096 individuals with and 169 514 matched individuals without prior PCR-confirmed infection (median age, 36 years; 73% male). Among BNT162b2-vaccinated persons, 159 reinfections occurred in those with and 2509 in those without prior infection 14 days or more after dose 2. Among mRNA-1273–vaccinated persons, 43 reinfections occurred in those with and 368 infections in those without prior infection. Cumulative infection incidence among BNT162b2-vaccinated individuals was an estimated 0.15% (95% CI, 0.12%-0.18%) in those with and 0.83% (95% CI, 0.79%-0.87%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio for breakthrough infection with prior infection, 0.18 [95% CI, 0.15-0.21]; $P < .001$). Cumulative infection incidence among mRNA-1273–vaccinated individuals was an estimated 0.11% (95% CI, 0.08%-0.15%) in those with and 0.35% (95% CI, 0.32%-0.40%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio, 0.35 [95% CI, 0.25-0.48]; $P < .001$). Vaccinated individuals with prior infection 6 months or more before dose 1 had statistically significantly lower risk for breakthrough infection than those infected less than 6 months before dose 1 (adjusted hazard ratio, 0.62 [95% CI, 0.42-0.92]; $P = .02$ for BNT162b2 and 0.40 [95% CI, 0.18-0.91]; $P = .03$ for mRNA-1273 vaccination).

CONCLUSIONS AND RELEVANCE Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021. The observational study design precludes direct comparisons of infection risk between the 2 vaccines.

Supplemental content

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JAMA. 2021;326(19):1930-1939. doi:10.1001/jama.2021.19623
Published online November 1, 2021. Corrected on November 22, 2021.

JAMA | Original Investigation

Effect of Amoxicillin Dose and Treatment Duration on the Need for Antibiotic Re-treatment in Children With Community-Acquired Pneumonia
The CAP-IT Randomized Clinical Trial

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IMPORTANCE The optimal dose and duration of oral amoxicillin for children with community-acquired pneumonia (CAP) are unclear.

OBJECTIVE To determine whether lower-dose amoxicillin is noninferior to higher dose and whether 3-day treatment is noninferior to 7 days.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, 2 × 2 factorial noninferiority trial enrolling 824 children, aged 6 months and older, with clinically diagnosed CAP, treated with amoxicillin on discharge from emergency departments and inpatient wards of 28 hospitals in the UK and 1 in Ireland between February 2017 and April 2019, with last trial visit on May 21, 2019.

INTERVENTIONS Children were randomized 1:1 to receive oral amoxicillin at a lower dose (35-50 mg/kg/d; n = 410) or higher dose (70-90 mg/kg/d; n = 404), for a shorter duration (3 days; n = 413) or a longer duration (7 days; n = 401).

MAIN OUTCOMES AND MEASURES The primary outcome was clinically indicated antibiotic re-treatment for respiratory infection within 28 days after randomization. The noninferiority margin was 8%. Secondary outcomes included severity/duration of 9 parent-reported CAP symptoms, 3 antibiotic-related adverse events, and phenotypic resistance in colonizing *Streptococcus pneumoniae* isolates.

RESULTS Of 824 participants randomized into 1 of the 4 groups, 814 received at least 1 dose of trial medication (median [IQR] age, 2.5 years [1.6-2.7]; 421 [52%] males and 393 [48%] females), and the primary outcome was available for 789 (97%). For lower vs higher dose, the primary outcome occurred in 12.6% with lower dose vs 12.4% with higher dose (difference, 0.2% [1-sided 95% CI −∞ to 4.0%]), and in 12.5% with 3-day treatment vs 12.5% with 7-day treatment (difference, 0.1% [1-sided 95% CI −∞ to 3.9]). Both groups demonstrated noninferiority with no significant interaction between dose and duration (P = .63). Of the 14 prespecified secondary end points, the only significant differences were 3-day vs 7-day treatment for cough duration (median 12 days vs 10 days; hazard ratio [HR], 1.2 [95% CI, 1.0 to 1.4]; P = .04) and sleep disturbed by cough (median, 4 days vs 4 days; HR, 1.2 [95% CI, 1.0 to 1.4]; P = .03). Among the subgroup of children with severe CAP, the primary end point occurred in 17.3% of lower-dose recipients vs 13.5% of higher-dose recipients (difference, 3.8% [1-sided 95% CI, −∞ to10%]; P value for interaction = .18) and in 16.0% with 3-day treatment vs 14.8% with 7-day treatment (difference, 1.2% [1-sided 95% CI, −∞ to 7.4%]; P value for interaction = .73).

CONCLUSIONS AND RELEVANCE Among children with CAP discharged from an emergency department or hospital ward (within 48 hours), lower-dose outpatient oral amoxicillin was noninferior to higher dose, and 3-day duration was noninferior to 7 days, with regard to need for antibiotic re-treatment. However, disease severity, treatment setting, prior antibiotics received, and acceptability of the noninferiority margin require consideration when interpreting the findings.

TRIAL REGISTRATION ISRCTN Identifier: ISRCTN76888927

JAMA. 2021;326(17):1713-1724. doi:10.1001/jama.2021.17843
Corrected on December 7, 2021.

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com

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ARTICLES
https://doi.org/10.1038/s41591-021-01583-4
nature medicine

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BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar

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With the global expansion of the highly transmissible SARS-CoV-2 Delta (B.1.617.2) variant, we conducted a matched test-negative case–control study to assess the real-world effectiveness of COVID-19 messenger RNA vaccines against infection with Delta in Qatar's population. BNT162b2 effectiveness against any, symptomatic or asymptomatic, Delta infection was 45.3% (95% CI, 22.0–61.6%) ≥14 d after the first vaccine dose, but only 51.9% (95% CI, 47.0–56.4%) ≥14 d after the second dose, with 50% of fully vaccinated individuals receiving their second dose before 11 May 2021. Corresponding mRNA-1273 effectiveness ≥14 d after the first or second dose was 73.7% (95% CI, 58.1–83.5%) and 73.1% (95% CI, 67.5–77.8%), respectively. Notably, effectiveness against Delta-induced severe, critical or fatal disease was 93.4% (95% CI, 85.4–97.0%) for BNT162b2 and 96.1% (95% CI, 71.6–99.5%) for mRNA-1273 ≥ 14 d after the second dose. Our findings show robust effectiveness for both BNT162b2 and mRNA-1273 in preventing Delta hospitalization and death in Qatar's population, despite lower effectiveness in preventing infection, particularly for the BNT162b2 vaccine.

Appreciable community transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) variant was first noted in Qatar by end of March 2021 (refs. [1–3]). Although Delta incidence has increased along with a recent surge in cases and hovered at about 200 cases per day in the summer of 2021, it remains low compared to earlier variant incidences with no signal for an epidemic wave materializing as of 19 September 2021. Between 23 March 2021 and 7 September 2021, 43% of diagnosed infections were Delta infections (Methods)[1,3]. Delta dominance was, however, preceded by two large consecutive SARS-CoV-2 Alpha (B.1.1.7) and Beta (B.1.351) waves earlier in 2021 (refs. [1–5]). The rapid scale-up of Coronavirus Disease 2019 (COVID-19) vaccination in Qatar may have impeded efficient Delta transmission. As of 19 September 2021, it is estimated that over 80% of Qatar's resident population has received two doses of either the BNT162b2 (ref. [6]) (Pfizer-BioNTech) vaccine or the mRNA-1273 (ref. [7]) (Moderna) vaccine[8]. This study assessed BNT162b2 and mRNA-1273 vaccines' real-world effectiveness against the Delta variant in Qatar from 23 March 2021 to 7 September 2021 and compared these estimates to those in other countries.

Results

Study population. From 21 December 2020 to 7 September 2021, 950,232 people had at least one BNT162b2 vaccine dose (median date of first dose was 21 April 2021) and 916,290 were fully vaccinated (median date of second dose was 11 May 2021). Administration of the second dose was within a median of 21 d after the first dose (interquartile range (IQR) 21–22 d), with full-vaccination of 97.4% of individuals within 30 d of first dose.

Over this timeframe, 564,468 individuals had at least one mRNA-1273 vaccine dose (median date of first dose was 19 May 2021) and 509,322 were fully vaccinated (median date of second dose was 24 May 2021); distributions for both doses were skewed with means of 16 May 2021 and 11 June 2021, respectively. Administration of the second dose was within a median of 28 d after the first dose (IQR 28–31 d), with full-vaccination of 74.7% of individuals within 30 d of the first dose.

With greater and regular vaccine availability, coverage for BNT162b2 has been steadily increasing since December 2020. In contrast, coverage for mRNA-1273 depended on dispatch of large shipments and did not reach considerable levels before March 2021.

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RESEARCH ARTICLE

Nasopharyngeal Expression of Angiotensin-Converting Enzyme 2 and Transmembrane Serine Protease 2 in Children within SARS-CoV-2-Infected Family Clusters

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ABSTRACT Lower levels of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) in the nasal epithelium of children may be related to a lower incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, compared to adults. However, no direct evidence is available to support this hypothesis. In this study, we compared the transcript levels of ACE2 and TMPRSS2 in nasopharyngeal swab samples (n = 234) from children and adult family members within SARS-CoV-2-exposed families and assessed the association with SARS-CoV-2 infection status. Transcript levels for ACE2, but not TMPRSS2, were higher in adults than in children (n = 129 adults and 105 children; $P < 0.05$). The expression of the two genes was not significantly different between SARS-CoV-2 positive and SARS-CoV-2 negative patients within the same age groups. However, in families with one or more SARS-CoV-2 positive adult family members, expression of both genes was significantly higher in SARS-CoV-2 positive children than in SARS-CoV-2 negative children ($P < 0.05$). By multivariate analysis, ACE2 expression adjusted for age and sex was significantly associated with SARS-CoV-2 infection in the overall population (odds ratio [OR], 1.112 [95% confidence interval [CI], 1.012 to 1.229]; $P < 0.05$). The degree of this association was higher (OR, 1.172 [95% CI, 1.034 to 1.347]; $P < 0.05$) in the subgroup of families with only SARS-CoV-2 positive adult family members. Our results suggest that children with lower levels of nasal ACE2 and TMPRSS2 are more likely to remain SARS-CoV-2 negative despite being exposed to a SARS-CoV-2 positive adult family member.

IMPORTANCE ACE2 and TMPRSS2 are well established in the literature as SARS-CoV-2 entry factors. Recent data suggest that lower levels of nasal ACE2 in children may be associated with their lower incidence of coronavirus disease 2019 (COVID-19). In this study, using data from nasopharyngeal swab specimens from adult and pediatric members of families in which one or more members of the family had laboratory-confirmed SARS-CoV-2 infection, we show that children with lower levels of ACE2 and TMPRSS2 are more likely to remain SARS-CoV-2 negative despite being exposed to a SARS-CoV-2 positive adult family member. These results provide new insights into the roles of nasopharyngeal ACE2 and TMPRSS2 in acquiring SARS-CoV-2 infection, and they show that the differential expression of these genes in adults versus children may contribute to differential rates of SARS-CoV-2 infection in these populations.

KEYWORDS angiotensin-converting enzyme 2, COVID-19, SARS-CoV-2, transmembrane serine protease 2, nasopharyngeal

The global pandemic of coronavirus disease 2019 (COVID-19) (1) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prompted urgent research on the pathogenesis and transmission of the virus, including

Citation Hasan MR, Ahmad MN, Dargham SR, Zayed H, Al Hashemi A, Ngwabi N, Perez Lopez A, Dobson S, Abu Raddad LJ, Tanga P. 2021. Nasopharyngeal expression of angiotensin-converting enzyme 2 and transmembrane serine protease 2 in children within SARS-CoV-2-infected family clusters. Microbiol Spectr 9: e00783-21. https://doi.org/10.1128/Spectrum.00783-21.

Editor Clinton J. Jones, Oklahoma State University, College of Veterinary Medicine

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Received 6 July 2021
Accepted 9 October 2021
Published 3 November 2021

Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT

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Declared competing interests of authors: David Dunn reports grants from the National Institute for Health Research during the conduct of the study (RP-PG-1212-20006). Saul N Faust reports personal fees or grants from AstraZeneca plc (Cambridge, UK)/Medimmune (Gaithersburg, MA, USA), Sanofi SA (Paris, France), Pfizer Inc. (New York, NY, USA), Seqirus UK Ltd (Maidenhead, UK), Sandoz (Holzkirchen, Germany), Merck KGAA (Darmstadt, Germany), GlaxoSmithKline plc (Brentford, UK) and Johnson & Johnson

Abstract

Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT

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Background: Data are limited regarding the optimal dose and duration of amoxicillin treatment for community-acquired pneumonia in children.

Objectives: To determine the efficacy, safety and impact on antimicrobial resistance of shorter (3-day) and longer (7-day) treatment with amoxicillin at both a lower and a higher dose at hospital discharge in children with uncomplicated community-acquired pneumonia.

Design: A multicentre randomised double-blind 2 × 2 factorial non-inferiority trial in secondary care in the UK and Ireland.

Setting: Paediatric emergency departments, paediatric assessment/observation units and inpatient wards.

Participants: Children aged > 6 months, weighing 6–24 kg, with a clinical diagnosis of community-acquired pneumonia, in whom treatment with amoxicillin as the sole antibiotic was planned on discharge.

Acta Biomed 2021; Vol. 92, N. 5: e2021481 DOI: 10.23750/abm.v92i5.12252

Myxedema coma in children and adolescents: A rare endocrine emergency - Personal experience and review of literature

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Abstract. Decompensated hypothyroidism, formerly known as myxedema coma, represents the most extreme clinical expression of severe primary or secondary hypothyroidism in which patients exhibit multiple organ abnormalities and progressive mental deterioration. The exact incidence of myxedema coma in adults is not known, but some authors have estimated that is approximately 0.22 per 100.0000 per year in the western world. Myxedema coma is more common in females and during winter months. The diagnosis of myxedema coma is primarily clinical with supportive evidence of the abnormal thyroid function tests. Clinical features vary depending on a several factors including the age of onset and the severity of the disease. In the majority of patients (95%), the cause of underlying hypothyroidism is autoimmunity, i.e., Hashimoto thyroiditis or congenital abnormalities. Rarely it occurs in secondary (central) hypothyroidism, due to thyrotropin deficiency related to pituitary disease, or pituitary-thyroid damage due to iron overload. Treatment consists of thyroid hormone replacement, correction of electrolyte disturbances, passive rewarming, treatment of infections, respiratory and hemodynamic support, and administration of stress-dose glucocorticoids. Prognosis seems to be better in children and adolescents compared to adults. The present review reports personal experience and the literature data on 13 patients. (www.actabiomedica.it)

Keywords: Myxedema coma, hypothyroidism, iron overload, aplastic anemia, Hashimoto thyroiditis, treatment, prognosis

Introduction

Decompensated hypothyroidism, formerly known as myxedema coma, is an endocrine emergency leading to altered mental status or mental slowing, associated with hypothermia, and other signs and symptoms associated with hypothermia and poor functioning of multiple organs due to severe primary or secondary hypothyroidism (1,2).

Primary hypothyroidism results from the inability of the thyroid gland to produce adequate amounts of thyroid hormone. Typically, patients with myxedema coma have primary hypothyroidism diagnosed by low serum levels of free-thyroxine (FT_4) and triiodothyronine (T_3) and a high thyroid stimulating hormone (TSH) level. However, primary hypothyroidism should be differentiated from secondary or tertiary hypothyroidism (low-normal or decreased TSH and

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RESEARCH ARTICLE

Fecal Carriage and Molecular Characterization of Carbapenemase-Producing *Enterobacterales* in the Pediatric Population in Qatar

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ABSTRACT Whole-genome sequencing was used to characterize carbapenemase-producing *Enterobacterales* (CPE) strains recovered from rectal screening swab samples obtained from children at a tertiary-care pediatric hospital in Qatar during a 3-year period. A total of 72 CPE isolates recovered from 61 fecal carriers were characterized. *Escherichia coli* (47 isolates [65.3%]) and *Klebsiella pneumoniae* (22 isolates [30.6%]) were the most common species identified. High levels of genetic diversity were observed for both species. These 72 isolates produced 78 carbapenemases, characterized as either NDM-type (41 enzymes [52.6%]) or OXA-48-type (37 enzymes [47.4%]). NDM-5 (24 enzymes [30.8%]), NDM-1 (15 enzymes [19.2%]), and OXA-181 (15 enzymes [19.2%]) were the most common variants detected within each type. Twenty-three NDM producers exhibited difficult-to-treat resistance, compared with only 2 of the OXA-48 producers. Multiple comorbidities were identified in 88.5% of the patients, whereas recent travel history to countries in which CPE are endemic was documented for 57.4% of the patients. All 9 bla_{OXA-48}-type-gene-containing *E. coli* sequence type 38 (ST38) strains were isolated from patients without international travel history. The mean quarterly incidence of fecal carriage decreased more than 6-fold after the implementation of coronavirus disease 2019 (COVID-19)-related international travel restrictions in Qatar in mid-March 2020. Our data suggest that NDM-type and OXA-48-type carbapenemases expressed by a large diversity of *E. coli* and *K. pneumoniae* genotypes are largely dominant in the pediatric population of Qatar. Although our data indicate successful local expansion of *E. coli* ST38 strains harboring $bla_{OXA-244}$ genes, at least within health care settings, bla_{OXA-48}-type and bla_{NDM}-type genes appear to have been mainly introduced sporadically by asymptomatic carriers who visited or received health care in some nearby countries in which the genes are endemic.

IMPORTANCE To the best of our knowledge, this is the first study addressing the molecular characteristics of CPE in a pediatric population in Qatar using whole-genome sequencing. Since several countries in the Arabian Peninsula share relatively similar demographic patterns and international links, it is plausible that the molecular characteristics of CPE in children, at least in the middle and eastern parts of the region, are similar to those observed in our study.

KEYWORDS *Escherichia coli*, *Klebsiella pneumoniae*, NDM, OXA-48, carbapenemase, carriage, children

The incidence of carbapenemase-producing *Enterobacterales* (CPE) is growing at an alarming pace in many regions of the world, including the Middle East (1, 2), jeopardizing the effectiveness of carbapenems, the last resort to treat infections caused by

Citation Pérez-López A, Sundararaju S, Tsui KM, Al-Mana H, Hasan MR, Suleiman M, Al Maslamani E, Imam O, Roscoe D, Tang P. 2021. Fecal carriage and molecular characterization of carbapenemase-producing *Enterobacterales* in the pediatric population in Qatar. Microbiol Spectr 9:e01122-21. https://doi.org/10.1128/Spectrum.01122-21.

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Received 3 August 2021
Accepted 20 October 2021
Published 10 November 2021

Research and Reports in Urology

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PERSPECTIVES

The Plate Objective Scoring Tool (POST): Further Reflections and Extended Applications

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Abstract: Hypospadias is a common birth defect of the male external genitalia. However, there are conflicting arguments about the optimal classification approach and ideal surgical technique. We have introduced the Plate Objective Scoring Tool (POST) to define critical glanular phenotypic landmarks of the urethral plate. We propose that POST can objectively, reproducibly, and accurately determine urethral plate quality, thus permitting robust comparison between the different surgical techniques commonly utilized in hypospadias repair. Furthermore, the POST scoring system represents a versatile tool that can objectively quantify key variables in hypospadiology that are currently not well defined. Further validation of POST should lead to better identification and management of postoperative complications.

Keywords: hypospadias, scoring tool, classification, POST, objective

Introduction

Hypospadias is considered a common birth defect of the external genitalia of boys.[1,2] However, several controversies surround the different classification approaches and ideal surgical techniques for correction.[3] We have introduced the Plate Objective Scoring Tool (POST) to define critical phenotypic landmarks of the urethral plate (UP) within the glans. POST allows objective and reproducible determination of urethral plate quality, thereby enabling comparison of the different surgical techniques commonly used for hypospadias repair.[4,5] The POST system originated from studying the normal configuration of the glans in children who were anesthetized for ritual circumcision,[6] leading to the determination of three key anatomical landmarks: A, B, and C (Figure 1). The area from A to B is the extent of the neo-meatal opening, while B to C is the extent of the vertical glanular fusion line. Having identified these reference points, the ratio (AB)/(BC) defines POST value, which represents urethral impression within the glans penis and thus overall quality of the urethral plate.

Embryological Basis of POST

The rationale behind POST scoring is well supported by a robust embryological evidence base. Developmentally, the opening zipper hypothesis begins with gradual canalization of the solid urethral plate within the penile shaft and glans to form the urethral groove, while the closing zipper depends on fusion of the urethral layers to form the final urethral tube.[7] Therefore, a shorter (AB) length is explained by arrest of the ventro-dorsal canalization process within the glans penis around gestational week 14. As a result, lower AB/BC ratio could represent an earlier stage of urethral development and thus more severe phenotypical stages.

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/yy_2-0aaCfw

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Received: 8 June 2021
Accepted: 13 August 2021
Published: 11 November 2021

[Intervention Review]

Growth hormone for in vitro fertilisation (IVF)

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2021.

Citation: Sood A, Mohiyiddeen G, Ahmad G, Fitzgerald C, Watson A, Mohiyiddeen L. Growth hormone for in vitro fertilisation (IVF). *Cochrane Database of Systematic Reviews* 2021, Issue 11. Art. No.: CD000099. DOI: 10.1002/14651858.CD000099.pub4.

ABSTRACT

Background

In an effort to improve outcomes of in vitro fertilisation (IVF) cycles, the use of growth hormone (GH) has been considered as adjuvant treatment in ovarian stimulation. Improving the outcomes of IVF is especially important for women with infertility who are considered 'poor responders'. We have compared the outcomes of IVF with adjuvant GH versus no adjuvant treatment in routine use, and specifically in poor responders.

Objectives

To assess the effectiveness and safety of growth hormone as an adjunct to IVF compared to standard IVF for women with infertility

Search methods

We searched the following databases (to November 2020): Cochrane Gynaecology and Fertility (CGF) Group specialised register, CENTRAL, MEDLINE, Embase, CINAHL, Epistemonikos database and trial registers together with reference checking and contact with study authors and experts in the field to identify additional trials.

Selection criteria

We included all randomised controlled trials (RCTs) of adjuvant GH treatment in IVF compared with no adjuvant treatment for women with infertility. We excluded trials where additional adjuvant treatments were used with GH. We also excluded trials comparing different IVF protocols.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. Two review authors independently performed assessment of trial risk of bias and extraction of relevant data. The primary review outcome was live birth rate. The secondary outcomes were clinical pregnancy rate, oocytes retrieved, embryo transfer, units of gonadotropin used and adverse events, i.e. ectopic pregnancy, multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), congenital anomalies, oedema.

Main results

We included 16 RCTs (1352 women). Two RCTs (80 women) studied GH in routine use, and 14 RCTs (1272 women) studied GH in poor responders. The evidence was low to very low certainty, the main limitations being risk of bias, imprecision and heterogeneity.

Adjuvant growth hormone compared to no adjuvant: routine use for in vitro fertilisation (IVF)

World Journal of Pediatrics (2021) 17:576–589
https://doi.org/10.1007/s12519-021-00476-3

ORIGINAL ARTICLE

Consensus statement on the epidemiology, diagnosis, prevention, and management of cow's milk protein allergy in the Middle East: a modified Delphi-based study

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Received: 26 July 2021 / Accepted: 17 October 2021 / Published online: 24 November 2021

Abstract

Background This study aimed to develop an expert consensus regarding the epidemiology, diagnosis, and management of cow's milk protein allergy (CMPA) in the Middle East.

Methods A three-step modified Delphi method was utilized to develop the consensus. Fifteen specialized pediatricians participated in the development of this consensus. Each statement was considered a consensus if it achieved an agreement level of ≥ 80%.

Results The experts agreed that the double-blind placebo-controlled oral challenge test (OCT) should be performed for 2–4 weeks using an amino acid formula (AAF) in formula-fed infants or children with suspected CMPA. Formula-fed infants with confirmed CMPA should be offered a therapeutic formula. The panel stated that an extensively hydrolyzed formula (eHF) is indicated in the absence of red flag signs. At the same time, the AAF is offered for infants with red flag signs, such as severe anaphylactic reactions. The panel agreed that infants on an eHF with resolved symptoms within 2–4 weeks should continue the eHF with particular attention to the growth and nutritional status. On the other hand, an AAF should be considered for infants with persistent symptoms; the AAF should be continued if the symptoms resolve within 2–4 weeks, with particular attention to the growth and nutritional status. In cases with no symptomatic improvements after the introduction of an AAF, other measures should be followed. The panel developed a management algorithm, which achieved an agreement level of 90.9%.

Conclusion This consensus document combined the best available evidence and clinical experience to optimize the management of CMPA in the Middle East.

Keywords Consensus Cow's milk protein allergy · Infant formula · Middle East · Milk hypersensitivity

Introduction

Cow's milk protein allergy (CMPA) is an abnormal immunological response to specific proteins, mainly casein and/or whey proteins, present in either formula or breast milk [1]. The current epidemiological figures highlight that CMPA is the prevalent form of food hypersensitivity in children younger than three years, affecting up to 7.5% of them in the first year of life [2]. In some Middle Eastern countries, the incidence of CMPA among infants younger than 2 years was reported to be 3.4% [3]. Positive family history of atopy and atopic dermatitis in early infancy are distinguished risk factors for CMPA [4, 5]. Based on the type of immunological reactions, the clinical presentation of the CMPA can be broadly divided into immediate and delayed-onset presentations. Eczema and allergic colitis are commonly present in breastfed infants [6].

CMPA is a clinical condition in which proper history taking and physical examination are the cornerstones for accurate identification of the patients [7]. However, the diagnosis of CMPA can be challenging, and further investigations are

Moustafa A. El-Hodhod and Mortada H. F. El-Shabrawi contributed equally to this work.

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BMJ Open

Identifying priority medicines policy issues for Qatar: exploring perspectives and experiences of healthcare professionals through a qualitative study

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To cite: Zia N, Ibrahim MIM, Adheir F, *et al*. Identifying priority medicines policy issues for Qatar: exploring perspectives and experiences of healthcare professionals through a qualitative study. *BMJ Open* 2021;**11**:e054150. doi:10.1136/bmjopen-2021-054150

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-054150).

Received 09 June 2021
Accepted 25 October 2021

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ABSTRACT

Objectives To identify priority medicines policy issues, including the 'use' and 'access to medicines' in Qatar.

Design In this qualitative study, general inductive method was used and semi-structured exploratory interviews conducted.

Setting Stakeholders from a broad range of academic and healthcare practitioners in Qatar.

Participants Exploratory, semi-structured interviews were conducted with 21 stakeholders throughout Qatar. The inclusion criteria include (a) participants working or involved in the Qatar's healthcare system, (b) participants having experience or working knowledge of medicine policy documents, different facets of it, use of medicines and access to medicines, (c) as well as participants well versed in the English language. It was intended to cover stakeholders from a broad range of healthcare and policy institutions in Qatar.

Primary and secondary outcome measures All participants were involved in semi-structured, audio-recorded interviews, which were then transcribed verbatim, coded into NVivo V.12 and followed by thematic analysis to identify the common themes. Perceptions, experiences and opinions regarding Qatar's medicines policy issues were recorded.

Results This study found challenges related to the availability of pharmaceuticals in Qatar, including medicines registration process. There is no comprehensive national medicines policy in Qatar, however, there are a number of rules, regulations, policies and procedures in place. The community pharmacy services provided are mostly 'traditional' with less emphasis on pharmacists' extended roles and/or cognitive services. The study identifies several areas for improvement including extending the role of the pharmacist, improve the prescribing of antibiotics, medicines compliance and counselling for consumers, pharmacovigilance, implementation of generic medicines policies, as well as the need for a national health record database.

Conclusions The findings suggest that in the last 20 years, Qatar has moved towards advancing healthcare; however, there are gaps and opportunities. The strategies need to be developed to resolve access to medicines issues, the priority being medicines registration, import and so on. With the rise of chronic diseases and a growing population, there is also a need to work to improve medicines adherence among patients.
A national medicines policy should be developed through a consultative broad-based process in which prescribers, physicians, pharmacists and healthcare professionals be given a chance to contribute.

Strengths and limitations of this study

- ► The strength of the study is that it is the first such study on the topic using a qualitative inductive approach to cover medicines policy in Qatar.
- ► An exploratory qualitative design is used to uncover healthcare professionals' opinions on medicines policy.
- ► The study emphasises the various facets of medicines policy including medicines use situation, community pharmacy practice, medicine registration, patients counselling, medicines access and medicines adherence issues.
- ► Sampling did not achieve the target composition of the participants. This may have limit the range of stakeholders by not including patient support groups or the pharmaceutical manufacturing sector.
- ► The study provides enough data and adds to our understanding of the medicines policy issues and future health challenges and opportunities for Qatar.

INTRODUCTION

As of 2020, the population of Qatar is 2.79 million.[1] Qatar has a public and private healthcare system and provides modern healthcare services to its Qataris and non-Qataris. The quality of healthcare in Qatar is very high.[2] The State of Qatar started its National Health Strategy 2018–2022 (Q-NHS 2018) in 2018 and the aim was to develop a comprehensive world-class healthcare system.[3] It is projected that Qatar will spend QAR

[Intervention Review]

Interventions for the management of abdominal pain in Crohn's disease and inflammatory bowel disease

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Contact: Anthony K Akobeng, aakobeng@sidra.org.

Editorial group: Cochrane Gut Group.
Publication status and date: New, published in Issue 11, 2021.

Citation: Sinopoulou V, Gordon M, Akobeng AK, Gasparetto M, Sammaan M, Vasiliou J, Dovey TM.. Interventions for the management of abdominal pain in Crohn's disease and inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2021, Issue 11. Art. No.: CD013531. DOI: 10.1002/14651858.CD013531.pub2.

ABSTRACT

Background

Crohn's disease is a remitting and relapsing disorder that can affect the whole gastrointestinal tract. Active disease symptoms include abdominal pain, fatigue, weight loss, and diarrhoea. There is no known cure; however, the disease can be managed, and therefore places a huge financial burden on healthcare systems. Abdominal pain is a common and debilitating symptom of Crohn's and other inflammatory bowel diseases (IBDs), and is multifaceted. Abdominal pain in Crohn's disease could be a symptom of disease relapse or related to medication adverse effects, surgical complications and strictures or adhesions secondary to IBD. In the absence of these factors, around 20 to 50% of people with Crohn's in remission still experience pain.

Objectives

To assess the efficacy and safety of interventions for managing abdominal pain in people with Crohn's disease and IBD (where data on ulcerative colitis and Crohn's disease could not be separated).

Search methods

We searched CENTRAL, MEDLINE, three other databases, and clinical trials registries on 29 April 2021. We also searched the references of trials and systematic reviews for any additional trials.

Selection criteria

All published, unpublished, and ongoing randomised trials that compared interventions for the management of abdominal pain in the setting of Crohn's disease and IBD, with other active interventions or standard therapy, placebo, or no therapy were included. We excluded studies that did not report on any abdominal pain outcomes.

Data collection and analysis

Five review authors independently conducted data extraction and 'Risk of bias' assessment of the included studies. We analysed data using Review Manager 5. We expressed dichotomous and continuous outcomes as risk ratios and mean differences with 95% confidence intervals. We assessed the certainty of the evidence using GRADE methodology.

Journal of Pediatric Urology (2022) **18**, 38.e1–38.e11

Bladder exstrophy: We need to improve. A lot

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Keywords
Bladder exstrophy; Long-term; Continence; Bladder lithiasis; Bladder augmentation; Sexual health

Abbreviations
BE, bladder exstrophy; QOL, quality of life; LMIC, low medium income country; BNR, bladder neck reconstruction; BNI, bladder neck injection; BNC, bladder neck closure; MACE, Malone-type antegrade colonic enema conduit; UTI, urinary tract infection; CIC, clean intermittent catheterization; HRQOL, health-related quality of life

Received 23 September 2021
Revised 5 November 2021
Accepted 9 November 2021
Available online 15 November 2021

Summary

Introduction
Bladder exstrophy (BE) affects continence and sexual function, impacting on social life and mental health. Long-term data from the patients' point of view are needed to get a real-life perspective on the problem.

Study design
A self-developed questionnaire concerning sexual, psychosexual and psychosocial outcomes was sent to the adult members of the Brazilian Exstrophy Group.

Results
Fifty out of 67 adults from the group (74.5%) responded to the questionnaire. Failure of initial bladder closure attained 62%. Almost $^{3}/_{4}$ of the patients had augmentation cystoplasty. Bladder lithiasis was common. Esthetic procedures were frequently done. Repetitive UTI (n = 32, 64%) and kidney scars/disease (n = 20, 40%) were frequent. Most (88%) patients either depend on CIC or remain incontinent. Sexual problems predominated in males. Surgery for continence often failed, requiring re-operations, but the prognosis without these procedures was comparatively worse. Continent patients underwent more surgeries (mean 18, 13 and 9 procedures in continent, imperfectly continent and incontinent patients, respectively). Augmented patients more frequently achieved dryness ($p = 0.0035$). Two-thirds of the women underwent vaginoplasties, but dyspareunia/feeling of "tight" vagina still affected a quarter of them. Four women (15.4%) delivered healthy children. 91.7% of the males reported "normal" erections, but sexual inhibition was common due to feeling of having a small penis (n = 18, 75%). Persistent dorsal curvature and abnormal ejaculation were common (58.3% and 77.1%, respectively). Patients' comments related mainly to mental health issues/need for specialized care, limitations of medicine to cure/treat their disease, unavailability of experts, especially adult specialists, embarrassment over deformities and insufficient information about disease/treatment/prognosis.

Discussion
Most BE patients are well-integrated into society, but feelings of sadness and low self-esteem are common. Most welcome procedures to become dry, despite self-catheterization. The results of bladder neck reconstruction are far from perfect, despite multiple attempts and bladder augmentation was often necessary. Volitional voiding is uncommon. Sexual problems are worse for males, and sexual avoidance is common. Sexual function and self-image are inter-related. It seems reasonable to offer selective esthetic procedures to improve social/sexual interaction. Obstetric complications are common, especially UTI, need for ureteral and/or conduit stenting, abnormal fetal positioning, uterine prolapse, technical problems during surgical deliveries and prematurity.

Conclusion
Continence/dryness in BE was mostly eventually achieved, usually depending on multiple interventions, bladder augmentation and self-catheterization. Despite multiple surgeries many adults remain incontinent. Sexual problems and avoidance are the rule in males, due to the feelings of penile inadequacy. Pregnant females deserve expert obstetric care.

https://doi.org/10.1016/j.jpurol.2021.11.007

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 November 21; 27(43): 7572-7581

DOI: 10.3748/wjg.v27.i43.7572

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

SYSTEMATIC REVIEWS

Minimum sample size estimates for trials in inflammatory bowel disease: A systematic review of a support resource

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Author contributions: Gordon M conceived the study, contributed to design, analysis and writing; Lakunina S led completion, analysis and write up; Sinopoulou V and Akobeng A contributed to analysis, reviewed and edited the write up.

Conflict-of-interest statement: None to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: United Kingdom

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B

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Abstract

BACKGROUND

Of 25% of randomised controlled trials (RCTs) on interventions for inflammatory bowel disease (IBD) have no power calculation.

AIM

To systematically review RCTs reporting interventions for the management of IBD and to produce data for minimum sample sizes that would achieve appropriate power using the actual clinical data.

METHODS

We included RCTs retrieved from Cochrane IBD specialised Trial register and CENTRAL investigating any form of therapy for either induction or maintenance of remission against control, placebo, or no intervention of IBD in patients of any age. The relevant data was extracted, and the studies were grouped according to the intervention used. We recalculated sample size and the achieved difference, as well as minimum sample sizes needed in the future.

RESULTS

A total of 105 trials were included. There was a large discrepancy between the estimated figure for the minimal clinically important difference used for the calculations (15% group differences observed *vs* 30% used for calculation) explaining substantial actual sample size deficits. The minimum sample sizes indicated for future trials based on the 25 years of trial data were calculated and grouped by the intervention.

CONCLUSION

A third of intervention studies in IBD within the last 25 years are underpowered, with large variations in the calculation of sample sizes. The authors present a sample size estimate resource constructed on the published evidence base for

Cureus

Open Access Case Report

DOI: 10.7759/cureus.19692

Vallecular Cyst: Reminder of a Rare Cause of Stridor and Failure to Thrive in Infants

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Review began 10/31/2021
Review ended 11/16/2021
Published 11/18/2021

Abstract

The vallecular cyst is a rare cause of stridor, respiratory distress, and failure to thrive in infants. Large vallecular cysts may present with serious complications such as life-threatening airway obstruction. This report is of an infant who presented with stridor and failure to thrive. The patient's condition was diagnosed as the presence of a vallecular cyst using flexible laryngoscopy. The vallecular cyst was successfully managed using endoscopic marsupialization. After the procedure, the patient was asymptomatic and dramatically gained weight within a few months. This case report serves as a reminder for clinicians to consider vallecular cysts as a differential diagnosis of stridor and failure to thrive in infants. It also emphasizes that early diagnosis and management lead to favorable clinical outcomes.

Categories: Family/General Practice, Pediatrics, Pulmonology
Keywords: respiratory distress, laryngoscopy, failure to thrive, stridor, vallecular cyst

Introduction

Vallecular cysts are rare, representing 10.5-20.1% of all congenital laryngeal cysts [1-2]. The overall incidence rate of these cysts is approximately 3.49-5.3 cases per 100,000 newborns [2-3]. Clinical features include stridor, respiratory distress, poor feeding, and failure to thrive [4-5]. Larger lesions may lead to life-threatening airway obstructions, which is of greater concern [6].

Herein, we present a case of vallecular cyst in an infant who presented with stridor and failure to thrive; the patient's condition markedly improved, and no complications occurred owing to the appropriate diagnostic procedure and treatment approach. We emphasize the importance of considering a vallecular cyst as a differential diagnosis for stridor and failure to thrive in infants and highlight that prompt diagnosis and proper management of vallecular cysts lead to favorable clinical outcomes.

Case Presentation

A three-month-old male infant presented with stridor and failure to thrive. He was delivered vaginally at full-term (birth weight 3.5 kg) and had an uncomplicated neonatal course. His parents reported that he had noisy and difficult breathing a few days after birth, which worsened over time and was associated with episodes of cyanosis and poor bottle feeding. A general pediatrician saw him at one month of age for stridor and poor weight gain, assumed a diagnosis of laryngomalacia, and advised the parents to increase the frequency of his feed. After that, his parents sought medical advice several times, including emergency department visits for significant respiratory distress, increasing stridor, and failure to thrive. He was then referred to our neurology clinic to assess hypotonia. No workup was performed, and he was not hospitalized before the referral. Physical examination revealed inspiratory stridor, suprasternal and subcostal retractions, tachypnea, and bilaterally reduced air entry. His oxygen saturation, which was 93% in room air, and improved slightly after oxygen supplementation. His weight at presentation was 4.2 kg, falling below the 3rd percentile of the WHO growth chart. No dysmorphic features were present.

Chest X-ray and regular laboratory test findings were normal, including serum electrolytes, complete blood counts, renal and liver functions, thyroid hormone levels, and blood gas analysis. The patient was taken to the operating room for an airway assessment based on the above findings. The patient underwent flexible laryngoscopy, which revealed a cystic mass measuring approximately 2 x 3 cm in size, arising from the lingual surface of the epiglottis and significantly occluding the laryngeal inlet (Figure *1*).

How to cite this article
Alnaimi A, Abushahin A (November 18, 2021) Vallecular Cyst: Reminder of a Rare Cause of Stridor and Failure to Thrive in Infants. Cureus 13(11): e19692. DOI 10.7759/cureus.19692

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 32 (2022) 142–149

www.elsevier.com/locate/nmd

Muscle "islands": An MRI signature distinguishing neurogenic from myopathic causes of early onset distal weakness

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Received 20 July 2021; received in revised form 12 October 2021; accepted 10 November 2021

Abstract

Muscle MRI has an increasing role in diagnosis of inherited neuromuscular diseases, but no features are known which reliably differentiate myopathic and neurogenic conditions. Using patients presenting with early onset distal weakness, we aimed to identify an MRI signature to distinguish myopathic and neurogenic conditions. We identified lower limb MRI scans from patients with either genetically ($n = 24$) or clinically ($n = 13$) confirmed diagnoses of childhood onset distal myopathy or distal spinal muscular atrophy. An initial exploratory phase reviewed 11 scans from genetically confirmed patients identifying a single potential discriminatory marker concerning the pattern of fat replacement within muscle, coined "islands". This pattern comprised small areas of muscle tissue with normal signal intensity completely surrounded by areas with similar intensity to subcutaneous fat. In the subsequent validation phase, islands correctly classified scans from all 12 remaining genetically confirmed patients, and 12/13 clinically classified patients. In the genetically confirmed patients MRI classification of neurogenic/myopathic aetiology had 100% accuracy (24/24) compared with 65% accuracy (15/23) for EMG, and 79% accuracy (15/19) for muscle biopsy. Future studies are needed in other clinical contexts, however the presence of islands appears to highly suggestive of a neurogenic aetiology in patients presenting with early onset distal motor weakness.

Keywords: MRI; Distal myopathy; Distal spinal muscular atrophy; Early-onset.

1. Introduction

In patients presenting with muscle weakness, initial localization of pathology to the peripheral nervous system and subsequent classification as neurogenic or myopathic is generally possible on clinical grounds supported by neurophysiology and laboratory investigations such as creatine kinase [1]. In cases where these data are conflicting or uninformative, muscle biopsy may be helpful but is an invasive investigation and is prone to sampling bias.

In patients with a pure motor distal presentation the distinction between neurogenic and myopathic aetiology can be particularly challenging .The distal myopathies are inherited disorders of muscle with initial or predominant distal

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https://doi.org/10.1016/j.nmd.2021.11.003
0960-8966/

Immunotherapy ADVANCES

Immunotherapy Advances, 2022, Vol. 2, No. 1, 1–13
https://doi.org/10.1093/immadv/ltab022
Advance Access Publication Date: 13 November 2021
Research Article

OXFORD

Research Article

A phase 1b open-label dose-finding study of ustekinumab in young adults with type 1 diabetes

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Received 23 June 2021; Revised 22 September 2021; Accepted 11 November 2021

Summary

Objectives: We assessed the safety of ustekinumab (a monoclonal antibody used in psoriasis to target the IL-12 and IL-23 pathways) in a small cohort of recent-onset (<100 days of diagnosis) adults

Abbreviations:AUC: Area under the curve; CD: Cluster of differentiation; CMV: Cytomegalovirus; DSMB: Data and safety monitoring board; EBV: Epstein-Barr virus; GAD65: Glutamate decarboxylase 65; GCP: Good clinical practice; GWAS: Genome-wide association studies; HIV: Human immunodeficiency virus; IA-2: Islet Antigen 2; ICH: International Conference of Harmonisation; IFN-γ: Interferon-γ; IL-12: Interleukin-12; IL-17A: Interleukin-17a; IL-23: Interleukin-23; IU: Insulin Units; LOB: Limits of blank; MMTT: Mixed meal tolerance test; NOD: Non-obese diabetic; PBMC: Peripheral blood mononuclear cells; SAE: Serious adverse events; SC: Subcutaneous; T1D: Type 1 diabetes; T2D: Type 2 diabetes; Tc: Cytotoxic T cells; Th: T helper cells; Treg: T regulatory cells; TYK2: Tyrosine kinase 2; ZnT8: Zinc transporter 8.

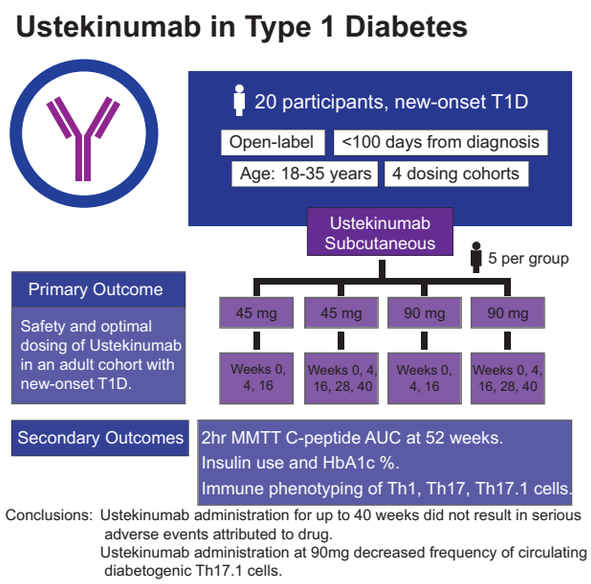
with type 1 diabetes (T1D) by conducting a pilot open-label dose-finding and mechanistic study (NCT02117765) at the University of British Columbia.

Methods: We sequentially enrolled 20 participants into four subcutaneous dosing cohorts: (i) 45 mg loading weeks 0/4/16, (ii) 45 mg maintenance weeks 0/4/16/28/40, (iii) 90 mg loading weeks 0/4/16, and (iv) 90 mg maintenance weeks 0/4/16/28/40. The primary endpoint was safety as assessed by an independent data and safety monitoring board (DSMB) but we also measured mixed meal tolerance test C-peptide, insulin use/kg, and HbA1c. Immunophenotyping was performed to assess immune cell subsets and islet antigen-specific T cell responses.

Results: Although several adverse events were reported, only two (bacterial vaginosis and hallucinations) were thought to be possibly related to drug administration by the study investigators. At 1 year, the 90 mg maintenance dosing cohort had the smallest mean decline in C-peptide area under the curve (AUC) (0.1 pmol/ml). Immunophenotyping showed that ustekinumab reduced the percentage of circulating Th17, Th1, and Th17.1 cells and proinsulin-specific T cells that secreted IFN-γ and IL-17A.

Conclusion: Ustekinumab was deemed safe to progress to efficacy studies by the DSMB at doses used to treat psoriasis in adults with T1D. A 90 mg maintenance dosing schedule reduced proinsulin-specific IFN-γ and IL-17A-producing T cells. Further studies are warranted to determine if ustekinumab can prevent C-peptide AUC decline and induce a clinical response.

Graphical Abstract



Keywords: ustekinumab, type 1 diabetes, clinical trial, immunomodulatory

Introduction

Type 1 diabetes (T1D) is an autoimmune disease that arises from the T cell-mediated destruction of pancreatic β-cells. Data generated from people (individuals) with recent-onset T1D [1], indicate that functional insulin-secreting β-cells are present at time of disease presentation. Thus, long-term interruption of T cell-mediated, autoimmune β-cell destruction at the time of clinical T1D presentation could preserve sufficient β-cells to maintain insulin secretion.

T1D pathogenesis involves defects in immune tolerance, particularly in $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs), permitting expansion of autoreactive $CD4^+$ and $CD8^+$ T cells [2], which destroy insulin-producing β-cells. Peripheral blood mononuclear cells (PBMC) from children with recent-onset T1D [3] have a higher proportion of

Gokul Erumbala[1], Sabu Anzar[1], Amjad Tonbari[1], Ramadan Salem[1], Colin Powell[1,2]

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Review

Stating the obvious: intravenous magnesium sulphate should be the first parenteral bronchodilator in paediatric asthma exacerbations unresponsive to first-line therapy

What is the most appropriate second-line intravenous bronchodilator treatment when a child with a severe asthma attack is not responsive to initial inhaled therapy? The second-line treatment options for acute asthma include parenteral β_2-agonists, methylxanthine and magnesium sulphate ($MgSO_4$). There is a poor evidence-base to inform this decision. This review argues that intravenous $MgSO_4$ is the obvious treatment of choice for this situation as the initial treatment based on current knowledge. We describe the mode of action, scope and limitations of $MgSO_4$, safety profile, economic impact, comparisons of the alternatives, and finally, what the guidelines say. This review explores the suitability of intravenous $MgSO_4$ as a pragmatic and safe initial second-line therapy for children unresponsive to initial asthma management.

Cite as: Erumbala G, Anzar S, Tonbari A, *et al*. Stating the obvious: intravenous magnesium sulphate should be the first parenteral bronchodilator in paediatric asthma exacerbations unresponsive to first-line therapy. *Breathe* 2021; 17: 210113.

Introduction

Acute exacerbation or "attacks" of asthma pose a significant burden to paediatric healthcare facilities and to patients and their families. Despite a consensus on the fundamental principles underpinning the management of an acute asthma exacerbation, considerable variations exist in the "second-line approach" recommendations in guidelines once initial inhaled bronchodilators and corticosteroids have not worked [1–4]. Most second-line treatment options for acute asthma include parenteral β_2-agonists, methylxanthine and magnesium sulphate ($MgSO_4$) [5–8]. There are few clinical trials comparing their relative efficacy and safety profiles [9]. This paucity of evidence can potentially lead to a clinical dilemma for the treating physician on selecting a safe and effective initial second-line agent in children unresponsive to the initial conventional approach.

With ever-increasing pressures on healthcare facilities, an ideal step-up treatment should be safe and effective with minimal resource implications. The traditional agents used in asthma escalation, such as parenteral β_2-agonists and aminophylline, are known to require complex calculations for rate and dilution and the need for high-dependency monitoring [1–4].

$MgSO_4$ has a distinct mechanism of action in acute asthma, and has been a subject of interest in research for well over half a century. $MgSO_4$ can be administered through inhalational and intravenous

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In acute asthma in children, when they are not responsive to maximal inhaled therapy, intravenous magnesium sulphate should be the first choice second-line intravenous treatment. https://bit.ly/3lvmH08

Pediatric Radiology (2021) 51:2598–2606
https://doi.org/10.1007/s00247-021-05173-x

ESPR

Surveillance of Fontan-associated liver disease: current standards and a proposal from the European Society of Paediatric Radiology Abdominal Task Force

Giulia Perucca[1] · Charlotte de Lange[2] · Stéphanie Franchi-Abella[3] · Marcello Napolitano[4] · Michael Riccabona[5] · Damjana Ključevšek[6] · Seema Toso[7] · Jochen Herrmann[8] · Samuel Stafrace[9,10] · Kassa Darge[11] · Maria Beatrice Damasio[12] · Costanza Bruno[13] · Magdalena Maria Woźniak[14] · Luisa Lobo[15] · Donald Ibe[16] · Anne M. Smets[17] · Philippe Petit[18] · Lil-Sofie Ording Müller[19]

Received: 8 June 2021 / Revised: 8 June 2021 / Accepted: 31 July 2021 / Published online: 15 October 2021

Abstract
Since Francis Fontan first introduced the eponymous technique, the Fontan procedure, this type of surgical palliation has allowed thousands of children affected by specific heart malformations to reach adulthood. Nevertheless, abdominal, thoracic, lymphatic and neurologic complications are the price that is paid by these patients. Our review focuses on Fontan-associated liver disease; the purpose is to summarize the current understanding of its physiopathology, the aim of follow-up and the specific radiologic follow-up performed in Europe. Finally, we as members of the Abdominal Task Force of the European Society of Paediatric Radiology propose a consensus-based imaging follow-up algorithm.

Keywords Adolescents · Children · Cirrhosis · Fontan procedure · Hepatocellular carcinoma · Liver · Liver fibrosis · Magnetic resonance imaging · Ultrasound

Introduction

The Fontan procedure was initially performed in 1968 for children affected by tricuspid atresia [1]. Since then, the surgical technique has been modified [2] and currently consists of a series of planned surgical interventions that occur from shortly after birth until 2–4 years of age, resulting in a direct connection between the caval veins and the pulmonary arteries (Fig. 1). This represents a palliation for children affected by pathologies with a single functional ventricle, the most common being hypoplastic left heart syndrome. The only definitive treatment is heart transplantation.

Venous congestion caused by this new circulation, as well as the pre-, peri- and postoperative cardiac conditions, can cause hepatic fibrosis, often leading to the development of liver cirrhosis. The aim of liver imaging in Fontan patients is to assess the presence and progression of fibrosis, with close surveillance for hepatic nodules to detect potential malignancy.

Although the Fontan procedure is now more than 50 years old, a universally accepted follow-up imaging protocol of the liver has not been established. Although some proposed follow-up algorithms have been published recently in North America [3, 4], these guidelines do not reflect European practice, as highlighted by a recent European Society of Paediatric Radiology (ESPR) Abdominal Task Force survey [5].

A common and more uniform liver imaging follow-up protocol would allow these children to have a more homogeneous diagnosis and ultimately more harmonized treatment across Europe. This would, in addition, improve and increase our knowledge of this pathology and permit clinicians to adjust liver surveillance protocols based on more solid and comparable data.

The main consequence of the artificially created circulation is an increased systemic venous pressure and a decreased systemic arterial output [6]. In addition, the pre-, peri- and postsurgical abnormal hemodynamic condition is likely to contribute to the complications [7]. These can affect several organs

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Pediatric Radiology (2021) 51:2607–2610
https://doi.org/10.1007/s00247-021-05172-y

ESPR

Radiologic follow-up in Fontan-associated liver disease in Europe: European Society of Paediatric Radiology survey demonstrates the need for a consensus protocol

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Received: 8 June 2021 / Revised: 8 June 2021 / Accepted: 31 July 2021 / Published online: 16 October 2021

Abstract

Fontan surgery is a life-saving procedure for newborns with complex cardiac malformations, but it originates complications in different organs. The liver is also affected, with development of fibrosis and sometimes cirrhosis and hepatocellular carcinoma. There is no general agreement on how to follow-up these children for the development of liver disease. To understand the current practice on liver follow-up, we invited members of the European Society of Paediatric Radiology (ESPR) to fill out an online questionnaire. The survey comprised seven questions about when and how liver follow-up is performed on Fontan patients. While we found some agreement on the use of US as screening tool, and of MRI for nodule characterization, the discrepancies on timing and the lack of a shared protocol make it currently impossible to compare data among centers.

Keywords Adolescents · Children · Cirrhosis · Fontan procedure · Hepatocellular carcinoma · Liver · Liver fibrosis · Magnetic resonance imaging · Ultrasound

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ORIGINAL ARTICLES

Clinical Management of End-Stage Renal Disease Patients on Dialysis Receiving Radioactive Iodine Treatment

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Clinical Nuclear Medicine: December 2021 - Volume 46 - Issue 12 - p 977-982
doi: 10.1097/RLU.0000000000003915

Abstract

Purpose

Radioactive iodine (RAI) is used to treat thyroid cancer patients with a clear paradigm for most patients. End-stage renal disease (ESRD) patients pose several challenges when undergoing RAI treatment, primarily due to the lack of renal clearance. We retrospectively report our experience with RAI treatment in a cohort of patients with ESRD and provide a set of recommendations on aspects such as the need for adjusted dose activity, balancing scheduling between RAI therapy and dialysis, and radiation safety precautions.

Patients and Methods

In this study, we report on 5 patients (6 cases), with ESRD on dialysis, treated with RAI for thyroid cancer. Retention measurements to determine individual biological clearance of RAI from the patient's body before and after dialysis sessions were assessed using external exposure dose rates measured at 1 m.

Early Human Development 163 (2021) 105505

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Cardiac structure and function in very preterm-born adolescents compared to term-born controls: A longitudinal cohort study

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ARTICLE INFO

Keywords:
Premature birth
Cardiovascular
Echocardiography
Adolescent

ABSTRACT

Background: There is emerging evidence of differences in cardiac structure and function in preterm-born adults and increased risk of heart failure. However, there is a paucity of data in populations who have been exposed to modern intensive care and the impact of perinatal factors is unclear.
Aims: To compare echocardiographic measures of cardiac structure and function in a regional cohort of 17-year-olds born very preterm compared to term-born peers and the influence of perinatal factors.
Study design: Observational longitudinal cohort study.
Subjects: A regional cohort of ninety-one 17-year-olds born at <32 weeks gestation compared to sixty-two term-born controls.
Outcome measures: Echocardiographic measures of cardiac structure and function.
Results: Left ventricular and right atrial volume and left ventricular mass, indexed to body surface area, were significantly smaller in preterm-born adolescents compared to term-born controls even when adjusted for sex. There were no between group differences in cardiac function. Within those born preterm we found a significant association between gestational age and birthweight z-score and measures of cardiac function at 17 years. Within the preterm group, those with a diagnosis of bronchopulmonary dysplasia had higher left ventricular posterior wall thickness, higher mitral deceleration time and lower left atrial area and tricuspid annular plane of systolic excursion.
Conclusions: Adolescents born very prematurely, who have received modern intensive care, have measurable differences in heart structure compared to their term-born peers but heart function is preserved. For those born preterm, gestational age, birthweight and bronchopulmonary dysplasia are associated with differences in cardiac function.

Abbreviations: LV, left ventricle or left ventricular; EDD, end-diastolic dimension; ESD, end-systolic dimension; IVS, interventricular septal thickness; PWT, posterior wall thickness; BSA, body surface area; FS, fractional shortening; EF, ejection fraction; SV, stroke volume; DT, deceleration time; RV, right ventricle or right ventricular; FAC, fractional area change; TAPSE, tricuspid annular plane of systolic excursion; GLS, global longitudinal strain; E_A, arterial elastance; E_{LV}, left ventricular elastance; BPD, bronchopulmonary dysplasia; SGA, small for gestational age; BMI, body mass index; VLBW, very low birth weight; cMRI, cardiac magnetic resonance imaging.

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https://doi.org/10.1016/j.earlhumdev.2021.105505
Received 25 July 2021; Received in revised form 31 October 2021; Accepted 2 November 2021
Available online 4 November 2021

J Nucl Med Technol. 2021 Dec 6;jnmt.121.263013. doi: 10.2967/jnmt.121.263013.
Online ahead of print.

Hybrid Imaging with SPECT-CT and SPECT-MR in Hepatic Splenosis

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Affiliations + expand

PMID: 34872916 DOI: 10.2967/jnmt.121.263013

Abstract

Splenosis, commonly occurs incidentally and locates to bowel surfaces, parietal peritoneum, mesentery, and diaphragm, but can potentially occur anywhere in the peritoneal cavity. Patients frequently have a history of splenectomy or trauma. On the other hand, hepatic splenosis is a rare entity and may present itself clinically. Indeterminate liver lesions can pose a clinical dilemma and may lead to additional investigations, anxiety, follow-up imaging and even to invasive procedures. MRI usually performs extremely well. In difficult cases, scintigraphy can be of great value -especially with novel SPECT-CT and SPECT-MR techniques-. We describe a case of a 29-year-old lady with hepatic splenosis and the impact of hybrid imaging.

Keywords: Correlative Imaging; Gastrointestinal; Hepatic splenosis; Hepatology; MRI; Molecular Imaging; Oncology: GI; Oncology: Liver; RBC scan; SPECT-CT; SPECT-MR; Sulfur colloid.

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

METHODS AND PROTOCOLS

Evaluation of Rapid Immunochromatographic Tests for the Direct Detection of Extended Spectrum Beta-Lactamases and Carbapenemases in Enterobacterales Isolated from Positive Blood Cultures

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ABSTRACT NG-Test CTX-M MULTI and NG-Test Carba 5 (NG Biotech) are two rapid *in vitro* immunochromatographic assays that are widely used for the detection of the most common extended spectrum beta-lactamases (ESBL) and carbapenemases in Enterobacterales. ESBL and carbapenemases are leading causes of morbidity and mortality worldwide and their rapid detection from positive blood cultures is crucial for early initiation of effective antimicrobial therapy in bloodstream infections (BSI) involving antibiotic-resistant organisms. In this study, we developed a rapid workflow for positive blood cultures for direct identification of Enterobacterales by MALDI-TOF mass-spectrometry, followed by detection of ESBL and carbapenemases using NG-Test CTX-M MULTI and NG-Test Carba 5 (NG Biotech). The workflow was evaluated using Enterobacterales isolates (n = 114), primarily *Klebsiella* species (n = 50) and *Escherichia coli* (n = 40). Compared to the standard testing approach in our institution using BD Phoenix, our new testing approach demonstrates 100% sensitivity and specificity for organism identification and detection of ESBL and carbapenemases. Implementation of a rapid workflow in diagnostic microbiology laboratories will enable more effective antimicrobial management of patients with BSI due to ESBL- and carbapenemase-producing Enterobacterales.

IMPORTANCE The incidence of bloodstream infections (BSI) with extended spectrum beta-lactamase (ESBL) producing and carbapenemase producing Enterobacterales (CPE) is increasing at an alarming rate, for which only limited therapeutic options remain available. Rapid identification of these bacteria along with their antibiotic resistance mechanisms in positive blood cultures with Gram-negative bacteria will allow for early initiation of effective therapy and limit the overuse of broad-spectrum antibiotics in BSI (1). In this study we evaluated a combined approach of testing positive blood cultures directly, using MALDI-TOF MS followed by rapid immunochromatographic tests, for the detection of ESBLs and CPEs. Our approach demonstrates 100% sensitivity and specificity for the identification of Enterobacterales and detection of ESBLs and CPEs in positive blood culture with a turnaround time (TAT) of ≤60 min compared to a TAT of 48 h required by conventional culture and susceptibility testing methods.

KEYWORDS NG-Test CARBA 5, CTX-M, ESBL, CPO

Extended-spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing Enterobacterales (CPE) have been reported as significant causes of morbidity and mortality worldwide. Over the last decades, the increasing prevalence of ESBL-producing

Editor William Lainhart, University of Arizona/Banner Health

Ad Hoc Peer Reviewer Janet Hindler, UCLA Medical Center

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Received 10 July 2021
Accepted 10 November 2021
Published 8 December 2021

JAMA | Original Investigation

Effect of Minimally Invasive Surfactant Therapy vs Sham Treatment on Death or Bronchopulmonary Dysplasia in Preterm Infants With Respiratory Distress Syndrome

The OPTIMIST-A Randomized Clinical Trial

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IMPORTANCE The benefits of surfactant administration via a thin catheter (minimally invasive surfactant therapy [MIST]) in preterm infants with respiratory distress syndrome are uncertain.

OBJECTIVE To examine the effect of selective application of MIST at a low fraction of inspired oxygen threshold on survival without bronchopulmonary dysplasia (BPD).

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial including 485 preterm infants with a gestational age of 25 to 28 weeks who were supported with continuous positive airway pressure (CPAP) and required a fraction of inspired oxygen of 0.30 or greater within 6 hours of birth. The trial was conducted at 33 tertiary-level neonatal intensive care units around the world, with blinding of the clinicians and outcome assessors. Enrollment took place between December 16, 2011, and March 26, 2020; follow-up was completed on December 2, 2020.

INTERVENTIONS Infants were randomized to the MIST group (n = 241) and received exogenous surfactant (200 mg/kg of poractant alfa) via a thin catheter or to the control group (n = 244) and received a sham (control) treatment; CPAP was continued thereafter in both groups unless specified intubation criteria were met.

MAIN OUTCOMES AND MEASURES The primary outcome was the composite of death or physiological BPD assessed at 36 weeks' postmenstrual age. The components of the primary outcome (death prior to 36 weeks' postmenstrual age and BPD at 36 weeks' postmenstrual age) also were considered separately.

RESULTS Among the 485 infants randomized (median gestational age, 27.3 weeks; 241 [49.7%] female), all completed follow-up. Death or BPD occurred in 105 infants (43.6%) in the MIST group and 121 (49.6%) in the control group (risk difference [RD], −6.3% [95% CI, −14.2% to 1.6%]; relative risk [RR], 0.87 [95% CI, 0.74 to 1.03]; P = .10). Incidence of death before 36 weeks' postmenstrual age did not differ significantly between groups (24 [10.0%] in MIST vs 19 [7.8%] in control; RD, 2.1% [95% CI, −3.6% to 7.8%]; RR, 1.27 [95% CI, 0.63 to 2.57]; P = .51), but incidence of BPD in survivors to 36 weeks' postmenstrual age was lower in the MIST group (81/217 [37.3%] vs 102/225 [45.3%] in the control group; RD, −7.8% [95% CI, −14.9% to −0.7%]; RR, 0.83 [95% CI, 0.70 to 0.98]; P = .03). Serious adverse events occurred in 10.3% of infants in the MIST group and 11.1% in the control group.

CONCLUSIONS AND RELEVANCE Among preterm infants with respiratory distress syndrome supported with CPAP, minimally invasive surfactant therapy compared with sham (control) treatment did not significantly reduce the incidence of the composite outcome of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age. However, given the statistical uncertainty reflected in the 95% CI, a clinically important effect cannot be excluded.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12611000916943

JAMA. 2021;326(24):2478-2487. doi:10.1001/jama.2021.21892
Published online December 13, 2021.

Editorial page 2475

Multimedia

Supplemental content

CME Quiz at jamacmelookup.com

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Group Information: A list of the OPTIMIST-A Trial Investigators appears in Supplement 4.

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Original Article

Predictors of Psychological Distress in Health Care Staff in Qatar during COVID-19 Pandemic

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ABSTRACT

Background & Objective: The Coronavirus disease 2019 (COVID-19) pandemic has caused widespread psychological distress. The aims of the study were a) to assess mental health symptoms experienced by expatriate hospital staff and b) to determine the impact of staff wellbeing interventions specific to pandemic related stress.

Methods: The study was conducted from June 2020 until August 2020. A 16-question survey was disseminated online via Survey Monkey to assess the mental health needs of hospital staff during the pandemic. Based on results, a virtual, tiered mental health support model was developed, and staff feedback was collected.

Results: Almost 46.2% of respondents (N: 1001) reported at least one mental health symptom in the initial survey. The most common symptoms were anxiety, low mood and feelings of isolation. Being single and in poor health status were predictors of developing mental health symptoms (P <0.01). Female gender was a predictor for experiencing fear of getting infected. Time constraints at work was the most common reason for not accessing mental health support.

Conclusions: As in other parts of the world, hospital staff in Qatar experienced mental health symptoms and significant fear related to the COVID-19 Pandemic. Being single and in poor health status were risk factors. Mental health interventions at work must take into account time constraints experienced by staff.

KEYWORDS: Mental health, Social isolation, Expatriates, Pandemic.

doi: https://doi.org/10.12669/pjms.37.7.4533

How to cite this:

Latif F, Ahmed SR, Farhan S, Watt F, Azeem MW. Predictors of Psychological Distress in Health Care Staff in Qatar during COVID-19 Pandemic. Pak J Med Sci. 2021;37(7):1782-1787. doi: https://doi.org/10.12669/pjms.37.7.4533

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* Received for Publication: April 8, 2021
* Revision Received: June 10, 2021
* Revision Accepted: July 5, 2021

INTRODUCTION

The WHO declared Coronavirus disease 2019 (COVID-19) a global pandemic on March 11th, 2020. The first case of the virus in the small gulf state of Qatar was reported on February 28th, 2020. As the rate of infections grew, the State of Qatar issued gradually tightening social restrictions starting early March, 2020.[1] The restrictions included closures of schools, shopping malls, parks and recreation venues and travel out of the country. In April, 2020 the Ministry of Public Health reported 106,648 cases of Coronavirus Disease (COVID-19) in Qatar, which has a population of 2.7 million. Total number of deaths was 157.[2]

Health care staff are at increased risk for experiencing adverse mental health symptoms during a pandemic.[3] Previous studies[4,5] have shown

PLOS MEDICINE

RESEARCH ARTICLE

Introduction and expansion of the SARS-CoV-2 B.1.1.7 variant and reinfections in Qatar: A nationally representative cohort study

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Citation: Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Coyle P, Malek JA, Ahmed AA, et al. (2021) Introduction and expansion of the SARS-CoV-2 B.1.1.7 variant and reinfections in Qatar: A nationally representative cohort study. PLoS Med 18(12): e1003879. https://doi.org/10.1371/journal.pmed.1003879

Academic Editor: Mirjam E. E. Kretzschmar, Universitair Medisch Centrum Utrecht, NETHERLANDS

Received: July 15, 2021

Accepted: November 30, 2021

Published: December 16, 2021

Data Availability Statement: The dataset of this study is the property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly. Future access to this dataset can be considered through a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/OurServices/eservices/Pages/Governmental-

Abstract

Background

The epidemiology of the SARS-CoV-2 B.1.1.7 (or Alpha) variant is insufficiently understood. This study's objective was to describe the introduction and expansion of this variant in Qatar and to estimate the efficacy of natural infection against reinfection with this variant.

Methods and findings

Reinfections with the B.1.1.7 variant and variants of unknown status were investigated in a national cohort of 158,608 individuals with prior PCR-confirmed infections and a national cohort of 42,848 antibody-positive individuals. Infections with B.1.1.7 and variants of unknown status were also investigated in a national comparator cohort of 132,701 antibody-negative individuals. B.1.1.7 was first identified in Qatar on 25 December 2020. Sudden, large B.1.1.7 epidemic expansion was observed starting on 18 January 2021, triggering the onset of epidemic's second wave, 7 months after the first wave. B.1.1.7 was about 60% more infectious than the original (wild-type) circulating variants. Among persons with a prior PCR-confirmed infection, the efficacy of natural infection against reinfection was estimated to be 97.5% (95% CI: 95.7% to 98.6%) for B.1.1.7 and 92.2% (95% CI: 90.6% to 93.5%) for

Systems biology analysis of human genomes points to key pathways conferring spina bifida risk

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Edited by Patrick Stover, Texas A&M AgriLife, College Station, TX; received April 12, 2021; accepted October 20, 2021

Spina bifida (SB) is a debilitating birth defect caused by multiple gene and environment interactions. Though SB shows non-Mendelian inheritance, genetic factors contribute to an estimated 70% of cases. Nevertheless, identifying human mutations conferring SB risk is challenging due to its relative rarity, genetic heterogeneity, incomplete penetrance, and environmental influences that hamper genome-wide association studies approaches to untargeted discovery. Thus, SB genetic studies may suffer from population substructure and/or selection bias introduced by typical candidate gene searches. We report a population based, ancestry-matched whole-genome sequence analysis of SB genetic predisposition using a systems biology strategy to interrogate 298 case-control subject genomes (149 pairs). Genes that were enriched in likely gene disrupting (LGD), rare protein-coding variants were subjected to machine learning analysis to identify genes in which LGD variants occur with a different frequency in cases versus controls and so discriminate between these groups. Those genes with high discriminatory potential for SB significantly enriched pathways pertaining to carbon metabolism, inflammation, innate immunity, cytoskeletal regulation, and essential transcriptional regulation consistent with their having impact on the pathogenesis of human SB. Additionally, an interrogation of conserved noncoding sequences identified robust variant enrichment in regulatory regions of several transcription factors critical to embryonic development. This genome-wide perspective offers an effective approach to the interrogation of coding and noncoding sequence variant contributions to rare complex genetic disorders.

neural tube defects | myelomeningocele | whole-genome sequence | rare variant enrichment | pathway analysis

The neural tube defect (NTD) spina bifida (SB), among the debilitating but survivable malformations in live births, is due to failed embryonic neural tube closure. Together, SB and the nonviable NTD anencephaly have a global prevalence ranging from one in 3,000 to one in 100 (1). Decades of clinical and animal model investigations have indicated that SB comprises a complex genetic disorder, requiring at least one (and probably several) of many genetic alterations or gene–environment interactions for neurulation to fail (2, 3). NTD-causing mutations have been reported in more than 250 mouse genes (4, 5), which has since grown to over 400 mutant genes currently listed in the Mouse Genome Informatics database, further underscoring the complex genetic origins of the disorder. Genetic heritability of human SB, or the proportion of cases that are attributable to genetic alteration, is estimated to be as much as 70% (6).

Maternal periconceptional supplementation with folic acid (vitamin B9) can reduce the occurrence of SB in offspring by as much as 70% in some populations (7–9). Despite folate supplementation campaigns and fortification of the US food supply since 1998, SB prevalence rates have only dropped 30%, suggesting that most benefits from folic acid have been achieved. Other agents such as vitamin B12, methionine, or inositol show some promise for effective prevention (10). However, the mechanisms through which these agents influence SB occurrence

Significance

Genetic investigations of most structural birth defects, including spina bifida (SB), congenital heart disease, and craniofacial anomalies, have been underpowered for genome-wide association studies because of their rarity, genetic heterogeneity, incomplete penetrance, and environmental influences. Our systems biology strategy to investigate SB predisposition controls for population stratification and avoids much of the bias inherent in candidate gene searches that are pervasive in the field. We examine both protein coding and noncoding regions of whole genomes to analyze sequence variants, collapsed by gene or regulatory region, and apply machine learning, gene enrichment, and pathway analyses to elucidate molecular pathways and genes contributing to human SB.

Author contributions: V.A.-P., J.M.M., C.E.M., R.H.F., and M.E.R. designed research; V.A.-P., P.W., E.E., N.C., T.C., and M.E.R. performed research; V.A.P., A.M.-F., E.E., G.T., A.A.A., N.C., T.C., J.A.-Z., Y.L., H.E.-B., A.A.-K., G.M.S., E.K., K.S., C.E.M., O.E., R.H.F., and M.E.R. contributed new reagents/analytic tools; V.A.-P., P.W., A.M.-F., E.E., G.T., Y.L., and O.E. analyzed data; and V.A.-P., P.W., E.E., J.M.M., G.M.S., O.E., R.H.F., and M.E.R. wrote the paper.

Competing interest statement. R.H.F. formerly held a leadership position with the now dissolved TeratOmic Consulting LLC. He also receives travel funds to attend editorial board meetings of the Journal of Reproductive and Developmental Medicine published out of the Red Hospital of Fudan University. E.E. consults for the DNA Diagnostics Center. P.S. and R.H.F. are coauthors on a 2020 paper resulting from an NIH workshop: Maruvada P et al., Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop. Am J Clin Nutr. 2020 Nov 11;112(5):1390-1403. doi: 10.1093/ajcn/nqaa259. PMID: 33022704; PMCID: PMC7657327.

This article is a PNAS Direct Submission.

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This article contains supporting information online at http://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2106844118/-/DCSupplemental.

Published December 16, 2021.

CLINICAL STUDIES

Seminal Studies in Facial Reanimation Surgery: Consensus and Controversies in the Top 50 Most Cited Articles

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The Journal of Craniofacial Surgery: July/August 2022 - Volume 33 - Issue 5 - p 1507-1513
doi: 10.1097/SCS.0000000000008436

Abstract

Facial paralysis can impair one's ability to form facial expressions that are congruent with internal emotion. This hinders communication and the cognitive processing of emotional experience. Facial reanimation surgery, which aims to restore full facial expressivity is a relatively recent undertaking which is still evolving. Due in large part to published techniques, refinements, and clinical outcomes in the scientific literature, consensus on best practice is gradually emerging, whereas controversies still exist.

Taking stock of how the discipline reached its current state can help delineate areas of agreement and debate, and more clearly reveal a path forward. To do this, the authors have analyzed the 50 seminal publications pertaining to facial reanimation surgery. In longstanding cases, the free gracilis transfer emerges as a clear muscle of choice but the nerve selection remains controversial with prevailing philosophies advocating cross facial nerve grafts (with or without the support of an ipsilateral

motor donor) or an ipsilateral motor donor only, of which the hypoglossal and nerve to masseter predominate. The alternative orthodoxy has refined the approach popularized by Gillies in 1934 and does not require the deployment of microsurgical principles. Although this citation analysis does not tell the whole story, surgeons with an interest in facial reanimation will find that this is a good place to start.

JAMA Internal Medicine | Original Investigation

Severity of Illness in Persons Infected With the SARS-CoV-2 Delta Variant vs Beta Variant in Qatar

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IMPORTANCE The Delta variant is now the predominant circulating SARS-CoV-2 strain worldwide. Severity of illness in persons infected with the SARS-CoV-2 Delta variant compared with the Beta variant is not known.

OBJECTIVE To directly compare clinical outcomes in persons infected with the SARS-CoV-2 Delta variant vs those infected with the Beta variant in Qatar.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the national COVID-19 database in Qatar, which includes information on all individuals who were ever tested for SARS-CoV-2 using a reverse transcriptase–polymerase chain reaction test and all individuals who received any SARS-CoV-2 vaccine in Qatar. Among persons with confirmed SARS-CoV-2 infection between March 22 and July 7, 2021, those infected with the Delta variant were identified and were propensity score matched with control individuals infected with the Beta variant. The variants were ascertained by variant genotyping of the positive samples.

EXPOSURES SARS-CoV-2 infection with the Delta or Beta variant.

MAIN OUTCOMES AND MEASURES The main outcomes were admission to the hospital, admission to the intensive care unit, use of supplemental oxygen, use of high-flow oxygen, receipt of mechanical ventilation, or death among those infected with the Delta or Beta variant overall and stratified by vaccination status.

RESULTS Among 1427 persons infected with the Delta variant (252 [55.9%] male; median age, 34 years [IQR, 17-43 years]) and 5353 persons infected with the Beta variant (233 [51.7%] male; median age, 34 years [IQR, 17-45 years]), 451 propensity score–matched pairs were identified. Persons infected with the Delta variant were more likely to be hospitalized (27.3% [95% CI, 23.2%-31.6%] vs 20.0% [95% CI, 16.4-24.0]; $P = .01$) or to have mild-moderate or severe-critical disease outcomes (27.9% [95% CI, 23.8%-32.3%] vs 20.2% [95% CI, 16.6%-24.2%]; $P = .01$) compared with persons infected with the Beta variant. Infection with the Delta variant was independently associated with higher odds of experiencing any adverse outcome (adjusted odds ratio [aOR], 2.53; 95% CI, 1.72-3.72). Compared with being unvaccinated, being vaccinated with a second dose more than 3 months before infection was associated with lower odds of any adverse outcome among persons infected with the Delta variant (aOR, 0.11; 95% CI, 0.04-0.26) and among those infected with the Beta variant (aOR, 0.22; 95% CI, 0.05-0.98). Protection was similar among those who received a second vaccine dose less than 3 months before infection, but having received only a single dose was not associated with a lower odds of any severe outcome among those infected with the Delta variant (aOR, 1.12; 95% CI, 0.41-3.06) or those infected with the Beta variant (aOR, 0.74; 95% CI, 0.20-2.72).

CONCLUSIONS AND RELEVANCE In this cohort study of persons with COVID-19 in Qatar, infection with the SARS-CoV-2 Delta variant was associated with more severe disease than was infection with the Beta variant. Being unvaccinated was associated with greater odds of severe-critical disease.

JAMA Intern Med. 2022;182(2):197-205. doi:10.1001/jamainternmed.2021.7949
Published online December 22, 2021.

Supplemental content

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AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

Performance and Impact on Initial Antibiotic Choice of Direct Identification of Pathogens from Pediatric Blood Culture Bottles Using an In-House MALDI-TOF MS Protocol

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ABSTRACT The performance and early therapeutic impact of direct identification by matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF; DIMT) on pediatric blood culture bottles using in-house-developed methods to obtain microbial pellets for spectrometric analysis have seldom been studied. During a 2-year period (June 2018 to May 2020), DIMT was performed on broths from positive pediatric blood culture bottles using an in-house-developed method. Organism identifications with a score of ≥1.6 were notified to treating clinicians. Therapeutic modifications that occurred after the communication of DIMT were reviewed through the electronic medical records. DIMT was performed on 530 pediatric positive blood culture bottles. Among 505 monomicrobial bottles, identifications from 298 (97.7%) deemed as bloodstream infections (BSI) and 189 (94.5%) as contaminations had DIMT notified to clinicians. All identifications were correct except for one *Streptococcus mitis* incorrectly reported as *Streptococcus pneumoniae*. Therapy modifications resulting from DIMT occurred in 27 (8.3%) patients with BSI. Deescalation from effective or ineffective broad-spectrum regimens occurred mainly in *Enterococcus faecalis* bacteremia, whereas appropriate escalation from an ineffective regimen with narrower spectrum occurred mainly in bacteremia caused by AmpC-β-lactamase-producing *Enterobacterales*. Escalation therapy was instituted significantly faster than deescalation therapy (median time, 0.75 versus 10.5 h [P = 0.01]). DIMT also enabled clinicians to confirm contamination in nearly one-half of patients with contaminated blood cultures. Our DIMT method applied to positive pediatric blood culture bottles demonstrated reliable performance for the rapid identification of pathogens. Our DIMT approach allowed therapeutic optimization in BSI, especially involving microorganisms with intrinsic antibiotic resistance, and was helpful in the early identification of likely contaminants.

IMPORTANCE We demonstrate the performance and early impact on the antimicrobial management of bloodstream infections of an inexpensive, in-house preparation method for direct identification of bloodstream pathogens in pediatric blood culture bottles by matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry.

KEYWORDS MALDI-TOF, blood culture, bloodstream infections, children

Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS) has now become an indispensable part of routine, microbial identification procedures in the clinical microbiology laboratories. MALDI-TOF MS has accelerated the turnaround time of bacterial and fungal identification from days to minutes, allowing early initiation of appropriate antimicrobial therapy and infection control measures. Apart from identification of microorganisms from colonies, MALDI-TOF MS is widely used for direct identification of pathogens from positive blood culture bottles (1, 2). One method for direct

Editor Jennifer Dien Bard, Children's Hospital Los Angeles, University of Southern California

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The authors declare no conflict of interest.

Received 14 October 2021
Accepted 23 November 2021
Published 22 December 2021

Received: 26 September 2021 | Revised: 9 November 2021 | Accepted: 16 November 2021

DOI: 10.1002/ccr3.5141

CASE REPORT

Clinical Case Reports Open Access WILEY

Maturity-onset diabetes of the young (MODY) due to PDX1 mutation in a sib-pair diabetes family from Qatar

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Funding information
This research was supported by the Qatar National Research Fund [QNRF-NPRP 10-6100017-AXX] awarded to Professor Khalid Hussain.

Abstract

Maturity-onset diabetes of young (MODY) is an autosomal dominant genetic disorder that causes insulin deficiency without autoimmunity. We present the first family with pancreatic duodenal homeobox 1 *(PDX1)* mutation causing diabetes from Qatar. Routine genetic screening of all antibody-negative diabetic patients with diabetes should be offered to avoid misdiagnosis.

KEYWORDS

MODY, PDX1, pediatric diabetes mellitus

1 | INTRODUCTION

Maturity-onset diabetes of the young (MODY) is an autosomal dominant genetic disorder characterized by impaired insulin secretion causing hyperglycemia at an early age, most commonly before 25 years of age. There is minimal or no defect in insulin action, absence of autoimmunity or insulin resistance.[1] Serum insulin and/or c-peptide with some residual pancreatic function is usually present. In the family history, typically multiple members will have diabetes.[2] MODY is the most common form of monogenic diabetes affecting 1%–5% of all patients with diabetes mellitus (DM).[3] However, these figures are based on studies in European and other western countries, with limited information about MODY in Middle Eastern countries.[2,3] MODY subjects are often misdiagnosed as type 1 or type 2 diabetes; however, they have different treatment modalities and prognosis. Diagnosis of MODY should be considered in subjects with autoantibody negative atypical diabetes with multiple affected family members.[1]

14 subtypes of MODY have been described in the literature, the most common being MODY due to glucokinase *(GCK)*, hepatocyte nuclear factor 1A *(HNF1A)*, and hepatocyte nuclear factor 4A *(HNF4A)* gene mutations.[4]

Journal of *Fungi*

MDPI

Article

Phylogenetic Relationships, Speciation, and Origin of *Armillaria* in the Northern Hemisphere: A Lesson Based on rRNA and Elongation Factor 1-Alpha

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Abstract: *Armillaria* species have a global distribution and play various roles in the natural ecosystems, e.g., pathogens, decomposers, and mycorrhizal associates. However, their taxonomic boundaries, speciation processes, and origin are poorly understood. Here, we used a phylogenetic approach with 358 samplings from Europe, East Asia, and North America to delimit the species boundaries and to discern the evolutionary forces underpinning divergence and evolution. Three species delimitation methods indicated multiple unrecognized phylogenetic species, and biological species recognition did not reflect the natural evolutionary relationships within *Armillaria*; for instance, biological species of *A. mellea* and *D. tabescens* are divergent and cryptic species/lineages exist associated with their geographic distributions in Europe, North America, and East Asia. While the species-rich and divergent Gallica superclade might represent three phylogenetic species (PS I, PS II, and *A. nabsnona*) that undergo speciation. The PS II contained four lineages with cryptic diversity associated with the geographic distribution. The genus *Armillaria* likely originated from East Asia around 21.8 Mya in early Miocene when Boreotropical flora (56–33.9 Mya) and the Bering land bridge might have facilitated transcontinental dispersal of *Armillaria* species. The Gallica superclade arose at 9.1 Mya and the concurrent vicariance events of Bering Strait opening and the uplift of the northern Tibetan plateau might be important factors in driving the lineage divergence.

Keywords: phylogeography; species delimitation; allopatric speciation; molecular clock; ancestral area reconstruction

Citation: Liang, J.; Pecoraro, L.; Cai, L.; Yuan, Z.; Zhao, P.; Tsui, C.K.M.; Zhang, Z. Phylogenetic Relationships, Speciation, and Origin of *Armillaria* in the Northern Hemisphere: A Lesson Based on rRNA and Elongation Factor 1-Alpha. *J. Fungi* **2021**, *7*, 1088. https://doi.org/10.3390/jof7121088

Academic Editors: Philippe Silar

Received: 8 November 2021
Accepted: 13 December 2021
Published: 17 December 2021

1. Introduction

Understanding the biogeographical pattern and origin of fungi is important, especially for those fungal plant pathogens that cause severe economic losses. However, studying fungal biogeography is challenging. This has been attributed to shortcomings in delimiting species based on morphological characteristics, poor knowledge of the phylogeny in most fungal groups, rare fossil records, and the long-distance dispersal ability of spores to overcome geographic barriers [1]. For example, it took over a century of efforts to figure out the origin and dispersal pattern of *Pyricularia oryzae*, the famous pathogen of rice blast, since it was first discovered in 1892 [2,3]. Benefiting from the development

frontiers in Microbiology

ORIGINAL RESEARCH
published: 10 December 2021
doi: 10.3389/fmicb.2021.772736

Can the Salivary Microbiome Predict Cardiovascular Diseases? Lessons Learned From the Qatari Population

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Background: Many studies have linked dysbiosis of the gut microbiome to the development of cardiovascular diseases (CVD). However, studies assessing the association between the salivary microbiome and CVD risk on a large cohort remain sparse. This study aims to identify whether a predictive salivary microbiome signature is associated with a high risk of developing CVD in the Qatari population.

Methods: Saliva samples from 2,974 Qatar Genome Project (QGP) participants were collected from Qatar Biobank (QBB). Based on the CVD score, subjects were classified into low-risk (LR < 10) ($n = 2491$), moderate-risk (MR = 10–20) ($n = 320$) and high-risk (HR > 30) ($n = 163$). To assess the salivary microbiome (SM) composition, 16S-rDNA libraries were sequenced and analyzed using QIIME-pipeline. Machine Learning (ML) strategies were used to identify SM-based predictors of CVD risk.

Results: *Firmicutes* and *Bacteroidetes* were the predominant phyla among all the subjects included. Linear Discriminant Analysis Effect Size (LEfSe) analysis revealed that *Clostridiaceae* and *Capnocytophaga* were the most significantly abundant genera in the LR group, while *Lactobacillus* and *Rothia* were significantly abundant in the HR group. ML based prediction models revealed that *Desulfobulbus, Prevotella*, and *Tissierellaceae* were the common predictors of increased risk to CVD.

Conclusion: This study identified significant differences in the SM composition in HR and LR CVD subjects. This is the first study to apply ML-based prediction modeling using the SM to predict CVD in an Arab population. More studies are required to better understand the mechanisms of how those microbes contribute to CVD.

Keywords: CVD, salivary microbiome, precision medicine, machine learning, QGP

OPEN ACCESS

Edited by:
Florence Carrouel, Université Claude Bernard Lyon 1, France

Reviewed by:
Ina Saliasi, Université Claude Bernard Lyon 1, France
Frédéric Denis, Université de Nantes, France

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Specialty section:
This article was submitted to Microbial Symbioses, a section of the journal Frontiers in Microbiology

Received: *08 September 2021*
Accepted: *17 November 2021*
Published: *10 December 2021*

Citation:
Murugesan S, Elanbari M, Bangarusamy DK, Terranegra A and Al Khodor S (2021) Can the Salivary Microbiome Predict Cardiovascular Diseases? Lessons Learned From the Qatari Population. Front. Microbiol. 12:772736. doi: 10.3389/fmicb.2021.772736

INTRODUCTION

Non-communicable Diseases (NCDs) are the leading cause of death globally (Allen et al., 2017). According to the World Health Organization [WHO] (2013) report, the global burden of non-communicable diseases (NCDs) raised to 82% by 2020. The most common NCDs are cardiovascular diseases (CVD), cancer, respiratory disorders, and diabetes (Balakumar et al., 2016).

frontiers in Immunology

ORIGINAL RESEARCH
published: 20 December 2021
doi: 10.3389/fimmu.2021.796065

Rubella Virus Infected Macrophages and Neutrophils Define Patterns of Granulomatous Inflammation in Inborn and Acquired Errors of Immunity

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Specialty section:
This article was submitted to Primary Immunodeficiencies, a section of the journal Frontiers in Immunology

Received: *15 October 2021*
Accepted: *30 November 2021*
Published: *20 December 2021*

Citation:
Perelygina L, Faisthalab R, Abernathy E, Chen M-h, Hao LJ, Bercovitch L, Bayer DK, Noroski LM, Lam MT, Cicalese MP, Al-Herz W, Nanda A, Hajjar J, Vanden Driessche K, Schroven S, Leysen J, Rosenbach M, Peters P, Raedler J, Albert MH, Abraham RS, Rangarjan HG, Buchbinder D, Kobrynski L, Pham-Huy A, Dhossche J, Cunningham Rundles C, Meyer AK, Theos A, Atkinson TP, Musiek A, Adeli M, Derichs U, Walz C, Krüger R, von Bernuth H, Klein C, Icenogle J, Hauck F and Sullivan KE (2021) Rubella Virus Infected Macrophages and Neutrophils Define Patterns of Granulomatous Inflammation in Inborn and Acquired Errors of Immunity. Front. Immunol. 12:796065. doi: 10.3389/fimmu.2021.796065

Rubella virus (RuV) has recently been found in association with granulomatous inflammation of the skin and several internal organs in patients with inborn errors of immunity (IEI). The cellular tropism and molecular mechanisms of RuV persistence and pathogenesis in select immunocompromised hosts are not clear. We provide clinical, immunological, virological, and histological data on a cohort of 28 patients with a broad spectrum of IEI and RuV-associated granulomas in skin and nine extracutaneous tissues to further delineate this relationship. Combined immunodeficiency was the most frequent diagnosis (67.8%) among patients. Patients with previously undocumented conditions, i.e., humoral immunodeficiencies, a secondary immunodeficiency, and a defect of innate immunity were identified as being susceptible to RuV-associated granulomas. Hematopoietic cell transplantation was the most successful treatment in this case series resulting in granuloma resolution; steroids, and TNF-α and IL-1R inhibitors were moderately effective. In addition to M2 macrophages, neutrophils were identified by immunohistochemical analysis as a novel cell type infected with RuV. Four patterns of RuV-associated granulomatous inflammation were classified based on the structural organization of granulomas and identity and location of cell types harboring RuV antigen. Identification of conditions that increase susceptibility to RuV-associated granulomas combined with structural characterization of the granulomas may lead to a better understanding of the pathogenesis of RuV-associated granulomas and discover new targets for therapeutic interventions.

Keywords: inborn errors of immunity, primary immunodeficiency, vaccine-derived rubella viruses, granulomatous inflammation, skin lesion, neutrophils, macrophages, granuloma treatments

INTRODUCTION

Inborn errors of immunity (IEI) are a heterogeneous group of more than 450 monogenic disorders affecting different components of the immune system and manifesting with increased susceptibly to autoinflammation, autoimmunity, atopy, infection, bone marrow failure, and/or malignancy (1, 2). Chronic infection in patients with IEI can trigger formation of histopathological immune structures around antigens, resulting in granulomas, which primarily consist of macrophages and lymphocytes (3). If the immune system fails to clear the antigen, granulomas themselves can become a significant pathology with damage to the affected organ. The estimated prevalence of all types of granulomas (both sterile and non-sterile) in individuals with IEI is 1-4% (4). Effective treatment of granulomatous inflammation depends on correct identification of the combined immunological and microbial etiology, and often presents a diagnostic and therapeutic challenge for clinicians and pathologists (5).

Rubella virus (RuV) is a single-stranded positive sense RNA virus from the *Matonaviridae* family. Both wild type RuV and the live-attenuated vaccine strain RA27/3, which is part of the MMR vaccine used in most countries, can cause persistent infection resulting in several associated pathologies (6). Persistent infection of the developing fetus with wild type RuV often results in an array of developmental abnormalities known as congenital rubella syndrome (7, 8). Detection of RuV antigen in brain progenitor cells, alveolar macrophages, cardiac and vascular fibroblasts, the ciliary body of the eye, and in placental capillary endothelium correlate with organ abnormalities in this syndrome (9, 10). Other less common pathologies caused by persistent wild type RuV infection include rubella encephalitis, Fuchs' uveitis, arthralgia, and arthritis (11–14).

Several cases of IEI with granuloma formation have recently been identified in association with RuV vaccine strain RA27/3 (15–20). Infectious immunodeficiency-related vaccine-derived rubella viruses (iVDRV) were isolated from granuloma biopsies and sequenced (16, 20). The iVDRV genomes contained multiple mutations which resulted in viruses with altered growth properties compared to the parental vaccine strain: iVDRV strains were less cytopathic, produced less infectious virus and could establish long-term persistent cultures in primary human fibroblasts (20). Patients with IEI develop rubella-associated granulomas from weeks to decades after MMR vaccination (18). The recent report of a patient with common variable immunodeficiency (CVID) with wild type RuV associated granulomas presenting in his 70s provides the first evidence that, in addition to vaccine virus strain, wild type RuV strains are also capable of long-term asymptomatic persistence and clinical re-emergence as symptomatic granulomas decades later (21). The cellular or tissue reservoir for latent iVDRV and wild type RuV, the mechanism of virus persistence, and the cause of virus-associated lesions in different organs is presently unknown. The risk factors and clinical manifestations remain incompletely described.

SJCAPP

Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 9:187-195 (2021) DOI 10.21307/sjcapp-2021-021

Research Article **Open Access**

Prevalence of elevated anxiety symptoms among children in quarantine with COVID-19 infection in the State of Qatar: A cross-sectional study

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Abstract

Background: Children are particularly vulnerable to the psychological effects of the COVID-19 pandemic. The disruption in daily life has impacted children significantly. Moreover, the increased worrying associated with the probability of getting infected or becoming seriously unwell due to infection can potentially precipitate anxiety disorders among children.
Objective: This study aimed to determine rates of elevated anxiety symptoms in children with COVID-19 infection. It also explored whether there were any differences in terms of age, gender, and residency status.
Method: A cross-sectional, questionnaire-based study with 88 participants (children aged 7-13 years, 54.5% males, 45.5% females) from two institutional quarantine centers. The Spence Children's Anxiety Scale and its validated Arabic version (self-reported questionnaires) were used to measure anxiety symptoms.
Results: 36.3% children reported elevated anxiety symptoms. A lower rate of 32.8% was reported in younger children (7-11 years) compared to 45.8% in older children (12 and 13 years). 70.4% and 57.9% children reported physical injury fears and separation anxiety respectively. A higher prevalence of overall anxiety was reported in children from expatriate families (40.6%) compared to native children (25%). The difference in the mean scores between the expatriate and native group of children was found statistically significant for obsessive-compulsive symptoms.
Conclusions: The prevalence of elevated anxiety symptoms among children in quarantine with COVID-19 infection can be much higher than that reported in the general population. Older children can have elevated anxiety symptoms more commonly than their younger counterparts can. Expatriate children are likely to be more vulnerable to the psychological impact of the pandemic compared to children from local families. Our results suggest the crucial need of focusing on the psychological impact of COVID-19 pandemic on children. The prioritization and effective management of the mental health needs of children should be a vital component of the overall, global response to the pandemic.

Keywords: Child and adolescent psychiatry; anxiety disorders; child behavior

Introduction

Worrying is considered a normal and adaptive component of emotional development in children. By the time they reach primary school, up to 70% of children report some kind of worrying (1). However, worrying can become pathological when excessive and persistent, and when it interferes with the child's functioning (2). Such pathological worrying in children usually exists as part of an anxiety or mood disorder (3). Anxiety disorders are the most common mental disorders with onset during childhood, with a prevalence that ranges from 10 to 30 percent (4-6). The worldwide prevalence of any anxiety disorder among children according to the Diagnostic and Statistical Manual (DSM) and International Statistical Classification of Diseases and Related Health Problems (ICD) is around 6.5% (7).

Journal of Pediatric Urology (2022) **18**, 151–159

Review Article

Evaluation of penile curvature in patients with hypospadias; gaps in the current practice and future perspectives

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Keywords
Hypospadias; Penile curvature; Chordee; 3D mapping

Received 12 May 2021
Revised 10 October 2021
Accepted 28 December 2021
Available online 31 December 2021

Summary

Background/Purpose
Penile curvature (PC) is a significant phenotypic anomaly associated with hypospadias that can affect hypospadias repair post-operative outcomes and impact on long-term quality of life as well as psychosexual wellbeing of affected patients. While several previous studies have attempted to define PC assessment criteria, there is still no accurate, reproducible, and reliable tool for quantifying severity. Our goal was to review the pros and cons of the current tools utilized for assessing the degree of PC in children, stressing on both strengths and limitations of each method.

Methods
A wide and deliberate review of the literature discussing the assessment of PC in hypospadias patients was conducted. We also draw on relevant methods employed in adults with PC and Peyronie's disease where a greater breadth of studies has been conducted.

Results
The appraisal outcomes combined with our recommendations were presented in a structured approach discussing the pre-, intra-, and post-operative evaluation of PC in patients with hypospadias. Critical appraisal of the evaluation tools in terms of availability, cost, objectivity, and potential reproducibility was presented.

Conclusion
This review reflects on current tools used for assessing the degree of PC in children, highlighting both strengths and limitations of each method. A wide variety of approaches are currently being practiced or investigated, with each method displaying particular utility and reliability characteristics. Several approaches are currently being explored with high potential to overcome the current difficulties encountered when measuring PC both in clinical practice and research studies.

Introduction

Hypospadias prevalence in the general population is approximately 1:250 male live births, with ~25–33% also displaying significant penile curvature (PC) [1–3], which refers to abnormal bending of the longitudinal axis of the penile shaft. Although PC can occur in various different settings, it is more common and presents sooner in patients with hypospadias, hence accurate evaluation and management are required at an earlier age. Causes of hypospadias-associated PC include embryological arrest of the ventral penile axis, as well as factors involving penile skin shortage, short urethral plate, ventro-dorsal corporeal disproportion, and dysplastic para-spongiosal tissues [4]. Despite clear clinical significance [5] and prognostic value [6], accurate and objective assessment of PC is not straightforward to reproduce between surgeons, and no proven protocols exist to rapidly evaluate PC in a consistent and standardized fashion [7].

Assessment of PC is considered a critical evaluation in patients with hypospadias. Standardized assessment of the degree of PC is therefore of paramount importance, since minor variations can change the surgical approach selected [8,9]. Consequently, varying degrees of PC have been proposed as appropriate cut-off values for considering staged surgical repair [8,9]. (Fig. 1) The threshold to treat penile curvature in hypospadias patients is variable according to the surgeon and the relevance of the curvature is subjective from patient to patient. At the same time, no universal agreement on ventral lengthening procedure based off of a certain cut off numbers however, different

https://doi.org/10.1016/j.jpurol.2021.12.015

Original Article

Current Urology

OPEN

Scrotal base distance: A new key genital measurement in males with hypospadias and cryptorchidism

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Abstract

Background: Anogenital distance (AGD) in both humans and animals is a known reflection of fetal endocrine effect on genital virilization and the related abnormalities, including cryptorchidism and hypospadias. However, we introduce here and investigate scrotal base distance (SBD) as a sensitive genital anthropometric biomarker in human infants with cryptorchidism and hypospadias, which are considered early manifestations of testicular dysgenesis syndrome. We aim to assess SBD in patients with cryptorchidism or hypospadias against healthy subjects.

Material and methods: Patients with hypospadias (n=61, age 17.4±6.3 months) or cryptorchidism (n=51, age 11.4±4.8 months) were enrolled for assessment of SBD, AGD, and penile length; and compared with a cohort of 102 full-term healthy boys for standard ritual circumcision by measuring age-specific standard deviation scores.

Results: Patients having hypospadias had lower mean SBD, AGD, and penile length standard deviation scores than the control group ($p < 0.01$). These values in patients with cryptorchidism were longer than mean values in boys with hypospadias ($p < 0.01$) and shorter than mean values in the control group.

Conclusions: We showed that SBD, AGD, and penile length were lower in patients with cryptorchidism or hypospadias compared to normative data measured from a control group of healthy boys for ritual circumcision. These results enforce the use of SBD as an objective anthropometric measurement and a viable biomarker to assess the effects of fetal endocrine imbalance on male external genitalia development.

Keywords: Cryptorchidism; Hypospadias; Scrotal base distance; Testicular dysgenesis syndrome

1. Introduction

It is well established now that the incidence of hypospadias, cryptorchidism, and testicular malignancy is globally increasing with a significant geographic variation that might be influenced by their etiological background.[1,2] Although there is no distinct causative delineation of this group of diseases yet, they stand under the umbrella of an entity called "testicular dysgenesis syndrome" (TDS). A hypothesis that can explain abnormal testicular development in this group of patients is fetal endocrine disruption secondary to exposure to different environmental chemicals.[3] Several animal experiments had supported this explanation.[4,5]

Anogenital distance (AGD) is sexually dimorphic in several mammals, where it is longer in males in comparison to females. AGD is also considered an objective biomarker of fetal endocrine disruption in human beings[6] and is considered as a true reflection of fetal exposure to androgens and antiandrogens. Therefore, AGD is frequently utilized in preclinical reproductive toxicology experiments.[7] Furthermore, testicular dysfunction in postpubertal males secondary to fetal exposure to endocrine disruption can be reflected by the shortening of the AGD.[8,9] It was also shown that patients with hypospadias and cryptorchidism had shortened AGD.[10,11]

Several animal experiments showed that male fetus needed suitable amounts of androgen exposure within a masculinization programming window to ensure the healthy development of the male reproductive system.[12–14] Abnormal development of both internal and external genitalia can result from suboptimal exposure to endocrine stimuli within this critical timeframe with an associated risk of developing hypospadias, undescended testes (UDT) and abnormal sperm production.[13]

We proposed and investigated the reliability of a new parameter, "scrotal base distance" (SBD), as a reflection of external genitalia development in relationship to TDS, including hypospadias and cryptorchidism, which are the most common anomaly of the genitalia in children. This measurement has been chosen because it reflects directly one of the genital structures, which is the scrotal size primarily and its internal contents, that is, the testes secondarily, hence it has a robust hypothetical justification of being a significant reflection of in utero genital development. This has not been studied previously and might add a useful noninvasive tool for the assessment of hypo-development of the external genitalia. Establishment of an association between the novel SBD and hypospadias or UDT, which are considered

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Current Urology, (2021) 15, 214–218

Received February 6, 2020; Accepted April 6, 2020.

http://dx.doi.org/10.1097/CU9.0000000000000031