PREFACE

The promise of precision medicine can only reach its true potential when patients become the center of everything we do — whether it's using WGS to end a diagnostic odyssey, cellular models to dissect disease pathways, or cell and gene therapies to cure a rare disease — every patient's journey can be enriched through research.

This past year proved a significant year of firsts at Sidra Medicine, all made possible by closer integration between the research branch and the hospital. On one end, our genomics laboratory team worked tirelessly with Sidra's pathology team to deliver clinical exomes and genomes – both firsts for the State of Qatar. On another end, our advanced cell therapy team managed to license and activate Qatar's first GMP laboratory, providing for the first time in Qatar stem cell CD34 selection procedure for a patient requiring bone marrow transplantation top-up at Sidra. This combination of clinical grade diagnostic and therapeutic manufacturing will usher in an era of personalized advanced therapies to Sidra patients, preparing us to undertake early phase clinical trials for rare and orphan conditions – a key priority for the coming years.

On the scientific discovery side, our Precision Medicine program continues to influence patient workup beyond standard of care. Our scientists and clinicians discovered tens of novel genes and biomarkers of disease in 2023, publishing over 200 papers, with close to 75% percent of Research Branch publications appearing in the top 15 percent (and 22% in the top 2%) of journals worldwide. Multi-disciplinary integration between research and clinical groups continued to grow, particularly across 5 strategic clinical research programs, whose members began meeting to identify 'gold cohorts' and design research plans that significantly improve diagnostic yield and enhance treatment outcomes for our patients. To support our growing research activities, our clinicians and scientists collectively applied for and won nearly 25M QAR in grants over the past 18 months. Notably, the proportion of applications to grant agencies outside Qatar continued to grow, and we were honored to receive the first $1M international grant awarded to Sidra Medicine.

Finally, 2023 was a stellar year in terms of demonstrating our commitment to capacity building. Altogether, nearly 70 students and interns spent time with us throughout last year, including almost 30 PhD and Masters degree candidates doing their thesis work at Sidra. Moreover, we had international visiting scientists training at Sidra labs from several countries including Mexico, France, Germany, Turkey, the US and the UK. We are proud to continue growing as a recognized brand for regional and global trainees seeking education and skill-development in biomedical and genomic research, and are thankful to our faculty and staff who take valuable time to host and train the next generation of precision medicine scientists and contribute to the vibrant knowledge-economy in Qatar.
In all, 2023 represented a year of growth, alignment, and innovation, with every step taking us closer to making precision medicine a reality for our patients. We extend our deepest gratitude to all team members across Sidra Medicine who remained focused on helping us deliver on this mission, and to all the families and patients who entrust Sidra Medicine to deliver the highest-quality, research-driven care.

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المقدمة

لا يمكن لوعد الطب الدقيق أن يصل إلى إمكاناته الحقيقية إلا حينما يصير المرضى هم محور كل ما نفعله - سواء أكان ذلك باستخدام تسلسل الجينوم الكامل لإنهاء ملحمة التشخيص، أو عبر النماذج الخلوية لتحليل مسارات المرض، أو بعلاجات الخلايا والجينات لشفاء مرض نادر - وقتها يمكن إثراء رحلة المريض بأكملها بفضل هجود الأبحاث.

لقد كان العام الماضي عامًا عظيمًا بتحقيق الإنجازات السبّاقة في سدرة للطب، أصبح كل هذا ممكنًا بفضل التكامل الوثيق بين فرع الأبحاث والمستشفى. فمن ناحية، عمل فريق مختبر الجينوم لدينا بلا كلل عمل فريق علم الأمراض في سدرة للطب من أجل تقديم الإكسوم والجينوم السريريين - وكلاهما الأول من نوعه في دولة قطر. ومن ناحية أخرى، تمكن فريق العلاج الخلوي المتقدم لدينا من ترخيص وتفعيل أول مختبر للممارسات الصناعية الجيدة في دولة قطر، وهو يتيح تصنيع وتسليم العلاجات المتقدمة لمرضى سدرة للطب، مما يجهزنا لإجراء تجارب سريرية في مرحلة مبكرة - وهي أولوية رئيسية في السنوات القادمة.

من ناحية الاكتشاف العلمي، يواصل برنامجنا للطب الدقيق تعزيز فحص المريض بما يتفوق على معايير الرعاية. اكتشف علماؤنا وأطباؤنا عشرات الجينات الجديدة والمؤشرات الحيوية للمرض في عام ٢٠٢٣، ونشروا أكثر من ٢٠٠ ورقة بحثية، مع ظهور نحو ٧٥٪ من منشورات فرع الأبحاث في ١٥٪ من أعلى المجلات (و ٢٢٪ من المنشورات في ٢٪ من أعلى المجلات) في كل أنحاء العالم. أخذ التكامل متعدد التخصصات بين المجموعات البحثية والسريرية يف النمو، لا سيما عبر ٥ برامج بحثية سريرية إستراتيجية، بدأ أعضاؤها الاجتماع لتحديد «المجموعات الذهبية» وتصميم خطط بحثية تحسن على نحو ملحوظ نتائج التشخيص وتعزز نتائج العلاج لدى مرضانا. بهدف دعم أنشطتنا البحثية المتنامية، تقدّم أطباؤنا وعلماؤنا جماعيًا للحصول على منح تقدر بنحو ٢٥ مليون ريال قطري على مدار ١٨ شهرًا الماضية وفازوا بها. من الجدير بالذكر، أن نسبة الطلبات المقدمة إلى وكالات المنح خارج قطر استمرت في التنامي، وتشرفنا بتلقي أول منحة دولية بقيمة مليون دولار فاز بها سدرة للطب.

أخيرا، كان عام ٢٠٢٣ عامًا متميزاً فيما يخص إظهار التزامنا ببناء القدرات. إجمالاً ، أمضى نحو ٧٠ طالبًا ومتدربًا الوقت معنا طوال العام الماضي، بما في ذلك نحو ٣٠ مرشحًا لنيل درجة الدكتوراه والماجستير أعدوا رسائلهم في سدرة للطب. علاوة على ذلك، قدمنا التدريب لعلماء زائرين دوليين في مختبرات سدرة للطب جاؤوا من عدة دول، بما في ذلك دول المكسيك وفرنسا وألمانيا وتركيا والولايات المتحدة والمملكة المتحدة. نحن فخورون بمواصلة نمونا بوصفنا علامة تجارية معترف بها للمتدربين الإقليميين والعالميين الذين يسعون إلى التعلم وتطوير المهارات في مجال البحوث الطبية الحيوية والجينومية، ونشعر بالامتنان لأعضاء هيئة التدريس والموظفين لدينا ممن يخصصون وقتهم الثمين لاستضافة وتدريب الجيل القادم من علماء الطب الدقيق والإسهام في الاقتصاد المعرفي بدولة قطر.

عمومًا، كان عام ٢٠٢٣ عاماً للنمو والمواءمة والابتكار، إذ جعلتنا كل خطوة نقترب من تحويل الطب الدقيق إلى حقيقة واقعة من أجل مرضانا. نعرب عن عميق امتناننا لكل الذين ظلوا مهتمين بمساعدتنا في تنفيذ هذه المهمة، ولجميع العائلات التي أسندت أمانة رعايتها إلى سدرة للطب.

الدكتور خالد فخرو
رئيس قسم الأبحاث

نور فيصل
مدير التحرير

Research Branch, 2023

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ARTICLE

Inherited human ITK deficiency impairs IFN-γ immunity and underlies tuberculosis

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Inborn errors of IFN-γ immunity can underlie tuberculosis (TB). We report three patients from two kindreds without EBV viremia or disease but with severe TB and inherited complete ITK deficiency, a condition associated with severe EBV disease that renders immunological studies challenging. They have CD4⁺ αβ T lymphocytopenia with a concomitant expansion of CD4⁻CD8⁻ double-negative (DN) αβ and Vδ2⁻ γδ T lymphocytes, both displaying a unique CD38⁺CD45RA⁺T-bet⁺EOMES⁻ phenotype. Itk-deficient mice recapitulated an expansion of the γδ T and DN αβ T lymphocyte populations in the thymus and spleen, respectively. Moreover, the patients' T lymphocytes secrete small amounts of IFN-γ in response to TCR crosslinking, mitogens, or forced synapse formation with autologous B lymphocytes. Finally, the patients' total lymphocytes secrete small amounts of IFN-γ, and CD4⁺, CD8⁺, DN αβ T, Vδ2⁺ γδ T, and MAIT cells display impaired IFN-γ production in response to BCG. Inherited ITK deficiency undermines the development and function of various IFN-γ–producing T cell subsets, thereby underlying TB.

Introduction

Tuberculosis (TB) is caused by virulent mycobacterial species from the *Mycobacterium tuberculosis* complex (MTBC), including *Mycobacterium tuberculosis* (*M. tb*) and *Mycobacterium bovis*. TB remains endemic in many countries (Houben and Dodd, 2016). The World Health Organization has estimated that there were ∼9 million new cases and ∼1.2 million deaths globally among HIV-negative individuals in 2019 (WHO, 2020). However, only ∼5–10% of individuals infected with *M. tb* develop TB in their

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Association of Juvenile Dermatomyositis Disease Activity With the Expansion of Blood Memory B and T Cell Subsets Lacking Follicular Markers

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Objective. This study was undertaken to identify blood markers of juvenile dermatomyositis (DM) disease activity (DA), which are needed to improve disease management.

Methods. The study comprised a total of 123 juvenile DM patients and 53 healthy controls. Results of laboratory tests (aldolase, creatinine kinase, lactate dehydrogenase [LDH], aspartate aminotransferase) and clinical measures of DA in patients with juvenile DM, including the Manual Muscle Testing in 8 muscles (MMT-8), Childhood Myositis Assessment Scale (CMAS), and disease activity scores (DAS) (total DAS for juvenile DM, the muscle DAS, and the skin DAS), were recorded when available. Surface phenotype of peripheral blood mononuclear cells was assessed using flow cytometry. Whole blood transcriptional profiles were studied using either RNA-sequencing or microarrays. Differential gene expression was determined using DESeq and compared by pathway and gene ontology analyses.

Results. Conventional memory (CD27+IgD–) B cells expressing low CXCR5 levels ($CXCR5^{low/-}$ CM B cells) were significantly increased in frequency and absolute numbers in 2 independent cohorts of juvenile DM patients compared with healthy controls. The frequency of CD4+ Th2 memory cells (CD45RA–CXCR5–CCR6–CXCR3–) was also increased in juvenile DM, especially in patients who were within <1 year from diagnosis. The frequency of $CXCR5^{low/-}$ CM B cells correlated with serum aldolase levels and with a blood interferon-stimulated gene transcriptional signature. Furthermore, both the frequency and absolute numbers of $CXCR5^{low/-}$ CM B cells correlated with clinical and laboratory measures of muscle DA (MMT-8, CMAS, aldolase, and LDH).

Conclusion. These findings suggest that both CM B cells lacking the CXCR5 follicular marker and CXCR5– Th2 cells represent potential biomarkers of DA in juvenile DM and may contribute to its pathogenesis.

INTRODUCTION

Juvenile dermatomyositis (DM) is a childhood-specific inflammatory myopathy characterized by proximal muscle weakness, unique skin manifestations, and systemic vasculopathy (1). Although mortality has decreased 10-fold in recent years (2), morbidity remains significant. Disease pathogenesis is not fully understood, and treatment relies on nonspecific immunosuppression (3,4).

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Network-based identification and prioritization of key transcriptional factors of diabetic kidney disease

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ABSTRACT

Diabetic nephropathy (DN) is one of the most established microvascular complications of diabetes and a key cause of end-stage renal disease. It is well established that gene susceptibility to DN plays a critical role in disease pathophysiology. Therefore, many genetic studies have been performed to categorize candidate genes in prominent diabetic cohorts, aiming to investigate DN pathogenesis and etiology. In this study, we performed a meta-analysis on the expression profiles of GSE1009, GSE30122, GSE96804, GSE99340, GSE104948, GSE104954, and GSE111154 to identify critical transcriptional factors associated with DN progression. The analysis was conducted for all individual datasets for each kidney tissue (glomerulus, tubules, and kidney cortex). We identified distinct clusters of susceptibility genes that were dysregulated in a renal compartment-specific pattern. Further, we recognized a small but a closely connected set of these susceptibility genes enriched for podocyte differentiation, several of which were characterized as genes encoding critical transcriptional factors (TFs) involved in DN development and podocyte function. To validate the role of identified TFs in DN progression, we functionally validated the three main TFs (DACH1, LMX1B, and WT1) identified through differential gene expression and network analysis using the hyperglycemic zebrafish model. We report that hyperglycemia-induced altered gene expression of the key TF genes leads to morphological abnormalities in zebrafish glomeruli, pronephric tubules, proximal and distal ducts. This study demonstrated that altered expression of these TF genes could be associated with hyperglycemia-induced nephropathy and, thus, aids in understanding the molecular drivers, essential genes, and pathways that trigger DN initiation and development.

1. Introduction

Diabetic nephropathy (DN), also known as diabetic kidney disease, is a main microvascular complication of diabetes mellitus (DM) and a key factor in increased morbidity and mortality in DM patients. Several factors, including hyperglycemia-generated metabolic fluctuations [1], age at onset [2], DM duration [3], hypertension [4] and genetic susceptibility [5], have been proven as significant contributors to the disease progression. It is majorly the glomerular damage, besides tubulointerstitial fibrosis, contributing to the pathogenesis of DN [6,7]. The current treatment for DN is controlling

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Molecular Cancer

REVIEW Open Access

CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances

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Abstract

In the last decade, Chimeric Antigen Receptor (CAR)-T cell therapy has emerged as a promising immunotherapeutic approach to fight cancers. This approach consists of genetically engineered immune cells expressing a surface receptor, called CAR, that specifically targets antigens expressed on the surface of tumor cells. In hematological malignancies like leukemias, myeloma, and non-Hodgkin B-cell lymphomas, adoptive CAR-T cell therapy has shown efficacy in treating chemotherapy refractory patients. However, the value of this therapy remains inconclusive in the context of solid tumors and is restrained by several obstacles including limited tumor trafficking and infiltration, the presence of an immunosuppressive tumor microenvironment, as well as adverse events associated with such therapy. Recently, CAR-Natural Killer (CAR-NK) and CAR-macrophages (CAR-M) were introduced as a complement/alternative to CAR-T cell therapy for solid tumors. CAR-NK cells could be a favorable substitute for CAR-T cells since they do not require HLA compatibility and have limited toxicity. Additionally, CAR-NK cells might be generated in large scale from several sources which would suggest them as promising off-the-shelf product. CAR-M immunotherapy with its capabilities of phagocytosis, tumor-antigen presentation, and broad tumor infiltration, is currently being investigated. Here, we discuss the emerging role of CAR-T, CAR-NK, and CAR-M cells in solid tumors. We also highlight the advantages and drawbacks of CAR-NK and CAR-M cells compared to CAR-T cells. Finally, we suggest prospective solutions such as potential combination therapies to enhance the efficacy of CAR-cells immunotherapy.

Keywords CAR-T, CAR-NK, CAR-M, Cellular immunotherapy, Solid tumors, Combined therapies

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Introduction

Cancer presents a paramount health issue with increasing annual incidence and mortality rates [1]. Conventional therapeutic approaches involving surgery, radiation therapy and chemotherapy have major drawbacks and many patients with metastatic or recurrent disease still face dismal outcomes [2, 3]. In the last decade, various targeted treatments have considerably evolved owing to increasing knowledge in cancer molecular medicine and in immuno-oncology, allowing the development of precision medicine as a more specific and less toxic way to manage cancer [4]. Antitumor immunotherapy provided a major advance in the treatment of cancer by modulating the immune system to enhance its ability to recognize and destroy the malignant cells [5]. A broadly successful antitumor cellular immunotherapy approach consists of engineering immune cells to express cell surface receptor/s capable of recognizing antigens expressed on the surface of tumor cells and destroying them [6]. Subsequently, genetically modified immune cells are redirected through the Chimeric Antigen Receptor (CAR) to the tumor cells [7]. Currently, approved CAR-T cell therapy targets are mostly the B cell maturation antigen (BCMA) for multiple myeloma (MM) [8, 9] and the B cell antigen CD19 for various lymphoid malignancies including B-cell leukemias [10–12] and some types of lymphomas [13, 14]. Indeed, according to published anti-BCMA CAR-T cell clinical trials, complete remission rates of 29 to 60% were reached in a total of 61 patients with relapsed/refractory multiple myeloma (r/r MM) [15]. CAR-T cells targeting CD19 led to initial complete remission in up to 85% of patients with acute lymphoblastic leukemia (ALL) [16] and in up to 100% of patients with refractory or relapsed B cell acute lymphoblastic leukemia (r/r B-ALL) [17]. CAR-T cells targeting large B cell lymphoma are currently approved for second-line therapy after chemotherapy failure [18]. The application of CAR-T cell therapy in hematological malignancies showed promising results that increases the prospect to use this strategy in other types of malignancies.

Currently, there are several ongoing clinical trials utilizing CAR-T cell therapy for solid tumors including glioblastoma [19], lung cancer [20], liver cancer [21], gastric cancer [22], renal cancer [23], prostate cancer [24], osteosarcoma, peritoneal carcinomatosis, pleural cancer, central nervous system tumors and neuroblastoma [25]. This immunotherapeutic approach generated promising clinical outcome. However, it has also shown several radical limitations such as difficulty of the cytotoxic T cells to infiltrate the tumor, insufficiency of T cell recruitment to the tumor site due to abnormal chemokines secreted by solid tumor cells and to the immunosuppressive tumor microenvironment [26, 27]. Moreover, other limitations are related to CAR-T cell side effects including the on-target off-tumor toxicities and the cytokine-released syndrome (CRS) which present the two major adverse events that restrain the therapeutic index [28, 29]. In addition, other toxicities induced by CAR-T cells, such as tumor lysate syndrome, neurotoxicity, cytopenia-related adverse events are also common limitations of this therapy [30]. In the interest of overcoming these obstacles, various innovative strategies are currently under investigation. In addition, scientists are seeking alternative immune effector cells that can be engineered with CARs to be used as antitumor cellular immunotherapy. The increasing understanding of the prominent characteristics of NK cells and macrophages, related to the interaction with other cellular components of the tumor microenvironment, expanded the research focus from CAR-T to CAR-NK and CAR-M cellular immunotherapy [31–35].

Here we discuss the current status, the challenges and prospects regarding the clinical applications of CAR-T, CAR-NK, and CAR-M cells in the management of patients with solid tumors. We also highlight the potential advantages of CAR-NK and CAR-M cells over CAR-T cells.

CAR-T cell therapy in solid tumors: applications, challenges and recent advances

In recent years, T cells engineered with CAR demonstrated promising outcomes against B cell leukemia and lymphoma, proving its therapeutic anti-cancer potential [36]. Indeed, two CAR-T cell therapies Tisagenlecleucel and Axicabtagen-ciloleucel, were approved by the European Medical Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma [37–40]. Two additional products have also been approved for these indications: brexucabtagene autoleucel (mantle lymphoma and ALL) and lisocabtagene maraleucel (DBCL, follicular lymphoma, high grade lymphoma). This success is largely due to the choice of the target, the B-cell marker CD19, generating a T cell immune response against the malignant B cells in a MHC-independent manner [41, 42]. Other target antigens: BCMA and CD38 are also found on myeloma cells [37, 38]. Therefore, cellular BCMA-CD38-CAR-T cell therapy is feasible in treating patients with relapsed and refractory multiple myeloma (r/r MM), with high response rate, low recurrence rate and manageable CRS [43]. Importantly, BCMA-CAR-T immunotherapies Ciltacabtagene-autoleucel and Idecabtagene-vicleucel are now available for the treatment of patients with relapsed and refractory multiple myeloma [44]. These significant achievements in the treatment of hematological malignancies advocate CAR-T cell application for the treatment of solid tumors. In recent years, an increasing number of CAR-T cell clinical trials

RESEARCH ARTICLE

REVISED Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: An observational cohort [version 2; peer review: 2 approved]

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Abstract

Background: Gestational diabetes mellitus (GDM) contributes to maternal and neonatal morbidity. As data from marginalized populations remains scarce, this study compares risk-factor-based to universal GDM screening in a low resource setting.
Methods: This is a secondary analysis of data from a prospective preterm birth cohort. Pregnant women were enrolled in the first trimester and completed a 75g oral glucose tolerance test (OGTT) at 24-32 weeks' gestation. To define GDM cases, Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO trial) criteria were used. All GDM positive cases were treated. Sensitivity and specificity of risk-factor-based selection for screening (criteria: age ≥30y, obesity (Body mass

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Human IRF1 governs macrophagic IFN-γ immunity to mycobacteria

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

Summary

Inborn errors of human IFN-γ-dependent macrophagic immunity underlie mycobacterial diseases, whereas inborn errors of IFN-α/β-dependent intrinsic immunity underlie viral diseases. Both types of IFNs induce the transcription factor IRF1. We describe unrelated children with inherited complete IRF1 deficiency and early-onset, multiple, life-threatening diseases caused by weakly virulent mycobacteria and related intramacrophagic pathogens. These children have no history of severe viral disease, despite exposure to many viruses, including SARS-CoV-2, which is life-threatening in individuals with impaired IFN-α/β immunity. In leukocytes or fibroblasts stimulated *in vitro*, IRF1-dependent responses to IFN-γ are, both quantitatively and qualitatively, much stronger than those to IFN-α/β. Moreover, IRF1-deficient mononuclear phagocytes do not control mycobacteria and related pathogens normally when stimulated with IFN-γ. By contrast, IFN-α/β-dependent intrinsic immunity to nine viruses, including SARS-CoV-2, is almost normal in IRF1-deficient fibroblasts. Human IRF1 is essential for IFN-γ-dependent macrophagic immunity to mycobacteria, but largely redundant for IFN-α/β-dependent antiviral immunity.

Graphical Abstract

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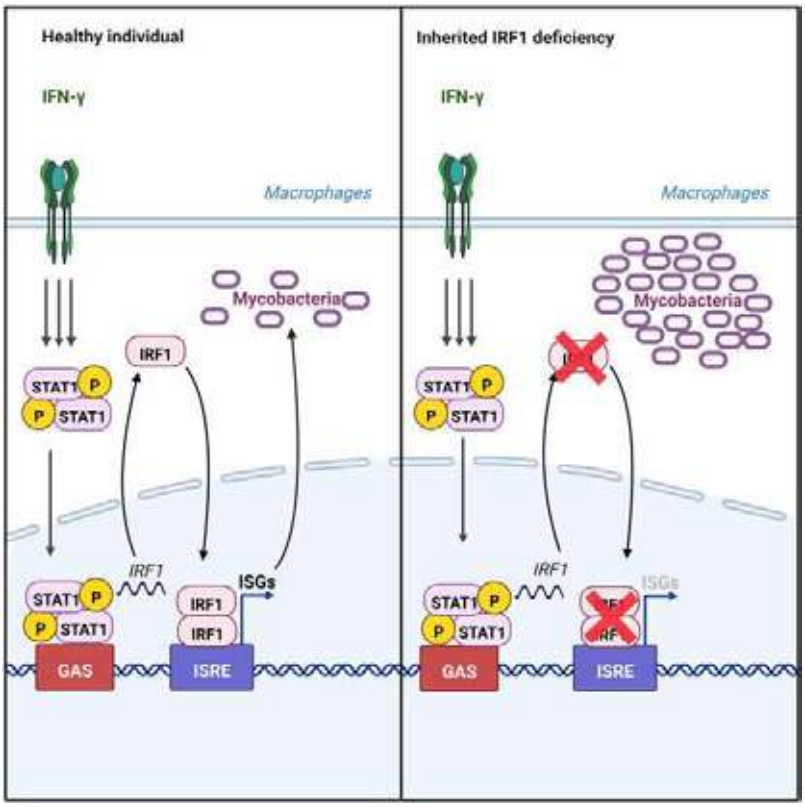
Authors Contributions

J.R., J.Bu., and J.-L.C. conceived the study, designed the experiments, interpreted the data, and drafted the manuscript. J.R., J.Bu., Y.S., and L.A. analyzed WES. J.R., A.-L.N., R.Y., J.L.P., M.B., W.D., M.Ma., D.Le. D.La., J.-M.D, A.G., M.O., P.B., H.M.H., M.M.-V., J.E.H., L.L., H.M.I., Z.L., H.Y.C., S-H.Y., A.C., T.L.V., T.S., Y.K.-D., R.B., J.Bo., Q.P., D.L., J.N.P, S.H., H.M., S.Z., M.Man., C.S., M.Mat., M.P., M.Mi., A.M., C.-O.Q, V.B., S.B-D., J.-F.E., and C.A.C, L.P., J.S., M.Ro., and M.-A.A performed experiments on cells, analyzed them, and generated figures. N.T., O.T., M.B., L.P., M.E.J.P., M.-L.G., and J.Bu. recruited patients. J.M., F.Ra., D.M., and P.Z. analyzed RNA-seq experiments. A-S.L. and F.Ro. performed serological tests for virology. T.K., F.A.A., M.M.A.A, M.Ra., and N.Mar. performed or analyzed PhIP-Seq. K.H., and N.L. provided iPSC cells. D.La., B.C.M., and J.H.F. performed experiments in mice. R.M.B., M.O., and R.L. analyzed data. M.Mi., and S.Ro. provided resources. A.S., S.R., H.F., L.A., S.B.-D., N.Mar., N.Man., M.R.M., N.L., V.B., C.S.M, S.G.T., J.P.D.S., A.N.S., Q.Z., S.Y.Z., J-.F.E., L.K., S.M.L., G.V., C.M.R., J.H.F., D.La., J-.L.C., P.G., and J.Bu. supervised experiments or analyses. All the authors discussed, revised, and approved the manuscript.

Declaration of Interests

J.-L.C. serves on the scientific advisory boards of ADMA Biologics Inc., Kymera Therapeutics, and Elixiron Immunotherapeutics. All other authors declare no competing interests.



In Brief

Studies in humans with interferon regulatory factor 1 (IRF1) deficiency reveal differences in how by type I and type II interferon immune responses protect humans against different types of pathogens.

Keywords

Inborn errors of immunity; *Mycobacterium* ; interferon-γ; interferon-stimulated gene; IRF1; viruses

Introduction

The discovery of inborn errors of immunity (IEI) underlying severe infectious diseases delineates the essential *versus* redundant functions of the corresponding human genes in host defense *in natura*, while clarifying the pathogenesis of these infections[1–3]. Mendelian susceptibility to mycobacterial disease (MSMD) is the most extensively studied monogenic susceptibility to a single type of infection in otherwise healthy individuals with apparently normal resistance to most other infections. Patients with MSMD are selectively vulnerable to weakly virulent mycobacteria — bacillus Calmette-Guérin (BCG) vaccines and environmental mycobacteria (EM) — and, in some cases, *Mycobacterium tuberculosis* and other intramacrophagic microorganisms[4–9]. MSMD is typically “isolated”, but can occasionally be “syndromic”, if associated with at least one other key infectious or non-

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ARTICLE

Human CARMIL2 deficiency underlies a broader immunological and clinical phenotype than CD28 deficiency

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Patients with inherited CARMIL2 or CD28 deficiency have defective T cell CD28 signaling, but their immunological and clinical phenotypes remain largely unknown. We show that only one of three CARMIL2 isoforms is produced and functional across leukocyte subsets. Tested mutant *CARMIL2* alleles from 89 patients and 52 families impair canonical NF-κB but not AP-1 and NFAT activation in T cells stimulated via CD28. Like CD28-deficient patients, CARMIL2-deficient patients display recalcitrant warts and low blood counts of CD4⁺ and CD8⁺ memory T cells and CD4⁺ T_{REG}s. Unlike CD28-deficient patients, they have low counts of NK cells and memory B cells, and their antibody responses are weak. CARMIL2 deficiency is fully penetrant by the age of 10 yr and is characterized by numerous infections, EBV⁺ smooth muscle tumors, and mucocutaneous inflammation, including inflammatory bowel disease. Patients with somatic reversions of a mutant allele in CD4⁺ T cells have milder phenotypes. Our study suggests that CARMIL2 governs immunological pathways beyond CD28.

Introduction

In the two-signal model of T cell activation, the first signal is delivered via the TCR following the recognition of antigenic peptides bound to MHC molecules. The second signal is provided by the CD28 co-stimulator, following its binding to its ligands (CD80 or CD86) on APC. After T cell activation, TCR and CD28 form microclusters that move toward the center of the immune synapse, forming a central supramolecular activation complex. Acting in synergy, the TCR and CD28 trigger the association of the cytosolic adaptor CARD11 with BCL10 and MALT1 to form the CBM (CARD11-BCL10-MALT1) complex, which stimulates NF-κB signaling (Thome et al., 2010; Jiang and Lin, 2012; Wang et al., 2012). In murine T cells, capping protein regulator and myosin 1 linker 2 (CARMIL2), previously known as RLTPR (RGD, leucine-rich repeat [LRR], tropomodulin, and proline-rich-containing protein), has been shown to be an essential scaffolding protein for CD28 costimulation (Liang et al., 2013). CARMIL2 interacts with CARD11 (Roncagalli et al., 2016), and, in T cells expressing a mutated CARMIL2 allele, the accumulation of CARD11 to the central supramolecular activation complex and NF-κB activation are abolished (Liang et al., 2013). In mice, CARMIL2 is also essential for the development of regulatory T cells (T_{REG}s; Liang et al., 2013), and the in vitro differentiation of type 1 helper T cells (T_{H1}) and T_{H17} cells, whereas it is redundant for T_{H2} differentiation (Roncagalli et al., 2016). Despite its expression by murine B cells, CARMIL2 deficiency affects only murine responses to T cell–dependent antigens, with T cell–independent responses remaining intact (Roncagalli et al., 2016). Finally, murine CARMIL2 is expressed in natural killer (NK) cells and plasmacytoid dendritic cells (pDCs), but its function in these cells remains unknown (Roncagalli et al., 2016).

In humans, biallelic *CARMIL2* loss-of-function (LOF) variants cause a combined immunodeficiency, with susceptibility to viral, bacterial, mycobacterial, and fungal infections, immune dysregulation in the gut and skin (Schober et al., 2017; Wang et al., 2016; Magg et al., 2019), and a particular susceptibility to EBV⁺ smooth muscle tumors (EBV⁺ SMTs; Schober et al., 2017; Magg et al., 2018). Affected individuals have abnormally low proportions of memory CD4⁺ T cells, T_{REG}s, and memory B cells (Wang et al., 2016). As in mice, mutant human T cells display impairments of CD28 signaling, T_{H1} and T_{H17} cell differentiation in vitro, an abnormal cytoskeletal organization interfering with T cell polarity and migration, and impaired B cell responses in vivo (Wang et al., 2016; Schober et al., 2017). The recent discovery of individuals with inherited biallelic CD28 deficiency has challenged our understanding of the role of CARMIL2 (Béziat et al., 2021). Studies of human CD28 deficiency have revealed that CD28 signaling is required for immunity to α- and γ-papillomaviruses (HPV) but otherwise largely redundant (Béziat et al., 2021). In turn, this suggested that impaired CD28 activation could account for susceptibility to HPV in CARMIL2-deficient individuals. Conversely, the apparently more severe and broader clinical phenotype of individuals with CARMIL2 deficiency than of those with CD28 deficiency suggests an involvement of CARMIL2 in additional signaling pathways. Consistent with this hypothesis, we previously reported an impairment of NF-κB activation downstream from surface IgM in CARMIL2-deficient B cells (Wang et al., 2016). However, we were unable to rescue any T or B cell phenotype in human cells with a WT copy of the "canonical" isoform of *CARMIL2* (Wang et al., 2016; Schober et al., 2017). Moreover, the clinical phenotypes of CARMIL2 and CD28 deficiencies have been determined from only small numbers of cases. It is, therefore, important to undertake an in-depth characterization of the genetic, immunological, and clinical features of inherited CARMIL2 deficiency, to set the stage for CARMIL2-signaling studies in humans.

Results

Only the *CARMIL2* isoform 3 is expressed in human leukocyte subsets

Two *CARMIL2* transcripts arising from alternative splicing are described as protein-coding in the Ensembl database (Fig. 1 A). The first (ENST00000334583.11; transcript 1) encodes a 1435-amino acid protein with 38 exons (isoform 1). The second (ENST00000545661.5; transcript 2) encodes a 1372-amino acid protein with 38 exons (isoform 2). Transcript 2 has 108 nucleotides fewer than transcript 1 due to the presence of an additional intron within exon 14, and the loss of exon 36, but it retains the same open reading frame. mRNA sequencing in adult T cell leukemia/lymphoma, cutaneous cytotoxic T cell lymphoma, and CD4⁺ primary human T cells has revealed a third transcript (transcript 3) not reported in Ensembl (Park et al., 2017; Uchida et al., 2021), encoding a 1399-amino acid protein with 39 exons (isoform 3). Transcript 3 also lacks part of exon 14, but it retains exon 36. The retention of part of exon 14 in isoform 1 is predicted to result in an additional loop projecting outside

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Human IL-23 is essential for IFN-γ-dependent immunity to mycobacteria

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Abstract

Patients with autosomal recessive (AR) IL-12p40 or IL-12Rβ1 deficiency display Mendelian susceptibility to mycobacterial disease (MSMD) due to impaired IFN-γ production and, less commonly, chronic mucocutaneous candidiasis (CMC) due to impaired IL-17A/F production. We report six patients from four kindreds with AR IL-23R deficiency. These patients are homozygous for one of four different loss-of-function *IL23R* variants. All six patients have a history of MSMD but only two suffered from CMC. We show that IL-23 induces IL-17A only in MAIT cells, possibly contributing to the incomplete penetrance of CMC in patients unresponsive to IL-23. By contrast, IL-23 is required for both baseline and *Mycobacterium*-inducible IFN-γ immunity in both Vδ2$^+$ γδ T and MAIT cells, probably contributing to the higher penetrance of MSMD in these patients. Human IL-23 appears to contribute to IL-17A/F-dependent immunity to *Candida* in a single lymphocyte subset, but is required for IFN-γ-dependent immunity to *Mycobacterium* in at least two lymphocyte subsets.

One-Sentence Summary:

IL-23 signaling is required for baseline and IL-23-inducible IFN-γ immunity in both Vδ2$^+$ γδ T and MAIT cells.

INTRODUCTION

Life-threatening disease during primary infection in otherwise healthy individuals can result from monogenic inborn errors of immunity (IEI) (1, 2). Studies of such IEIs can shed light on the essential and redundant roles of the corresponding human genes in host defense *in natura,* while clarifying mechanisms of disease (3–6). Mendelian susceptibility to

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Conflicts of interest/Competing interests
The authors have no conflict of interest to declare.

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REVIEW ARTICLE

Potential roles of lncRNA-XIST/miRNAs/mRNAs in human cancer cells

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Abstract
Long non-coding RNAs (lncRNAs) are non-coding RNAs that contain more than 200 nucleotides but do not code for proteins. In tumorigenesis, lncRNAs can have both oncogenic and tumor-suppressive properties. X inactive-specific transcript (XIST) is a known lncRNA that has been implicated in X chromosome silencing in female cells. Dysregulation of XIST is associated with an increased risk of various cancers. Therefore, XIST can be a beneficial prognostic biomarker for human malignancies. In this review, we attempt to summarize the emerging roles of XIST in human cancers.

Keywords Cancer · LncRNAs · XIST · Pathogenesis · Tumorigenesis

Introduction

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nt in length with no apparent protein-coding potential [1, 2]. These RNAs are mostly transcribed by the non-coding regions of the human genome such as intergenic, exonic, and tronic regions [1, 3]. Accumulating evidence suggests that lncRNAs are key regulators of the main cellular processes including proliferation, migration, differentiation, invasion, and apoptosis [4]. The lncRNAs function is through regulation of target gene expression at different levels of transcriptional, translational, epigenetic, and chromatin remodeling [5]. Hence, the detection of lncRNAs in body fluids has served them as prognostic and diagnostic biomarkers for monitoring cancer progression and is also considered a therapeutic target for human cancer [6, 7]. X-inactive specific transcript (XIST) as a lncRNA is located on chromosome Xq13.2 and is involved in X chromosome

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Technical assessment of different extraction methods and transcriptome profiling of RNA isolated from small volumes of blood

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Transcriptome profiling of human whole blood is used to discover biomarkers of diseases and to assess phenotypic traits. Recently, finger-stick blood collection systems have allowed a less invasive and quicker collection of peripheral blood. Such non-invasive sampling of small volumes of blood offers practical advantages. The quality of gene expression data is strictly dependent on the steps used for the sample collection, extraction, preparation and sequencing. Here we have: (i) compared the manual and automated RNA extraction of small volumes of blood using the Tempus Spin RNA isolation kit and the MagMAX for Stabilized Blood RNA Isolation kit , respectively; and (ii) assessed the effect of TURBO DNA Free treatment on the transcriptomic data of RNA isolated from small volumes of blood. We have used the QuantSeq 3′ FWD mRNA-Seq Library Prep kit to prepare RNA-seq libraries, which were sequenced on the Illumina NextSeq 500 system. The samples isolated manually displayed a higher variability in the transcriptomic data as compared to the other samples. The TURBO DNA Free treatment affected the RNA samples negatively, decreasing the RNA yield and reducing the quality and reproducibility of the transcriptomic data. We conclude that automated extraction systems should be preferred over manual extraction systems for data consistency, and that the TURBO DNA Free treatment should be avoided when working on RNA samples isolated manually from small volumes of blood.

Transcriptome profiling is a reference research field, and it is applied especially for the study of human diseases[1,2]. The analysis of the human transcriptome allows us to understand the human genome at the gene expression level and also provides a window to understand gene regulation and genome plasticity[2–4]. However, gene expression profiling can only be of value when the RNA under study is representative of the starting material[5]. Unfortunately, several pre-analytical factors affect the RNA yield and quality and might hamper the representativeness of the starting RNA[5], including RNA isolation methods, DNase treatments, library preparation etc. The ex vivo instability of RNA can be reduced if the blood is freshly extracted and processed for RNA isolation immediately. However, this is not a feasible option and, in most cases, blood is collected with variations in timing and storage conditions, which have been proven to affect transcriptomic profiles to some degree[6]. Different RNA stabilizers are employed to overcome the limitation of using fresh blood for RNA isolation[7–9]. Such stabilizer solutions immediately lyse cells chemically and stabilize nucleic acids. Cellular RNases are inactivated, and the RNA is selectively precipitated, leaving proteins and genomic DNA in solution. One of the most common RNA stabilizer solutions is represented by Tempus Blood RNA (Thermo Fisher Scientific, MA, USA). Tempus system uses a solid-phase, silica-based isolation strategy and its performance has been proven higher than other systems[10]. Yet, Tempus Blood RNA utility is limited by the requirement of a venous blood samples of at least 3.0 ml. Recently,

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finger-stick blood collection systems have made it possible to collect peripheral blood without the need of medical infrastructures, offering practical and logistic advantages[11]. Nevertheless, technical improvements are required to make the gene expression profiling of small volumes of blood a reliable and reproducible technique[12]. Automated workflows offer several advantages for large-scale projects, as they increase sample throughput and reduce cost and manual errors[13–16]. The MagMAX for Stabilized Blood RNA Isolation kit (Thermo Fisher Scientific, MA, USA) employs a magnetic bead-based technology to purify RNA from blood stored in Tempus solution. Because of its bead-based approach, it can easily be implemented on automated systems. The MagMax workflow includes a TURBO DNase step that removes contaminating DNA and can also be implemented in automation systems, such as the KingFisher Magnetic Particle Processors (Thermo Fisher Scientific, MA, USA). However, there currently exist many liquid-handling workstations on the market, each one of them offers different degrees of flexibility. Hamilton Robotics (Hamilton, NV, USA), for instance, offers autonomous programming[15]. In this study the Hamilton NGS Star platform has been employed for automated RNA extraction.

Here, we have compared the manual RNA isolation of small volumes of blood (Tempus Blood RNA kit) and an automated workflow implemented in-house by using the MagMAX for Stabilized Blood RNA Isolation kit on the Hamilton NGS Star platform (Hamilton, NV, USA); we have also evaluated the effect of the TURBO DNA Free treatment (Thermo Fisher Scientific, MA, USA) on the reproducibility and reliability of the transcriptomic data. Transcriptome sequencing was performed by using the Lexogen QuantSeq 3′ mRNA-Seq Library Prep FWD kit (Lexogen GmbH, Austria) with unique molecular identifiers (UMI), because of its streamlined protocol and its relatively lower cost as compared to other systems.

Here we demonstrate that the automated extraction workflow produces more consistent data as compared to the manual extraction method and that the TURBO DNA Free treatment should be avoided when working on RNA isolated manually from small volumes of blood.

Methods

RNA isolation. Whole blood was collected from healthy donors as previously described[11]. Ethical approvals were collected from Sidra Institutional Review Board committee (IRB Protocol #1707011887). An informed consent was obtained from the study subjects and all methods were performed in accordance with the relevant guidelines and regulations. Different conditions were tested for each healthy donor recruited, as shown in Fig. 1. For the manual process, the Tempus Spin RNA Isolation kit was used to isolate and purify RNA from blood collected in the capillary tubes according to the manufacturer's instructions and adjusting the reagents volumes to maintain the working ratios required by the protocol. For the automated process, the MagMAX for Stabilized Blood RNA Isolation kit was used on the Hamilton NGS Star platform using a protocol developed in-house. The protocol developed in house includes some initial manual steps. Figure 2 summarizes the manual and automated steps of the protocol developed in-house with the MagMAX for Stabilized Blood RNA Isolation kit . Supplementary Fig. 1 displays the deck layout of the Hamilton NGS STAR. The MagMAX for Stabilized Blood RNA Isolation kit uses a magnetic bead-based technology and includes a DNase treatment step (TURBO DNA Free treatment). After extraction, RNA was quantified on the NanoDrop 8000 Spectrophotometer (Thermo Fisher Scientific, MA, USA) to evaluate the concentration and purity. The amount of RNA present in each sample was then detected on the Qubit 2.0 Fluorometer (Thermo Fisher Scientific, MA, USA) using the Qubit RNA HS Assay kit (Thermo Fisher Scientific, MA, USA). The RNA profile and integrity of all samples was assessed using

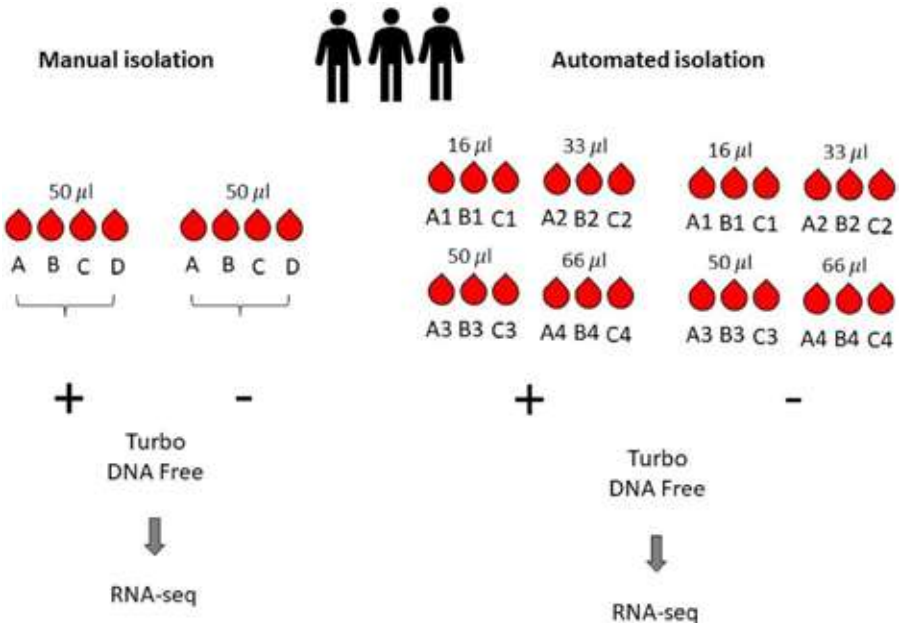

Figure 1. Outline of the RNA samples isolated in this study for the manual and automated workflows.

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The link between glycemic control measures and eye microvascular complications in a clinical cohort of type 2 diabetes with microRNA-223-3p signature

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Abstract

Background Type 2 diabetes (T2D) is a critical healthcare challenge and priority in Qatar which is listed amongst the top 10 countries in the world, with its prevalence presently at 17% double the global average. MicroRNAs (miRNAs) are implicated in the pathogenesis of (T2D) and long-term microvascular complications including diabetic retinopathy (DR).

Methods In this study, a T2D cohort that accurately matches the characteristics of the general population was employed to find microRNA (miRNA) signatures that are correlated with glycemic and β cell function measurements. Targeted miRNA profiling was performed in (471) T2D individuals with or without DR and (491) (non-diabetic) healthy controls from the Qatar Biobank. Discovery analysis identified 20 differentially expressed miRNAs in T2D compared to controls, of which miR-223-3p was significantly upregulated (fold change:5.16, p = 3.6e−02) and positively correlated with glucose and hemoglobin A1c (HbA1c) levels (p-value = 9.88e−04 and 1.64e−05, respectively), but did not show any significant associations with insulin or C-peptide. Accordingly, we performed functional validation using a miR-223-3p mimic (overexpression) under control and hyperglycemia-induced conditions in a zebrafish model.

Results Over-expression of miR-223-3p alone was associated with significantly higher glucose (42.7 mg/dL, n = 75 vs 38.7 mg/dL, n = 75, p = 0.02) and degenerated retinal vasculature, and altered retinal morphology involving changes in the ganglion cell layer and inner and outer nuclear layers. Assessment of retinal angiogenesis revealed significant upregulation in the expression of vascular endothelial growth factor and its receptors, including kinase insert domain receptor. Further, the pancreatic markers, pancreatic and duodenal homeobox 1, and the insulin gene expressions were upregulated in the miR-223-3p group.

Conclusion Our zebrafish model validates a novel correlation between miR-223-3p and DR development. Targeting miR-223-3p in T2D patients may serve as a promising therapeutic strategy to control DR in at-risk individuals.

†Equally contributed, co-first authors can prioritize their names when citing this paper's reference in their communication or resumes.

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Role of E2F transcription factor in oral cancer: Recent insight and advancements

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ABSTRACT

The family of mammalian E2F transcription factors (E2Fs) comprise of 8 members (E2F1-E2F8) classified as activators (E2F1-E2F3) and repressors (E2F4-E2F8) primarily regulating the expression of several genes related to cell proliferation, apoptosis and differentiation, mainly in a cell cycle-dependent manner. E2F activity is frequently controlled via the retinoblastoma protein (pRb), cyclins, p53 and the ubiquitin-proteasome pathway. Additionally, genetic or epigenetic changes result in the deregulation of E2F family genes expression altering S phase entry and apoptosis, an important hallmark for the onset and development of cancer. Although studies reveal E2Fs to be involved in several human malignancies, the mechanisms underlying the role of E2Fs in oral cancer lies nascent and needs further investigations. This review focuses on the role of E2Fs in oral cancer and the etiological factors regulating E2Fs activity, which in turn transcriptionally control the expression of their target genes, thus contributing to cell proliferation, metastasis, and drug/therapy resistance. Further, we will discuss therapeutic strategies for E2Fs, which may prevent oral tumor growth, metastasis, and drug resistance.

Abbreviations: Akt, RAC (Rho family)-alpha serine/threonine-protein kinase; AP-1, Activator protein 1; APAF1, Apoptotic protease activating factor 1; APC/C, Anaphase-promoting complex; AS1, Antisense RNA 1; ASK1, Apoptosis signal-regulating kinase 1; ATM, Ataxia Telangiectasia Mutated; BCL, B-cell CLL/lymphoma; BMP2, Bone morphogenetic protein 2; BRCA, Breast cancer gene; BZLF1, BamHI Z fragment leftward open reading frame 1; CCNA/CCNE, Cyclin; CCND1, Cyclin D1; CCNF, F box protein cyclin F; Cdc, Cell division control protein; CDH1, Cadherin 1; CDK, Cyclin dependent kinase; CENPM, Centromere Protein M ChIP, Chromatin immunoprecipitation; CHK, Checkpoint kinase; CKS, Cyclin Dependent Kinase Regulatory Subunit; c-Myc, cellular Myelocytomatosis; DDR1, Discoidin domain receptor 1; DNA, Deoxyribonucleic acid; DP, Dimerization partner; E2F, Adenoviral early region 2 binding factor; EBNA, Epstein-Barr virus latent antigen; EBV, Epstein-Barr virus; FOXC2, Forkhead box protein C2; HIF, Hypoxia inducible factor; HN1, Hematopoietic and neurologic expressed 1; HNSCC, Head and neck squamous cell carcinoma; HOXB7, Homeobox 7; HPV, Human papillomavirus; HSV, Herpes simplex virus; IL, Interleukin; KIF4A, Kinesin family member 4A; LMP, Latent membrane protein; lncRNAs, long non-coding RNAs; lncPCAT1, Prostate cancer-associated ncRNA transcript-1; LZ, Leuzine zipper; MAP3K5, Mitogen-Activated Protein Kinase Kinase Kinase 5; MB, Marked box; miR/miRNA, Micro ribonucleic acid; MLH, MutL homolog; MSH, MutS homolog; mTOR, Mammalian target of Rapamycin; NF-κB, Nuclear factor-kappa B; NSD2, Nuclear receptor binding SET domain protein 2; OPSCC, Oropharyngeal squamous cell carcinoma; OSCC, Oral squamous cell carcinoma; PI3K, Phosphatidylinositol 3-kinase; PIKK, Phosphoinositide-3 kinase like kinase; PPARγ, Peroxisome proliferator-activated receptor-γ; pRb, Retinoblastoma protein; RAN, Raw areca nut; RPA, Replication protein A; SASP, Senescence associated secretory phenotype; SCC, Squamous cell carcinoma; SCCOC, Squamous cell carcinoma of oral cavity; SCCOP, Squamous cell carcinoma of the oropharynx; SNAIL, Zinc finger protein SNAI1; SNHG12, Small nucleolar RNA host gene 12; SNP, Single nucleotide polymorphism; SOX2, SRY (sex determining region Y)-box 2; SSCRP1, Structure specific recognition protein 1; STAT, Signal transducer and activators of transcription; TCGA, The Cancer Genome Atlas; TEAD4, TEA Domain Transcription Factor 4; TGB, Target gene bias; TGF-β:, Transforming growth factor-β; TP53, Tumor protein 53; TP73, Tumor protein 73; TSCC, Tongue squamous cell carcinoma; UHRF1, Ubiquitin-like with PHD and ring finger domains 1; UTR, Untranslated region; VEGFA, Vascular endothelial growth factor A; Wnt, Wingless; YBX2, Y-box binding protein 2; ZNF750, Zinc-finger protein 750.

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1. Introduction

Oral cancer comprises 95% of all head and neck cancers that arise in the oral mucosa and encompasses cancers of lip and all sub-sites of the oral cavity and oropharynx [1]. It is the sixth most common cancer worldwide with 90% of the cases being histologically squamous cell carcinoma (SCC) [2,3]. Etiologically, oral cancer is multifactorial and its most common predisposing risk factors include: tobacco, excess alcohol consumption, poor oral hygiene, premalignant conditions, exposure to UV radiations as well as the oral microbiome and exposure to viral infections; as in human papillomavirus (HPV) and Epstein-Barr virus (EBV) [4,5], as shown in Fig. 1. In addition, like most cancers, oral cancer is associated with old age, as cancer cases escalate exponentially over the age of 40, particularly epithelial carcinomas [6]. Nevertheless, although this association has been firmly established [6,7]; therapeutic avenues are yet to respond to this association with clear targeted therapeutic strategies that take into consideration the phenotypic changes associated with the aging milieu.

Oral cancers progress chronologically from hyperplasia to dysplasia and finally carcinoma [8]. At the point of their presentation, they are considered a highly aggressive disease, since in the majority of cases, patients are diagnosed with advanced stages (III-IV) coupled with metastasis to distant organs [9,10]. Prognostic tools include age, presence of lymph node metastasis, primary tumor size and location [11]. Today, the 5-year survival rate of oral cancers is 50% with a significant favorable outcome in women, which necessitates the development of novel therapeutic targets [12]. From a therapeutic standpoint, oral cancers are divided into HPV positive (HPV+) and negative (HPV-) cases, with HPV+ ones being generally more responsive to treatment [13]. Interestingly, when it comes to their molecular pathways, both HPV+ and HPV- cases effect the E2F family of transcription factors albeit via different upstream factors [13]. Therefore, novel targeted approaches are gaining popularity by targeting various specific molecular pathways [14–16], as shown in Fig. 1. In this regard, transcription factors are considered as one of the most favorable therapeutic targets in the management of human cancers, including oral. However, given the crucial role that some of these factors play in normal cellular development, a clear understanding of the effect of different upstream signaling

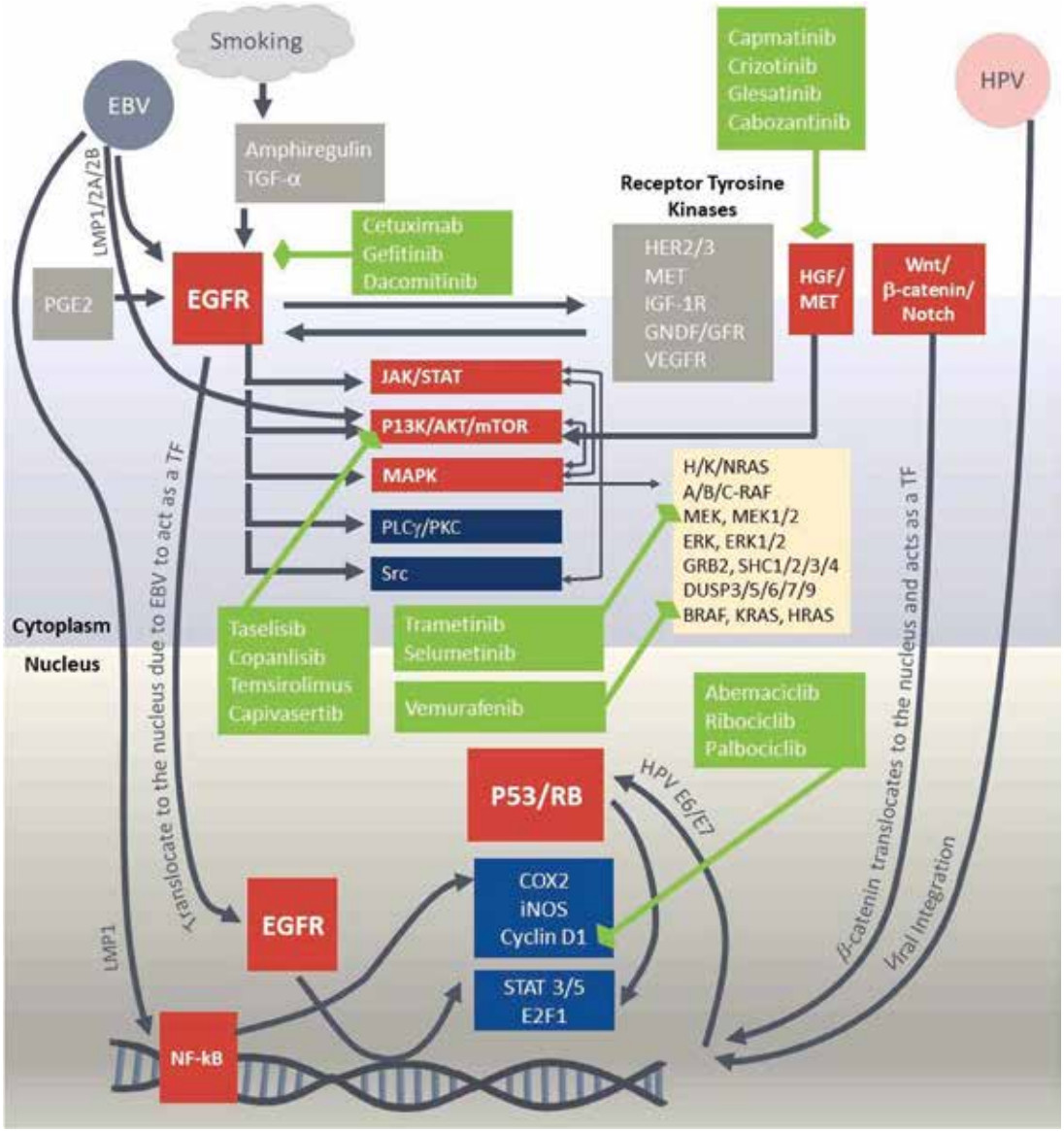

Fig. 1. Major oral cancer signaling pathways (in red), and their downstream targets. Major established therapeutic avenues against oral cancer (in green) and their molecular target.

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Bell Palsy: Facts and Current Research Perspectives

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Abstract

Bell palsy is a non-progressive neurological condition characterized by the acute onset of ipsilateral seventh cranial nerve paralysis. People who suffer from this type of facial paralysis develop a droop on one side of their face, or sometimes both. This condition is distinguished by a sudden onset of facial paralysis accompanied by clinical features such as mild fever, postauricular pain, dysgeusia, hyperacusis, facial changes, and drooling or dry eyes. Epidemiological evidence suggests that 15 to 23 people per 100,000 are affected each year, with a recurrence rate of 12%. It could be caused by ischaemic compression of the seventh cranial nerve, which could be caused by viral inflammation. Pregnant women, people with diabetes, and people with respiratory infections are more likely to have facial paralysis than the general population. Immune, viral, and ischemic pathways are all thought to play a role in the development of Bell paralysis, but the exact cause is unknown. However, there is evidence that Bell's hereditary proclivity to cause paralysis is a public health issue that has a greater impact on patients and their families. Delay or untreated Bell paralysis may contribute to an increased risk of facial impairment, as well as a negative impact on the patient's quality of life. For management, antiviral agents such as acyclovir and valacyclovir, and steroid treatment are recommended. Thus, early diagnosis accompanied by treatment of the uncertain etiology of the disorder is crucial. This paper reviews mechanistic approaches, and emerging medical perspectives on recent developments that encounter Bell palsy disorder.

Keywords: Bell palsy; cranial nerve; current research perspectives; epidemiology; ipsilateral paralysis; management of bell palsy.

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A GHRHR founder mutation causes isolated growth hormone deficiency type IV in a consanguineous Pakistani family

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Background: Isolated growth hormone deficiency (IGHD) is caused by a severe shortage or absence of growth hormone (GH), which results in aberrant growth and development. Patients with IGHD type IV (IGHD4) have a short stature, reduced serum GH levels, and delayed bone age.

Objectives: To identify the causative mutation of IGHD in a consanguineous family comprising four affected patients with IGHD4 (MIM#618157) and explore its functional impact *in silico*.

Methods: Clinical and radiological studies were performed to determine the phenotypic spectrum and hormonal profile of the disease, while whole-exome sequencing (WES) and Sanger sequencing were performed to identify the disease-causing mutation. *In-silico* studies involved protein structural modeling and docking, and molecular dynamic simulation analyses using computational tools. Finally, data from the Qatar Genome Program (QGP) were screened for the presence of the founder variant in the Qatari population.

Results: All affected individuals presented with a short stature without gross skeletal anomalies and significantly reduced serum GH levels. Genetic mapping revealed a homozygous nonsense mutation [NM_000823:c.G214T:p.(Glu72*)] in the third exon of the growth-hormone-releasing hormone receptor gene *GHRHR* (MIM#139191) that was segregated in all patients. The substituted amber codon (UAG) seems to truncate the protein by deleting the C-terminus GPCR domain, thus markedly disturbing the GHRHR receptor and its interaction with the growth hormone-releasing hormone.

Conclusion: These data support that a p.Glu72* founder mutation in *GHRHR* perturbs growth hormone signaling and causes IGHD type IV. *In-silico* and biochemical analyses support the pathogenic effect of this nonsense mutation, while our comprehensive phenotype and hormonal profiling has established the

genotype–phenotype correlation. Based on the current study, early detection of *GHRHR* may help in better therapeutic intervention.

KEYWORDS

isolated growth hormone deficiency (IGHD4), Pakistani family, whole-exome sequencing, GHRHR, modeling, docking and simulation

Introduction

Isolated growth hormone deficiency (IGHD) is a condition characterized by growth retardation and development failure in affected children as a result of reduced growth hormone (GH) levels. It is estimated that between 1:3,480 and 1:10,000 live births are affected by IGHD (1–4). There are four IGHD types, IGHD I–IV, differentiated by their clinical spectrum, inheritance pattern, and associated genetic factors. Two IGHD I subtypes, IGHD IA (MIM# 262400) and IGHD 1B (MIM# 612781), are caused by *GH1* (MIM# 139250) and *GHRHR* (MIM# 139191) gene defects, respectively. In addition, a mutation at 17q23.3 on *GH1* underlies both IGHD 1B (MIM# 617281) and IGHD II (MIM# 173100). IGHD III (MIM# 307200) is caused by a genetic defect in *BTK* (MIM# 300300) located on Xq22, and IGHD IV (MIM# 618157) is caused by a genetic defect in *GHRHR* (MIM# 139191) located on 7p14.3. IGHD IA and IV occur most frequently, while types II and III are rare (OMIM database, accessed on 20 August 2022).

Both IGHD types IA and IB are autosomal recessive conditions characterized by short stature. In type IA, there is an absence of serum GH, and those affected produce anti-GH antibodies after GH treatment (5, 6). In type IB, there are low (but detectable) serum GH levels and no evidence of antibody production after GH treatment (7). IGHD type II, however, is an autosomal dominant condition; as with type IB, low serum GH levels are detectable and no anti-GH antibodies are produced upon GH treatment (8). IGHD type III usually segregates in an X-linked manner and is often associated with agammaglobulinemia (9). IGHD type IV is a recessive condition characterized by early and severe growth failure. Those affected exhibit a reduced GH response to various provocation tests (e.g., tests for determining growth hormone level) and low insulin-like growth factor-I (IGF1) and IGF-binding protein-3 (IGFBP3) levels, but a good response to GH treatment. At the cellular level, we know that human GH binds to human growth receptor (GHR) molecules and induces signal transduction through receptor dimerization (10). When GHRH interacts with its corresponding transmembrane domains on somatotropic (GH-producing) cells, a G protein-mediated interaction with ion channels causes an increase in intracellular cAMP accumulation, which ultimately promotes GH release from secretory granules (10–12). Indeed, elevated cAMP causes protein kinase A to phosphorylate and activate CREB (13, 14), whose target genes include the pituitary-specific transcription factor *Pit-1* (also known as *GHF-1*) (15–17). Pit-1 is a prototypic POU domain protein that is required for the proper regulation of *GH* gene activity in somatotropic cells, thereby providing a pathway by which a GHRH signal can lead to increased pituitary GH synthesis. Somatostatin, an inhibitory peptide, is thought to interact with this same signaling pathway *via* G protein-mediated suppression of the cAMP pathway (18, 19). Indeed, the malfunctioning or underexpression of endogenous CREB protein in pituitary somatotropic cells causes somatotroph hypoplasia and dwarfism in mice (20). It is now clear that any disruption to this multistep GH signaling pathway can result in GH deficiency and ultimately lead to short stature and various other clinical problems.

Here, we analyzed a Pakistani family comprising four affected individuals with IGHD4. Whole-exome sequencing in this family revealed a nonsense mutation NM_000823:c.G214T:p.Glu72* in the third exon of *GHRHR*. The identified mutation presumably creates a premature terminator codon in the extracellular domain of the GHRHR and results in the synthesis of a truncated and non-functional receptor. *In-silico* findings and biochemical analysis support the pathogenic effect of the reported nonsense mutation.

Methods

Study design, declarations, and approvals

This study was approved by the Ethical Review Board of Gomal University, Dera Ismail Khan, Pakistan. Informed consent to perform genetic, molecular, and clinical analyses and to publish patient data and images was obtained from all study participants. The family was identified in Tehsil Paroa of District Dera Ismail Khan, Pakistan, through a local street-to-street survey. The genealogy was ascertained to assess the mode of disease inheritance and determine the level of consanguinity between the parents. Then, the blood samples were collected, and DNA was isolated using a GeneJET Genomic DNA purification kit (Thermo Fisher Scientific, USA, Cat# K0721), according to the manufacturer's instructions.

Whole-exome sequencing and data analysis

All the patients (V-4, V-10, V-11, V-12) were siblings and exhibited the same phenotype (Table 1). Therefore, due to the high probability of harboring common genetic variants, WES was performed on two randomly selected patients (V-4 and V-10). A sequencing library was constructed using an xGen Exome Research Panel v2.0 Kit (Integrated DNA Technologies, Coralville, IA, USA) and sequenced on a NovaSeq 6000 (Illumina, San Diego, CA, USA).

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Treatment with decitabine induces the expression of stemness markers, PD-L1 and NY-ESO-1 in colorectal cancer: potential for combined chemoimmunotherapy

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Abstract

Background The mechanism of tumor immune escape and progression in colorectal cancer (CRC) is widely investigated *in-vitro* to help understand and identify agents that might play a crucial role in response to treatment and improve the overall survival of CRC patients. Several mechanisms of immune escape and tumor progression, including expression of stemness markers, inactivation of immunoregulatory genes by methylation, and epigenetic silencing, have been reported in CRC, indicating the potential of demethylating agents as anti-cancer drugs. Of these, a chemotherapeutic demethylating agent, Decitabine (DAC), has been reported to induce a dual effect on both DNA demethylation and histone changes leading to an increased expression of target biomarkers, thus making it an attractive anti-tumorigenic drug.

Methods We compared the effect of DAC in primary 1076 Col and metastatic 1872 Col cell lines isolated and generated from patients' tumor tissues. Both cell lines were treated with DAC, and the expression of the NY-ESO-1 cancer-testis antigen, the PD-L1 immunoinhibitory marker, and the CD44, Nanog, KLF-4, CD133, MSI-1 stemness markers were analyzed using different molecular and immunological assays.

Results DAC treatment significantly upregulated stemness markers in both primary 1076 Col and meta-static 1872 Col cell lines, although a lower effect occurred on the latter: CD44 (7.85 fold; ***$p = 0.0001$ vs. (4.19 fold; *$p = 0.0120$), Nanog (4.1 fold; ***$p < 0.0001$ vs.1.69 fold; ***$p = 0.0008$), KLF-4 (4.33 fold; ***$p < 0.0001$ vs.2.48 fold; ***$p = 0.0005$), CD133 (16.77 fold; ***$p = 0.0003$ vs.6.36 fold; *$p = 0.0166$), and MSI-1 (2.33 fold; ***$p = 0.0003$ vs.2.3 fold; ***$p = 0.0004$), respectively. Interestingly, in the metastatic 1872 Col cells treated with DAC, the expression of both PD-L1 and NY-ESO-1 was increased tenfold (*$p = 0.0128$) and fivefold (***$p < 0.0001$), respectively.

Conclusions We conclude that the upregulation of both stemness and immune checkpoint markers by DAC treatment on CRC cells might represent a mechanism of immune evasion. In addition, induction of NY-ESO-1 may

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Original Research

Performance Evaluation of a New Fluorescent-Based Lateral Flow Immunoassay for Quantification of Hemoglobin A1c (HBA1c) in Diabetic Patients

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Abstract

Background: Rapid hemoglobin A1C (HbA1c) level monitoring is essential in slowing the progression of diabetes. This need becomes challenging in low resources countries where the social burden of the disease is overwhelming. Recently, fluorescent-based lateral flow immunoassays (LFIAs) gained wide attention for small laboratories and population surveillance. **Aim**: We aim to evaluate the performance of Finecare™ HbA1c Rapid Test, certified by CE, NGSP, and IFCC, for the quantitative measurement of hemoglobin A1C (HbA1c) along with its reader. **Methods**: A total of 100 (fingerstick and venepuncture whole blood) samples were analyzed by Wondfo Finecare™ HbA1c Rapid Quantitative Test and the results were compared with the reference assay Cobas Pro c503. **Results**: A strong correlation was observed between Finecare™/Cobas Pro c503 with fingerstick ($r > 0.93$, $p < 0.0001$) and venous ($r > 0.97$, $p < 0.0001$) blood samples. Finecare™ measurements showed excellent agreement and compliance with Roche Cobas Pro c503 as the mean bias was negligible; 0.05 (Limits-of-agreement: –0.58–0.68) with fingerstick and 0.003 (Limits-of-agreement: –0.49–0.50) with venous blood. Interestingly, a very small mean bias (0.047) was also shown between the fingerstick and the venepuncture data, indicating that the type of sample used does not affect the results and the high reproducibility of the assay. Finecare™ showed 92.0% (95% CI: 74.0–99.0) sensitivity and 94.7% (95% CI: 86.9–98.5) specificity compared to the Roche Cobas Pro c503 using fingerstick whole blood samples. Finecare™ showed 100% (95% CI: 86.3–100) sensitivity and 98.7% (95% CI: 92.8–100) specificity compared to the Cobas Pro c503 using venepuncture samples. Cohen's Kappa denoted excellent agreement with Cobas Pro c503; 0.84 (95% CI: 0.72–0.97) and 0.97 (95% CI: 0.92–1.00) using fingerstick and venous blood samples, respectively. Most importantly, Finecare™ showed a significant difference between normal, pre-diabetic, and diabetic samples ($p < 0.0001$). Similar results were obtained when an additional 47 samples (from different participants; mainly diabetic) were analyzed in a different lab using different Finecare™ analyzer and different kit lot number. **Conclusions**: Finecare™ is a reliable and rapid assay (5 min) which can be easily implemented for long-term monitoring of HbA1c in diabetic patients, particularly in small laboratory settings.

Keywords: serology; lateral flow immunoassay; LFIA; HbA1c; diabetes

1. Introduction

The prevalence of diabetes mellitus is significantly expanding at an alarming pace all over the globe. The worldwide burden of diabetes mellitus (DM) has increased from 30 million in 1985 to 382 million in 2014, and current trends indicate that these rates will continue to expand [1]. According to the most recent projections reported by the International Diabetes Federation (IDF), the number of people living with diabetes mellitus will rise to 643 million by 2030 [2].

Glycated hemoglobin (HbA1c) serves as a reliable indicator of glycemic status in diabetic patients over a period of two to three months [3]. HbA1c is produced once hemoglobin is chemically linked to glucose [3]. Tradi-

tionally, high plasma glucose levels were used for DM diagnosis. Plasma glucose level is typically measured after fasting or two hours after an oral glucose (75 g) tolerance test in symptomatic patients [4]. Recently, the American Diabetes Association and the World Health Organisation (WHO) recommended the use of HbA1c (≥6.5%) for DM diagnosis [5]. This was based on the fact that HbA1c can predict clinical outcomes of the disease. In this context, many studies showed that HbA1c strongly correlates with chronic microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy [6,7]. Most importantly, HbA1c levels have also been proven to be helpful in algorithms for calculating cardiovascular risk (CVD), along with gender, age, blood pressure, smoking status, and cholesterol [8–10], and thus may be a relevant biomarker to be considered in CVD prevention strategies [11]. HbA1c testing offers significant practical advantages while typically being more expensive than blood glucose testing, with an average net cost of 13.6 times that of a plasma glucose measurement [12]. HbA1c testing may be done at any time of day and does not need any specific pre-test preparation by the patient (such as overnight fasting) [12,13]. Therefore, monitoring HbA1c levels in diabetic patients in a timely and consistent manner helps in slowing the progression of the disease. However, this need becomes challenging in settings with low resources and an absence of laboratory infrastructure, which are also places where the societal impact of the illness is often overwhelming [14]. The current laboratory diagnostic techniques for HbA1c, such as cation-exchange HPLC, capillary electrophoresis, and affinity chromatography, involve expensive instruments, are laborious, and require a longer turnaround time [15].

Lateral flow immunoassays (LFIAs) are attractive for small or point-of-care (POC) settings and population surveillance. They are rapid, inexpensive, simple to use, most importantly, rely on easily accessible samples such as whole blood from a fingerstick [16,17]. Finecare™ HbA1c Rapid Quantitative Test is a fluorescence immunoassay for the quantitative determination of HbA1c in human blood (venepuncture or fingerstick). In this study, we aimed to evaluate the performance of Finecare™ HbA1c Rapid Quantitative Test by using samples obtained by fingerstick and venepuncture. In addition, to compare the performance of Finecare™ HbA1c Rapid Quantitative Test with the reference technique, Cobas Pro c503 clinical chemistry analyzer from Roche Diagnostics.

2. Materials and Methods

2.1 Sample Collection and Ethical Approval

In collaboration with the Ministry of Health (MOH) in Jordan, Wondfo Biotech (Guangzhou, China) conducted two validation studies on Finecare™ HbA1c Rapid Quantitative Test; one was performed in a private referral laboratory (n = 100 samples) and the other was performed in a public health laboratory that belongs to the MOH (n = 47 samples), and the other was performed in a private referral laboratory (n = 100 samples). HbA1c was measured from collected fingerstick and matched venous blood samples for a total of 147 participants from both laboratories. Testing results were provided to our lab for analysis, and that data was unaccompanied by any patient identifications or private information other than the primary demographic data, including age and gender. Accordingly, an Ethical approval exemption (QU-IRB 1766-E/22) was granted by Qatar University.

2.2 Wondfo Finecare™ HbA1c Rapid Quantitative Test

Finecare™ HbA1c Rapid Quantitative Test is based on fluorescence immunoassay technology and measures the level of HbA1c in human blood using a sandwich immunodetection approach. According to the manufacturer's test leaflets and flyer, the Fincare™ HbA1c POC test, according to the manufacturer's test leaflets and flyer, is traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method for measuring HbA1c and is certified by the National Glycohemoglobin Standardization Program (NGSP) as having documented traceability to the Diabetes Control and Complications Trial (DCCT) reference method [18,19]. The NGSP awards certification to manufacturers for successfully meeting specific performance criteria [20]. The test was carried out according to the manufacturer instructions. The LFA reaction time is 5 min, and the measuring range is 4.0–14.5%

2.3 Roche Cobas Pro c503 Reference Method

The Tina-quant Hemoglobin A1cDx assay is intended to diagnose diabetic patients. It is *in vitro* diagnostics assay to quantify hemoglobin A1c (mmol/mol) and % hemoglobin A1c in whole venous blood on the cobas pro c503 clinical chemistry analyzers. This approach is based on the turbidimetric inhibition immunoassay of blood samples that have been hemolyzed. The anti-HbA1c antibody forms a soluble complex with a single binding site on HbA1c. Polyhaptens react with excess anti-HbA1c antibodies to generate an insoluble compound, which is evaluated by turbidimetry. The measuring range is 4.0–14.5%.

2.4 Statistical Method

Finecare™ and the reference technique, Cobas Pro c503, were compared using correlation and linear regression analysis. Because our data was not normally distributed, we estimated the spearman correlation coefficient (r), with r values of 0–0.39 indicating a weak correlation, 0.40–0.59 indicating a moderate connection, 0.6–0.77 indicating a high correlation, and 0.8–1 indicating a very strong correlation [21]. In addition, we assessed the area under the curve (AUC) of the Receiver-Operating Characteristic (ROC) curve, which measures the accuracy of a quantitative diagnostic test [22]. An AUC of 0.9–1.0 is denoted as excellent, 0.8–0.9 is denoted as very good, 0.7–0.8 is denoted

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Abundance of *ACVR1B* transcript is elevated during septic conditions: Perspectives obtained from a hands-on reductionist investigation

Anucha Preechanukul[1], Thatcha Yimthin[1], Sarunporn Tandhavanant[1], Tobias Brummaier[2,3], Chalita Chomkatekaew[4], Sukanta Das[4,5], Basirudeen Syed Ahamed Kabeer[6], Mohammed Toufiq[6], Darawan Rinchai[6], T. Eoin West[1,7,8], Damien Chaussabel[6], Narisara Chantratita[1,4]* and Mathieu Garand[6,9]*

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Sepsis is a complex heterogeneous condition, and the current lack of effective risk and outcome predictors hinders the improvement of its management. Using a reductionist approach leveraging publicly available transcriptomic data, we describe a knowledge gap for the role of ACVR1B (activin A receptor type 1B) in sepsis. ACVR1B, a member of the transforming growth factor-beta (TGF-beta) superfamily, was selected based on the following: 1) induction upon *in vitro* exposure of neutrophils from healthy subjects with the serum of septic patients (GSE49755), and 2) absence or minimal overlap between ACVR1B, sepsis, inflammation, or neutrophil in published literature. Moreover, *ACVR1B* expression is upregulated in septic melioidosis, a widespread cause of fatal sepsis in the tropics. Key biological concepts extracted from a series of PubMed queries established indirect links between ACVR1B and "cancer", "TGF-beta superfamily", "cell proliferation", "inhibitors of activin", and "apoptosis". We confirmed our observations by measuring ACVR1B transcript abundance in buffy coat samples obtained from healthy individuals (n=3) exposed to septic plasma (n = 26 melioidosis sepsis cases) *ex vivo*. Based on our re-investigation of publicly available transcriptomic data and newly generated *ex vivo* data, we provide perspective on the role of ACVR1B during sepsis. Additional experiments for addressing this knowledge gap are discussed.

KEYWORDS

activin A, sepsis, melioidosis, innate immunity, blood transcriptomics

Introduction

Sepsis is a heterogeneous syndrome that arises from a dysregulated host inflammatory response to an infection (1–3). The response is accompanied by activation of vascular endothelial cells, neutrophils and platelets which together can contribute to collateral tissue damage in the vasculature. Inflammation worsen with the influx of neutrophils to the site of infection. Subsequent clearance of infected neutrophils are part of the way to the resolution of inflammation (4, 5). Clinical biomarkers of sepsis have been assessed (reviewed in (6)). Some, like C-reactive protein and procalcitonin, are routinely used in clinical practice but have significant limitations. The lack of clinical biomarkers for risk and outcome prediction hinders the improvement of sepsis management. As early detection and treatment of sepsis are key to favorable outcomes, predictive markers (e.g., gene expression signatures) are needed (7).

In tropical countries, melioidosis is a common cause of community-acquired infection and associated with high mortality. Melioidosis is caused by the environmental bacterium, *Burkholderia pseudomallei* via ingestion, inhalation or inoculation. The global incidence of melioidosis is estimated to be 165,000 cases with a mortality rate of approximately 89,000 cases per year (8). To improve the outcome of melioidosis patients, there is a need to understand the immunopathogenesis of severe sepsis from melioidosis.

The ACVR1B gene (*ACVR1B*) encodes the activin A receptor type 1B. Activins are a pluripotent growth and differentiation factors, believed to be involved in numerous processes such as male germ cell development (9), follicle development (10), stem cell differentiation (11) as well as immune response (12). Activin isoforms are dimeric protein complexes and belong to the transforming growth factor-beta (TGF-beta) superfamily (13). Activin A is released rapidly into the circulation during inflammation and has been shown to modulate the inflammatory response by alteration of cytokine secretion, induction of nitric oxide production, and regulation of immune cell activity (14). Activin signaling pathways involve activins binding to a heteromeric complex of receptors that consist of at least two type I and two type II receptors. Both types of receptors possess serine-threonine kinase activity and regulation of gene expression is signaled via SMAD proteins. The ACVR1B gene encodes a type I receptor which is essential for activin signaling. Mutations in this gene are associated with cancer (15), cell proliferation (16).

High-throughput profiling technologies have revolutionized biomedical research by enabling assessment of physiological as well as pathological states of biological systems at an unprecedented depth. Moreover, an increasing amount of research data is available in public repositories (e.g., NCBI Gene Expression Omnibus [GEO]). These vast data collections have been postulated to serve as valuable training materials for the next generation of biomedical data scientists (17). Here, we report the upregulation of the ACVR1B gene during sepsis in human melioidosis and discuss additional possible avenues to investigate its putative role in the pathogenesis of sepsis. We acknowledge that the definition of sepsis may vary in each study and that it is challenging to properly summarize all interpretations. Also, the pathophysiology of sepsis is known to differ between age groups, e.g., neonates vs. adults. In this study, we were interested in the host response to severe infection across lifespan, experimental settings, and cell types, therefore, we use the word sepsis or septic as a broad term to encompass this syndrome which is often appreciated as a continuum of clinical presentation.

Materials and methods

In silico reductionist approach

Public repositories of articles and data, such as PubMed and GEO, constitute a vast resource but they can be difficult to explore. Here we present a logical reductionist approach to investigate putative novel biomarkers for sepsis.

The steps consist of 1) identifying a gene of interest based on its differential expression in the pathological/physiological context of interest, 2) confirming the reproducibility of the initial observation, 3) determining the current body of literature linking the gene and topic, 4) extracting the known biological concepts concerning the gene, and 5) inferring putative novel roles for the gene with literature support.

All datasets were obtained from GEO and used to confirm the initial findings in relevant clinical settings/samples. Datasets were selected without prior knowledge of ACVR1B expression levels and consisted only of human studies in which transcriptome profiles were generated in septic patients and compared to uninfected controls (Table 1). The task of identifying datasets was facilitated by using an interactive database recently created by our group and called SysInflam HuDB (sepsis.gxbsidra.org/dm3/geneBrowser/filteredSampleSets) (18). Other relevant information was retrieved from each GEO entry, such as: the geographic localization of the patient population, and the type of biological samples.

Ethical approval

The work involving human subjects was approved by the ethical committee of Faculty of Tropical Medicine, Mahidol University (approval no. MUTM 2015-002-04, MUTM 2018-046-01 and MUTM 2018-039-02), Udon Thani Hospital (approval no.6/2561), Nakhon Phanom Hospital (approval no. IEC-NKP1-No.15/2558), Roi Et Hospital (approval no. 166/2559), Buriram Hospital (approval no. BR 0032, 102.3/57), and Surin Hospital (approval no. 21/2560). This study was conducted in accordance with the principles of the Declaration of Helsinki (2008) and the International Council for Harmonization and Good Clinical Practice guidelines. Written informed consent/assent form was obtained from all participants or their legal guardians.

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EXPERT REVIEW OPEN

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Neuroimaging genetics approaches to identify new biomarkers for the early diagnosis of autism spectrum disorder

Sabah Nisar[1,4] and Mohammad Haris[1,2,3]✉

Autism-spectrum disorders (ASDs) are developmental disabilities that manifest in early childhood and are characterized by qualitative abnormalities in social behaviors, communication skills, and restrictive or repetitive behaviors. To explore the neurobiological mechanisms in ASD, extensive research has been done to identify potential diagnostic biomarkers through a neuroimaging genetics approach. Neuroimaging genetics helps to identify ASD-risk genes that contribute to structural and functional variations in brain circuitry and validate biological changes by elucidating the mechanisms and pathways that confer genetic risk. Integrating artificial intelligence models with neuroimaging data lays the groundwork for accurate diagnosis and facilitates the identification of early diagnostic biomarkers for ASD. This review discusses the significance of neuroimaging genetics approaches to gaining a better understanding of the perturbed neurochemical system and molecular pathways in ASD and how these approaches can detect structural, functional, and metabolic changes and lead to the discovery of novel biomarkers for the early diagnosis of ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disability that manifests in early childhood and is characterized by deficits in social skills, behaviors, and communication. According to the World Health Organization, approximately 1 in 160 children worldwide [1] and about 1 in 44 children in the United States have ASD [2], which can occur in all racial and ethnic groups, and is four times more prevalent in boys than in girls [3]. Individuals with ASD can have co-occurring conditions, such as attention deficit hyperactivity disorder (ADHD), bipolar disorder, depression, intellectual disability, language and developmental delays, speech disorder, and gastrointestinal symptoms [4]. Although the cause of ASD is ambiguous, genetic and non-genetic factors most likely contribute to its development [5].

ASD is associated with several genetic syndromes, a high incidence of chromosomal rearrangements, and the presence of common and rare variants [6]. Methodologic advances have revealed that common, heritable polygenic risk accounts for ~50% of ASD cases; major-affect mutations account for 15%; and rare de novo copy number variations (CNVs) and single-nucleotide variants (SNVs) that alter the structural genome account for ~5% [7]. No theory posits a clear unifying mechanism of ASD at the molecular or cellular level, because it remains unclear whether ASD is many disorders converging on a few molecular pathways or a few disorders with complex, diverse mechanisms [8].

The cellular and molecular bases of autism can be attributed to increased local connectivity in brain regions, neuronal migration deficits, excitatory/inhibitory imbalance, and synaptic dysregulation [9–12]. Many studies have highlighted the genetic heterogeneity underlying ASD and indicated that several ASD-associated gene or protein products interact with neuronal, synaptic, and other neurodevelopmental pathways [13, 14]. Neurologic disorders, such as ASD, cause microdamage to the brain, and detection of the resulting structural and functional changes requires the use of high-resolution, noninvasive imaging techniques, such as magnetic resonance imaging (MRI). Furthermore, neuroimaging studies have provided evidence of altered cortical and subcortical structures, impaired white matter (WM) connectivity, and atypical connectivity in the frontal and temporal brain regions involved in various cognitive functions [15].

Because genes directly affect brain development and function, genetic polymorphisms or aberrations might be strongly associated with the functioning of the compromised neural systems and behavioral outcomes [16]. Neuroimaging can be used to investigate the effect of genetic variations on brain structure, function, and connectivity; this approach is known as "neuroimaging genetics" [17]. Neuroimaging genetics can delineate the molecular mechanisms induced by genetic variants (common and rare) linked to neurodevelopmental disorders (NDDs). Neuroimaging genetics enables us to investigate gene-specific effects on different functional brain systems, which will contribute to future diagnosis of various NDDs, including ASD.

In this review, we will explore various neuroimaging techniques that can be used to assess the impact of genetic factors on brain structure, function, and metabolism. In addition, we will discuss the neuroimaging genetics approach can be used to identify novel biomarkers for the early diagnosis of ASD.

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Encephalitis and poor neuronal death-mediated control of herpes simplex virus in human inherited RIPK3 deficiency

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[#], [&], [*]equal contributions.

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RESEARCH Open Access

Ubiquitin specific peptidase 37 and PCNA interaction promotes osteosarcoma pathogenesis by modulating replication fork progression

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Abstract

Background Osteosarcoma is a type of bone cancer that predominantly affects young individuals, including children and adolescents. The disease progresses through heterogeneous genetic alterations, and patients often develop pulmonary metastases even after the primary tumors have been surgically removed. Ubiquitin-specific peptidases (USPs) regulate several critical cellular processes, such as cell cycle progression, transcriptional activation, and signal transduction. Various studies have revealed the significance of USP37 in the regulation of replication stress and oncogenesis.

Methods In this study, the Cancer Genome Atlas (TCGA) database was analyzed to investigate USP37 expression. RNA sequencing was utilized to assess the impact of USP37 overexpression and depletion on gene expression in osteosarcoma cells. Various molecular assays, including colony formation, immunofluorescence, immunoprecipitation, and DNA replication restart, were employed to examine the physical interaction between USP37 and PCNA, as well as its physiological effects in osteosarcoma cells. Additionally, molecular docking studies were conducted to gain insight into the nature of the interaction between USP37 and PCNA. Furthermore, immunohistochemistry was performed on archived tissue blocks from osteosarcoma patients to establish a correlation between USP37 and PCNA expression.

Results Analysis of the TCGA database revealed that increased expression of USP37 was linked to decreased progression-free survival (PFS) in osteosarcoma patients. Next-generation sequencing analysis of osteosarcoma cells demonstrated that overexpression or knockdown of USP37 led to the expression of different sets of genes. USP37 overexpression provided a survival advantage, while its depletion heightened sensitivity to replication stress in osteosarcoma cells. USP37 was found to physically interact with PCNA, and molecular docking studies indicated that the interaction occurs through unique residues. In response to genotoxic stress, cells that overexpressed USP37 resolved DNA damage foci more quickly than control cells or cells in which USP37 was depleted. The expression of USP37 varied in archived osteosarcoma tissues, with intermediate expression seen in 52% of cases in the cohort examined.

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METHOD ARTICLE

REVISED Organizing training workshops on gene literature retrieval, profiling, and visualization for early career researchers [version 2; peer review: 2 approved]

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Abstract

Early-career researchers must acquire the skills necessary to effectively search and extract information from biomedical literature. This ability is for instance crucial for evaluating the novelty of experimental results, and assessing potential publishing opportunities. Given the rapidly growing volume of publications in the field of biomedical research, new systematic approaches need to be devised and adopted for the retrieval and curation of literature relevant to a specific theme. In this context, we present a hands-on training curriculum aimed at retrieval, profiling, and visualization of literature associated with a given topic. The curriculum was implemented in a workshop in January 2021. Here we provide supporting material and step-by-step implementation guidelines with the ISG15 gene literature serving as an illustrative use case. Workshop participants can learn several skills, including: 1) building and troubleshoot PubMed queries in order to retrieve the literature associated with a gene of interest; 2) identifying key concepts relevant to given themes (such as cell types, diseases, and biological processes); 3) measuring the prevalence of these concepts in the gene literature; 4) extracting key information from relevant articles, and 5) developing a background section or summary on the basis of this information. Finally, trainees can learn to consolidate the structured information captured through this process for presentation via an interactive web application.

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Anti-angiogenic effect of nano-formulated water soluble kaempferol and combretastatin in an in vivo chick chorioallantoic membrane model and HUVEC cells

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ABSTRACT

The present study evaluated the efficacy of nano-formulated water-soluble kaempferol and combretastatin alone and combined against the native kaempferol and combretastatin on angiogenesis. The solvent evaporation method was used to synthesize the nano-formulated water-soluble kaempferol and combretastatin and characterized using various analyses such as dynamic light scattering (DLS) and Fourier-transform infrared (FT-IR) spectroscopy.The anti-angiogenic activity of native, nano-formulated water-soluble kaempferol and combretastatin was investigated by cell viability on HUVEC and A498 cell lines, while chick chorioallantoic membrane (CAM) assay was utilized to assess morphometric and histopathological changes, and mRNA expressions of VEGF-A and FGF2 using qRT-PCR. MTT assay results revealed that the combination of nano-formulated water-soluble kaempferol and combretastatin significantly reduced the cell viability compared to control, individual treatments of native, nano-formulated water-soluble kaempferol, and combretastatin. Morphometric analysis of CAM showed that treatment with nano-formulated water-soluble kaempferol and combretastatin caused a substantial decrease in density, vessel network, branch points, and nets of CAM blood vessels. The histopathological results of CAM showed the irregular shape of blood vessels at the thin stratum of chronic endoderm, and blood capillaries were diminished compared to the control. In addition, the mRNA expression levels of VEGF-A and FGF2 were significantly decreased compared with native forms. Therefore, the findings of this study indicate that nano-formulated water-soluble combretastatin and kaempferol suppress angiogenesis by preventing the activation of endothelial cells and suppressing factors of angiogenesis. Moreover, a combination of nano-formulated water-soluble kaempferol and combretastatin worked much better than individual treatments.

Abbreviations: NF-K, , Nano-formulated water-soluble kaempferol; NF-C, , Nano-formulated water-soluble Combretastatin; VEGFR2, , Vascular endothelial growth factor receptor-2; VEGF-A, , Vascular endothelial growth factor-A; FGF2, , Fibroblast growth factor-2; CAM, , chick chorioallantoic membrane; RT-PCR, Reverse Transcriptase- Polymerase Chain Reaction; mRNA, , messenger RNA; ERK, , extracellular signal-regulated kinases; MAPK, , mitogen-activated protein kinases; CRP, , C-reactive protein; NF-kB, , nuclear factor-kB; PBS, , Phosphate buffer saline; ANOVA,, Analysis of Variance; DLS, , Dynamic Light Scattering; FT-IR, , Fourier Transition-Infrared spectroscopy; LSCC, , Lung Squamous Cell Carcinoma; EMT, , Epithelial-Mesenchymal transition.

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Review

OPEN

The Promise of Precision Nutrition for Modulation of the Gut Microbiota as a Novel Therapeutic Approach to Acute Graft-versus-host Disease

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Abstract. Acute graft-versus-host disease (aGVHD) is a severe side effect of allogeneic hematopoietic stem cell transplantation (aHSCT) that has complex phenotypes and often unpredictable outcomes. The current management is not always able to prevent aGVHD. A neglected actor in the management of aGVHD is the gut microbiota. Gut microbiota dysbiosis after aHSCT is caused by many factors and may contribute to the development of aGVHD. Diet and nutritional status modify the gut microbiota and a wide range of products are now available to manipulate the gut microbiota (pro-, pre-, and postbiotics). New investigations are testing the effect of probiotics and nutritional supplements in both animal models and human studies, with encouraging results. In this review, we summarize the most recent literature about the probiotics and nutritional factors able to modulate the gut microbiota and we discuss the future perspective in developing new integrative therapeutic approaches to reducing the risk of graft-versus-host disease in patients undergoing aHSCT.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (aHSCT) is applied as first-line therapy in a wide variety of severe immunodeficiencies and bone marrow failures or as definitive treatment in high-risk hematologic malignancies. Today, aHSCT is a standard clinical practice in hundreds of specialized clinical centers, serving as a potentially life-saving treatment for tens of thousands of patients every year, throughout the world.

A major limitation of its application is the graft-versus-host disease (GVHD) complication, occurring in acute GVHD (aGVHD) involving gastrointestinal (GI) tract, liver, and skin in 35%–50% of cases and in chronic GVHD (cGVHD) in 30%–40% of cases.[1,2] Furthermore, the outcomes of aGVHD vary unpredictably between the mild and severe forms. Thus, at present, the clinical outcome for these patients is dismal, with long-term morbidity in 10%–50% of adult aGVHD cases and 50%–70% of pediatric cases.

For many decades now, aGVHD has been a focus of intense research designed to discover new biomarkers and therapeutic targets to improve clinical outcomes. Interestingly, one of the most recent important discoveries focused on 2 GI biomarkers: suppressor of tumorigenesis 2 (ST2) and regenerating islet-derived 3 alpha (REG3α). Both molecules, combined in an algorithm, predicted GVHD severity and treatment response, achieving therefore an exceptional performance.[3] The GI tract is indeed a key component in the biology of aGVHD, representing an interphase between the gut lumen microbiota composition[4] and epithelium-associated immune tissues. As such, the GI tract is the first mediator of inflammatory signals, typically in the case of chemo/radiotherapy damages after aHSCT conditioning. ST2 and Reg3α are both biomarkers of GI crypt damage, proving the key importance of the disruption of GI barriers, and implying the relevance of finding biological targets for drugs in this ecosystem.

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Serum immune mediators as novel predictors of response to anti-PD-1/PD-L1 therapy in non-small cell lung cancer patients with high tissue-PD-L1 expression

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related morbidity and mortality worldwide. Immune checkpoint inhibitors (ICIs) including anti-PD-1 and anti-PD-L1 antibodies, have significantly changed the treatment outcomes with better overall survival, but only 15-40% of the patients respond to ICIs therapy. The search for predictive biomarkers of responses is warranted for better clinical outcomes. We aim here to identify pre-treatment soluble immune molecules as surrogate biomarkers for tissue PD-L1 (TPD-L1) status and as predictors of response to anti-PD-1/PD-L1 therapy in NSCLC patients. Sera from 31 metastatic NSCLC patients, eligible for anti-PD-1/PD-L1 or combined chemoimmunotherapy, were collected prior to treatment. Analysis of soluble biomarkers with TPD-L1 status showed significant up/down regulation of the immune inhibitory checkpoint markers (sSiglec7, sSiglec9, sULBP4 and sPD-L2) in patients with higher TPD-L1 (TPD-L1 >50%) expression. Moreover,

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Assessment of Broadly Reactive Responses in Patients With MERS-CoV Infection and SARS-CoV-2 Vaccination

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RESEARCH ARTICLE

small methods
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V_4C_3 MXene Immune Profiling and Modulation of T Cell-Dendritic Cell Function and Interaction

Laura Fusco, Arianna Gazzi, Christopher E. Shuck, Marco Orecchioni, Eiman I Ahmed, Linda Giro, Barbara Zavan, Açelya Yilmazer, Klaus Ley, Davide Bedognetti, Yury Gogotsi, and Lucia Gemma Delogu**

Although vanadium-based metallodrugs are recently explored for their effective anti-inflammatory activity, they frequently cause undesired side effects. Among 2D nanomaterials, transition metal carbides (MXenes) have received substantial attention for their promise as biomedical platforms. It is hypothesized that vanadium immune properties can be extended to MXene compounds. Therefore, vanadium carbide MXene (V_4C_3) is synthetized, evaluating its biocompatibility and intrinsic immunomodulatory effects. By combining multiple experimental approaches in vitro and ex vivo on human primary immune cells, MXene effects on hemolysis, apoptosis, necrosis, activation, and cytokine production are investigated. Furthermore, V_4C_3 ability is demonstrated to inhibit T cell-dendritic cell interactions, evaluating the modulation of CD40–CD40 ligand interaction, two key costimulatory molecules for immune activation. The material biocompatibility at the single-cell level on 17 human immune cell subpopulations by single-cell mass cytometry is confirmed. Finally, the molecular mechanism underlying V_4C_3 immune modulation is explored, demonstrating a MXene-mediated downregulation of antigen presentation-associated genes in primary human immune cells. The findings set the basis for further V_4C_3 investigation and application as a negative modulator of the immune response in inflammatory and autoimmune diseases.

1. Introduction

Thanks to their outstanding physicochemical properties, the 2D transition metal carbides/carbonitrides (MXenes)[1,2] are currently studied for biomedical applications ranging from artificial organs,[3] intraocular lenses,[4] and theranostics[5,6] to implantable and epidermal electrodes,[7] and many others.[5,6,8–16] In particular, MXene nanosheets exhibit high photothermal-conversion efficiency and localized surface plasmon resonance effect, expanding the field of photodynamic and photothermal therapy,[17] and a high surface area suitable for drug delivery.[18–20] Notably, the high metallic conductivity of MXenes is accompanied by hydrophilicity,[21,22] a fundamental aspect for biomedical purposes.[23]

We recently explored the immune profile of Nb_4C_3, $Mo_2Ti_2C_3$, and Ta_4C_3 MXenes revealing their ability to interact with a broad range of immune cells.[24] 2D MXenes have also been investigated

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REVIEW Open Access

Statistical methods and resources for biomarker discovery using metabolomics

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Abstract

Metabolomics is a dynamic tool for elucidating biochemical changes in human health and disease. Metabolic profiles provide a close insight into physiological states and are highly volatile to genetic and environmental perturbations. Variation in metabolic profiles can inform mechanisms of pathology, providing potential biomarkers for diagnosis and assessment of the risk of contracting a disease. With the advancement of high-throughput technologies, large-scale metabolomics data sources have become abundant. As such, careful statistical analysis of intricate metabolomics data is essential for deriving relevant and robust results that can be deployed in real-life clinical settings. Multiple tools have been developed for both data analysis and interpretations. In this review, we survey statistical approaches and corresponding statistical tools that are available for discovery of biomarkers using metabolomics.

Keywords: Metabolomics, Metabolomics tools, Statistical methods, Analytical workflow, Univariate, Multivariate

Overview of metabolomics

The term metabolome was first coined in 1998 [1] and became widely established in the early 2000 [2]. Metabolomics profiling is a high-throughput technique that quantifies the levels of endogenous metabolites in a sample (biological fluids, tissues, etc.). [3]. The study of metabolites or metabolite profiling has been gaining popularity in the past decade, thanks to the recent advances in analytical platforms such as Fourier-Transform Infrared spectrometry (FT-IR), Nuclear magnetic resonance (NMR), mass spectrometry (MS) coupled to separation techniques such as gas-chromatography (GC–MS), liquid chromatography (LC–MS), Fourier Transform mass spectrometry (FT-MS), Ultra-high performance liquid chromatography (UPLC–MS), Capillary electrophoresis (CE–MS), Inductively coupled plasma (IPC–MS), Ion chromatography (IC–MS) [4] etc. Metabolites are key molecules in cellular functions. Many biological disturbances involve a cascade of metabolic changes, making metabolites close descriptors for the phenotype. There are two main analytical techniques that are used in the quantification of metabolites (in a cell, tissue, or body fluids): NMR and MS [5–7] through a process that can be untargeted or targeted. The former is a comprehensive technique measuring

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Exploring the potential of microRNA as a diagnostic tool for gestational diabetes

Duaa Ahmed Elhag[1] and Souhaila Al Khodor[1*]

Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that play critical roles in regulating host gene expression. Recent studies have indicated a role of miRNAs in the pathogenesis of gestational diabetes mellitus (GDM), a common pregnancy-related disorder characterized by impaired glucose metabolism. Aberrant expression of miRNAs has been observed in the placenta and/or maternal blood of GDM patients, suggesting their potential use as biomarkers for early diagnosis and prognosis. Additionally, several miRNAs have been shown to modulate key signaling pathways involved in glucose homeostasis, insulin sensitivity, and inflammation, providing insights into the pathophysiology of GDM. This review summarizes the current knowledge on the dynamics of miRNA in pregnancy, their role in GDM as well as their potential as diagnostic and therapeutic targets.

Keywords Diabetes, OGTT, Pregnancy complications, BMI, Macrosomia

Introduction

According to the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO), Gestational Diabetes Mellitus (GDM) is defined as a pregnancy-related carbohydrate intolerance that is first diagnosed during pregnancy [1, 2]. This results in varying degrees of hyperglycemia and is associated with potential complications such as pre-eclampsia, premature rupture of membranes, cesarean section, preterm delivery, high blood pressure, and babies with large birth weight [3–6]. The worldwide prevalence of GDM is around 14%, varying based on the population ethnicity and the diagnostic test used [6–8]. The American Diabetes Association (ADA) recommends performing the oral glucose tolerance test (OGTT) for the diagnosis of GDM in the second trimester (between 24 and 28 weeks) for low-risk pregnant women, but early diagnosis in the first trimester can identify those at high risk for GDM and prevent adverse complications by adjusting the cut-off points of the OGTT plasma glucose test [9, 10]. Despite that the OGTT can detect up to 80.3% of GDM cases, there is a need for additional diagnostic biomarkers to achieve 100% diagnostic accuracy for GDM cases as early as the first trimester. This would improve outcomes for pregnant women and their infants.

Pregnancy is characterized by physiological and metabolic changes that prepare the mother's body for fetal growth, which is a well-established fact [11, 12]. These include temporal variations in the expression profile of microRNAs (miRNAs), particularly in the first trimester [13]. miRNAs have the potential to identify pregnant women with complications such as preeclampsia (PE), or GDM [13]. These non-coding and highly conserved RNAs are typically 18–22 nucleotides in length and are known to regulate targeted gene expression by binding to their 3'UTR [14]. They are among the most commonly emerging epigenetic regulators for metabolic adaptation during pregnancy [15–17]. However, their dysregulation has been associated with several pregnancy complications, including PE, intrauterine growth restriction (IUGR), miscarriage, preterm birth, and GDM

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Novel fluorobenzothiazole as a dual inhibitor of gyrase B and topoisomerase IV against Gram-positive pathogens

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Abstract

Aim: The development of a novel inhibitor targeting gyrase B and topoisomerase IV offers an opportunity to combat multidrug resistance. **Methods:** We investigated the activity of RBx 10080758 against Gram-positive bacteria *in vitro* and *in vivo*. **Results:** RBx 10080758 showed a potent 50% inhibitory concentration of 0.13 µM and 0.25 µM against gyrase B and topoisomerase IV, respectively, and exhibited strong whole-cell *in vitro* activity with MIC ranges of 0.015-0.06 and 0.015-0.03 µg/ml against *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In a rat thigh infection model with methicillin-resistant *S. aureus*, RBx 10080758 at 45 mg/kg exhibited a >3 $\log_{10}$ CFU reduction in thigh muscles. **Conclusion:** RBx 10080758 displayed potent activity against multiple multidrug-resistant Gram-positive bacteria with a dual-targeting mechanism of action.

Keywords: Gram-positive bacteria; dual inhibitors; fluorobenzothiazole; gyrase B; rat thigh infection; topoisomerase IV.

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Long non-coding RNAs modulate tumor microenvironment to promote metastasis: novel avenue for therapeutic intervention

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Cancer is a devastating disease and the primary cause of morbidity and mortality worldwide, with cancer metastasis responsible for 90% of cancer-related deaths. Cancer metastasis is a multistep process characterized by spreading of cancer cells from the primary tumor and acquiring molecular and phenotypic changes that enable them to expand and colonize in distant organs. Despite recent advancements, the underlying molecular mechanism(s) of cancer metastasis is limited and requires further exploration. In addition to genetic alterations, epigenetic changes have been demonstrated to play an important role in the development of cancer metastasis. Long non-coding RNAs (lncRNAs) are considered one of the most critical epigenetic regulators. By regulating signaling pathways and acting as decoys, guides, and scaffolds, they modulate key molecules in every step of cancer metastasis such as dissemination of carcinoma cells, intravascular transit, and metastatic colonization. Gaining a good knowledge of the detailed molecular basis underlying lncRNAs regulating cancer metastasis may provide previously unknown therapeutic and diagnostic lncRNAs for patients with metastatic disease. In this review, we concentrate on the molecular mechanisms underlying lncRNAs in the regulation of cancer metastasis, the cross-talk with metabolic reprogramming, modulating cancer cell anoikis resistance, influencing metastatic microenvironment, and the interaction with pre-metastatic niche formation. In addition, we also discuss the clinical utility and therapeutic potential of lncRNAs for cancer treatment. Finally, we also represent areas for future research in this rapidly developing field.

KEYWORDS

cancer, metastasis, long non-coding RNAs, tumor microenvironment, anoikis resistance, metabolic reprogramming, immune modulation

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Identification of a novel candidate HSD3B2 gene variant for familial hypospadias by whole-exome sequencing

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Introduction: Hypospadias [MIM: 300633] is one of the most frequent congenital malformations of male external genitalia. The spectrum of genetic variants causing hypospadias is varied, with studies commonly implicating genes critical in the fetal steroidogenic pathway. This is the first genetic study on hypospadias from the Yemen ethnicity and the second to report *HSD3B2* mutations in more than one affected individual from the same family.

Material and methods: Surgical hypospadias repair was performed on two hypospadias-affected siblings from a consanguineous family. Whole-exome sequencing (WES) was performed to identify the potential pathogenic variant for hypospadias, which was later confirmed by Sanger sequencing. The identified variant was further analyzed for its pathogenicity by using *in silico* tools such as SIFT, PolyPhen-2, MutationAssessor, MutationTaster, FATHMM, and ConSurf.

Results: We identified a novel missense mutation (Chr1:119964631T>A, c.507T>A, p. N169K) in 3β-hydroxysteroid 2-dehydrogenase (*HSD3B2*) gene by WES. Sanger sequencing confirmed that the variant segregated the disease in the family between the affected and non-affected individuals. Both patients are homozygous, while parents and two unaffected siblings are heterozygous carriers, indicating an autosomal recessive pattern of inheritance. The *in silico* analysis by all six *in silico* tools (SIFT, PolyPhen-2, MutationAssessor, MutationTaster, FATHMM, and ConSurf) predicted the variant to be pathogenic/deleterious.

Discussion: An abnormal fetal steroidogenic pathway due to genetic influences may affect the development of the male genital tract, including the urethral tract closure and morphogenesis of male genitalia. Furthermore, the pathogenicity of the observed variant in this study, confirmed by multiple *in silico* tools, characterizes the influence HSD3B2 gene variants may have in the etiology of hypospadias.

Abbreviations: DHEA, dehydroepiandrotone; HSD3B2, 3β-hydroxysteroid 2-dehydrogenase; WES, whole-exome sequencing.

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REVIEW Open Access

Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments

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Abstract

Traditional cancer treatments use nonspecific drugs and monoclonal antibodies to target tumor cells. Chimeric antigen receptor (CAR)-T cell therapy, however, leverages the immune system's T-cells to recognize and attack tumor cells. T-cells are isolated from patients and modified to target tumor-associated antigens. CAR-T therapy has achieved FDA approval for treating blood cancers like B-cell acute lymphoblastic leukemia, large B-cell lymphoma, and multiple myeloma by targeting CD-19 and B-cell maturation antigens. Bi-specific chimeric antigen receptors may contribute to mitigating tumor antigen escape, but their efficacy could be limited in cases where certain tumor cells do not express the targeted antigens. Despite success in blood cancers, CAR-T technology faces challenges in solid tumors, including lack of reliable tumor-associated antigens, hypoxic cores, immunosuppressive tumor environments, enhanced reactive oxygen species, and decreased T-cell infiltration. To overcome these challenges, current research aims to identify reliable tumor-associated antigens and develop cost-effective, tumor microenvironment-specific CAR-T cells. This review covers the evolution of CAR-T therapy against various tumors, including hematological and solid tumors, highlights challenges faced by CAR-T cell therapy, and suggests strategies to overcome these obstacles, such as utilizing single-cell RNA sequencing and artificial intelligence to optimize clinical-grade CAR-T cells.

†Tariq Masoodi, Sabah Nisar and Maysaloun Merhi have contributed equally.

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RESEARCH Open Access

Salivary microbiome and hypertension in the Qatari population

Selvasankar Murugesan[1] and Souhaila Al Khodor[1*]

Abstract

Background The prevalence of hypertension in Qatar is 33 percent of the adult population. It is postulated that the salivary microbiome can regulate blood pressure (BP). However, limited investigations exist to prove this hypothesis. Therefore, we examined the difference in the salivary microbiome composition between hypertensive and normotensive Qatari subjects.

Methods A total of 1190 Qatar Genome Project (QGP) participants (Mean age = 43 years) were included in this study. BP for all participants was classified into Normal (n = 357), Stage1 (n = 336), and Stage2: (n = 161) according to the American Heart Association guidelines. 16S-rRNA libraries were sequenced and analyzed using QIIME-pipeline, and PICRUST was used to predict functional metabolic routes. Machine Learning (ML) strategies were applied to identify salivary microbiome-based predictors of hypertension.

Results Differential abundant analysis (DAA) revealed that *Bacteroides* and *Atopobium* were the significant members of the hypertensive groups. Alpha and beta diversity indices indicated dysbiosis between the normotensive and hypertensive groups. ML-based prediction models revealed that these markers could predict hypertension with an AUC (Area under the curve) of 0.89. Functional predictive analysis disclosed that Cysteine and Methionine metabolism and the sulphur metabolic pathways involving the renin-angiotensin system were significantly higher in the normotensive group. Therefore, members of *Bacteroides* and *Atopobium* can serve as predictors of hypertension. Likewise, *Prevotella*, *Neisseria,* and *Haemophilus* can be the protectors that regulate BP via nitric acid synthesis and regulation of the renin-angiotensin system.

Conclusion It is one of the first studies to assess salivary microbiome and hypertension as disease models in a large cohort of the Qatari population. Further research is needed to confirm these findings and validate the mechanisms involved.

Keywords 16S ribosomal RNA, Qatar biobank, Saliva, Hypertension, Cardiovascular disease, Qatari population

Introduction

Hypertension is one of the risk factors for cardiovascular disease (CVD), its prevalence has doubled globally in the last three decades [1]. According to the World Health Organization (WHO), hypertension accounts for 12.8% of all deaths [2]. Factors contributing to hypertension include sedentary lifestyles, unhealthy diets that are high in fat and low in fiber, ethnicity, inappropriate medication use, and stress [3, 4]. Moreover, hypertension can cause damage to the body before symptoms appear, and if left untreated, it can cause several health complications,

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A Genomic Study of the Japanese Population Focusing on the Glucocorticoid Receptor Interactome Highlights Distinct Genetic Characteristics Associated with Stress Response

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Abstract

All living organisms have been programmed to maintain a complex inner equilibrium called homeostasis, despite numerous adversities during their lifespan. Any threatening or perceived as such stimuli for homeostasis is termed a stressor, and a highly conserved response system called the stress response system has been developed to cope with these stimuli and maintain or reinstate homeostasis. The glucocorticoid receptor, a transcription factor belonging to the nuclear receptors protein superfamily, has a major role in the stress response system, and research on its interactome may provide novel information regarding the mechanisms underlying homeostasis maintenance. A list of 149 autosomal genes that have an essential role in GR function or are prime examples of GRE-containing genes was composed in order to gain a comprehensive view of the GR interactome. A search for SNPs on those particular genes was conducted on a dataset of 3554 Japanese individuals, with mentioned polymorphisms being annotated with relevant information from the ClinVar, LitVar, and dbSNP databases. Forty-two SNPs of interest and their genomic locations were identified. These SNPs have been associated with drug metabolism and neuropsychiatric, metabolic, and immune system disorders, while most of them were located in intronic regions. The frequencies of those SNPs were later compared with a dataset consisting of 1465 Korean individuals in order to find population-specific characteristics based on some of the identified SNPs of interest. The results highlighted.that rs1043618 frequencies were different in the two populations, with mentioned polymorphism having a potential role in chronic obstructive pulmonary disease in response to environmental stressors. This SNP is located in the HSPA1A gene, which codes for an essential GR co-chaperone, and such information showcases that similar gene may be novel genomic targets for managing or combatting stress-related pathologies.

Keywords: Biomarkers; Genetics; Glucocorticoid receptor; Homeostasis; Population analysis; SNPs; Stress response system.

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The antioxidant L-Ergothioneine prevents cystine lithiasis in the *Slc7a9*$^{-/-}$ mouse model of cystinuria

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ABSTRACT

The high recurrence rate of cystine lithiasis observed in cystinuria patients highlights the need for new therapeutic options to address this chronic disease. There is growing evidence of an antioxidant defect in cystinuria, which has led to test antioxidant molecules as new therapeutic approaches. In this study, the antioxidant L-Ergothioneine was evaluated, at two different doses, as a preventive and long-term treatment for cystinuria in the *Slc7a9*$^{-/-}$ mouse model. L-Ergothioneine treatments decreased the rate of stone formation by more than 60% and delayed its onset in those mice that still developed calculi. Although there were no differences in metabolic parameters or urinary cystine concentration between control and treated mice, cystine solubility was increased by 50% in the urines of treated mice. We also demonstrate that L-Ergothioneine needs to be internalized by its transporter OCTN1 (*Slc22a4*) to be effective, as when administrated to the double mutant *Slc7a9*$^{-/-}$*Slc22a4*$^{-/-}$ mouse model, no effect on the lithiasis phenotype was observed. In kidneys, we detected a decrease in GSH levels and an impairment of maximal mitochondrial respiratory capacity in cystinuric mice that L-Ergothioneine treatment was able to restore. Thus, L-Ergothioneine administration prevented cystine lithiasis in the *Slc7a9*$^{-/-}$ mouse model by increasing urinary cystine solubility and recovered renal GSH metabolism and mitochondrial function. These results support the need for clinical trials to test L-Ergothioneine as a new treatment for cystinuria.

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The Plant Genome

ORIGINAL ARTICLE

Genome-wide association of dry (Tamar) date palm fruit color

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Abstract

Date palm (*Phoenix dactylifera*) fruit (dates) are an economically and culturally significant crop in the Middle East and North Africa. There are hundreds of different commercial cultivars producing dates with distinctive shapes, colors, and sizes. Genetic studies of some date palm traits have been performed, including sex determination, sugar content, and fresh fruit color. In this study, we used genome sequences and image data of 199 dry dates (Tamar) collected from 14 countries to identify genetic loci associated with the color of this fruit stage. Here, we find loci across multiple linkage groups (LG) associated with dry fruit color phenotype. We recover both the previously identified *VIRESCENS* (VIR) genotype associated with fresh fruit yellow or red color and new associations with the lightness and darkness of dry fruit. This study will add resolution to our understanding of date color phenotype, especially at the most commercially important Tamar stage.

1 | INTRODUCTION

Date palm (*Phoenix dactylifera*) is one of the oldest and most economically important fruit crops in the Middle East and North Africa (Chao & Krueger, 2007; Weiss et al., 2012). While there are thousands of cultivars or varieties, likely, only a few hundred are commercially important (Zaid & Arias-Jimenez, 1999). These cultivars produce fruit (dates) that vary in shape, color, and size. Fruit development and ripening involve many complex biological processes, with color changes of the fruit being an important factor closely associated with the ripening stage (Abbas & Ibrahim, 1998). Dates have five different development stages: Hababauk, Kimri, Khalal, Rutab, and Tamar (Al-Mssallem et al., 2013; Siddiq & Greiby, 2013). During the first development stages of Hababauk and Kimri, the fruit skin color is whitish-green. In the Khalal stage, dates partially ripen and gain maximum size and weight and the color changes from green to yellow or red depending on the cultivar. Dates fully mature in the Rutab stage, and the color begins its change to brown. Tamar is the final stage of ripening, during which fruit water content is reduced to less than 25%, sugar content increases to 70%–80%, and the color turns dark brown. Dates are harvested and sold mainly in three different stages of development:

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RESEARCH ARTICLE

WILEY

A variant in sperm-specific glycolytic enzyme enolase 4 (*ENO4*) causes human male infertility

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Abstract

Background: Although defects in sperm morphology and physiology lead to male infertility, in many instances, the exact disruption of molecular pathways in a given patient is often unknown. The glycolytic pathway is an essential process to supply energy in sperm cell motility. Enolase 4 (*ENO4*) is crucial for the glycolytic process, which provides the energy for sperm cells in motility. *ENO4* is located in the sperm principal piece and is essential for the motility and organization of the sperm flagellum. In the present study, we characterized a family with asthenozoospermia and abnormal sperm morphology as a result of a variant in the enolase 4 (*ENO4*) gene.

Methods: Computer-assisted semen analysis, papanicolaou smear staining and scanning electron microscopy were used to examine sperm motility and morphology for semen analysis in patients. For genetic analysis, whole-exome sequencing followed by Sanger sequencing was performed.

Results: Two brothers in a consanguineous family were being clinically investigated for sperm motility and morphology issues. Genetic analysis by whole-exome sequencing revealed a homozygous variant [c.293A>G, p.(Lys98Arg)] in the *ENO4* gene that segregated with infertility in the family, shared by affected but not controls.

Conclusions: In view of the association of asthenozoospermia and abnormal sperm morphology in *Eno4* knockout mice, we consider this to be the first report describing the involvement of *ENO4* gene in human male infertility. We also explore the possible involvement of another variant in explaining other phenotypic features in this family.

Shoaib Nawaz and Shabir Hussain, contributed equally to this work.

CHAPTER SIX

Epigenetic inhibitors and their role in cancer therapy

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Article

Genetic Variation and Sensory Perception of a Pediatric Formulation of Ibuprofen: Can a Medicine Taste Too Good for Some?

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Abstract: There is wide variation in how individuals perceive the chemosensory attributes of liquid formulations of ibuprofen, encompassing both adults and children. To understand personal variation in the taste and chemesthesis properties of this medicine, and how to measure it, our first scientific strategy centered on utilizing trained adult panelists, due to the complex and time-consuming psychophysical tasks needed at this initial stage. We conducted a double-blind cohort study in which panelists underwent whole-genome-wide genotyping and psychophysically evaluated an over-the-counter pediatric medicine containing ibuprofen. Associations between sensory phenotypes and genetic variation near/within irritant and taste receptor genes were determined. Panelists who experienced the urge to cough or throat sensations found the medicine less palatable and sweet, and more irritating. Perceptions varied with genetic ancestry; panelists of African genetic ancestry had fewer chemesthetic sensations, rating the medicine sweeter, less irritating, and more palatable than did those of European genetic ancestry. We discovered a novel association between *TRPA1* rs11988795 and tingling sensations, independent of ancestry. We also determined for the first time that just tasting the medicine allowed predictions of perceptions after swallowing, simplifying future psychophysical studies on diverse populations of different age groups needed to understand genetic, cultural–dietary, and epigenetic factors that influence individual perceptions of palatability and, in turn, adherence and the risk of accidental ingestion.

Keywords: genetic ancestry; ibuprofen; pediatric formulations; taste; irritation; chemesthesis; single nucleotide polymorphisms

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1. Introduction

How medications are delivered often differs between children and adults. While adults typically take medicine as solid formulations, encapsulating unpleasant-tasting active pharmaceutical ingredients (APIs), young children, unable or unwilling to swallow pills or capsules, are treated with liquid formulations that contain sugars, salts, and flavor volatiles to improve palatability [1–4]. There are cultural exceptions to this generalization, however.

cancers

MDPI

Review

Exploring the Role of microRNAs in Glioma Progression, Prognosis, and Therapeutic Strategies

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Simple Summary: Despite advancements in healthcare and research, the occurrence of gliomas, a type of brain tumor, continues to rise. Emerging evidence has proven that dysregulated microRNAs play a significant role in the initiation, progression, prognosis, and recurrence of gliomas. Not only can these micro-RNAs serve as diagnostic tools, but they also hold promise for the development of targeted therapeutic treatments. It is therefore of great importance to have a comprehensive understanding of the specific microRNAs involved, the different pathways they are involved in, and the potential outcomes of mutations. This is ultimately the focus of this review, which establishes a solid foundation for the development of targeted therapeutic agents, also highlighting the possible challenges that may be encountered.

Abstract: Gliomas, which arise from glial cells in the brain, remain a significant challenge due to their location and resistance to traditional treatments. Despite research efforts and advancements in healthcare, the incidence of gliomas has risen dramatically over the past two decades. The dysregulation of microRNAs (miRNAs) has prompted the creation of therapeutic agents that specially target them. However, it has been reported that they are involved in complex signaling pathways that contribute to the loss of expression of tumor suppressor genes and the upregulation of the expression of oncogenes. In addition, numerous miRNAs promote the development, progression, and recurrence of gliomas by targeting crucial proteins and enzymes involved in metabolic pathways such as glycolysis and oxidative phosphorylation. However, the complex interplay among these pathways along with other obstacles hinders the ability to apply miRNA targeting in clinical practice. This highlights the importance of identifying specific miRNAs to be targeted for therapy and having a complete understanding of the diverse pathways they are involved in. Therefore, the aim of this review is to provide an overview of the role of miRNAs in the progression and prognosis of gliomas, emphasizing the different pathways involved and identifying potential therapeutic targets.

Keywords: microRNA; glioma; cancer stem cells; prognosis; targeted therapy

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1. Introduction

Brain malignancies are among the most dreaded forms of cancer because of their immediate impact on cognitive function and well-being and unfavorable prognosis. These tumors exhibit irregular growth patterns and invade surrounding healthy brain tissue. The location and size of the tumor can lead to a variety of symptoms, including headaches, seizures, numbness, and difficulties with speech and vision. Glial cells, which provide support and protection to neurons, can transform into gliomas, the most prevalent type of primary malignant brain tumor [1].

Gliomas comprise various subtypes, including oligodendrogliomas, astrocytomas, and ependymomas, representing 24% of all primary brain and CNS malignancies worldwide.

Cell Genomics

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Perspective

Equity, diversity, and inclusion at the Global Alliance for Genomics and Health

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SUMMARY

A lack of diversity in genomics for health continues to hinder equitable leadership and access to precision medicine approaches for underrepresented populations. To avoid perpetuating biases within the genomics workforce and genomic data collection practices, equity, diversity, and inclusion (EDI) must be addressed. This paper documents the journey taken by the Global Alliance for Genomics and Health (a genomics-based standard-setting and policy-framing organization) to create a more equitable, diverse, and inclusive environment for its standards and members. Initial steps include the creation of two groups: the Equity, Diversity, and Inclusion Advisory Group and the Regulatory and Ethics Diversity Group. Following a framework that we call "Reflected in our Teams, Reflected in our Standards," both groups address EDI at different stages in their policy development process.

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Genome-Wide RNA Tomography in the Mouse Whole Olfactory Mucosa

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Abstract

Spatial transcriptomics allows for the genome-wide profiling of topographic gene expression patterns within a tissue of interest. Here, we describe our methodology to generate high-quality RNA-seq libraries from cryosections from fresh frozen mouse whole olfactory mucosae. This methodology can be extended to virtually any vertebrate organ or tissue sample.

Keywords: Cryosectioning; Low-input RNA; Olfaction; RNA-sequencing; Spatial transcriptomics; Tomo-seq; Whole olfactory mucosa.

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Stressed target cancer cells drive nongenetic reprogramming of CAR T cells and solid tumor microenvironment

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The poor efficacy of chimeric antigen receptor T-cell therapy (CAR T) for solid tumors is due to insufficient CAR T cell tumor infiltration, in vivo expansion, persistence, and effector function, as well as exhaustion, intrinsic target antigen heterogeneity or antigen loss of target cancer cells, and immunosuppressive tumor microenvironment (TME). Here we describe a broadly applicable nongenetic approach that simultaneously addresses the multiple challenges of CAR T as a therapy for solid tumors. The approach reprograms CAR T cells by exposing them to stressed target cancer cells which have been exposed to the cell stress inducer disulfiram (DSF) and copper (Cu)(DSF/Cu) plus ionizing irradiation (IR). The reprogrammed CAR T cells acquire early memory-like characteristics, potent cytotoxicity, enhanced in vivo expansion, persistence, and decreased exhaustion. Tumors stressed by DSF/Cu and IR also reprogram and reverse the immunosuppressive TME in humanized mice. The reprogrammed CAR T cells, derived from peripheral blood mononuclear cells of healthy donors or metastatic female breast cancer patients, induce robust, sustained memory and curative anti-solid tumor responses in multiple xenograft mouse models, establishing proof of concept for empowering CAR T by stressing tumor as a promising therapy for solid tumors.

Chimeric antigen receptor T-cell therapy (CAR T) has achieved unprecedented success as a novel immunotherapy with curative potential for certain hematologic cancers[1]. In contrast, results from clinical trials of CAR T for solid tumors have been disappointing[2,3]. Many factors contribute to the poor efficacy of CAR T for solid tumors. These include insufficient infiltration, expansion, persistence, and effector function, resulting in the ultimate exhaustion of adoptively transferred CAR T cells and an immunosuppressive tumor microenvironment (TME)[4]. In addition, intrinsic target antigen heterogeneity and/or antigen loss due to selective pressure by targeted therapies[5,6] also contribute to the resistance of solid tumors to CAR T[7,8]. Significant efforts have been made to genetically engineer modified CAR T cells to promote more effective treatments for solid tumors. These include, but are not limited to, altering an array of tumor-specific CAR T cells to

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BMC Cancer

RESEARCH Open Access

Associations between telomere attrition, genetic variants in telomere maintenance genes, and non-small cell lung cancer risk in the Jammu and Kashmir population of North India

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Abstract

Background Telomeres are repetitive DNA sequences located at the ends of chromosomes, playing a vital role in maintaining chromosomal integrity and stability. Dysregulation of telomeres has been implicated in the development of various cancers, including non-small cell lung cancer (NSCLC), which is the most common type of lung cancer. Genetic variations within telomere maintenance genes may influence the risk of developing NSCLC. The present study aimed to evaluate the genetic associations of select variants within telomere maintenance genes in a population from Jammu and Kashmir, North India, and to investigate the relationship between telomere length and NSCLC risk.

Methods We employed the cost-effective and high-throughput MassARRAY MALDI-TOF platform to assess the genetic associations of select variants within telomere maintenance genes in a population from Jammu and Kashmir, North India. Additionally, we used TaqMan genotyping to validate our results. Furthermore, we investigated telomere length variation and its relation to NSCLC risk in the same population using dual-labeled fluorescence-based qPCR.

Results Our findings revealed significant associations of TERT rs10069690 and POT1 rs10228682 with NSCLC risk (adjusted *p*-values = 0.019 and 0.002, respectively), while TERF2 rs251796 and rs2975843 showed no significant associations. The TaqMan genotyping validation further substantiated the associations of TERT rs10069690 and rs2242652 with NSCLC risk (adjusted *p*-values = 0.02 and 0.003, respectively). Our results also demonstrated significantly shorter telomere lengths in NSCLC patients compared to controls ($p = 0.0004$).

Conclusion This study highlights the crucial interplay between genetic variation in telomere maintenance genes, telomere attrition, and NSCLC risk in the Jammu and Kashmir population of North India. Our findings suggest that TERT

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Immunologic constant of rejection as a predictive biomarker of immune checkpoint inhibitors efficacy in non-small cell lung cancer

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Abstract

Background Anti-PD1/PDL1 immune checkpoint inhibitors (ICI) transformed the prognosis of patients with advanced non-small cell lung cancer (NSCLC). However, the response rate remains disappointing and toxicity may be life-threatening, making urgent identification of biomarkers predictive for efficacy. Immunologic Constant of Rejection signature (ICR) is a 20-gene expression signature of cytotoxic immune response with prognostic value in some solid cancers. Our objective was to assess its predictive value for benefit from anti-PD1/PDL1 in patients with advanced NSCLC.

Methods We retrospectively profiled 44 primary tumors derived from NSCLC patients treated with ICI as single-agent in at least the second-line metastatic setting. Transcriptomic analysis was performed using the nCounter® analysis system and the PanCancer Immune Profiling Panel. We then pooled our data with clinico-biological data from four public gene expression data sets, leading to a total of 162 NSCLC patients treated with single-agent anti-PD1/PDL1. ICR was applied to all samples and correlation was searched between ICR classes and the Durable Clinical Benefit (DCB), defined as stable disease or objective response according to RECIST 1.1 for a minimum of 6 months after the start of ICI.

Results The DCB rate was 29%; 22% of samples were classified as ICR1, 30% ICR2, 22% ICR3, and 26% ICR4. These classes were not associated with the clinico-pathological variables, but showed enrichment from ICR1 to ICR4 in quantitative/qualitative markers of immune response. ICR2-4 class was associated with a 5.65-fold DCB rate when compared with ICR1 class. In multivariate analysis, ICR classification remained associated with DCB, independently from PDL1 expression and other predictive immune signatures. By contrast, it was not associated with disease-free survival in 556 NSCLC TCGA patients untreated with ICI.

Conclusion The 20-gene ICR signature was independently associated with benefit from anti-PD1/PDL1 ICI in patients with advanced NSCLC. Validation in larger retrospective and prospective series is warranted.

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Article

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Guadecitabine plus ipilimumab in unresectable melanoma: five-year follow-up and integrated multi-omic analysis in the phase 1b NIBIT-M4 trial

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Association with hypomethylating agents is a promising strategy to improve the efficacy of immune checkpoint inhibitors-based therapy. The NIBIT-M4 was a phase Ib, dose-escalation trial in patients with advanced melanoma of the hypomethylating agent guadecitabine combined with the anti-CTLA-4 antibody ipilimumab that followed a traditional 3 + 3 design (NCT02608437). Patients received guadecitabine 30, 45 or 60 mg/m^2/day subcutaneously on days 1 to 5 every 3 weeks starting on week 0 for a total of four cycles, and ipilimumab 3 mg/kg intravenously starting on day 1 of week 1 every 3 weeks for a total of four cycles. Primary outcomes of safety, tolerability, and maximum tolerated dose of treatment were previously reported. Here we report the 5-year clinical outcome for the secondary endpoints of overall survival, progression free survival, and duration of response, and an exploratory integrated multi-omics analysis on pre- and on-treatment tumor biopsies. With a minimum follow-up of 45 months, the 5-year overall survival rate was 28.9% and the median duration of response was 20.6 months. Re-expression of immunomodulatory endogenous retroviruses and of other repetitive elements, and a mechanistic signature of guadecitabine are associated with response. Integration of a genetic immunoediting index with an adaptive immunity signature stratifies patients/lesions into four distinct subsets and discriminates 5-year overall survival and progression free survival. These results suggest that coupling genetic immunoediting with activation of adaptive immunity is a relevant requisite for achieving long term clinical benefit by epigenetic immunomodulation in advanced melanoma patients.

Immune checkpoint inhibitors (ICI) are drugs targeting regulatory pathways in T cells to enhance antitumor immune responses[1]. Treatment with ICI has dramatically improved the clinical outcome of patients with tumors of different histotypes[2], including melanoma[3], and lung cancer[4]. However, the percentage of subjects who benefit from ICI therapy is still low, and novel therapeutic strategies are eagerly awaited to fully exploit their clinical potential. Indeed, even in the most responsive tumor types, both intrinsic[5] and acquired resistance[6,7] limit the efficacy of ICI therapy. The cellular and molecular characterization of human tumor samples by high-throughput and deep phenotyping approaches define the role of the immune microenvironment in driving the

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Role of the vaginal microbiome in miscarriage: exploring the relationship

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Miscarriage is a devastating pregnancy loss that affects many women worldwide. It is characterized as a spontaneous miscarriage that occurs before 20 weeks of gestation which affects more than 25% of pregnancies. While the causes of miscarriage are complex and multifactorial, recent research has suggested a potential role of the vaginal microbiota. The vaginal microbiome is a dynamic ecosystem of microbes that are essential for preserving vaginal health and avoiding infections. Vaginal dysbiosis has been accompanied with numerous adverse pregnancy complications, such as preterm birth. However, the effect of the vaginal microbiome in miscarriage is not fully understood. This review aims to investigate the link between vaginal microbiota and miscarriage. Also, we investigate the various mechanisms through which the vaginal microbiota may affect miscarriage. Additionally, we examine the implications of these research findings, specifically the possibility of vaginal microbiome screening and targeted interventions to prevent miscarriage.

KEYWORDS

pregnancy complications, pregnancy loss, vaginal microbiota, vaginal dysbiosis, inflammation

1 Introduction

Miscarriage is a prevalent issue in obstetrics, affecting approximately 25% of pregnancies worldwide. Miscarriages can be divided into two categories based on time: early miscarriages, which occur before to 12 weeks of gestation, and late losses, which occurs between 12 and 22 weeks of pregnancy (Larsen et al., 2013; Al-Memar et al., 2020). Despite being common, the causes of the majority of miscarriages are still unknown (Larsen et al., 2013). Possible factors include uterine abnormalities (Chan et al., 2011), incorrect embryo selection (Kiecka et al., 2021), genetic (Demey et al., 1991; Branch et al., 2010) and epigenetic issues (Daher et al., 2012; Yin et al., 2012),, diseases of the embryo, immunological factors (Holers et al., 2002; Calleja-Agius et al., 2012),, endocrine variables (Cocksedge et al., 2009) chromosomal problems and lifestyle choices (Larsen et al., 2013) which may contribute to its occurrence.

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Positive regulation of oxidative phosphorylation by nuclear myosin 1 protects cells from metabolic reprogramming and tumorigenesis in mice

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Metabolic reprogramming is one of the hallmarks of tumorigenesis. Here, we show that nuclear myosin 1 (NM1) serves as a key regulator of cellular metabolism. NM1 directly affects mitochondrial oxidative phosphorylation (OXPHOS) by regulating mitochondrial transcription factors TFAM and PGC1α, and its deletion leads to underdeveloped mitochondria inner cristae and mitochondrial redistribution within the cell. These changes are associated with reduced OXPHOS gene expression, decreased mitochondrial DNA copy number, and deregulated mitochondrial dynamics, which lead to metabolic reprogramming of NM1 KO cells from OXPHOS to aerobic glycolysis.This, in turn, is associated with a metabolomic profile typical for cancer cells, namely increased amino acid-, fatty acid-, and sugar metabolism, and increased glucose uptake, lactate production, and intracellular acidity. NM1 KO cells form solid tumors in a mouse model, suggesting that the metabolic switch towards aerobic glycolysis provides a sufficient carcinogenic signal. We suggest that NM1 plays a role as a tumor suppressor and that NM1 depletion may contribute to the Warburg effect at the onset of tumorigenesis.

Functional mitochondria are crucial for a healthy cell as they maintain intracellular calcium levels, communicate with the nucleus via metabolites produced by the Krebs cycle to initiate epigenetic changes and modulate their dynamics to fit the bio-energetic demands of cells[1–4]. However, their primary role is to produce energy in the form of up to 36 ATP molecules via OXPHOS. In hypoxic conditions, cells switch to the less efficient glycolysis pathway, which converts glucose to lactate and produces only 2 molecules of ATP per molecule of glucose. As the majority of cells use OXPHOS as a primary energy source, the expression of both nuclear and mitochondrial genes encoding macromolecular complexes involved in the OXPHOS electron transport chain is tightly regulated[5]. This is not true for highly proliferating

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Harnessing large language models (LLMs) for candidate gene prioritization and selection

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Abstract

Background Feature selection is a critical step for translating advances afforded by systems-scale molecular profiling into actionable clinical insights. While data-driven methods are commonly utilized for selecting candidate genes, knowledge-driven methods must contend with the challenge of efficiently sifting through extensive volumes of biomedical information. This work aimed to assess the utility of large language models (LLMs) for knowledge-driven gene prioritization and selection.

Methods In this proof of concept, we focused on 11 blood transcriptional modules associated with an Erythroid cells signature. We evaluated four leading LLMs across multiple tasks. Next, we established a workflow leveraging LLMs. The steps consisted of: (1) Selecting one of the 11 modules; (2) Identifying functional convergences among constituent genes using the LLMs; (3) Scoring candidate genes across six criteria capturing the gene's biological and clinical relevance; (4) Prioritizing candidate genes and summarizing justifications; (5) Fact-checking justifications and identifying supporting references; (6) Selecting a top candidate gene based on validated scoring justifications; and (7) Factoring in transcriptome profiling data to finalize the selection of the top candidate gene.

Results Of the four LLMs evaluated, OpenAI's GPT-4 and Anthropic's Claude demonstrated the best performance and were chosen for the implementation of the candidate gene prioritization and selection workflow. This workflow was run in parallel for each of the 11 erythroid cell modules by participants in a data mining workshop. Module M9.2 served as an illustrative use case. The 30 candidate genes forming this module were assessed, and the top five scoring genes were identified as BCL2L1, ALAS2, SLC4A1, CA1, and FECH. Researchers carefully fact-checked the summarized scoring justifications, after which the LLMs were prompted to select a top candidate based on this information. GPT-4 initially chose BCL2L1, while Claude selected ALAS2. When transcriptional profiling data from three reference datasets were provided for additional context, GPT-4 revised its initial choice to ALAS2, whereas Claude reaffirmed its original selection for this module.

Conclusions Taken together, our findings highlight the ability of LLMs to prioritize candidate genes with minimal human intervention. This suggests the potential of this technology to boost productivity, especially for tasks that require leveraging extensive biomedical knowledge.

Keywords Transcriptomics, Erythroid cells, Feature selection, Large language models, Generative artificial intelligence

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ARTICLE OPEN

Control of TGFβ signalling by ubiquitination independent function of E3 ubiquitin ligase TRIP12

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Transforming growth factor β (TGFβ) pathway is a master regulator of cell proliferation, differentiation, and death. Deregulation of TGFβ signalling is well established in several human diseases including autoimmune disorders and cancer. Thus, understanding molecular pathways governing TGFβ signalling may help better understand the underlying causes of some of those conditions. Here, we show that a HECT domain E3 ubiquitin ligase TRIP12 controls TGFβ signalling in multiple models. Interestingly, TRIP12 control of TGFβ signalling is completely independent of its E3 ubiquitin ligase activity. Instead, TRIP12 recruits SMURF2 to SMAD4, which is most likely responsible for inhibitory monoubiquitination of SMAD4, since SMAD4 monoubiquitination and its interaction with SMURF2 were dramatically downregulated in *TRIP12*$^{-/-}$ cells. Additionally, genetic inhibition of *TRIP12* in human and murine cells leads to robust activation of TGFβ signalling which was rescued by re-introducing wildtype TRIP12 or a catalytically inactive C1959A mutant. Importantly, TRIP12 control of TGFβ signalling is evolutionary conserved. Indeed, genetic inhibition of *Drosophila TRIP12* orthologue, *ctrip*, in gut leads to a reduced number of intestinal stem cells which was compensated by the increase in differentiated enteroendocrine cells. These effects were completely normalised in *Drosophila* strain where *ctrip* was co-inhibited together with *Drosophila SMAD4* orthologue, *Medea*. Similarly, in murine 3D intestinal organoids, CRISPR/Cas9 mediated genetic targeting of *Trip12* enhances TGFβ mediated proliferation arrest and cell death. Finally, CRISPR/Cas9 mediated genetic targeting of *TRIP12* in MDA-MB-231 breast cancer cells enhances the TGFβ induced migratory capacity of these cells which was rescued to the wildtype level by re-introducing wildtype TRIP12. Our work establishes TRIP12 as an evolutionary conserved modulator of TGFβ signalling in health and disease.

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INTRODUCTION

TGFβ family is a group of multifunctional cytokines involved in various cellular processes including embryogenesis, immune cell function, cell cycle regulation, tissue homoeostasis, extracellular matrix production, and tissue remodelling and repair [1–3]. TGFβ exerts its function via binding to and activating specific heteromeric serine-threonine activin receptor like kinases (ALK4/5) also known as type I and type II serine-threonine kinases [4]. The active TGFβ/Activin type I receptor directly phosphorylate the receptor-regulated SMADs (R-SMADs), SMAD2 and SMAD3 respectively. Phosphorylated R-SMADs interact with the common interacting partner and the major regulator of TGFβ/BMP signalling, SMAD4. The R-SMADs/SMAD4 heteromeric complex translocates to the nucleus leading to robust activation of downstream TGFβ pathway genes [5, 6].

In healthy tissues, TGFβ pathway activation leads to cell cycle arrest and apoptosis [7]. Due to its strong cytostatic ability, TGFβ is a potent tumour suppressor, and several members of TGFβ signalling pathway are frequently mutated in human cancers including colon and pancreatic cancer [8, 9]. Additionally, TGFβ may promote cancer growth by promoting epithelial-to-mesenchymal transition (EMT), cancer metastasis and invasion, and modulation of tumour microenvironment [10, 11]. Thus, TGFβ activity is tightly regulated by different mechanisms. For example, *SMAD7*, one of the downstream TGFβ pathway genes, contributes to the resolution of TGFβ activity by recruiting of E3 ubiquitin ligase SMURF2 to the TGFβR1 thereby facilitating its polyubiquitination and proteasome mediated degradation [12]. In addition, monoubiquitination of SMAD4 leads to its dissociation from the active R-SMADs complex and termination of TGFβ response [13]. Different E3 ubiquitin ligases including SMURF2 and TRIM33 have been implicated in inhibitory SMAD4 monoubiquitination [14–16].

The thyroid hormone receptor interactor protein 12 (TRIP12), also known as the E3 ubiquitin ligase for Arf, is a HECT-domain E3 ubiquitin ligase. TRIP12 is involved in DNA damage response, oncogenic stress, cell cycle control, and neurodegeneration [17–21]. Additionally, TRIP12 regulates response to PARP inhibitors in breast cancer cells [22] and we have shown that the genetic

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Original article

In vitro evaluation of Neosetophomone B inducing apoptosis in cutaneous T cell lymphoma by targeting the FOXM1 signaling pathway

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ABSTRACT

Background: Cutaneous T cell lymphoma (CTCL) is a T cell-derived non-Hodgkin lymphoma primarily affecting the skin, with treatment posing a significant challenge and low survival rates.
Objective: In this study, we investigated the anti-cancer potential of Neosetophomone B (NSP-B), a fungal-derived secondary metabolite, on CTCL cell lines H9 and HH.
Methods: Cell viability was measured using Cell counting Kit-8 (CCK8) assays. Apoptosis was measured by annexin V/PI dual staining. Immunoblotting was performed to examine the expression of proteins. Applied Biosystems' high-resolution Human Transcriptome Array 2.0 was used to examine gene expression.
Results: NSP-B induced apoptosis in CTCL cells by activating mitochondrial signaling pathways and caspases. We observed downregulated expression of BUB1B, Aurora Kinases A and B, cyclin-dependent kinases (CDKs) 4 and 6, and polo-like kinase 1 (PLK1) in NSP-B treated cells, which was further corroborated by Western blot analysis. Notably, higher expression levels of these genes showed reduced overall and progression-free survival in the CTCL patient cohort. FOXM1 and BUB1B expression exhibited a dose-dependent reduction in NSP-B-treated CTCL cells.FOXM1 silencing decreased cell viability and increased apoptosis via BUB1B downregulation. Moreover, NSP-B suppressed FOXM1-regulated genes, such as Aurora Kinases A and B, CDKs 4 and 6, and PLK1. The combined treatment of Bortezomib and NSP-B showed greater efficacy in reducing CTCL cell viability and promoting apoptosis compared to either treatment alone.
Conclusion: Our findings suggest that targeting the FOXM1 pathway may provide a promising therapeutic strategy for CTCL management, with NSP-B offering significant potential as a novel treatment option.

1. Introduction

Cancer is a leading cause of human mortality, responsible for over 9.6 million deaths annually [1]. The growing incidence is attributed to aging populations, genetic predispositions, and epigenetic factors like unhealthy lifestyles or drug-induced immunosuppression [1,2]. Current projections estimate that one in eight men and one in ten women will develop cancer during their lifetimes. By 2030, cancer is expected to cause 13 million deaths annually [3]. Cutaneous lymphoma, a lymphocyte cancer, is the

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RESEARCH ARTICLE

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Neosetophomone B induces apoptosis in multiple myeloma cells via targeting of AKT/SKP2 signaling pathway

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Abstract

Multiple myeloma (MM) is a hematologic malignancy associated with malignant plasma cell proliferation in the bone marrow. Despite the available treatments, drug resistance and adverse side effects pose significant challenges, underscoring the need for alternative therapeutic strategies. Natural products, like the fungal metabolite neosetophomone B (NSP-B), have emerged as potential therapeutic agents due to their bioactive properties. Our study investigated NSP-B's antitumor effects on MM cell lines (U266 and RPMI8226) and the involved molecular mechanisms. NSP-B demonstrated significant growth inhibition and apoptotic induction, triggered by reduced AKT activation and downregulation of the inhibitors of apoptotic proteins and S-phase kinase protein. This was accompanied by an upregulation of p21Kip1 and p27Cip1 and an elevated Bax/BCL2 ratio, culminating in caspase-dependent apoptosis. Interestingly, NSP-B also enhanced the cytotoxicity of bortezomib (BTZ), an existing MM treatment. Overall, our findings demonstrated that NSP-B induces caspase-dependent apoptosis, increases cell damage, and suppresses MM cell proliferation while improving the cytotoxic impact of BTZ. These findings suggest that NSP-B can be used alone or in combination with other medicines to treat MM, highlighting its importance as a promising phytoconstituent in cancer therapy.

KEYWORDS

AKT, caspases, drug synergy, multiple myeloma, neosetophomone B, SKP2

Association of intestinal dysbiosis with susceptibility to multiple sclerosis: Evidence from different population studies (Review)

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Abstract. Understanding the relationship between microorganisms that live in our intestines and neuroinflammatory and neurodegenerative pathologies of the central nervous system (CNS) is essential, since they have been shown to have an immunomodulatory effect in neurological disorders, such as multiple sclerosis (MS). The gut microbiota can be affected by several environmental factors, including infections, physical and emotional stress and diet, the latter known as the main modulator of intestinal bacteria. An abrupt shift in the gut microbiota composition and function is known as dysbiosis, a state of local and systemic inflammation produced by pathogenic bacteria and its metabolites responsible for numerous neurological symptoms. It may also trigger neuronal damage in patients diagnosed with MS. Intestinal dysbiosis affects the permeability of the intestine, allowing chronic low-grade bacterial translocation from the intestine to the circulation, which may overstimulate immune cells and cells resident in the CNS, break immune tolerance and, in addition, alter the permeability of the blood-brain barrier (BBB). This way, toxins, inflammatory molecules and oxidative stress molecules can pass freely into the CNS and cause extensive damage to the brain. However, commensal bacteria, such as the *Lactobacillus* genus and *Bacteroides fragilis*, and their metabolites (with anti-inflammatory potential), produce neurotransmitters such as γ-aminobutyric acid, histamine, dopamine, norepinephrine, acetylcholine and serotonin, which are important for neurological regulation. In addition, reprogramming the gut microbiota of patients with MS with a healthy gut microbiota may help improve the integrity of the gut

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Abbreviations: AFB1, aflatoxin B1; AhR, aryl hydrocarbon receptor; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CIS, clinically isolated syndrome; CNS, central nervous system; CVD, cardiovascular disease; EAE, experimental autoimmune encephalomyelitis; ENS, enteric nervous system; FMT, fecal microbiota transplantation; FoxP3, forkhead box protein 3; FXR, farnesoid receptor X; GA, glatiramer acetate; GABA, γ-aminobutyric acid; GALT, gut-associated lymphoid tissue; GPBAR1, G-protein-coupled bile acid receptor 1; GM, gut microbiota; IBS, irritable bowel syndrome; IFN-γ, interferon-γ; IL-2, interleukin 2; IL-10Rα, IL-10 receptor α; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharides; miRNA, microRNA; MS, multiple sclerosis; NF-κB, nuclear factor κB; NMR, nuclear magnetic resonance; NLR, nucleotide-binding oligomerization domain-like receptors; NLRP6, pyrimidine domain of inflammasome 6; RCT, randomized controlled trial; ROS, reactive oxygen species; RRMS, relapsing-remitting multiple sclerosis; rRNA, ribosomal RNA; RXR, receptor X retinoide; SCFAs, short-chain fatty acids; SPMS, secondary progressive multiple sclerosis; T1DM, type 1 diabetes mellitus; Th, T-helper cell; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell; VDR, vitamin D receptor

Key words: multiple sclerosis, gut microbiota, intestinal dysbiosis, neuroinflammation, neurodegenerative disease

Molecular Therapy
Nucleic Acids
Review

Progress and harmonization of gene editing to treat human diseases: Proceeding of COST Action CA21113 GenE-HumDi

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Human MCTS1-dependent translation of JAK2 is essential for IFN-γ immunity to mycobacteria

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

Abstract

Human inherited disorders of IFN-γ immunity underlie severe mycobacterial diseases. We report X-linked recessive MCTS1 deficiency in men with mycobacterial disease from kindreds of different ancestries (from China, Finland, Iran, and Saudi Arabia). Complete deficiency of this translation re-initiation factor impairs the translation of a subset of proteins, including the kinase JAK2 in all cell types tested, including T lymphocytes and phagocytes. JAK2 expression is sufficiently low to impair cellular responses to IL-23 and partially IL-12, but not other JAK2-dependent cytokines. Defective responses to IL-23 preferentially impair the production of IFN-γ by innate-like adaptive MAIT and γδ T lymphocytes upon mycobacterial challenge. Surprisingly, the lack of MCTS1-dependent translation re-initiation and ribosome recycling seems to be otherwise physiologically redundant in these patients. These findings suggest that X-linked recessive human MCTS1 deficiency underlies isolated mycobacterial disease by impairing JAK2 translation in innate-like adaptive T lymphocytes, thereby impairing the IL-23-dependent induction of IFN-γ.

One-Sentence Summary:

X-linked recessive human MCTS1 deficiency underlies mycobacterial disease by impairing JAK2 translation in innate-like T lymphocytes, thereby decreasing the IL-23-dependent production of IFN-γ by these cells upon mycobacterial challenge.

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Author Contributions

J.Bo., J.Bu., Q.Zha. and J.-L.C. conceived the study, designed the experiments, interpreted the data, and drafted the manuscript. J.Bo., Q.Zho., Q.Zha., C.C., Y.S., A.C., and L.A. analyzed WES data. J.Bo, Q.Zho., M.R. Q.P., J.R., M.O., A.-L.N., C.A.A.F., A.S.LH., L.E., J.E.H., C.Sc., C.So., T.L.-V., M.E., M.M., M.R., M.S., N.M., T.K., T.V., D.B., A.E., R.Y., A.Y., J.Pe., J.Pu., M.M.-V., M.M.-F., F.S., V.B., S.B-D., and Z.J., performed experiments and generated figures. S.S., E.S., M.A-S., G.E.G., N.Y., T.N., S.H., M.S., N.P., N.R., X.W., Q.Zha., and J.Bu. recruited patients and coordinated the clinical study protocol and sample collection. J.Bo., M.O., P.Z., and D.R. analyzed RNA-seq experiments. S.B.-D., A.T., J-.L.C., Q.Zha., and J.Bu. supervised experiments or analyses. All the authors discussed, revised, and approved the manuscript.

Declaration of interests

J.-L.C. serves on the scientific advisory boards of ADMA Biologics Inc., Kymera Therapeutics, and Elixiron Immunotherapeutics.

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RESEARCH Open Access

Unveiling the dynamics of the breast milk microbiome: impact of lactation stage and gestational age

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Abstract

Background Breast milk (BM) provides complete nutrition for infants for the first six months of life and is essential for the development of the newborn's immature immune and digestive systems. While BM was conventionally believed to be sterile, recent advanced high throughput technologies have unveiled the presence of diverse microbial communities in BM. These insights into the BM microbiota have mainly originated from uncomplicated pregnancies, possibly not reflecting the circumstances of mothers with pregnancy complications like preterm birth (PTB).

Methods In this article, we investigated the BM microbial communities in mothers with preterm deliveries (before 37 weeks of gestation). We compared these samples with BM samples from healthy term pregnancies across different lactation stages (colostrum, transitional and mature milk) using 16S rRNA gene sequencing.

Results Our analysis revealed that the microbial communities became increasingly diverse and compositionally distinct as the BM matured. Specifically, mature BM samples were significantly enriched in *Veillonella* and *lactobacillus* (Kruskal Wallis; $p < 0.001$) compared to colostrum. The comparison of term and preterm BM samples showed that the community structure was significantly different between the two groups (Bray Curtis and unweighted unifrac dissimilarity; $p < 0.001$). Preterm BM samples exhibited increased species richness with significantly higher abundance of *Staphylococcus haemolyticus, Propionibacterium acnes, unclassified Corynebacterium species*. Whereas term samples were enriched in *Staphylococcus epidermidis, unclassified OD1,* and *unclassified Veillonella* among others.

Conclusion Our study underscores the significant influence of pregnancy-related complications, such as preterm birth (before 37 weeks of gestation), on the composition and diversity of BM microbiota. Given the established significance of the maternal microbiome in shaping child health outcomes, this investigation paves the way for identifying modifiable factors that could optimize the composition of BM microbiota, thereby promoting maternal and infant health.

Keywords Breast milk, Microbiome, Preterm birth, Breastfeeding, Prematurity

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Original Article

MOLECULAR METABOLISM

Short-term consumption of highly processed diets varying in macronutrient content impair the sense of smell and brain metabolism in mice

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ABSTRACT

Objective: Food processing greatly contributed to increased food safety, diversity, and accessibility. However, the prevalence of highly palatable and highly processed food in our modern diet has exacerbated obesity rates and contributed to a global health crisis. While accumulating evidence suggests that chronic consumption of such foods is detrimental to sensory and neural physiology, it is unclear whether its short-term intake has adverse effects. Here, we assessed how short-term consumption (<2 months) of three diets varying in composition and macronutrient content influence olfaction and brain metabolism in mice.

Methods: The diets tested included a grain-based standard chow diet (CHOW; 54% carbohydrate, 32% protein, 14% fat; #8604 Teklad Rodent diet , Envigo Inc.), a highly processed control diet (hpCTR; 70% carbohydrate, 20% protein, 10% fat; #D12450B, Research Diets Inc.), and a highly processed high-fat diet (hpHFD; 20% carbohydrate, 20% protein, 60% fat; #D12492, Research Diets Inc.). We performed behavioral and metabolic phenotyping, electro-olfactogram (EOG) recordings, brain glucose metabolism imaging, and mitochondrial respirometry in different brain regions. We also performed RNA-sequencing (RNA-seq) in the nose and across several brain regions, and conducted differential expression analysis, gene ontology, and network analysis.

Results: We show that short-term consumption of the two highly processed diets, but not the grain-based diet, regardless of macronutrient content, adversely affects odor-guided behaviors, physiological responses to odorants, transcriptional profiles in the olfactory mucosa and brain regions, and brain glucose metabolism and mitochondrial respiration.

Conclusions: Even short periods of highly processed food consumption are sufficient to cause early olfactory and brain abnormalities, which has the potential to alter food choices and influence the risk of developing metabolic disease.

Keywords Highly processed food; Diet; Olfaction; Metabolism; Obesity

1. INTRODUCTION

The evolutionary history of modern humans is riddled with seismic shifts in their patterns of food, production, consumption, and physical activity [1,2]. The rapid evolution of food processing, driven by industrialization and globalization of food systems in recent decades, has led to a wide range of processed foods, which greatly enhanced both food security (i.e., enough food for everyone) and nutrition security (i.e., adding important nutrients to processed foods) [3,4]. Presently, a substantial proportion of individuals in Western societies lead sedentary lifestyles within a fast-paced environment, constantly exposed to a multitude of sensory cues that promote the excessive consumption of

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RESEARCH Open Access

Modulation of SLFN11 induces changes in DNA Damage response in breast cancer

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Abstract

Background Lack of Schlafen family member 11 (SLFN11) expression has been recently identified as a dominant genomic determinant of response to DNA damaging agents in numerous cancer types. Thus, several strategies aimed at increasing SLFN11 are explored to restore chemosensitivity of refractory cancers. In this study, we examined various approaches to elevate SLFN11 expression in breast cancer cellular models and confirmed a corresponding increase in chemosensitivity with using the most successful efficient one. As oncogenic transcriptomic downregulation is often driven by methylation of the promotor region, we explore the demethylation effect of 5-aza-2′-deoxycytidine (decitabine), on the SLFN11 gene. Since SLFN11 has been reported as an interferon inducible gene, and interferon is secreted during an active anti-tumor immune response, we investigated the in vitro effect of IFN-γ on SLFN11 expression in breast cancer cell lines. As a secondary approach to pick up cross talk between immune cells and SLFN11 expression we used indirect co-culture of breast cancer cells with activated PBMCs and evaluated if this can drive SLFN11 upregulation. Finally, as a definitive and specific way to modulate SLFN11 expression we implemented SLFN11 dCas9 (dead CRISPR associated protein 9) systems to specifically increase or decrease SLFN11 expression.

Results After confirming the previously reported correlation between methylation of SLFN11 promoter and its expression across multiple cell lines, we showed in-vitro that decitabine and IFN-γ could increase moderately the expression of SLFN11 in both BT-549 and T47D cell lines. The use of a CRISPR-dCas9 UNISAM and KRAB system could increase or decrease SLFN11 expression significantly (up to fivefold), stably and specifically in BT-549 and T47D cancer cell lines. We then used the modified cell lines to quantify the alteration in chemo sensitivity of those cells to treatment with DNA Damaging Agents (DDAs) such as Cisplatin and Epirubicin or DNA Damage Response (DDRs) drugs like Olaparib. RNAseq was used to elucidate the mechanisms of action affected by the alteration in SLFN11 expression. In cell lines with robust SLFN11 promoter methylation such as MDA-MB-231, no SLFN11 expression could be induced by any approach.

Conclusion To our knowledge this is the first report of the stable non-lethal increase of SLFN11 expression in a cancer cell line. Our results show that induction of SLFN11 expression can enhance DDA and DDR sensitivity in breast

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vaccines

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Review

CAR-T-Cell Therapy in Multiple Myeloma: B-Cell Maturation Antigen (BCMA) and Beyond

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Abstract: Significant progress has been achieved in the realm of therapeutic interventions for multiple myeloma (MM), leading to transformative shifts in its clinical management. While conventional modalities such as surgery, radiotherapy, and chemotherapy have improved the clinical outcomes, the overarching challenge of effecting a comprehensive cure for patients afflicted with relapsed and refractory MM (RRMM) endures. Notably, adoptive cellular therapy, especially chimeric antigen receptor T-cell (CAR-T) therapy, has exhibited efficacy in patients with refractory or resistant B-cell malignancies and is now also being tested in patients with MM. Within this context, the B-cell maturation antigen (BCMA) has emerged as a promising candidate for CAR-T-cell antigen targeting in MM. Alternative targets include SLAMF7, CD38, CD19, the signaling lymphocyte activation molecule CS1, NKG2D, and CD138. Numerous clinical studies have demonstrated the clinical efficacy of these CAR-T-cell therapies, although longitudinal follow-up reveals some degree of antigenic escape. The widespread implementation of CAR-T-cell therapy is encumbered by several barriers, including antigenic evasion, uneven intratumoral infiltration in solid cancers, cytokine release syndrome, neurotoxicity, logistical implementation, and financial burden. This article provides an overview of

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RESEARCH ARTICLE

Development and validation of an Arabic language eye-tracking paradigm for the early screening and diagnosis of autism spectrum disorders in Qatar

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Abstract

Abnormal eye gaze is a hallmark characteristic of autism spectrum disorder (ASD). The primary aim of the present research was to develop an Arabic version of an objective measure of ASD, the "autism index" (AI), based on eye gaze tracking to social and nonsocial stimuli validated initially in the United States. The initial phase of this study included the translation of English language eye-tracking stimuli into stimuli appropriate for an Arabic-speaking culture. During the second phase, we tested it on a total of 144 children with ASD, and 96 controls. The AI had excellent internal consistency and test–retest reliability. Moreover, the AI showed good differentiation of ASD from control cases (AUC = 0.730, SE = 0.035). The AI was significantly positively correlated with SCQ total raw scores ($r = 0.46$, $p < 0.001$). ADOS-2 scores were only available in the ASD group and did not show a significant relationship with AI scores ($r = 0.10$, $p = 0.348$), likely due to the restricted range. The AI, when implemented using Arabic-translated stimuli in a Qatari sample, showed good diagnostic differentiation and a strong correlation with parent-reported ASD symptoms. Thus, the AI appears to have cross-cultural validity and may be useful as a diagnostic aide to inform clinical judgment and track ASD symptom levels as part of the evaluation process.

Lay Summary

This study aimed to create an Arabic version of a tool called the "autism index" (AI), which uses eye gaze tracking to assess autism spectrum disorder (ASD). The researchers translated the AI's eye-tracking tests into Arabic and tested it on

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Inflammatory protein signatures in individuals with obesity and metabolic syndrome

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There is variability in the metabolic health status among individuals presenting with obesity; some may be metabolically healthy, while others may have developed the metabolic syndrome, a cluster including insulin resistance, hypertension, dyslipidemia, and increased risk of cardiovascular disease and type 2 diabetes. The mechanisms contributing to this metabolic heterogeneity are not fully understood. To address this question, plasma samples from 48 individuals with BMI ≥ 35 kg/m^2 were examined (27 with and 21 without metabolic syndrome). Fasting plasma samples were subjected to Olink proteomics analysis for 184 cardiometabolic and inflammation-enriched proteins. Data analysis showed a clear differentiation between the two groups with distinct plasma protein expression profiles. Twenty-four proteins were differentially expressed (DEPs) between the two groups. Pathways related to immune cell migration, leukocyte chemotaxis, chemokine signaling, mucosal inflammatory response, tissue repair and remodeling were enriched in the group with metabolic syndrome. Functional analysis of DEPs revealed upregulation of 15 immunological pathways. The study identifies some of the pathways that are altered and reflect metabolic health in individuals with obesity. This provides valuable insights into some of the underlying mechanisms and can lead to identification of therapeutic targets to improve metabolic health in individuals with obesity.

The prevalence of obesity (defined as a body mass index [BMI] of ≥ 30 kg/m^2) has increased significantly posing a serious public health challenge. According to the World Obesity Federation, 813 million adults aged 20 years and older were affected by obesity worldwide in 2020 and it has been estimated that this figure will almost double by 2035[1] Whilst obesity, defined by BMI, is often associated with multiple health consequences including the metabolic syndrome (characterized by central adiposity, hypertension, dyslipidemia, and hyperglycaemia), type 2 diabetes and cardiovascular disease, many individuals within the obesity BMI threshold do not experience these obesity complications. About one-third of individuals with obesity present with no evidence of the metabolic syndrome and have been referred to as having "obesity only" (OBO). About half of OBO individuals may transition to a state of "obesity with metabolic syndrome" (OBM) over a period of 10 years[2]. Studying the pathophysiological processes underlying OBO and OBM will allow a more in depth understanding that will help better classification of obesity as a disease and potentially identify therapeutic targets for the cardiometabolic consequences of obesity. Previously, we have observed that the OBO and OBM phenotypes have differential miRNA and metabolic signatures[3,4]. In this case–control study, we examined differences in specific proteins, using a high throughput plasma protein-screening assay, between OBO and OBM groups.

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Shrinking the battlefield in cancer therapy: Nanotechnology against cancer stem cells

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Highlights

- Current cancer therapies face hurdles such as lack of specificity, cytotoxicity, and drug resistance.
- Tumors contain stem-like cells that can drive cancer progression and recurrence.
- Successful eradication of cancer stem cells is crucial for preventing cancer relapse and achieving effective treatment.
- Nanomaterials have the potential to enhance drug efficacy and bioavailability, offering a promising approach to target cancer stem cells.
- With their tunable properties, nanomaterials offer vast possibilities in cancer, prognosis, and treatment at both cellular and molecular levels.

Abstract

Cancer remains one of the leading causes of mortality worldwide, presenting a significant healthcare challenge owing to the limited efficacy of current treatments. The application of nanotechnology in cancer treatment leverages the unique optical, magnetic, and electrical attributes of nanomaterials to engineer innovative, targeted therapies. Specifically, manipulating nanomaterials allows for enhanced drug loading efficiency, improved bioavailability, and targeted delivery systems, reducing the non-specific cytotoxic effects characteristic of conventional chemotherapies. Furthermore, recent advances in nanotechnology have demonstrated encouraging results in specifically targeting CSCs, a key development considering the role of these cells in disease recurrence and resistance to treatment. Despite these breakthroughs, the clinical approval rates of nano-drugs have not kept pace with research advances, pointing to existing obstacles that must be addressed. In conclusion, nanotechnology presents a novel, powerful tool in the fight against cancer, particularly in targeting the elusive and treatment-resistant CSCs. This comprehensive review delves into the intricacies of nanotherapy, explicitly targeting cancer stem cells, their markers, and associated signaling pathways.

Graphical abstract

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Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards

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Abstract

Owing to advances in genomics that enable differentiation of molecular aetiologies, patients with monogenic inflammatory bowel disease (mIBD) potentially have access to genotype-guided precision medicine. In this Expert Recommendation, we review the therapeutic research landscape of mIBD, the reported response to therapies, the medication-related risks and systematic bias in reporting. The mIBD field is characterized by the absence of randomized controlled trials and is dominated by retrospective observational data based on case series and case reports. More than 25 off-label therapeutics (including small-molecule inhibitors and biologics) as well as cellular therapies (including haematopoietic stem cell transplantation and gene therapy) have been reported. Heterogeneous reporting of outcomes impedes the generation of robust therapeutic evidence as the basis for clinical decision making in mIBD. We discuss therapeutic goals in mIBD and recommend standardized reporting (mIBD REPORT (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards) to stratify patients according to a genetic diagnosis and phenotype, to assess treatment effects and to record safety signals. Implementation of these pragmatic standards should help clinicians to assess the therapy responses of individual patients in clinical practice and improve comparability between observational retrospective studies and controlled prospective trials, supporting future meta-analysis.

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Review

A comprehensive review of genomics, transcriptomics, proteomics, and metabolomic insights into the differentiation of *Pseudomonas aeruginosa* from the planktonic to biofilm state: A multi-omics approach

Mustafa Vohra [a b], Avleen Kour [a], Nitin Pal Kalia [c], Manoj Kumar [d], Sarika Sharma [e], Sundeep Jaglan [f], Narayan Kamath [b g], Sandeep Sharma [a]

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Highlights

- Omics-based technology is critical for targeted study of biofilm differential gene expression and essential biological macromolecules (DNA, RNA, proteins, metabolome) involved in biofilm formation.
- Deciphering spatial resolution within a biofilm will resolve biofilm localized gene expression.
- Multi-omics and AI-based approach helps to predict biofilm-based pathways based on molecular markers.

Abstract

Biofilm formation *by Pseudomonas aeruginosa* is primarily responsible for chronic wound and lung infections in humans. These infections are persistent owing to the biofilm's high tolerance to antimicrobials and constantly changing environmental factors. Understanding the mechanism governing biofilm formation can help to develop therapeutics explicitly directed against the molecular markers responsible for this process. After numerous years of research, many genes responsible for both in vitro and in vivo biofilm development remain unidentified. However, there is no “all in one” complete in vivo or in vitro biofilm model. Recent findings imply that the shift from planktonic bacteria to biofilms is a complicated and interrelated differentiation process. Research on the applications of omics technologies in *P. aeruginosa* biofilm development is ongoing, and these approaches hold great promise for expanding our knowledge of the mechanisms of biofilm formation. This review discusses the different factors that affect biofilm formation and compares *P. aeruginosa* biofilm formation using the omics approaches targeting essential biological macromolecules, such as DNA, RNA, Protein, and metabolome. Furthermore, we have outlined the application of currently available omics tools, such as genomics, proteomics, metabolomics, transcriptomics, and integrated multi-omics methodologies, to understand the differential gene expression (biofilm vs. planktonic bacteria) of *P. aeruginosa* biofilms.

Graphical abstract

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ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Identifying candidate genes underlying isolated congenital anosmia

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Abstract

An estimated 1 in 10 000 people are born without the ability to smell, a condition known as congenital anosmia, and about one third of those people have non-syndromic, or isolated congenital anosmia (ICA). Despite the significant impact of olfaction for our quality of life, the underlying causes of ICA remain largely unknown. Using whole exome sequencing (WES) in 10 families and 141 individuals with ICA, we identified a candidate list of 162 rare, segregating, deleterious variants in 158 genes. We confirmed the involvement of CNGA2, a previously implicated ICA gene that is an essential component of the olfactory transduction pathway. Furthermore, we found a loss-of-function variant in SREK1IP1 from the family gene candidate list, which was also observed in 5% of individuals in an additional non-family cohort with ICA. Although SREK1IP1 has not been previously associated with olfaction, its role in zinc ion binding suggests a potential influence on olfactory signaling. This study provides a more comprehensive understanding of the spectrum of genetic alterations and their etiology in ICA patients, which may improve the diagnosis, prognosis, and treatment of this disorder and lead to better understanding of the mechanisms governing basic olfactory function.

KEYWORDS
anosmia, CNGA2, olfaction, smell loss

1 | INTRODUCTION

Prior to the COVID-19 pandemic, it was estimated that 5% of the population experienced anosmia, or total loss of smell.[1] A smaller segment of the anosmic population (~3%[2,3] experience anosmia from birth, termed congenital anosmia (CA), which can be isolated (or non-syndromic; ICA) or exist as a symptom of a syndrome, such as Kallmann syndrome.[3] Despite the importance of olfaction for quality of life, the genetic bases for ICA remain largely unknown. Although more than a 100 genes are implicated in inherited deficits of both vision and hearing,[4,5] to date, only nine genes have been implicated in ICA (CNGA2, TENM1, PROKR2, PROK2, FGFR1, SEM3A, CHD7, ANOS1, FGF8).[6–12] Similar to inherited deficits in other sensory systems, ICA is a genetically heterogeneous disorder[3,6–8,10,13–15]; therefore, it is uncommon to find the same underlying gene responsible for ICA in unrelated families. Consequently, we expect that many genes contribute to anosmia, operating through a variety of distinct mechanisms.

A large portion of our understanding of the olfactory system is derived from non-human species and remains to be confirmed in humans.[16,17] Identifying human genes that correlate with anosmia can provide insight into the essential components of human olfaction. Previous research into the genetics of ICA often focused on a targeted search for genes identified as part of the rodent olfactory transduction pathway (i.e., CNGA2, GNAL, ACY3),[13,18–20] genes identified in

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Transitional circulation and hemodynamic monitoring in newborn infants

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Transitional circulation is normally transient after birth but can vary markedly between infants. It is actually in a state of transition between fetal (in utero) and neonatal (postnatal) circulation. In the absence of definitive clinical trials, information from applied physiological studies can be used to facilitate clinical decision making in the presence of hemodynamic compromise. This review summarizes the peculiar physiological features of the circulation as it transitions from one phenotype into another in term and preterm infants. The common causes of hemodynamic compromise during transition, intact umbilical cord resuscitation, and advanced hemodynamic monitoring are discussed.

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IMPACT:

- Transitional circulation can vary markedly between infants.
- There are alterations in preload, contractility, and afterload during the transition of circulation after birth in term and preterm infants.
- Hemodynamic monitoring tools and technology during neonatal transition and utilization of bedside echocardiography during the neonatal transition are increasingly recognized.
- Understanding the cardiovascular physiology of transition can help clinicians in making better decisions while managing infants with hemodynamic compromise.
- The objective assessment of cardio-respiratory transition and understanding of physiology in normal and disease states have the potential of improving short- and long-term health outcomes.

INTRODUCTION

Understanding the physiological changes that occur during the transition to newborn life is essential to correctly interpret the hemodynamic issues that may occur during and after this process. It is challenging for neonatologists to manage circulatory failure during the transition;[1] issues can differ between extreme preterm infants and term infants because premature infants have an immature circulation,[2] whereas circulatory systems can be malformed in term infants. Hence, the approach should be adopted for specific pathophysiological conditions such as patent ductus arteriosus (PDA), hypotension, intraventricular hemorrhage, birth asphyxia, severe growth restriction and pulmonary hypertension as the circulation transitions.[3–5]

This review summarizes the distinct features of transitional circulation and intact umbilical cord resuscitation during the transition. Some newer concepts of hemodynamic monitoring (neonatologist performing echocardiography, near-infrared spectroscopy (NIRS), electrical velocimetry) during the transition are also discussed that are being increasingly utilized at the bedside.

PHYSIOLOGY OF FETAL CIRCULATION

In the fetus, blood oxygenation occurs in the placenta as the fetal lungs are filled with liquid and do not function as an organ of gas exchange.[6,7] In humans, the single umbilical vein carries oxygenated blood from the placenta to the left atrium via the ductus venosus, which joins the IVC close to the IVC-right atrial junction. At the same time, deoxygenated blood from the lower part of the body flows via the IVC into the right atrium. Interestingly, these two (oxygenated and deoxygenated blood) flows do not mix due to the shape of the ductus venosus and the presence of the ridge of Eustachian valve. Therefore, most of the oxygenated blood flows toward the foramen ovale and enters the left atrium and reaches the left ventricle. As a result, in the fetus, the left ventricle receives its preload primarily from the organ of gas exchange (placenta) just like the adult (lung). Deoxygenated blood from IVC mixes with the SVC flow and enters the right ventricle.[4,8,9]

In the fetus, the right ventricle pumps deoxygenated blood into the main pulmonary artery during systole. However, because

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Diabetes Care
American Diabetes Association

Simplified Meal Announcement Versus Precise Carbohydrate Counting in Adolescents With Type 1 Diabetes Using the MiniMed 780G Advanced Hybrid Closed Loop System: A Randomized Controlled Trial Comparing Glucose Control

Goran Petrovski, Judith Campbell, Maheen Pasha, Emma Day, Khalid Hussain, Amel Khalifa, and Tim van den Heuvel

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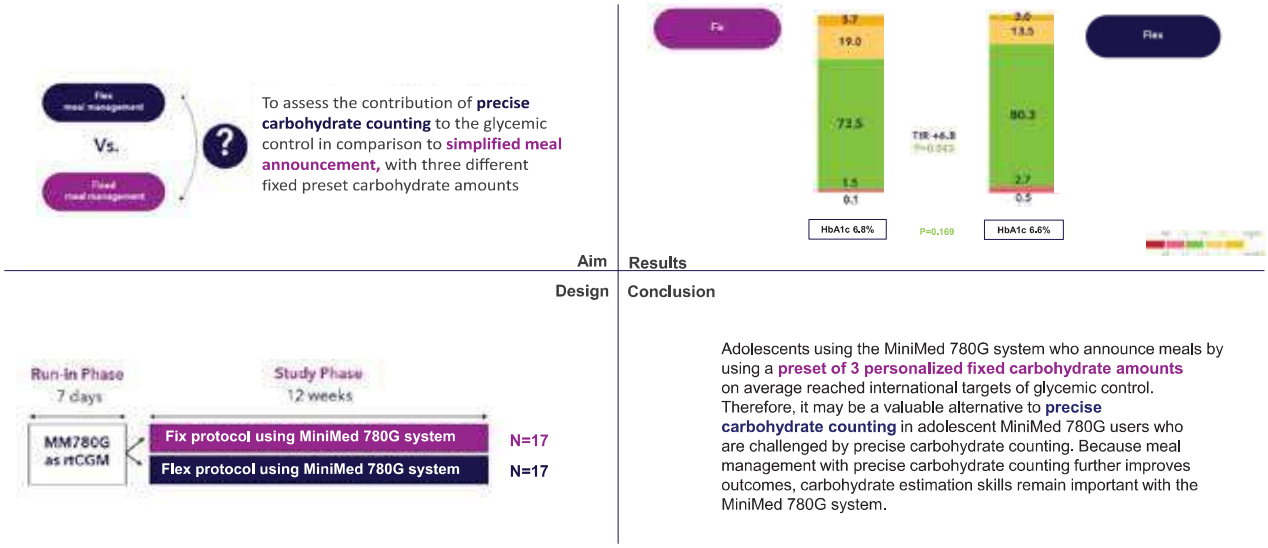

ARTICLE HIGHLIGHTS

- Adolescents using the MiniMed 780G system that announces meals by using a preset of three personalized fixed carbohydrate amounts on average reached international targets of glycemic control.
- This method may be a valuable alternative to precise carbohydrate counting in adolescent MiniMed 780G users who are challenged by precise carbohydrate counting.
- Meal management with precise carbohydrate counting further improves outcomes, and carbohydrate estimation skills remain important with the MiniMed 780G system.

BMC Health Services Research

RESEARCH

Open Access

Applying value-based strategies to accelerate access to novel cancer medications: guidance from the Oncology Health Economics Expert Panel in Qatar (Q-OHEP)

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Abstract

Background In line with global trends, cancer incidence and mortality may have decreased for specific types of cancer in Qatar. However, the cancer-related burden on patients, healthcare systems, and the economy is expected to expand; thus, cancer remains a significant public healthcare issue in Qatar. Qatar's free access to cancer care represents a considerable economic burden. Ensuring the best utilization of financial resources in the healthcare sector is important to provide unified and fair access to cancer care for all patients. Experts from the Qatar Oncology Health Economics Expert Panel (Q-OHEP) aimed to establish a consistent and robust base for evaluating oncology/hematology medications; involve patients' insights to accelerate access to cutting-edge medications; increase the value of cancer care; and reach a consensus for using cost-effective strategies and efficient methodologies in cancer treatment.

Methods The Q-OHEP convened on 30 November 2021 for a 3-hour meeting to discuss cancer management, therapeutics, and health economics in Qatar, focusing on four domains: (1) regulatory, (2) procurement, (3) treatment, and (4) patients. Discussions, guided by a moderator, focused on a list of suggested open-ended questions.

Results Some of the salient recommendations included the development of a formal, fast-track, preliminary approval pathway for drugs needed by patients with severe disease or in critical condition; and encouraging and promoting the conduct of local clinical trials and real-world observational studies using existing registry data. The Q-OHEP also recommended implementing a forecast system using treatment center data based on the supply/demand of formulary oncology drugs to detect treatment patterns, estimate needs, expedite procurement, and prevent shortages/delays. Furthermore, the panel discussed the needs to define value concerning cancer treatment in Qatar, implement value-based models for reimbursement decision-making such as health technology assessment and multiple-criteria

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CORRESPONDENCE

Protection against Reinfection with the Omicron BA.2.75 Subvariant

TO THE EDITOR: The BA.2.75 sublineage of the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may escape neutralizing antibodies. The BA.2.75 sublineage (primarily the BA.2.75.2 subvariant) became the predominant sublineage in Qatar by September 10, 2022 (Section S1 and Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We estimated the effectiveness of previous infection with SARS-CoV-2 in preventing reinfection with BA.2.75 using a test-negative, case–control study design (Section S2).[1]

In this study, the effectiveness of previous SARS-CoV-2 infection in preventing reinfection with BA.2.75 was defined as the proportional reduction in susceptibility to infection among persons who had had a previous infection as compared with those who had not been infected. We extracted data regarding SARS-CoV-2 laboratory testing, clinical infection, vaccination, and demographic details from the national SARS-CoV-2 databases, which include the results of all polymerase-chain-reaction and rapid antigen tests conducted at health care facilities in Qatar. Case participants (persons with positive SARS-CoV-2 tests) and controls (persons with negative SARS-CoV-2 tests) were matched exactly according to specific factors in order to balance observed confounders among the study groups (Fig. 1).[1,2] Previous infections were classified as pre-omicron infections if the positive test result was obtained before the onset of the omicron wave on December 19, 2021, and as omicron infections if the positive test result was obtained on or after that date.[2] Omicron infections were further classified according to subvariant or sublineage on the basis of the time period during which such infections were predominant: between December 19, 2021, and June 7, 2022, for BA.1 and BA.2 infections[2]; between June 8, 2022, and September 9, 2022, for BA.4 and BA.5 infections[2]; and between September 10, 2022, and October 18, 2022, for BA.2.75 infections.

Figure S2 shows the process for selecting the study population. Table S1 summarizes the characteristics of the study population, which was found to be broadly representative of the overall population of Qatar (Table S2). Most persons had been vaccinated with the mRNA vaccines that target the ancestral strain.

The effectiveness of previous pre-omicron infection against reinfection with BA.2.75, irrespective of the presence of symptoms, was 6.0% (95% confidence interval [CI], 1.5 to 10.4) (Fig. 1A and Table S3). The effectiveness of previous BA.1 or BA.2 infection was 49.9% (95% CI, 47.6 to 52.1), and the effectiveness of previous BA.4 or BA.5 infection was 80.6% (95% CI, 71.2 to 87.0). The effectiveness of previous pre-omicron infection, followed by BA.1 or BA.2 infection, against BA.2.75 reinfection was 56.4% (95% CI, 50.5 to 61.6). The effectiveness of previous pre-omicron infection, followed by BA.4 or BA.5 infection, was 91.6% (95% CI, 65.1 to 98.0).

We found similar but slightly higher effectiveness against symptomatic BA.2.75 reinfection (Table S3). Sensitivity analyses with adjustment for differences in testing frequency among the study groups confirmed the study results (Table S4). Analyses that were stratified according to the duration of time since the previous infection showed that the effectiveness of previous infection against any BA.2.75 reinfection was higher with more recent previous infection (Fig. 1B and Table S5). Analyses that were stratified according to vaccination status indicated that the effectiveness of previous infection was higher among persons who had had previous omicron infection and had been vaccinated than among those who had had previous omicron infection and had not been vaccinated (Fig. 1C and 1D and Table S5). These results confirm those of earlier reports, which indicated that previous pre-omicron infection or vaccination followed by omicron infection enhances protection against future omicron infection.[3,4] Cases of severe SARS-CoV-2 infection were rare (Section

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BASIC SCIENCE ARTICLE OPEN

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Vaccine evaluation and genotype characterization in children infected with rotavirus in Qatar

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BACKGROUND: We characterized and identified the genetic and antigenic variations of circulating rotavirus strains in comparison to used rotavirus vaccines.
METHODS: Rotavirus-positive samples ($n = 231$) were collected and analyzed. The VP7 and VP4 genes were sequenced and analyzed against the rotavirus vaccine strains. Antigenic variations were illustrated on the three-dimensional models of surface proteins.
RESULTS: In all, 59.7% of the hospitalized children were vaccinated, of which only 57.2% received two doses. There were no significant differences between the vaccinated and non-vaccinated groups in terms of clinical outcome. The G3 was the dominant genotype (40%) regardless of vaccination status. Several amino acid changes were identified in the VP7 and VP4 antigenic epitopes compared to the licensed vaccines. The highest variability was seen in the G3 (6 substitutions) and P[4] (11 substitutions) genotypes in comparison to RotaTeq®. In comparison to Rotarix®, G1 strains possessed three amino acid changes in 7-1a and 7-2 epitopes while P[8] strains possessed five amino acid changes in 8-1 and 8-3 epitopes.
CONCLUSIONS: The current use of Rotarix® vaccine might not be effective in preventing the infection due to the higher numbers of G3-associated cases. The wide range of mutations in the antigenic epitopes compared to vaccine strains may compromise the vaccine's effectiveness.

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IMPACT:

- The reduced rotavirus vaccine effectiveness necessitate regular evaluation of the vaccine content to ensure optimal protection.
- We characterized and identified the genetic and antigenic variations of circulating rotavirus strains in comparison to the Rotarix vaccine strain that is used in Qatar.
- The study highlight the importance for regular monitoring of emerging rotavirus variants and their impact on vaccine effectiveness in young children.

INTRODUCTION

Rotavirus (RV) is a leading cause of severe diarrheal infections among children under the age of 5 years. RV is estimated to cause 200K deaths and hundreds of thousands hospitalizations among children every year.[1,2] Binary classification of RV is used to designate rotaviruses into G and P genotypes based on the genetic diversity of the capsid proteins, VP7 and VP4 segments, respectively.[3,4] So far, 36 G and 51 P genotypes have been identified with G1, G2, G3, G4, G9, and G12 in combination with P[4], P[6], or P[8] being the most common genotypes associated with human infections.[5–8]

According to the World Health Organization (WHO) and Center of Disease Control (CDC), RV vaccination is the best way to protect against severe gastrointestinal disease.[9,10] Four oral, live-attenuated RVA vaccines are currently available worldwide: Rotarix®, RotaTeq®, Rotavac®, and RotaSiil®. All four vaccines are approved by WHO and considered highly effective in preventing severe gastrointestinal disease among infected children (WHO). Rotarix® (RVA1) (GlaxoSmithKline, Brentford, United Kingdom) is a monovalent RV vaccine consisting of a single human G1P[8] strain.[11] On the other hand, RotaTeq® (RVA5) (Merck & Co., Inc., United States), is a pentavalent human–bovine reassortant RV strain representing the most commonly circulating human RV genotypes (G1–G4 and P[8]). The implementation of RV vaccinations has subsequently lessened the burden of RV.[12–14] However, the RV continues to evolve, necessitating continuous monitoring of the circulating strains worldwide.

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IMAGES IN EMERGENCY MEDICINE

Obstetrics and Gynecology

Adolescent female with right lower abdominal pain

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Qatar National Library

1 | INTRODUCTION

A 12-year-old girl presented with severe right lower abdominal pain for 12 hours associated with nausea and multiple episodes of vomiting, which was non-bloody and non-bilious in nature. No history of dysuria, urgency, or vaginal discharge existed. Past medical history was unremarkable. The physical examination suggested right lower quadrant tenderness to palpation. The laboratory workup was normal complete blood cell count, blood electrolytes, and urinalysis. Ultrasound of the abdomen and pelvis showed no signs of acute appendicitis and normal-sized ovaries with normal blood flow. A right adnexal cystic lesion measuring 5.4 × 4.0 × 4.2 cm located in the right hemipelvis between the uterus and right ovary was identified (Figure 1A). Considering the intensity and persistence of the pain, the patient was taken to the operating room. The laparoscopy revealed fallopian tube torsion secondary to para ovarian cyst (Figure 1B).

2 | DIAGNOSIS

Torsion of fallopian tube secondary to para-ovarian cyst. Para-ovarian cysts or para-tubal cysts account for up to 20% of all adnexal masses and are found in females of all ages. The incidence of para-ovarian cysts in the pediatric and adolescent population is approximately 7%.[1] Like ovaries, the para-ovarian cyst can also undergo torsion with similar symptoms of abdominal pain, nausea, and vomiting. The chances of para-ovarian cyst torsion are not associated with the size or appearance of the cyst on ultrasound.[2] The para-ovarian cyst can torse on itself and cause fallopian tube torsion. The fallopian tube torsions are a rare cause of acute abdomen and are difficult to diagnose because symptoms are similar to other causes of adnexal torsion. Although ultrasound with color doppler is the initial diagnostic modality in adnexal pain, para-ovarian cysts are not easily identified. If clinical suspicion of adnexal torsion is high and ultrasound is normal, magnetic resonance imaging or diagnostic laparoscopy can be considered.[3] In our patient the ultrasound identified a cyst with normal color doppler of both ovaries but, owing to persistent pain, laparoscopy was performed and torsion of fallopian tube secondary to para-ovarian cyst was identified (Figure 1B). In summary, para-ovarian cyst can cause torsion of adnexal structures.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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Orphanet Journal of Rare Diseases

REVIEW Open Access

Genetic epidemiology of Woodhouse-Sakati Syndrome in the Greater Middle East region and beyond: a systematic review

Amira Kohil[1], Atiyeh M. Abdallah[1], Khalid Hussain[2] and Mashael Al-Shafai[1*]

Abstract

Background Woodhouse-Sakati syndrome (WSS) is a rare, autosomal recessive genetic disorder with variable clinical manifestations mainly affecting the endocrine and nervous systems. The aim of this study was to systematically review the genetic basis of WSS and report the genetic variants and clinical phenotypes associated with the disease.

Methods PubMed, Science Direct, Scopus, and Web of Science databases were searched from the time of inception until June 2022. Broad search terms were used to capture the literature describing all genetic variants associated with WSS. The search keywords used are "Woodhouse Sakati" along with the term "mutation" OR "gene" OR "variant" OR "polymorphism".

Results Twenty-five eligible studies were included in this study. One hundred and eighty-five patients in 97 families from 12 different countries were diagnosed with WSS. In patients from the Greater Middle East (GME) region, consanguineous marriages were common (67%). Thirteen different *DCAF17* variants were associated with WSS development (including 8 identified in the GME region). The most frequent variant was a frameshift deletion variant (c.436delC, p.Ala147Hisfs*9) unique to Arabs that was reported in 11 cases from Tunisia, Kuwait, Qatar, Bahrain, and Saudi Arabia. There were no clear genotype–phenotype correlations for the different variants.

Conclusions This systematic review highlights the molecular basis and clinical manifestations of WSS globally, including the GME region, where the disease is prevalent due to consanguinity. Additional studies are now needed to understand the genotype–phenotype correlation for different *DCAF17* variants and their impact on the phenotypic heterogeneity observed in WSS patients.

Keywords Woodhouse-Sakati, Variants, *DCAF17*, Arabs, Middle East, Consanguinity

Background

Woodhouse-Sakati syndrome (WSS), first described in a consanguineous Saudi Arabian family in 1983 [1], is a rare, autosomal recessive genetic disorder [2]. WSS is characterized by a variety of predominantly endocrine and nervous system abnormalities including hypogonadism, diabetes mellitus (DM; in 95% of patients), hypothyroidism, low insulin-like growth factor (IGF-1) levels, deafness, alopecia, and electrocardiographic abnormalities [3, 4]. The prevalence of WSS is estimated to be < 1/1,000,000 of the population [2]. There is no clear age of onset for the disorder, but the different clinical manifestations can present at different times; for example, hypogonadism is often detected around the time of puberty (12–14 years of age); DM and hypothyroidism during adolescence up to the age of 25 years of age; and

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Pediatric Brain Tumors in the Molecular Era: Updates for the Radiologist

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Abbreviations

LGG, low-grade glioma; HGG, high-grade glioma; ATRT, atypical teratoid/rhabdoid tumor; MAPK, mitogen-activated protein kinase; SHH, sonic hedgehog; Wnt, wingless; LGG/GNT, low-grade gliomas , glioneuronal tumors, and neuronal tumors; SNV, single nucleotide variation; PXA, pleomorphic xanthoastrocytomas; PA, pilocytic astrocytoma

Introduction

Brain and other central nervous system (CNS) tumors are the most common group of solid tumors and the leading cause of tumor-related mortality in children, with an average annual age-adjusted mortality rate of 0.70 per 100,000 in the United States. Its incidence has surpassed leukemia for 2014-2018, with an overall calculated incidence rate of 5.85 per 100,000 population.[1] Over the past decade, there has been a plethora of research exploring the molecular landscape of various CNS tumors and accordingly endorsing targeted therapy strategies. These updates are highlighted in the fifth edition, 2021 WHO classification of tumors of the CNS. In this review, we will discuss the molecular landscape of common pediatric brain tumors, including pediatric Low-grade gliomas, glioneuronal tumors, neuronal tumors (LGG/GNT), pediatric high-grade gliomas (HGGs), ependymomas, medulloblastomas, and atypical teratoid/rhabdoid tumors (ATRTs), their clinical correlation and impact on outcome and treatment strategies. Finally, imaging features, including key radiogenomic clues, will be explored.

Radiomics and Radiogenomics

The recent surge of CNS tumor molecular information has shown that the molecular profile of a tumor may often trump histopathology and imaging as a prognostication tool and one that is used to tailor treatment approaches. Nonetheless, imaging remains the first diagnostic step in the work-up for children with CNS malignancies and the primary mean of follow-up. Consequently, the concepts of “radiogenomic” and “radiomics” have come into existence to investigate how imaging phenotype correlates with and may 1 day predict the molecular phenotype of the tumor, thereby determining the treatment strategy even earlier in the patient journey.

Radiogenomics focuses on correlating conventional and radiomic imaging features with the genetic and molecular background of the disease, aiming to provide a simple, non-invasive tool for inference to the genetic and molecular information from medical imaging.[2,3] Radiomics is a newly emerging technique that extracts unseen medical imaging features and correspondingly quantifies the phenotypic characteristics in an automated, high-throughput manner.[4] The extracted radiomics features may aid in the differential diagnosis, disease classification, prognosis prediction, or treatment response assessment.[4,5]

Cureus

Open Access Case Report

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Optic Neuritis in a Child With Poorly Controlled Type 1 Diabetes Mellitus: A Case Report

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Abstract

Type 1 diabetes stands among the most prevalent endocrinological diseases in the pediatric age group. The incidence rate continues to rise globally. Optic neuritis has been described in the literature in association with type 2 diabetes; however, cases of optic neuritis with type 1 diabetes are very few. Here we describe a rare case of a 15-year-old patient with type 1 diabetes mellitus presenting with optic neuritis. Due to the hyperglycemia that steroids can induce in some patients, management with steroids can be difficult. A multidisciplinary team approach is required to ensure that these patients' optic neuritis is properly handled while avoiding steroid side effects.

Categories: Endocrinology/Diabetes/Metabolism, Ophthalmology
Keywords: pediatric diabetes, diabetic eye disease, ophthalmology, diabetes type 1, optic neuritis

Introduction

Type 1 diabetes stands among the most prevalent endocrinological diseases in the pediatric age group. The incidence rate continues to rise globally, reaching up to 2.9 new cases per year per 100 000 persons below 15 years of age [1]. Looking at the gulf region, the prevalence of diabetes appears to be one of the highest globally. The percentages of diabetic patients (both type 1 and type 2) in five countries located in the gulf peninsula (Kuwait (21.1%), Qatar (20.2%), Saudi Arabia (20.0%), Bahrain (19.9%) and UAE (19.2%)) rank among the highest 10 countries in the world. In 2020, Qatar particularly reported an incidence rate of Type 1 diabetes mellitus (T1DM) of 38.05 per 100,000 individuals [2]. The increased number of T1DM cases has been reflected in the number of diabetes-related complications and associated diseases that come to medical attention, mainly ocular diseases. Some of these diseases are well known, like diabetic retinopathy, and others are rare; for example, Anterior ischemic optic neuropathy (AION) and diabetic papillopathy. Optic neuritis has been described in the literature in association with type 2 diabetes [3]; however, cases of optic neuritis with type 1 diabetes are very few. Here, we describe a rare case of a 15-year-old patient with type 1 diabetes mellitus presenting with optic neuritis.

Case Presentation

The patient is a 15-year-old girl who was diagnosed with type one diabetes mellitus in 2013. She has positive glutamic acid decarboxylase (GAD) antibodies and highly positive islet insulin antibodies. Her screening at the time of diagnosis was negative for celiac and autoimmune thyroid diseases. Her height was 138 cm, which is on the 0.02 centile, and her weight was 44 kg (on the 14th centile) with no recent loss. Menarche occurred two months back at Tanner's stage 4 of breast development. She was on a basal-bolus insulin regimen, receiving 20 glargine units in the evening and three fixed doses of Aspart insulin (five units before breakfast, 10 units before lunch, and five units before dinner). This regimen was the most suitable for her as she had great difficulty doing carbohydrate counting and giving insulin accordingly. Despite that, she had poor compliance due to social reasons, leading to unsatisfactory glycemic control. Her latest HbA1C at that time was 13.9% (Table *1*). After multiple missed clinic visits, the patient attended her first annual diabetic retinopathy screening after nine years of diabetes onset, in which her optic disc and fundus color photos showed early hard exudate in the background of the fundi in both eyes, with normal optic discs and no evidence of retinal microvascular abnormalities at this stage. Visual acuity was 6/29 in both eyes using Snellen's chart. She was scheduled for another annual ophthalmological screening test but missed her appointment. Her most recent annual diabetic nephropathy screening was significant for microalbuminuria (Albumin: Creatinine ratio 9.6 mg/mmol). Since her diagnosis, she has been admitted to the hospital four times with moderate diabetic ketoacidosis.

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REVIEW

Managing Severe Hypoglycaemia in Patients with Diabetes: Current Challenges and Emerging Therapies

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Abstract: Hypoglycaemia is common in patients with diabetes mellitus and is a limiting factor for achieving adequate glycaemic control. In the vast majority of cases, hypoglycaemia develops due to the imbalance between food intake and insulin injections. As recurrent hypoglycaemia leads to significant morbidity and mortality, the recognition and immediate treatment of hypoglycaemia in diabetic patients is thus important. In the last 20 years, the introduction of improved insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), and sensor-augmented pump therapy have all made significant improvements in helping to reduce and prevent hypoglycaemia. In terms of treatment, the American Diabetes Association recommends oral glucose as the first-line treatment option for all conscious patients with hypoglycaemia. The second line of treatment (or first line in unconscious patients) is the use of glucagon. Novel formulations of glucagon include the nasal form, the Gvoke HypoPen which is a ready-to-deliver auto-injector packaged formulation and finally a glucagon analogue, Dasiglucagon. The Dasiglucagon formulation has recently been approved for the treatment of severe hypoglycaemia. It is a ready-to-use, similar to endogenous glucagon and its potency is also the same as native glucagon. It does not require reconstitution before injection and therefore ensures better compliance. Thus, significant improvements including development of newer insulin analogues, insulin pump therapy, continuous glucose monitoring (CGM), sensor-augmented pump therapy and novel formulations of glucagon have all contributed to reducing and preventing hypoglycaemia in diabetic individuals. However, considerable challenges remain as not all patients have access to diabetes technologies and to the newer glucagon formulations to help reduce and prevent hypoglycaemia.

Keywords: hypoglycaemia, type 1 diabetes, type 2 diabetes, glucagon, counterregulatory hormone

Introduction

Hypoglycaemia is the most common and severe complication of type 1 diabetes mellitus (T1DM).[1] It interferes with daily activities, poses a source of fear for diabetic individuals and their families, impairs quality of life, and accounts for one of the limiting factors that affects achieving glycaemic control.[2] Avoiding severe and recurrent hypoglycemia is one of the main goals of diabetes management. Hypoglycemia can lead to acute and permanent neurological complications. Thus, addressing this severe clinical issue is paramount from the management point of the view.

Hypoglycemia is an important limiting factor in achieving glycaemic control diabetic individuals.[2] The American Diabetes Association (ADA) recommends glycosylated haemoglobin (HbA1c) target <7% for diabetic patients in all age groups, and the American Association of Clinical Endocrinologists (AACE) recommends an HbA1c <6.5% in subjects with no increased risk of hypoglycaemia.[3,4] In the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Trial, it has been shown that intensive glycaemic control can prevent or delay the development of microvascular complications such as retinopathy, nephropathy, and neuropathy in T1DM and type 2 diabetes (T2DM). However, there is an increased risk of hypoglycaemia with aggressive glycaemic targets.[5] Achieving tight glycaemic

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ORIGINAL ARTICLE

WILEY

Results from the second WHO external quality assessment for the molecular detection of respiratory syncytial virus, 2019–2020

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Abstract

Background: External quality assessments (EQAs) for the molecular detection of human respiratory syncytial virus (RSV) are necessary to ensure the standardisation of reliable results. The Phase II, 2019–2020 World Health Organization (WHO) RSV EQA included 28 laboratories in 26 countries. The EQA panel evaluated performance in the molecular detection and subtyping of RSV-A and RSV-B. This manuscript describes the preparation, distribution, and analysis of the 2019–2020 WHO RSV EQA.

Thomas Williams and Sandra Jackson contributed equally to this study.

WHO RSV Surveillance Group members are detailed in Appendix A.

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CASE REPORT

JIMD REPORTS SSIEM WILEY

Severe neonatal onset neuroregression with paroxysmal dystonia and apnoea: Expanding the phenotypic and genotypic spectrum of *CARS2*-related mitochondrial disease

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Abstract

Disorders of mitochondrial function are a collectively common group of genetic diseases in which deficits in core mitochondrial translation machinery, including aminoacyl tRNA synthetases, are key players. Biallelic variants in the *CARS2* gene (NM_024537.4), which encodes the mitochondrial aminoacyl-tRNA synthetase for cysteine (CARS2, mt-aaRS^{cys}; MIM*612800), result in childhood onset epileptic encephalopathy and complex movement disorder with combined oxidative phosphorylation deficiency (MIM#616672). Prior to this report, eight unique pathogenic variants in the *CARS2* gene had been reported in seven individuals. Here, we describe a male who presented in the third week of life with apnoea. He rapidly deteriorated with paroxysmal dystonic crises and apnoea resulting in death at 16 weeks. He had no evidence of seizure activity or multisystem disease and had normal brain imaging. Skeletal muscle biopsy revealed a combined disorder of oxidative phosphorylation. Whole-exome sequencing identified biallelic variants in the *CARS2* gene: one novel (c.1478T>C, p.Phe493Ser), and one previously reported (c.655G>A,

Cosmetic Medicine

Review Article

Photobiomodulation: A Systematic Review of the Oncologic Safety of Low-Level Light Therapy for Aesthetic Skin Rejuvenation

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www.aestheticsurgeryjournal.com

Abstract

Photobiomodulation (PBM) therapy is an increasingly popular modality for aesthetic skin rejuvenation. PBM induces genomic, proteomic, and metabolomic processes within target cells, but such manipulation of cell behavior has led to concerns about oncologic safety. This article presents a summary of the clinical and preclinical evidence for the oncologic safety of PBM for aesthetic skin rejuvenation. A focused systematic review was performed, in which safety data from clinical trials of PBM for skin rejuvenation was supplemented by analyses of in vitro data obtained from cells derived from human skin and human neoplastic cells and in vivo data of tumors of the skin, oral cavity, and breast. Within established parameters, red and near infrared light mainly enhances proliferation of healthy cells without a clear pattern of influence on cell viability. The same light parameters mainly reduce neoplastic cell proliferation and viability or else make no difference. Invasiveness potential (appraised by cell migration assays and/or differential gene expression) is equivocal. PBM does not induce dysplastic change in healthy cells. In vivo tumor models yield varied results with no clear pattern emerging. There are no relevant clinical trial data linking PBM with any significant adverse events, including the finding of a new or recurrent malignancy.

Current clinical and preclinical evidence suggests that PBM is oncologically safe for skin rejuvenation, and there is no evidence to support the proposition that it should be avoided by patients who have previously undergone treatment for cancer.

Level of Evidence: 4

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Photobiomodulation (PBM), synonymous with low-level light (laser) therapy (LLLT) has gained traction as a noninvasive therapy for skin rejuvenation, including treatment of facial rhytids, dyschromias, and acne vulgaris; wound healing including scar management; body contouring (either alone or as a means of enhancing the removal of fat during liposculpture); and androgenic alopecia.[1] The therapeutic potential of PBM is becoming generally accepted as clinical trial data continues to provide evidence of efficacy and safety. However, controversies remain.[2-4] One of the most pertinent discussion points is the issue of oncologic safety, with theoretical concerns expressed on account of the upregulation of cellular metabolic activity on exposure to red and near infrared laser light.[5-8]

Dr Glass is an attending plastic and craniofacial surgeon, Department of Surgery, Sidra Medicine, Doha, Qatar, a clinical editor for *Aesthetic Surgery Journal*, and a Cosmetic Medicine contributing editor for *ASJ Open Forum*.

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Case report

Severe Growth Hormone Deficiency in an Indian Boy Caused By a Novel 6 kb Homozygous Deletion Spanning the *GH1* Gene

Haris et al. GH1 Deletion Causing Familial Short Stature

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What is already known on this topic
- Mutations in *GH1* genes are associated with a rare condition called Isolated Growth Hormone Deficiency.
- The most common *GH1* deletions reported are 6.7 and 7.6 kb in size.
- The largest reported deletion is 45 kb in size.

What this study adds
- We report a 3 year old boy with extreme short stature with a deletion in *GH1* gene.
- The deletion is 6 kb in size which has not been reported before.
- The proband is homozygous for the deletion and the parents who are also short have a heterozygous deletion.

Abstract
Growth disorders resulting in extreme short stature are often a result of deficiency in growth hormone released from the pituitary gland or defective growth hormone releasing receptor. Genetic defects in the *GH1* and *GHRHR* genes account for around 11.1-20% of extreme short stature cases, resulting in a rare condition called Isolated Growth Hormone Deficiency. We describe the characterization of a *GH1* genetic defect discovered in a 3-year-old male patient with extreme short stature, developmental failure and undetectable serum levels of growth hormone. There is a familial history of short stature with both parents being short. Whole genome sequencing of the patient DNA revealed a large novel 6 kb homozygous deletion spanning the entire *GH1* gene in the patient. While the deletion was homozygous in the subjects, it was found in a heterozygous state in the parents. Thus we report a novel homozygous deletion including the *GH1* gene leading to Isolated Growth Hormone Deficiency- Type 1A associated with extreme short stature.
Keywords: *GH* gene deletion, Short stature, Familial short stature

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Introduction
Growth disorders resulting in extreme short stature are often a result of deficiency in growth hormone released from the pituitary gland (*GH1* gene, located on chromosome 17q23) or defective growth hormone releasing receptor (*GHRHR* gene, located on chromosome 7p14.3). Genetic defects in the *GH1* and *GHRHR* genes account for around 11.1-20% of extreme short stature cases, resulting in a rare condition called Isolated Growth Hormone Deficiency (IGHD). This frequency is reported to be 18.6 % higher in familial cases of IGHD [1].
IGHD is a disorder with varying prevalence in different populations ranging from 1:1800 in Sri-Lanka to 1:30,000 in the United Kingdom [2]. Familial IGHD is often grouped into 4 main subtypes: Type IA, Type IB, Type II and Type III [3]. These subtypes have a wide range in phenotype including extreme short stature, symptoms of doll-like facies, central obesity, highly pitched voices and puberty that is often delayed [4]. Type IA and IB often manifest as Extreme Short Stature (ESS) [3, 5] and follow an autosomal recessive or compound heterozygous inheritance pattern [6].
GH is a peptide hormone that contains two active sites for Growth Hormone Receptor (GHR) binding; a class I cytokine receptor. GHRs exist in a broad range of tissue cellular membranes including kidney cells, hepatocytes, adipocytes, myocytes, and many others. One GH molecule binds with two GHRs causing dimerization and this tertiary complex activates JAK-2 (Janus Kinase 2) bound to GHR [7]. Here JAK phosphorylates STAT5, a signal transducer and transcriptional activator, which enters the nucleus to induce GH-mediated genes expression. GH's mode of action relies on the secretion of IGF-1 from cells and stimulation of chondrocytes (cartilage cells) [8] leading to its differentiation. IGF-1 has an important role in stimulating growth at the end/growth plates of bones as well as muscle cells. In addition to the JAK-STAT pathway, the dimerization of GHR further causes the initiation of other cascades including the MAPK (Mitogen

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Case Report

Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome in a Child with Cystic Fibrosis

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Background. Drug reaction with eosinophilia and systemic symptoms (DRESSs) syndrome is an idiosyncratic drug-induced reaction that rarely occurs in children but can lead to serious complications. It manifests most commonly with fever, extensive skin eruptions, and eosinophilia. Symptoms typically develop two to six weeks after the initiation of the inciting drug. Visceral organ involvement especially the liver can also occur and if not recognized early and the inciting drug is not stopped immediately, it can lead to liver failure. Therefore, early diagnosis is important but can be very challenging because of disease rarity, lack of a diagnostic test, and its overlap with other common pediatric allergic and infectious conditions. *Case Presentation.* A 2.5-year-old boy with known diagnosis of cystic fibrosis, bilateral bronchiectasis, pancreatic insufficiency, and chronic airway colonization with *Pseudomonas aeruginosa* was admitted to our hospital with acute pulmonary exacerbation of CF lung disease. He was treated with intravenous piperacillin-tazobactam and intravenous amikacin in addition to airway clearance. On day 18 of treatment, the patient developed high grade fever followed by diffuse erythematous and pruritic maculopapular rash. Blood tests showed high eosinophilia, high C-reactive protein (CRP), and high liver enzymes levels. The clinical features and the laboratory findings were consistent with the DRESS syndrome. Therefore, all antibiotics were discontinued. Progressive resolution of the symptoms was observed within two days. Laboratory abnormalities were also normalized in the follow-up clinic visit 4 months later. *Conclusion.* Our case demonstrates the importance of early recognition of the DRESS syndrome in children who develop fever and skin rashes with eosinophilia while undergoing long-term antibiotic treatment. Prompt discontinuation of the offending drug is the cornerstone therapy and results in the resolution of symptoms and prevention of serious complications.

1. Background

Drug reaction with eosinophilia and systemic symptoms (DRESSs) is a very rare but potentially severe drug-induced hypersensitivity reaction that can occur in children and adults [1]. The pathophysiology of DRESS is not completely characterized, but it is hypothesized to be multifactorial and results from a delayed T-cell-dependent allergic reaction to an inciting drug [2].

Patients with the DRESS syndrome usually present with fever, skin eruptions, and eosinophilia within days to weeks of drug exposure. The liver, the kidney, and the lung injury can also occur [3]. DRESS may rarely affect the heart but is associated with high mortality [4]. The degree of symptoms and the extent of organ involvement in patients with the DRESS syndrome can range from mild to severe. Substantial mortality can result from a severe disease and estimated at approximately 5% of all affected children and 10% of all affected adults [1, 5]. Death in patients with severe DRESS syndrome occurs mainly due to liver failure. Therefore, early recognition of the condition and immediate discontinuation of the inciting drug is paramount.

The diagnosis of DRESS syndrome can be easily overlooked, especially in children, because of its rarity and because of its overlap with other more common pediatric allergic, autoimmune, and infectious conditions [1, 6]. Therefore, clinicians should be aware of this condition in order to effectively treat the disease and prevent the development of serious complications.

Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Longitudinal Assessment of Chest CT Findings and Pulmonary Function after COVID-19 Infection

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* X.H. and L.C. contributed equally to this work.

** Q.Y. and H.S. are co-senior authors.

Conflicts of interest are listed at the end of this article.

See also the editorial by van Beek in this issue.

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Background: Information on pulmonary sequelae and pulmonary function 2 years after recovery from SARS-CoV-2 infection is lacking.

Purpose: To longitudinally assess changes in chest CT abnormalities and pulmonary function in individuals after SARS-CoV-2 infection.

Materials and Methods: In this prospective study, participants discharged from the hospital after SARS-CoV-2 infection from January 20 to March 10, 2020, were considered for enrollment. Participants without chest CT scans at admission or with complete resolution of lung abnormalities at discharge were excluded. Serial chest CT scans and pulmonary function test results were obtained 6 months (June 20 to August 31, 2020), 12 months (December 20, 2020, to February 3, 2021), and 2 years (November 16, 2021, to January 10, 2022) after symptom onset. The term interstitial lung abnormality (ILA) and two subcategories, fibrotic ILAs and nonfibrotic ILAs, were used to describe residual CT abnormalities on follow-up CT scans. Differences between groups were compared with the χ^2 test, Fisher exact test, or independent samples *t* test.

Results: Overall, 144 participants (median age, 60 years [range, 27–80 years]; 79 men) were included. On 2-year follow-up CT scans, 39% of participants (56 of 144) had ILAs, including 23% (33 of 144) with fibrotic ILAs and 16% (23 of 144) with nonfibrotic ILAs. The remaining 88 of 144 participants (61%) showed complete radiologic resolution. Over 2 years, the incidence of ILAs gradually decreased (54%, 42%, and 39% of participants at 6 months, 12 months, and 2 years, respectively; $P < .001$). Respiratory symptoms (34% vs 15%, $P = .007$) and abnormal diffusing capacity of lung for carbon monoxide (43% vs 20%, $P = .004$) occurred more frequently in participants with ILAs than in those with complete radiologic resolution.

Conclusion: More than one-third of participants had persistent interstitial lung abnormalities 2 years after COVID-19 infection, which were associated with respiratory symptoms and decreased diffusion pulmonary function.

Chinese Clinical Trial Registry no. ChiCTR2000038609

Supplemental material is available for this article.

Globally, by February 23, 2023, more than 750 million people had recovered from COVID-19, but concerns remain that some organs, especially the lungs, may have long-term damage after infection (1,2). At present, several prospective studies and meta-analyses have investigated pulmonary sequelae in patients within 1 year after COVID-19 infection (3–7), but the proportion of overall CT abnormalities greatly varied (8.3%–84%). This variation may be attributed to the small study cohorts and the wide range in disease severity. Additional studies have shown that recovered patients have different degrees (26%–33%) of lung diffusion dysfunction (diffusing capacity of lung for carbon monoxide [DLCO] <80%) (8,9). Therefore, these individuals should be followed to detect and manage pulmonary sequelae and functional impairment.

Residual lung abnormalities after discharge from the hospital mainly include ground-glass opacities (GGOs), subpleural reticulations (4,10), cystic changes (4), traction bronchiectasis (9,11), honeycombing (9), and parenchymal bands and/or architectural distortion (11). These features fit the imaging definition of interstitial lung abnormalities (ILAs), which are potentially compatible with interstitial lung disease (12).

OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Craniofacial/Pediatric

Parents of Children with Cleft Lip Exhibit Heightened Visual Attention to the Perioral Area

Israa Abuelezz, MSc*
Marwa K. Qaraqe, PhD*
Mitchell A. Stotland, MD, MS, FRCSC†

Background: Following high-quality surgical repair, children born with a cleft lip anomaly may still display lasting visual differences. We exposed control adults and parents of affected children to images of children with cleft deformity and compared their visual tracking patterns. The protocol investigated whether parental exposure to secondary cleft deformity heightens or diminishes visual attraction to this type of structural facial variation.

Method: Twenty participants (10 control adults, 10 parents of affected children) assessed 40 colored images of children's faces while their eye movements were tracked. Twenty-four control images and 16 repaired cleft lip images were displayed to observers. Nine bilateral facial aesthetic zones were considered as regions of interest. Percentage of time visually fixating within each region, and statistical differences in fixation duration percentage between the two participant groups and across the bilateral regions of interest were analyzed.

Results: While both groups of observers directed more visual attention to the nasal and oral regions of the cleft images than control images, parents of children with cleft lip spent significantly more time fixating on these areas (25% and 24% of the time, respectively) than did unaffected adults (14.6% and 19.3%; $P < 0.001$).

Conclusions: These results demonstrate that parents of cleft lip children exhibit heightened attention to this type of facial difference relative to the naive observer. These findings highlight that observer profile can meaningfully influence the perception of a facial deformity. Awareness of this information may enhance communication between surgeon and parents of an affected child by providing added insight into parental perspective. *(Plast Reconstr Surg Glob Open 2023; 11:e4790; doi: 10.1097/GOX.0000000000004790; Published online 13 February 2023.)*

INTRODUCTION

When observing a face, individuals focus primarily on central discriminating features such as the eyes, nose, and mouth.[1] Faces that are disfigured in some way are visually perceived differently than unaffected faces. This difference exists because structural outliers generally attract an observer's visual attention. Cleft lip (CL) with or without cleft palate is one of the most common congenital facial deformities.[2,3] After surgical repair of CL, the secondary deformity can vary from barely detectable to significant, and has been shown to be associated with psychosocial ramifications such as low self-esteem.[4] Eye-tracking research has confirmed that the attention of naive observers is drawn toward areas of the face distorted by congenital or acquired forms of facial difference, including CL.[5,6] These eye-tracking studies have tended to exclude as observers those who are affected by—or who possess some sort of direct personal history with—CL. In terms of the perception and attitudes of parents of children with CL, relatively little has been written.[7,8] In the current study, we endeavored to determine whether parental exposure to secondary cleft deformity heightens (sensitizes) or diminishes (desensitizes) visual attraction to these structural variations.

For healthcare providers involved in the management of CL (or other facial differences), there is inherent value in understanding how patients, their family, and naive observers instinctively perceive facial difference. While a legitimate surgical treatment goal should be to achieve anatomic symmetry and landmark alignment resulting in a face that is eye-tracked normally, an

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[Intervention Review]

Probiotics for management of functional abdominal pain disorders in children

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ABSTRACT

Background

Functional abdominal pain is pain occurring in the abdomen that cannot be fully explained by another medical condition and is common in children. It has been hypothesised that the use of micro-organisms, such as probiotics and synbiotics (a mixture of probiotics and prebiotics), might change the composition of bacterial colonies in the bowel and reduce inflammation, as well as promote normal gut physiology and reduce functional symptoms.

Objectives

To assess the efficacy and safety of probiotics in the treatment of functional abdominal pain disorders in children.

Search methods

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and two clinical trials registers from inception to October 2021.

Selection criteria

Randomised controlled trials (RCTs) that compare probiotic preparations (including synbiotics) to placebo, no treatment or any other interventional preparation in patients aged between 4 and 18 years of age with a diagnosis of functional abdominal pain disorder according to the Rome II, Rome III or Rome IV criteria.

Data collection and analysis

The primary outcomes were treatment success as defined by the primary studies, complete resolution of pain, improvement in the severity of pain and improvement in the frequency of pain. Secondary outcomes included serious adverse events, withdrawal due to adverse events, adverse events, school performance or change in school performance or attendance, social and psychological functioning or change in social and psychological functioning, and quality of life or change in quality life measured using any validated scoring tool. For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI). For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CI.

Main results

We included 18 RCTs assessing the effectiveness of probiotics and synbiotics in reducing the severity and frequency of pain, involving a total of 1309 patients.

Original Article

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Awareness and knowledge of familial Mediterranean fever among medical scope students in Syrian universities: A cross-sectional study

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Abstract

Introduction: Familial Mediterranean fever is an autoinflammatory autosomal recessive disorder common among individuals of Mediterranean descent. It is characterized by recurrent episodes of fever accompanied by peritonitis, pleurisy, pericarditis, and/or arthritis, sometimes accompanied by an erysipelas-like rash. Mimicking manifestation of other inflammatory conditions and the diversity of symptoms leads to insufficient knowledge and understanding. General knowledge about this disease is considered low in most populations, but this bears greater consequences in people with high incidence rates. This study investigates the knowledge of familial Mediterranean fever among a group of medical students in public and private Syrian universities.

Methods: A cross-sectional study was conducted in May 2022, and an international standard-based electronic questionnaire was adopted. The study included 758 current undergraduate medical scope students from public and private universities in Syria. The survey used for this study included inquiries made to assess awareness using global standards. It was divided into 2 sections, with 7 questions focusing on sociodemographic characteristics and 17 questions assessing the students' understanding of Familial Mediterranean fever.

Results: Our analysis showed strong correlations between the knowledge of Familial Mediterranean fever and certain specialization, college, academic year, and marital status. The mean score of answers was 9.39 out of 17 for all participants. The mean score of answers for medical students was 10.01 out of 17, while it was 8.81 for pharmaceutical students and 6.51 for dental students. These differences were statistically significant, p-value <0.001. This means medical students know better than pharmaceutical students, who already have better knowledge than dental students.

Conclusion: We conclude that medical scope students' knowledge about the disease of Familial Mediterranean fever and its management is ineffective, especially among dental students, even in a country with high prevalence rates for Familial Mediterranean fever like Syria.

Keywords
FMF, medical education, Syria

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Introduction

Familial Mediterranean fever (FMF) is the most common hereditary periodic fever syndrome. The responsible gene for this autosomal recessive genetic disorder is the *MEFV* gene.[1] It is most common in populations in the Mediterranean region or of Mediterranean origin. Populations at high risk include Arabs, Turkish, Armenian, and Jews.[2] The prevalence of FMF varies among countries but is highest in the previously mentioned populations, with a rate of 1 in 200 to 1000 people. Previous studies suggest that over 100,000

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RESEARCH PAPER

Clinical Presentation and Outcome of Multiple Rare Earth Magnet Ingestions in Children of Qatar. A Single-Center Experience

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ABSTRACT

Introduction: Rare earth magnets are powerful magnets that can have several negative effects if ingested. The goal of our study is to describe the result of multiple rare earth magnets ingested by children in Qatar.

Materials and methods: This is observational research. We conducted a retrospective chart review and descriptive analysis of all cases of multiple rare earth magnetic ingestion that werepresented to the Emergency Department of Sidra Medicine between January 2018 and July 2022. We obtained an exemption for this study from our institutional review board (IRB).

Results: In our research, we identified 21 children having multiple rare earth magnetic ingestions. The predominant symptoms were abdominal pain and vomiting which were observed in 57% (n = 12) and 48% (n = 10) of the patients respectively. The most common sign was abdominal tenderness,observed in 14% (n = 3) of the patients. In our sample, 38% (n = 8) of the patients were managed conservatively whereas 62% (n = 13) needed intervention. In our study, 48% (n = 10) of the patients sustained complications. The frequent complications were intestinal perforation appreciated in 24% (n = 5) and intestinal perforation with fistula formation in 19% (n = 4) of the patients. The median age of these patients was two years while the median number of magnets ingested was six. The ingestions were unwitnessed, and the duration of ingestions was unknowninthemajorityofpatientswhoexperienced-complications (n = 8/10).

Conclusion: If numerous rare earth magnetis ingested, children are in high danger of harm. It can be difficult to pinpoint the cases in younger children due to poor

BMJ Open Respiratory Research

International perspective on research priorities and outcome measures of importance in the care of children with acute exacerbations of asthma: a qualitative interview study

Charmaine S Gray,[1,2] Yao Xu,[3,4] Franz E Babl,[5,6] Stuart Dalziel,[7,8] Colin V E Powell,[9,10] Shu-Ling Chong,[11] Damian Roland ,[12,13] Mark D Lyttle,[14,15] Ricardo M Fernandes ,[16,17] Javier Benito,[18] Mike Johnson,[19] Adriana Yock-Corrales,[20] Indumathy Santhanam,[21] Suzanne Schuh,[22,23] Baljit Cheema,[24] Jenny Couper,[1] Simon Craig ,[4,25] On behalf of the Pediatric Emergency Research Network (PERN)

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ABSTRACT

Background Acute exacerbations of asthma are common in children, however, treatment decisions for severe exacerbations are challenging due to a lack of robust evidence. In order to create more robust research, a core set of outcome measures needs to be developed. In developing these outcomes, it is important to understand the views of clinicians who care for these children in particular, views that relate to outcome measures and research priorities.

Methods To determine the views of clinicians, a total of 26 semistructured interviews based on the theoretical domains framework were conducted. These included experienced clinicians from emergency, intensive care and inpatient paediatrics across 17 countries. The interviews were recorded, and later transcribed. All data analyses were conducted in Nvivo by using thematic analysis.

Results The length of stay in hospital and patient-focused parameters, such as timing to return to school and normal activity, were the most frequently highlighted outcome measures, with clinicians identifying the need to achieve a consensus on key core outcome measure sets. Most research questions focused on understanding the best treatment options, including the role of novel therapies and respiratory support.

Conclusion Our study provides an insight into what research questions and outcome measures clinicians view as important. In addition, information on how clinicians define asthma severity and measure treatment success will assist with methodological design in future trials. The current findings will be used in parallel with a further Paediatric Emergency Research Network study focusing on the child and family perspectives and will contribute to develop a core outcome set for future research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute exacerbations of asthma are common in children, however, treatment decisions for severe exacerbations are challenging due to a lack of robust evidence.

WHAT THIS STUDY ADDS

⇒ An understanding of clinician perspectives relating to important outcome measures and research questions in acute exacerbations of asthma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current findings will be used in parallel with a further Paediatric Emergency Research Network study focusing on child and family perspectives to develop an internationally agreed core outcome set for future research in trials of acute severe asthma in children.

INTRODUCTION

An acute exacerbation of asthma, in children, is a common reason for emergency department (ED) presentation and subsequent admission to hospital.[1] Hospital admissions for asthma are increasing and are associated with a significant economic burden.[2–4] While many children have mild to moderate exacerbations and are discharged home, a recently published study of 14 029 children presenting to Australasian EDs found that 36% of children with acute asthma are admitted to hospital, with 1.1% requiring paediatric intensive care unit admission (PICU).[5] In addition, recent studies document increasing PICU admission for severe acute asthma worldwide.[4] Despite this concerning scenario, the evidence base informing treatments for these high-risk patients with severe presentations is weak.[6] Current knowledge is limited due to

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The Feasibility of Telemedicine in the Implementation and Management of Therapeutic Hypothermia for Infants with Neonatal Hypoxic-Ischemic Encephalopathy in a Resource-Limited Country

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Abstract

Background Telemedicine is widely used in neonatal services in developed countries, though its outcomes in low- and middle-income countries are controversial. Lack of expertise and/or facilities, however, has limited its use in developing countries and around areas of military conflicts. We aim to study the implementation and management of therapeutic hypothermia (TH) in infants with hypoxic-ischemic encephalopathy (HIE) with the help of telemedicine in a resource-limited country.

Methodology This is a retrospective study, evaluating patients who received TH, guided by telemedicine, through a mobile app (Telegram), an application that allows sharing and archiving of information with other beneficial features. We assessed the feasibility of utilizing telemedicine in guiding the application of TH to infants affected with HIE in the North-West of Syria between July 2020 and July 2021. Feasibility was measured by parameters related to the time gaps between initiation of consultation and treatment and clinical short-term outcomes.

Results Out of 5,545 newborn infants delivered during the study period, 22 patients were eligible for TH guided by telemedicine. Patients were referred for consultation at a median (interquartile range [IQR]) of 137 (35–165) minutes of life. A median (IQR) of 12 (3–18) minutes elapsed between the call for a consultation and the consultant response and a median (IQR) of 30 (0–42) minutes elapsed between seeking the consultation and the

Keywords
- hypoxic-ischemic encephalopathy
- therapeutic hypothermia
- cooling therapy
- NICU
- telemedicine

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Review

An updated review of contribution of long noncoding RNA-NEAT1 to the progression of human cancers

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Abstract

Long non-coding RNAs (lncRNAs) present pivotal roles in cancer tumorigenesis and progression. Recently, nuclear paraspeckle assembly transcript 1 (NEAT1) as a lncRNA has been shown to mediate cell proliferation, migration, and EMT in tumor cells. NEAT1 by targeting several miRNAs/mRNA axes could regulate cancer cell behavior. Therefore, NEAT1 may function as a potent biomarker for the prediction and treatment of some human cancers. In this review, we summarized various NEAT1-related signaling pathways that are critical in cancer initiation and progression.

Previous Next

Abbreviations

lncRNAs, Long non-coding RNAs; NEAT1, nuclear paraspeckle assembly transcript 1; WHO, World Health Organization; ceRNA, competing endogenous RNA; miRNAs, microRNAs; MEN, multiple endocrine neoplasia; SFPQ, splicing factor proline/glutamine rich; PSPC1, paraspeckle component 1; YTHDF2, YTH N6-methyladenosine RNA binding protein 2; Ezh2, Enhancer of zeste homolog 2; HIFs, hypoxia-inducible factors; PRC2, polycomb repressive complex 2; E2F3, E2F transcription factor 3; KLF3, Krüppel-like factor 3; si-NEAT1, small interfering RNA of NEAT; SMAD2, SMAD family member 2; MMP2, matrix metalloproteinase 2; OSCC, oral squamous cell carcinoma; IMR-1, Recruitment-1; ccRCC, clear cell renal cell carcinoma; m6A, N6-methyladenosine; METTL14, methyltransferase-like 14; ATG3, autophagy related 3; LAGE3, L-antigen family member 3; CNN2, Calponin 2; SMO, frizzled class receptor; STAT3, signal transducer and activator of transcription-3; PTBP3, Polypyrimidine tract-binding proteins 3; VCP, Valosin-containing protein; Tim-3, T-cell immunoglobulin and mucin domain protein 3; GABARAP, Gamma-aminobutyric acid receptor-associated protein; OS, osteosarcoma cell; HOXA13,, Homeobox A13; DNMT1, DNA methyltransferases 1; CCND1, cycle-related cyclin D1; PrC, prostate cancer cells; CDC5L, Cell division cycle 5-like protein; ACSL4, Acyl-CoA synthetase 4; m6A, 4 credible N6-methyladenosine; HMGA2, high-mobility group A; Erα, oestrogen receptor alpha; AR, androgen receptor; SRC3, steroid receptor co-activator3; RET, rearranged during transfection; KCTD20, potassium channel tetramerization protein domain containing 20; mTOR, mammalian target of rapamycin; SOX2, sex determining region Y-box protein 2; ITGAV, integrin α5; FAK, focal adhesion kinase; GC, gastric cancer; STAMBPL1, STAM binding protein-like 1; GADD45A, Growth arrest and DNA damageinducible 45 alpha; BRG1, Brahma-related gene-1; GCC, gastric carcinoma cells; XBP-1, X-box binding protein-1; LSCC, laryngeal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinomas; BJAB, Burkitt's lymphoma cell line; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; DCLK1, doublecortin like kinase 1; LSCC, lung squamous cell carcinoma; NSCLC, non-small cell lung cancer; ACSL4, acyl-CoA synthetase long-chain family member 4; HMGB2, high-mobility group box 2; ATF2, activating transcription factor 2; LUAD, lung adenocarcinoma cells; USF1, upstream stimulatory factor 1; TRIM6, tripartite motif containing 6; EGCG, green tea polyphenol; CTR1, copper transporter 1; PC, pancreatic cancer; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; ELF3, E74 like ETS transcription factor 3; PDA, pancreatic ductal adenocarcinoma; ADCs, antibody-drug conjugates; EMT, epithelial-mesenchymal transition

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See Online for appendix

BNT162b2 antigen dose and SARS-CoV-2 omicron infection in adolescents

COVID-19 vaccine antigen dose might affect protection against SARS-CoV-2 infection,[1,2] but direct evidence to quantify this effect is absent. We conducted a matched, retrospective, cohort study using a regression discontinuity design[3] to emulate a randomised controlled trial in Qatar between Feb 3, 2022, and Nov 8, 2022, to provide a head-to-head, controlled comparison of protection induced by two different antigen doses of the BNT162b2 (Pfizer–BioNTech) vaccine (appendix pp 4–10).

The study compared incidence of infection with the omicron (B.1.1.529) variant in the national cohort of adolescents aged 12 years who received the two-dose 30 µg BNT162b2 primary series with that in the national cohort of adolescents aged 11 years who received the two-dose pediatric 10 µg BNT162b2 primary series.

Data for SARS-CoV-2 laboratory testing, vaccination, and demographic information were extracted from Qatar's national SARS-CoV-2 databases (appendix pp 5–6). Adolescents in the 30 µg cohort were matched exactly one-to-one by sex, ten nationality groups, number of coexisting conditions, previous infection status (no previous infection, or previous infection with either pre-omicron or omicron viruses, or previous infections with both viruses) to adolescents in the 10 µg cohort, to balance observed confounders between exposure groups. Matching was also done by calendar month of the second vaccine dose to control for time since the second vaccine dose. Each matched pair was followed up from the calendar day 14 days after the adolescent in the 30 µg cohort received the second dose. Associations were estimated using Cox proportional hazard regression models.

The study population selection process is presented in the appendix (p 20). Of 4085 adolescents in the 30 µg cohort and 5323 in the 10 µg cohort, 2999 matched pairs were included. Baseline characteristics

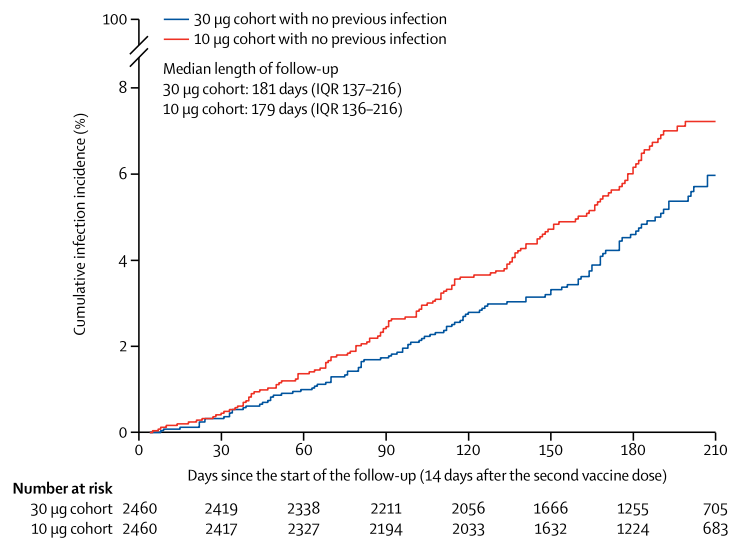

Figure: **Cumulative incidence of infection with the omicron variant of SARS-CoV-2 in adolescents vaccinated with two doses of 30 µg BNT162b2 versus two doses of 10 µg BNT162b2**

	30 µg cohort*	10 µg cohort*	HR (95% CI) for infection		Effectiveness against infection, % (95% CI)†
			Unadjusted	Adjusted†	
Matched cohorts with no previous infection			0·77 (0·60 to 0·99)	0·77 (0·60 to 0·98)	23·4% (1·6 to 40·4)
Total follow-up time, person-weeks	60 230	59 604	..	..	..
Number of incident infections	109	140	..	..	..
Incidence rate of infection, per 10 000 person-weeks (95% CI)	18·1 (15·0 to 21·8)	23·5 (19·9 to 27·7)	..	..	..
Matched cohorts with previous infection			1·50 (0·72 to 3·11)	1·50 (0·72 to 3·12)	−33·3% (−68·0 to 27·5)
Total follow-up time, person-weeks	12 212	12 222	..	..	..
Number of incident infections	18	12	..	..	..
Incidence rate of infection, per 10 000 person-weeks (95% CI)	14·7 (9·3 to 23·4)	9·8 (5·6 to 17·3)	..	..	..

HR=hazard ratio. *Each adolescent vaccinated with the 30 µg BNT162b2 vaccine was matched exactly one-to-one (by sex, ten nationality groups, number of coexisting conditions, previous infection status, and calendar month of the second vaccine dose) to the first eligible adolescent vaccinated with the pediatric 10 µg BNT162b2 vaccine who was alive and did not have a SARS-CoV-2 positive test in the 90 days before the start of the follow-up (14 days after the second vaccine dose of their match). †Vaccine effectiveness in the 30 µg cohort relative to that in the 10 µg cohort, estimated using hazard ratios derived from Cox regression analysis adjusted for sex, ten nationality groups, number of coexisting conditions, previous infection status, and calendar month of the second vaccine dose.

***Table*: Risk of and vaccine effectiveness against infection with the omicron variant of SARS-CoV-2 in adolescents vaccinated with two doses of 30 µg BNT162b2 versus two doses of 10 µg BNT162b2**

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Profiling of Immunomodulatory Genes and Quantification of CD25+ Cells in Different Types of Early Pregnancy Loss

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Affiliations + expand

PMID: 36861642 DOI: 10.1177/10935266231156327

Abstract

Introduction: Maternal regulatory T (Treg) cells play a pivotal role in establishing general immune homeostasis in the decidua for maintenance of pregnancy. We aimed in this study to investigate the relationship between mRNA expression of immunomodulatory genes and CD25+ Treg cells with early pregnancy losses.

Methods: Our study included 3 groups of early pregnancy losses including sporadic spontaneous abortions, recurrent spontaneous abortions, sporadic spontaneous abortions post IVF treatment and the control group. We performed RT-PCR for analyzing mRNA expression levels of 6 immunomodulatory genes and CD25 immunohistochemistry for quantification of Treg cells.

Results: Only *FOXP3, CD274 (PDL1)*, and *TGFβ1* mRNA expression levels were significantly decreased in the miscarriage groups in comparison to the control group, whereas there was no significant mRNA expression change of *CD4, IL2RA*, and *IL10*. We also found significantly lower number of CD25+ cells in the miscarriages.

Conclusion: We conclude that decreased expression of *FOXP3* and *PD-L1* may play a significant role in the pathogenesis of spontaneous abortion cases whereas decreased expression of *TGFβ1* gene may be associated with the occurrence of early loss in IVF-treated pregnancies. Additional immunoprofiling of Treg cell population is needed to quantify Treg cells in early pregnancy losses.

Keywords: early pregnancy loss; immune tolerance; in vitro fertilization; miscarriage; recurrent spontaneous abortion; regulatory T cells.

PLOS ONE

RESEARCH ARTICLE

Factors associated with common mental disorders among breastfeeding mothers in tertiary hospital nurseries in Nigeria

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Abstract

Background

Several studies have shown that the impact of maternal mental health disorders on newborns' well-being in low and middle-income countries (LMIC) are underreported, multidimensional and varies over time and differs from what is reported in high-income countries. We present the prevalence and risk factors associated with common mental disorders (CMDs) among breastfeeding mothers whose infants were admitted to Nigerian tertiary care facilities.

Methods

This was a national cross-sectional study involving mothers of hospitalised babies from eleven Nigerian tertiary hospitals. We used the WHO self-reporting Questionnaire 20 and an adapted WHO/UNICEF ten-step breastfeeding support package to assess mothers' mental health and breastfeeding support.

Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting: a retrospective population-based cohort study

Hiam Chemaitelly, Houssein H Ayoub, Patrick Tang, Peter Coyle, Hadi M Yassine, Asmaa A Al Thani, Hebah A Al-Khatib, Mohammad R Hasan, Zaina Al-Kanaani, Einas Al-Kuwari, Andrew Jeremijenko, Anvar Hassan Kaleeckal, Ali Nizar Latif, Riyazuddin Mohammad Shaik, Hanan F Abdul-Rahim, Gheyath K Nasrallah, Mohamed Ghaith Al-Kuwari, Adeel A Butt, Hamad Eid Al-Romaihi, Mohamed H Al-Thani, Abdullatif Al-Khal, Roberto Bertollini, Jeremy Samuel Faust, Laith J Abu-Raddad

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See Comment page 767

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Summary

Background Long-term effectiveness of COVID-19 mRNA boosters in populations with different previous infection histories and clinical vulnerability profiles is inadequately understood. We aimed to investigate the effectiveness of a booster (third dose) vaccination against SARS-CoV-2 infection and against severe, critical, or fatal COVID-19, relative to that of primary-series (two-dose) vaccination over a follow-up duration of 1 year.

Methods This observational, matched, retrospective, cohort study was done on the population of Qatar in people with different immune histories and different clinical vulnerability to infection. The source of data are Qatar's national databases for COVID-19 laboratory testing, vaccination, hospitalisation, and death. Associations were estimated using inverse-probability-weighted Cox proportional-hazards regression models. The primary outcome of the study is the effectiveness of COVID-19 mRNA boosters against infection and against severe COVID-19.

Findings Data were obtained for 2 228 686 people who had received at least two vaccine doses starting from Jan 5, 2021, of whom 658 947 (29·6%) went on to receive a third dose before data cutoff on Oct 12, 2022. There were 20 528 incident infections in the three-dose cohort and 30 771 infections in the two-dose cohort. Booster effectiveness relative to primary series was 26·2% (95% CI 23·6–28·6) against infection and 75·1% (40·2–89·6) against severe, critical, or fatal COVID-19, during 1-year follow-up after the booster. Among people clinically vulnerable to severe COVID-19, effectiveness was 34·2% (27·0–40·6) against infection and 76·6% (34·5–91·7) against severe, critical, or fatal COVID-19. Effectiveness against infection was highest at 61·4% (60·2–62·6) in the first month after the booster but waned thereafter and was modest at only 15·5% (8·3–22·2) by the sixth month. In the seventh month and thereafter, coincident with BA.4/BA.5 and BA.2·75* subvariant incidence, effectiveness was progressively negative albeit with wide CIs. Similar patterns of protection were observed irrespective of previous infection status, clinical vulnerability, or type of vaccine (BNT162b2 *vs* mRNA-1273).

Interpretation Protection against omicron infection waned after the booster, and eventually suggested a possibility for negative immune imprinting. However, boosters substantially reduced infection and severe COVID-19, particularly among individuals who were clinically vulnerable, affirming the public health value of booster vaccination.

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Introduction

With waning of vaccine and previous infection protection against SARS-CoV-2 infection and against severe COVID-19,[1–3] repeat booster vaccination could sustain immune protection against infection and disease.[4,5] However, the global population carries heterogeneous immune histories due to varying exposures to infection from different viral variants and vaccination.[6] Booster effectiveness can vary by previous infection and vaccination history, previous variant exposure, and by age and clinical vulnerability to severe COVID-19. Immune imprinting, a phenomenon in which the specific sequence of immunological events (due to infection or vaccination, or both) can enhance or compromise a person's future immune protection, could affect the utility of booster vaccination.[6–8] The optimal public health effect of boosters might not be achieved through a one size fits all approach.

We aimed to investigate the long-term real-world effectiveness of a booster (third dose) vaccination against SARS-CoV-2 infection and against severe,[9] critical,[9] or fatal[10] COVID-19, relative to that of primary-series (two-dose) vaccination, in people with different immune histories and different clinical vulnerability to infection, over a follow-up duration of 1 year.

Risk of suicide in children and adolescents in the emergency department—is universal screening the answer?

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ABSTRACT

Objective Suicide is a leading cause of death among children and adolescents. Suicide risk screening tools can detect the risk of suicide among patients presenting to healthcare settings. The aim of this review was to describe the effectiveness of universal suicide risk screening (all patients) compared with selective screening (behavioural health patients only) in children and adolescents in emergency departments (EDs).

Method A literature search was conducted on PubMed for articles related to suicide risk screening in paediatric EDs between January 2016 and February 2022.

Results 8 studies met the selection criteria. The review showed that 46%–93% of patients that screened positive for suicide risk had presented with a medical concern. These patients would have been missed without universal suicide risk screening. In both selective and universal screening scenarios, use of a suicide risk screening tool was better at detecting suicide risk compared with use of presenting problem alone. Suicide risk screening was found to be acceptable without increasing length of stay in the ED.

Conclusion Based on this review, using a suicide screening tool can help detect patients at risk who would otherwise have been missed.

INTRODUCTION

Suicide is one of the most common causes of death worldwide, and mortality due to suicide is increasing over time.[1–4] Suicide attempts are a rising problem in children and adolescents.[5] It is the fourth most common cause of death in general for adolescents between the ages of 15 and 19 as per reports from the WHO.[6] According to a survey conducted in 2018, in the USA, 18.8% of high school students had thought about suicide seriously, 15.7% had devised a plan and 8.9% had a suicide attempt one or more times in the year before the survey.[7] Deaths caused by suicide among children aged 10–14 years have recently exceeded those caused by automobile accidents.[8]

Over 80% of children and adolescents with suicide attempts visited a healthcare professional a year before the attempt, and 40% saw a healthcare professional a month before the attempt.[9 10] The rate of death by suicide is higher immediately after discharge from psychiatric hospitals.[11] This provides ample opportunity for early detection of suicidal risk and prevention in inpatient, primary healthcare and emergency department (ED) settings.[12] During routine care in the ED, referral to behavioural health assessments is usually based on chief complaint. Therefore, if the presenting complaint is medical or not suicide related, patients with suicide risk may be missed. The use of validated screening tools to detect risk of suicide has been proposed to be superior to detecting suicide risk through clinical judgement alone.[13 14] In general, suicide risk screening detects the presence of suicidal ideation, while assessment tools further stratify risk based on the intensity and severity of ideation and suicidal behaviours and the presence of risk and protective factors.[15] In healthcare settings, suicide risk screening can be either universal (all patients presenting to a clinical setting) or selective (patients presenting with a behavioural health concern).[16]

The aim of this review was to describe the effectiveness of universal suicide risk screening compared with selective screening in children and adolescents presenting to the ED.

METHODS

A comprehensive literature search of the electronic database PubMed was conducted. We used the search terms suicide*, suicide risk*, screening*, screening tool*, assessment tool*, pediatric*, and children and adolescents*. 'And' and 'Or' were used to combine the search terms. Studies were then selected using the following filters: human subjects, English language, full-text articles, published articles, and articles from January 2016 until February 2022. Then, two authors went through the papers independently and disagreements related to selection criteria were addressed by a face to face discussion. Authors selected articles that were focused on actual implementation of standardised universal or selective suicide risk screening workflow in the child and adolescent population (age 18 years or younger) in the ED. Studies focused on use of suicide risk screening tools solely for validation purposes were excluded. On the basis of heterogeneity of the literature, a narrative synthesis was undertaken.

Suicide risk screening tools used in the studies included the Ask Suicide-Screening Questions (ASQ),[17–20] Columbia-Suicide Severity Rating Scale (CSSRS)[21–23] and Patient Health Questionaire-9 (PHQ-9).[21] ASQ is a brief (4-question) screening tool with high sensitivity.[24] The ASQ can be self-administered, thus not requiring an increase in ED length of stay or valuable clinical provider hours. The CSSRS is a 6-question tool that can further stratify risk with good sensitivity and specificity.[25] The PHQ-9 is a 9-item tool that is used to detect depression and assess the severity of depression. It has a single question that asks about suicidal ideation.[26]

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RESEARCH

Aromatic L-amino acid decarboxylase deficiency in countries in the Middle East: a case series and literature review

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Abstract

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare inherited neurometabolic disorder that can lead to severe physical and developmental impairment. This report includes 16 patients from the Middle East and is the largest series of patients with confirmed AADC deficiency from this region reported to date. The patients displayed a range of signs and symptoms at presentation and almost all failed to reach major motor milestones. Missed and delayed diagnoses were common leading to the late introduction of targeted treatments. Eight unique variants were identified in the *DDC* gene, including six missense and two intronic variants. A previously undescribed variant was identified: an intronic variant between exons 13 and 14 (c.1243-10A>G). The patients were mostly treated with currently recommended medications, including dopamine agonists, vitamin B6, and monoamine oxidase inhibitors. One patient responded well, but treatment outcomes were otherwise mostly limited to mild symptomatic improvements. Five patients had died by the time of data collection, confirming that the condition is associated with premature mortality. There is an urgent need for earlier diagnosis, particularly given the potential for gene therapy as a transformative treatment for AADC deficiency when provided at an early age.

Conclusions: Delays in the diagnosis of AADC deficiency are common. There is an urgent need for earlier diagnosis, particularly given the potential for gene therapy as a transformative treatment for AADC deficiency when provided at an early age.

What is Known:
- *Aromatic L-amino acid decarboxylase deficiency is a rare neurometabolic disorder that can lead to severe physical and developmental impairment.*
- *Currently recommended medications provide mostly mild symptomatic improvements.*

What is New:
- *The clinical presentation of sixteen patients with confirmed AADC deficiency varied considerably and almost all failed to reach major motor milestones.*
- *There is an urgent need for earlier diagnosis, given the potential for gene therapy as a transformative treatment for AADC deficiency when provided at an early age.*

Keywords AADC deficiency · Delayed diagnosis · Developmental delay · Whole exome sequencing · Case report

Introduction

First described in 1990, aromatic L-amino acid decarboxylase (AADC) deficiency is an ultrarare, autosomal recessive, neurotransmitter metabolic disorder resulting from pathogenic variants within the dopa decarboxylase (*DDC*) gene [1, 2]. To date, at least 261 cases have been reported in the medical literature [3] and, as of June 2022, there are currently 420 variants listed in the Pediatric Neurotransmitter Disease database (PNDdb; available at: http://biopku.org/pnddb/home.asp), including 370 that are associated with a neurotransmitter deficiency phenotype. Although the global prevalence of AADC deficiency is unknown, it is believed to be higher in Asian populations owing to the presence of the founder variant c.714+4A>T [4]. In Taiwan, a pilot newborn

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ORIGINAL ARTICLE

Stage I epithelial or stromal type Wilms tumors are low risk tumors: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies (2001–2020)

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Abstract

Background: Patients treated with preoperative chemotherapy with stage I intermediate-risk Wilms tumor (IR-WT) represent the largest group of patients with Wilms tumor (WT), and they have excellent outcomes.

Methods: The authors performed a retrospective analysis of patients with stage I epithelial (ET-WT) or stromal type WT (ST-WT) treated pre- and postoperatively according to the International Society of Paediatric Oncology-WT-2001 protocol in the UK Children's Cancer and Leukaemia Group and Gesellschaft für Pädiatrische Onkologie und Hämatologie groups' participation in the relevant WT trials and studies (2001–2020).

Results: There were 880 patients with stage I IR-WT, including 124 with ET-WT, 156 with ST-WT, and 600 with other IR-WT (oIR-WT). Patients with stage I ET-WT or ST-WT were significantly younger than patients with oIR-WT, represented a large proportion of stage I WTs in their groups, and tumors showed poor histologic response to preoperative chemotherapy. The 5-year event-free survival (EFS) estimates for patients with stage I ET-WT (96.8% ± 1.8 SE) or ST-WT (96.8% ± 1.6 SE) were significantly better than for patients with oIR-WT (90.3% ± 1.3 SE) ($p = .014$ and $p = .009$, respectively). A multivariate analysis showed that histologic type (ET-WT or ST-WT) remained a significant factor for EFS when adjusted for age and gender ($p = .032$ and $p = .022$, respectively). In both groups, relapses occurred in 3.2% of patients, and the overall survival was 99.2%.

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ORIGINAL ARTICLE

End-of-life care in Brazilian Pediatric Intensive Care Units

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KEYWORDS
Terminal care;
End-of-life care;
Biomedical ethics;
Palliative care;
Pediatric intensive care units

Abstract

Objective: Most deaths in Pediatric Intensive Care Units involve forgoing life-sustaining treatment. Such deaths required carefully planned end-of-life care built on compassion and focused on palliative care measures. This study aims to assess topics related to the end of life care in Brazilian pediatric intensive care units from the perspective of a multidisciplinary team.

Method: The authors used a tested questionnaire, utilizing Likert-style and open-ended questions. After ethics committee approval, it was sent by email from September to November/2019 to three Pediatric Intensive Care Units in the South and Southeast of Brazil. One unit was exclusively dedicated to oncology patients; the others were mixed units.

Results: From 144 surveys collected (23% response rate) 136 were analyzed, with 35% physicians, 30% nurses, 21% nurse technicians, and 14% physiotherapists responding. Overall, only 12% reported enough end-of-life care training and 40% reported never having had any, albeit this was not associated with the physician's confidence in forgoing life-sustaining treatment. Furthermore, 60% of physicians and 46% of other professionals were more comfortable with non-escalation than withdrawing therapies, even if this could prolong suffering. All physicians were uncomfortable with palliative extubation; 15% of all professionals have witnessed it. The oncologic team uniquely felt that "resistance from the teams of specialists" was the main barrier to end-of-life care implementation.

Conclusion: Most professionals felt unprepared to forego life-sustaining treatment. Even for terminally ill patients, withholding is preferred over the withdrawal of treatment. Socio-cultural

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MDPI

Article

Comparative Analysis of Clinical and CT Findings in Patients with SARS-CoV-2 Original Strain, Delta and Omicron Variants

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Abstract: Objectives: To compare the clinical characteristics and chest CT findings of patients infected with Omicron and Delta variants and the original strain of COVID-19. Methods: A total of 503 patients infected with the original strain (245 cases), Delta variant (90 cases), and Omicron variant (168 cases) were retrospectively analyzed. The differences in clinical severity and chest CT findings were analyzed. We also compared the infection severity of patients with different vaccination statuses and quantified pneumonia by a deep-learning approach. Results: The rate of severe disease decreased significantly from the original strain to the Delta variant and Omicron variant (27% vs. 10% vs. 4.8%, $p < 0.001$). In the Omicron group, 44% (73/168) of CT scans were categorized as abnormal compared with 81% (73/90) in the Delta group and 96% (235/245, $p < 0.05$) in the original group. Trends of a gradual decrease in total CT score, lesion volume, and lesion CT value of AI evaluation were observed across the groups ($p < 0.001$ for all). Omicron patients who received the booster vaccine had less clinical severity ($p = 0.015$) and lower lung involvement rate than those without the booster vaccine (36% vs. 57%, $p = 0.009$). Conclusions: Compared with the original strain and Delta variant, the Omicron variant had less clinical severity and less lung injury on CT scans.

Keywords: SARS-CoV-2; Delta variant; Omicron variant; original strain; CT imaging

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1. Introduction

Over three years after the first described COVID-19 patient of the original strain in December 2019 [1,2], multiple variants of concern of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged, varying in transmissibility and severity [3]. The Delta variant was first identified in India in October 2020 and became the dominant strain detected globally in June 2021. Subsequently, the Omicron variant, which was first reported in South Africa on 24 November 2021, quickly replaced the Delta variant and became the predominant strain globally. The SARS-CoV-2 variants carry signature amino acid substitutions in key areas of the immunodominant spike protein, with evidence of altered virus characteristics [4]. Hence, the variances in clinical and imaging characteristics of SARS-CoV-2 variants and vaccine effectiveness gained public concern.

Numerous studies have revealed the clinical manifestations [5], imaging characteristics [6], and outcomes [7] of the first wave of SARS-CoV-2 (original strain). However, clinical and lung CT findings of the Omicron and Delta variants are lacking. Two recent studies [8,9] from the UK and South Korea have indicated that the CT severity of infection

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What are the barriers to sustaining a safe sleep program for infants within hospital settings: An integrative review of the literature

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Highlights

- This article highlights the need for continued safe sleep practices within hospital settings
- Continuing education is needed for both families and staff
- Education needs to fit the cultural context of each situation

Abstract

Problem

Safe sleep programs have been existing since the concept was first defined in 1969. The need for health care providers to model safe sleep practices is essential for successful adherence; however, barriers to promoting safe sleep practices hinder healthcare providers' ability to implement safe sleep in hospital settings.

Aim

To determine the barriers to promoting safe sleep practices amongst healthcare workers in the hospital setting.

Methods

Whittemore & Knafl's framework (2005) guided this integrative review. CINAHL, PubMed, and Academic Search Complete databases were used as a search strategy. Inclusion criteria was limited to studies between 2010 and 2021, were peer-reviewed, in English, and quality improvement projects consisting of barriers to implementing safe sleep practices within hospitals. To assess quality of the included studies, the Mixed Methods Appraisal Tool and Standards for Quality Improvement Reporting Excellence were used. The studies were analyzed by two of the authors with data further categorized using the Social Ecological Model (SEM) to develop themes.

Results

Findings of the 10 included studies were presented in the form of a data display matrix. The authors used the SEM to categorize the findings under three main categories at the organizational, individual, and cultural levels.

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STANDARD ARTICLE

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ACVIM American College of Veterinary Internal Medicine

Electroencephalographic evaluation under standing sedation using sublingual detomidine hydrochloride in Egyptian Arabian foals for investigation of epilepsy

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Abstract

Background: A standardized protocol for electroencephalography (EEG) under standing sedation for the investigation of epilepsy in foals is needed.

Hypothesis/Objectives: To evaluate a modified standardized EEG protocol under standing sedation using sublingual detomidine hydrochloride in Egyptian Arabian foals.

Animals: Nineteen foals (controls, 9; juvenile idiopathic epilepsy [JIE], 10).

Methods: Descriptive clinical study. Foals were classified as controls or epileptic based on history or witnessed seizures and neurological examination. Foals were sedated using sublingual detomidine hydrochloride at a dosage of 0.08 mg/kg to avoid stress associated with injectable sedation. Once foals appeared sedated with their heads low to the ground and with wide base stance (30 minutes), topical lidocaine hydrochloride was applied at the determined locations of EEG electrodes. Fifteen minutes were allowed for absorption and electrodes were placed, protected, and EEG recording performed.

Results: Level of sedation was considered excellent with no need of redosing. The EEG recording lasted from 27 to 51 minutes and provided interpretable data. Epileptic discharges (ED) were noted predominantly in the central-parietal region in 9 of 10 epileptic foals. Photic stimulation triggered ED in 7 of 10 epileptic foals and in none of the controls. Foals were not oversedated and recovered uneventfully.

Conclusions and Clinical Importance: Sublingual detomidine hydrochloride is a safe, painless, simple, and effective method of sedation for EEG recording in foals. Sublingual sedation allowed the investigation of cerebral electrical activity during states of sleep and arousal, and during photic stimulation for the investigation of epilepsy in foals.

KEYWORDS
electroencephalogram, epilepsy, paroxysmal, photic, sedation, seizures

Abbreviations: ECG, electrocardiogram; ED, epileptic discharges; EEG, electroencephalogram; JIE, juvenile idiopathic epilepsy; PD, photic driving; SWS, slow wave sleep.

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Original Investigation | Pediatrics

Interventions to Reduce Severe Brain Injury Risk in Preterm Neonates
A Systematic Review and Meta-analysis

Abdul Razak, MD; Waseemoddin Patel, MD; Naveed Ur Rehman Durrani, MD; Abdul Kareem Pullattayil, MISt

Abstract

IMPORTANCE Interventions to reduce severe brain injury risk are the prime focus in neonatal clinical trials.

OBJECTIVE To evaluate multiple perinatal interventions across clinical settings for reducing the risk of severe intraventricular hemorrhage (sIVH) and cystic periventricular leukomalacia (cPVL) in preterm neonates.

DATA SOURCES MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases were searched from inception until September 8, 2022, using prespecified search terms and no language restrictions.

STUDY SELECTION Randomized clinical trials (RCTs) that evaluated perinatal interventions, chosen a priori, and reported 1 or more outcomes (sIVH, cPVL, and severe brain injury) were included.

DATA EXTRACTION AND SYNTHESIS Two co-authors independently extracted the data, assessed the quality of the trials, and evaluated the certainty of the evidence using the Cochrane GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Fixed-effects pairwise meta-analysis was used for data synthesis.

MAIN OUTCOMES AND MEASURES The 3 prespecified outcomes were sIVH, cPVL, and severe brain injury.

RESULTS A total of 221 RCTs that assessed 44 perinatal interventions (6 antenatal, 6 delivery room, and 32 neonatal) were included. Meta-analysis showed with moderate certainty that antenatal corticosteroids were associated with small reduction in sIVH risk (risk ratio [RR], 0.54 [95% CI, 0.35-0.82]; absolute risk difference [ARD], −1% [95% CI, −2% to 0%]; number needed to treat [NNT], 80 [95% CI, 48-232]), whereas indomethacin prophylaxis was associated with moderate reduction in sIVH risk (RR, 0.64 [95% CI, 0.52-0.79]; ARD, −5% [95% CI, −8% to −3%]; NNT, 20 [95% CI, 13-39]). Similarly, the meta-analysis showed with low certainty that volume-targeted ventilation was associated with large reduction in risk of sIVH (RR, 0.51 [95% CI, 0.36-0.72]; ARD, −9% [95% CI, −13% to −5%]; NNT, 11 [95% CI, 7-23]). Additionally, early erythropoiesis-stimulating agents (RR, 0.68 [95% CI, 0.57-0.83]; ARD, −3% [95% CI, −4% to −1%]; NNT, 34 [95% CI, 22-67]) and prophylactic ethamsylate (RR, 0.68 [95% CI, 0.48-0.97]; ARD, −4% [95% CI, −7% to 0%]; NNT, 26 [95% CI, 13-372]) were associated with moderate reduction in sIVH risk (low certainty). The meta-analysis also showed with low certainty that compared with delayed cord clamping, umbilical cord milking was associated with a moderate increase in sIVH risk (RR, 1.82 [95% CI, 1.03-3.21]; ARD, 3% [95% CI, 0%-6%]; NNT, −30 [95% CI, −368 to −16]).

(continued)

Key Points

Question Which perinatal interventions associated with reducing the risk of severe intraventricular hemorrhage (sIVH) in neonates born at less than 37 weeks' gestation?

Findings In this systematic review and meta-analysis of 221 randomized clinical trials that assessed 44 perinatal interventions, antenatal corticosteroids for lung maturation (small decrease) and indomethacin prophylaxis (moderate decrease) were found with moderate certainty to be associated with reduced risk of sIVH in preterm neonates. With low certainty, volume-targeted ventilation (large decrease), early erythropoiesis-stimulating agents (moderate decrease), and prophylactic ethamsylate (moderate decrease) were associated with reduced sIVH risk, whereas umbilical cord milking (moderate increase) was associated with increased risk of sIVH in preterm neonates.

Meaning Findings of this study suggest a few interventions were associated with reduced sIVH risk; however, clinicians need to consider all of the critical factors that may affect applicability in these interventions, including certainty of the evidence, before applying them to clinical practice.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Deep learning based automated quantification of urethral plate characteristics using the plate objective scoring tool (POST)

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Hypospadias; Machine Learning; Artifical Intelligence; Urethral plate

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Summary

Introduction
The plate objective scoring tool (POST) was recently introduced as a reproducible and precise approach to quantifying urethral plate (UP) characteristics and guide to selecting particular surgical techniques. However, defining the landmarks mandatory for the POST score from captured images can potentially leads to variability. Although artificial intelligence (AI) is yet to be wholly accepted and explored in hypospadiology, it has certainly brought new possibilities to light.

Objectives
To explore the capacity of deep learning algorithm to further streamline and optimize UP characteristics appraisal on 2D images using the POST, aiming to increase the objectivity and reproducibility of UP appraisal in hypospadias repair.

Methods
The five key POST landmarks were marked by specialists in a 691-image dataset of prepubertal boys undergoing primary hypospadias repair. This dataset was then used to develop and validate a deep learning-based landmark detection model. The proposed framework begins with glans localization and detection, where the input image is cropped using the predicted bounding box. Next, a deep convolutional neural network (CNN) architecture is used to predict the coordinates of the five POST landmarks. These predicted landmarks are then used to assess UP characteristics in distal hypospadias.

Results
The proposed model accurately localized the glans area, with a mean average precision (mAP) of 99.5% and an overall sensitivity of 99.1%. A normalized mean error (NME) of 0.07152 was achieved in predicting the coordinates of the landmarks, with a mean squared error (MSE) of 0.001 and a 2.5% failure rate at a threshold of 0.2 NME.

Discussion
Our results support the possibility of further standardizing UP assessment from captured hypospadias images, and the use of machine learning algorithms and image recognition shows that these novel artificial intelligence technologies are useful for scoring hypospadias. External validation can provide valuable information on the generalizability and reliability of deep learning algorithms, which can aid in assessments, decision-making and predictions for surgical outcomes.

Conclusions
This deep learning application shows robustness and high precision in using POST to appraise UP characteristics. Further assessment using international multi-centre image-based databases is ongoing.

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Original article

Molecular characterization of *Candida auris* outbreak isolates in Qatar from patients with COVID-19 reveals the emergence of isolates resistant to three classes of antifungal drugs

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ABSTRACT

Objectives: During the COVID-19 pandemic in Qatar, many patients who were severely ill were colonized and infected by *Candida auris*, an invasive multidrug-resistant yeast pathogen that spreads through nosocomial transmission within healthcare facilities. Here, we investigated the molecular epidemiology of these *C. auris* isolates and the mechanisms associated with antifungal drug resistance.

Methods: Whole genomes of 76 clinical *C. auris* isolates, including 65 from patients with COVID-19 collected from March 2020 to June 2021, from nine major hospitals were sequenced on Illumina NextSeq. Single nucleotide polymorphisms were used to determine their epidemiological patterns and mechanisms for antifungal resistance. The data were compared with those published prior to the COVID-19 pandemic from 2018 to 2020 in Qatar.

Results: Genomic analysis revealed low genetic variability among the isolates from patients with and without COVID-19, confirming a clonal outbreak and ongoing dissemination of *C. auris* among various healthcare facilities. Based on antifungal susceptibility profiles, more than 70% (22/28) of isolates were resistant to both fluconazole and amphotericin B. Variant analysis revealed the presence of multi-antifungal resistant isolates with prominent amino acid substitutions: Y132F in *ERG11* and V704L in *CDR1* linked to reduced azole susceptibility and the emergence of echinocandin resistance samples bearing mutations in *FKS1* in comparison with pre-COVID-19 pandemic samples. One sample (CAS109) was resistant to three classes of antifungal drugs with a unique premature stop codon in *ERG3* and novel mutations in *CDR2*, which may be associated with elevated amphotericin B and azole resistance.

Discussion: *Candida auris* isolates from patients with COVID-19 and from most patient samples without COVID-19 in Qatar were highly clonal. The data demonstrated the emergence of multidrug-resistant strains that carry novel mutations linked to enhanced resistance to azoles, echinocandins, and amphotericin B. Understanding the epidemiology and drug resistance will inform the infection control strategy and drug therapy. **Fatma Ben Abid, Clin Microbiol Infect 2023;■:1**

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Automated measurement of penile curvature using deep learning-based novel quantification method

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Objective: Develop a reliable, automated deep learning-based method for accurate measurement of penile curvature (PC) using 2-dimensional images.
Materials and methods: A set of nine 3D-printed models was used to generate a batch of 913 images of penile curvature (PC) with varying configurations (curvature range 18° to 86°). The penile region was initially localized and cropped using a YOLOv5 model, after which the shaft area was extracted using a UNet-based segmentation model. The penile shaft was then divided into three distinct predefined regions: the distal zone, curvature zone, and proximal zone. To measure PC, we identified four distinct locations on the shaft that reflected the mid-axes of proximal and distal segments, then trained an HRNet model to predict these landmarks and calculate curvature angle in both the 3D-printed models and masked segmented images derived from these. Finally, the optimized HRNet model was applied to quantify PC in medical images of real human patients and the accuracy of this novel method was determined.
Results: We obtained a mean absolute error (MAE) of angle measurement <5° for both penile model images and their derivative masks. For real patient images, AI prediction varied between 1.7° (for cases of ~30° PC) and approximately 6° (for cases of 70° PC) compared with assessment by a clinical expert.
Discussion: This study demonstrates a novel approach to the automated, accurate measurement of PC that could significantly improve patient assessment by surgeons and hypospadiology researchers. This method may overcome current limitations encountered when applying conventional methods of measuring arc-type PC.

KEYWORDS

penile curvature, artificial intelligence, machine learning, YOLO, UNET, HRNet, hypospadias, chordee

1. Introduction

Congenital penile curvature (PC) is typically caused by abnormalities in genital development, such as chordee or hypospadias. Approximately 1 in 300 newborn males exhibit hypospadias (1, 2), with an estimated one-third of individuals also presenting with notable PC (3, 4). This condition is thought to result from arrested embryological development of the ventral axis of the penile shaft, often leading to insufficient skin, abnormally short urethral plate, and ventro-dorsal corporeal disproportion (5–7). In some

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Case report: Neonatal autoimmune lymphoproliferative syndrome with a novel pathogenic homozygous *FAS* variant effectively treated with sirolimus

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Background: Autoimmune lymphoproliferative syndrome (ALPS) is a rare disease characterized by defective *FAS* signaling, which results in chronic, nonmalignant lymphoproliferation and autoimmunity accompanied by increased numbers of "double-negative" T-cells (DNTs) (T-cell receptor αβ+ CD4−CD8−) and an increased risk of developing malignancies later in life.
Case presentation: We herein report a case of a newborn boy with a novel germline homozygous variant identified in the *FAS* gene, exon 9, c.775del, which was considered pathogenic. The consequence of this sequence change was the creation of a premature translational stop signal p.(Ile259*), associated with a severe clinical phenotype of ALPS-*FAS*. The elder brother of the proband was also affected by ALPS and has been found to have the same *FAS* homozygous variant associated with a severe clinical phenotype of ALPS-*FAS*, whereas the unaffected parents are heterozygous carriers of this variant. This new variant has not previously been described in population databases (gnomAD and ExAC) or in patients with *FAS*-related conditions. Treatment with sirolimus effectively improved the patient clinical manifestations with obvious reduction in the percentage of DNTs.

Abbreviations

ALPS, autoimmune lymphoproliferative syndrome; CADD, combined annotation-dependent depletion; DNT, "double-negative" T-cells; *FAS* gene, *Fas* cell surface death receptor gene; NICU, neonatal intensive care unit; CBC, complete blood count; NIV, noninvasive ventilation; CSF, cerebrospinal fluid; US, ultrasound; s*FASL*, soluble *Fas* ligand; WES, whole exome sequencing; FADD, *Fas*-associated death domain; AD, autosomal dominant; NK cells, natural killer cells; MMF, mycophenolate mofetil; mTOR, the mammalian target of rapamycin; CD4 cells, T-lymphocytes or "helper T-cells"; CD8 cells, cytotoxic T-lymphocytes; CD7 cells, transmembrane glycoprotein expressed by T-cells and NK cells and their precursors; CD3 cells, (cluster of differentiation 3) is a protein complex and T-cell co-receptor that is involved in activating both the cytotoxic T-cell (CD8+ naive T-cells); CD2 cells, (cluster of differentiation 2) is a cell adhesion molecule found on the surface of T-cells and NK cells; CD5 cells, T-cell surface glycoprotein that negatively regulates TCR signaling from the onset of T-cell activation; CD38 cells, cluster of differentiation 38; CD25 cells, cluster of differentiation 25; CD19+ (B cells), cluster of differentiation 19 B-lymphocyte antigen CD19; CD19-(E1) cells, CD19 (cluster of differentiation 19), also known as B-Lymphocyte Surface Antigen B4; CD3−/CD56+ (NK cells), NK cells have been defined as CD3−, CD16+, and/or CD56+ lymphocytes; IL-10, interleukin-10; PLAD, pre-ligand binding assembly domain; CRD1, cysteine rich domain 1; Phred, phred proprietary software.

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Short communication

Burnout among healthcare professionals in Qatar: A systematic review

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ABSTRACT

This systematic review aims to cover studies addressing the topic of burnout among the various types of healthcare professionals in Qatar. PubMed, Scopus and Google Scholar were searched with no filters. All studies using the Maslach Burnout Inventory (MBI) were included. The Newcastle-Ottawa Scale was used for quality assessment of the studies included. The reporting of the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The results indicate that the pooled prevalence rate of burnout among healthcare professionals in Qatar are, 17% and 20% based on fixed effect and random effect models, respectively.

1. Introduction

Burnout syndrome refers to the psychological consequences of ongoing and long-term work-related stress (Schaufeli et al., 1993), which is defined as a group of symptoms caused by chronic workplace stress involving emotional exhaustion, feelings of helplessness, depersonalization, negative attitudes, job satisfaction, job performance, vulnerability to illnesses, and interpersonal relationships (American Thoracic Society, 2016). The Maslach Burnout Inventory (MBI) is commonly used to assess burnout in medical professionals (Maslach et al., 2001). Other tools include the Copenhagen Burnout Inventory, the Shirom Melamed Burnout Questionnaire, and the Oldenburg Burnout Inventory (De Hert, 2020).

Reports have shown that burnout can occur in any working force (Lindblom et al., 2006). Others have shown high levels of burnout among medical service employees, with marginally higher levels among females (De Hert, 2020). Others have shown higher rates among physicians when compared to the general population (Shanafelt et al., 2012). At any given time, one-third of physicians suffer from burnout (De Hert, 2020). A systematic review that covered 45 countries, reported a wide range of burnout among physicians (0–80.5%) (Rotenstein et al., 2018). A second systematic review of burnout among healthcare providers in the Middle East showed that burnout is highly prevalent with estimates ranging from 40% to 60% (Chemali et al., 2019). Another review of burnout among healthcare providers in Sub-Saharan Africa reported a high level of burnout among all healthcare providers, with the highest levels being found among nurses (Dubale et al., 2019). More recently, a systematic review of physician burnout in the Eastern Mediterranean region showed high levels of burnout on all three subcomponents of the syndrome, with more than one-third of physicians reporting at least one component of the burnout syndrome (Doraiswamy et al., 2021).

Interestingly enough, very little is known about the collective burden of burnout and its effects on healthcare professionals in the Middle East in general and in Qatar more specifically. Few studies in Qatar have reported burnout among different categories of healthcare professionals, such as general physicians, ICU clinicians, psychiatrists, medical residents, and nurses. This systematic review aims to cover these studies.

2. Methods

On 26 June 2022, a search was carried out on PubMed, Scopus and Google scholar for literature related to burnout among healthcare professionals in Qatar. The search used no filters. The following terms were used: Qatar, Burnout, and Healthcare Professionals. A manual search, along with snowballing (Wohlin, 2014), was utilized as well.

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Article

Transcatheter closure of perimembranous ventricular septal defect using a novel fully bioabsorbable occluder: multicenter randomized controlled trial

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ABSTRACT

Although the use of bioabsorbable occluder is expected to reduce the risk of metal occluder-related complications, it has not been approved due to incomplete degradation and new complications. Novel fully bioabsorbable occluders were designed to overcome such limitations. The aim of this study was to investigate the efficacy and safety of a fully biodegradable occluder in patients with ventricular septal defects. 125 patients with perimembranous ventricular septal defect (VSD) larger than 3 mm were screened from April 2019 to January 2020 in seven centers. 108 patients were enrolled and randomized into the bioabsorbable occluder group (n = 54 patients) and nitinol occluder group (n = 54). A non-inferiority design was utilized and all patients underwent transcatheter device occlusion. Outcomes were analyzed with a 24-month follow-up. All patients were successfully implanted and completed the trial. No residual shunt >2 mm was observed during follow-up. Transthoracic echocardiography showed a hyperechoic area corresponding to the bioabsorbable occluder which decreased primarily during the first year after implantation and disappeared within 24 months. Postprocedural arrhythmia was the only occluder-related complication with an incidence of 5.56% and 14.81% for the bioabsorbable and nitinol groups, respectively (P = 0.112). The incidence of sustained conduction block was lower in the bioabsorbable occluder group (0/54 vs. 6/54, P = 0.036) at 24-month follow-up. In conclusion, the novel fully bioabsorbable occluder can be successfully and safely implanted under echocardiography guidance and reduce

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RESIDENT & FELLOW SECTION

Teaching Video NeuroImage: Oculomotor Apraxia as the Only Presentation of Diffuse Intrinsic Pontine Glioma

Farouq Thabet, MD, Mohammed Sawahreh, MD, Dana Thaher, MD, and Fatima Al Maadid, MD

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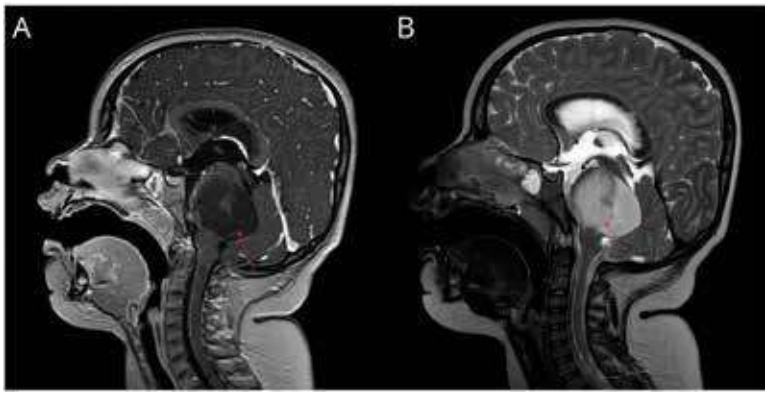
Figure MRI of the Brain Showing Diffuse Intrinsic Pontine Glioma



MRI of the brain T1-weighted image (sagittal view) showing a mass centered in the pons (arrow) with significant expansion and mild extension to the midbrain as well as a posterior exophytic component obliterating the 4th ventricle leading to early hydrocephalus (A). T2-weighted image showing high signal intensity of the tumor (B).

A 5-year-old typically developing boy presented with a 4-week history of moving his head to follow objects due to inability to move his eyes side to side. His neurologic examination was normal except for this inability to voluntarily move his eyes horizontally, consistent with oculomotor apraxia (Video 1). MRI of the brain showed pontine mass suggestive of diffuse high-grade glioma (DIPG) (Figure). The patient underwent radiotherapy, and a ventriculoperitoneal shunt was placed for hydrocephalus.

In pediatric patients, oculomotor apraxia may be seen in ataxia with oculomotor apraxia, Cogan syndrome, Joubert syndrome, and ataxia telangiectasia. In our case, the brainstem tumor disrupted the structural connectivity between the frontal eye fields and oculomotor network including the pons, the superior colliculus, and caudate nucleus leading to oculomotor apraxia.[1]

DIPG is an aggressive pediatric tumor with a median survival of 9–12 months. It classically presents with cranial nerve palsies, long tract signs, and ataxia.[2]

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Video

Teaching slides
links.lww.com/WNL/C786

Author Contributions

F. Thabet: drafting/revision of the manuscript for content, including medical writing for content. Mohammed Sawahreh: drafting/revision of the manuscript for content, including medical writing for content. D. Thaher: major role in the acquisition of data. F.A. Maadid: major role in the acquisition of data.

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Exploring ChatGPT's Potential in Facilitating Adaptation of Clinical Guidelines: A Case Study of Diabetic Ketoacidosis Guidelines

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Abstract

Background

This study aimed to evaluate the efficacy of ChatGPT, an advanced natural language processing model, in adapting and synthesizing clinical guidelines for diabetic ketoacidosis (DKA) by comparing and contrasting different guideline sources.

Methodology

We employed a comprehensive comparison approach and examined three reputable guideline sources: Diabetes Canada Clinical Practice Guidelines Expert Committee (2018), Emergency Management of Hyperglycaemia in Primary Care, and Joint British Diabetes Societies (JBDS) 02 The Management of Diabetic Ketoacidosis in Adults. Data extraction focused on diagnostic criteria, risk factors, signs and symptoms, investigations, and treatment recommendations. We compared the synthesized guidelines generated by ChatGPT and identified any misreporting or non-reporting errors.

Results

ChatGPT was capable of generating a comprehensive table comparing the guidelines. However, multiple recurrent errors, including misreporting and non-reporting errors, were identified, rendering the results unreliable. Additionally, inconsistencies were observed in the repeated reporting of data. The study highlights the limitations of using ChatGPT for the adaptation of clinical guidelines without expert human intervention.

Conclusions

Although ChatGPT demonstrates the potential for the synthesis of clinical guidelines, the presence of multiple recurrent errors and inconsistencies underscores the need for expert human intervention and validation. Future research should focus on improving the accuracy and reliability of ChatGPT, as well as exploring its potential applications in other areas of clinical practice and guideline development.

Categories: Quality Improvement, Healthcare Technology, Health Policy
Keywords: ai chatbot, healthcare technology, evidence-based medicine, evidence-based recommendations, chatgpt, medical informatics, healthcare management, prompt design, artificial intelligence, clinical guidelines

Introduction

Artificial intelligence (AI) has become increasingly important in healthcare due to its potential to improve patient care and outcomes. From diagnosis to treatment and management of various health conditions, AI has shown promise in a wide range of applications [1]. Large language models (LLMs) and natural language processing (NLP) are of particular interest to the medical field as they have the potential to assist in the adaptation of clinical guidelines. Clinical guidelines provide evidence-based recommendations to guide the diagnosis, treatment, and management of different health conditions, but their development is a resource-intensive process. Adapting these guidelines to reflect the latest scientific evidence and local contexts may be less resource-intensive but can be a complex process.

ChatGPT, an AI chatbot that uses NLP, can extract, summarize, compare, and contrast information from different guidelines and integrate findings into a comprehensive guideline [2]. Language models such as ChatGPT have demonstrated the potential to assist in medical academic research and clinical decision-making throughout the clinical workflow, from triage to diagnosis to management [3,4]. However, it is important to note that ChatGPT may generate incomplete, inconsistent, or irrelevant information that does not match user intentions or expectations [5,6].

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Congenital heart disease: addressing the need for novel lower-risk percutaneous interventional strategies

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Affiliations + expand

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Abstract

Introduction: With the advent of improved neonatal care, increasingly vulnerable higher-risk patients with complex congenital heart anomalies are presenting for intervention. This group of patients will always have a higher risk of an adverse event during a procedure but by recognizing this risk and with the introduction of risk scoring systems and thus the development of novel lower risk procedures, the rate of adverse events can be reduced.

Area covered: This article reviews risk scoring systems for congenital catheterization and demonstrates how they can be used to reduce the rate of adverse events. Then, novel low risk strategies are discussed for low-weight infants e.g. patent ductus arteriosus (PDA) stent insertion; premature infants e.g. PDA device closure; and transcatheter pulmonary valve replacement. Finally, how risk is assessed and managed within the inherent bias of an institution is discussed.

Expert opinion: There has been a remarkable improvement in the rate of adverse events in congenital cardiac interventions, but now, as the benchmark of mortality rate is switched to morbidity and quality of life, continued innovation into lower risk strategies and understanding the inherent bias when assessing risk will be key to continuing this improvement.

Keywords: Congenital heart disease; Interventional cardiology; Low weight infants; Risk management; Risk scores.

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RESEARCH

Access to Care and Therapy for Kawasaki Disease in the Arab Countries: A Kawasaki Disease Arab Initiative (Kawarabi) Multicenter Survey

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Abstract

Kawasaki Disease (KD) is still the most common acquired heart disease in children below the age of five years; it has been well described in the developed world; however, data from the Arab world are limited to case reports or single-center case series. In an effort of optimizing KD research in the Arab world, a group of physicians and researchers established the KD Arab Initiative (Kawarabi) in 2021, and published the first survey, which showed disparities in the availability of intravenous immunoglobulin (IVIG); this had prompted Kawarabi to assess the access to care and therapy of KD patients in Arab countries. A 32 structured questions survey was conducted in thirteen Arab countries and addressed KD patients' access to healthcare in urban and rural settings. The survey results showed that access to care was uniform across large, mid-size cities and rural areas in 7/13 (54%) countries, while in 6/13 (46%) countries, it was in favor of large and mid-size cities over rural areas. The quality of medical services received by children with KD in large cities was rated as excellent in 6/13 or good in 7/13 countries compared to fair in 4/13 or poor in 4/13 countries in rural areas. Availability of IVIG was limited (23%) in mid-size cities and almost impossible (23%) in rural areas. The KD patients in mid-size cities and rural areas have limited access to standard healthcare in the Arab world. This survey laid the foundation for future Kawarabi endeavors to improve the care of children with KD.

Keywords Kawasaki Disease · Arab · Treatment · Intravenous Immunoglobulins

Introduction

Kawasaki disease (KD) is an acute febrile illness of childhood resulting in medium-size vasculitis, affecting the coronary arteries primarily. It is the most common cause of acquired heart disease in children under 5 y of age in developed countries. When missed or not treated promptly, coronary artery aneurysms (CAAs) develop in up to 25% of KD patients leading to myocardial infarction or death [1].

KD's primary etiology is still unclear, yet it is well described in the developed world. The experience of the Arab world is limited to single-center case series, and case reports [2, 3]. In an effort to optimize KD research in Arab nations and ethnicities, a group of physicians and researchers established the KD Arab Initiative (Kawarabi) in 2021 [4]. In its first survey, Kawarabi noted disparities in the availability of intravenous immunoglobulin (IVIG), the mainstay therapy for children with KD, and a decreased awareness of the disease among the general population. This report aimed to assess further the diagnostic and therapeutic resources available in Arab countries members of Kawarabi for the diagnosis, management, and follow-up of children with KD by means of an online based survey. Results from this survey are expected to highlight unmet needs and ultimately help develop strategies to meet those needs.

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[Intervention Review]

Remote care through telehealth for people with inflammatory bowel disease

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ABSTRACT

Background

People with inflammatory bowel disease (IBD) require intensive follow-up with frequent consultations after diagnosis. IBD telehealth management includes consulting by phone, instant messenger, video, text message, or web-based services. Telehealth can be beneficial for people with IBD, but may have its own set of challenges. It is important to systematically review the evidence on the types of remote or telehealth approaches that can be deployed in IBD. This is particularly relevant following the coronavirus disease 2019 (COVID-19) pandemic, which led to increased self- and remote-management.

Objectives

To identify the communication technologies used to achieve remote healthcare for people with inflammatory bowel disease and to assess their effectiveness.

Search methods

On 13 January 2022, we searched CENTRAL, Embase, MEDLINE, three other databases, and three trials registries with no limitations on language, date, document type, or publication status.

Selection criteria

All published, unpublished, and ongoing randomised controlled trials (RCTs) that evaluated telehealth interventions targeted at people with IBD versus any other type of intervention or no intervention.

We did not include studies based on digital patient information resources or education resources, unless they formed part of a wider package including an element of telehealth. We excluded studies where remote monitoring of blood or faecal tests was the only form of monitoring.

Data collection and analysis

Two review authors independently extracted data from the included studies and assessed their risk of bias. We analysed studies on adult and paediatric populations separately. We expressed the effects of dichotomous outcomes as risk ratios (RRs) and the effects of continuous

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ORIGINAL ARTICLE

JAK Inhibition in Aicardi-Goutières Syndrome: a Monocentric Multidisciplinary Real-World Approach Study

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Abstract

The paradigm type I interferonopathy Aicardi-Goutières syndrome (AGS) is most typically characterized by severe neurological involvement. AGS is considered an immune-mediated disease, poorly responsive to conventional immunosuppression. Premised on a chronic enhancement of type I interferon signaling, JAK1/2 inhibition has been trialed in AGS, with clear improvements in cutaneous and systemic disease manifestations. Contrastingly, treatment efficacy at the level of the neurological system has been less conclusive. Here, we report our real-word approach study of JAK1/2 inhibition in 11 patients with AGS, providing extensive assessments of clinical and radiological status; interferon signaling, including in cerebrospinal fluid (CSF); and drug concentrations in blood and CSF. Over a median follow-up of 17 months, we observed a clear benefit of JAK1/2 inhibition on certain systemic features of AGS, and reproduced results reported using the AGS neurologic severity scale. In contrast, there was no change in other scales assessing neurological status; using the caregiver scale, only patient comfort, but no other domain of everyday-life care, was improved. Serious bacterial infections occurred in 4 out of the 11 patients. Overall, our data lead us to conclude that other approaches to treatment are urgently required for the neurologic features of AGS. We suggest that earlier diagnosis and adequate central nervous system penetration likely remain the major factors determining the efficacy of therapy in preventing irreversible brain damage, implying the importance of early and rapid genetic testing and the consideration of intrathecal drug delivery.

Keywords Aicardi-Goutières syndrome (AGS) · interferon · JAK inhibitors

Introduction

The paradigm type I interferonopathy Aicardi-Goutières syndrome (AGS) encompasses 9 genotypes (AGS1-9), proposed to share a common pathophysiology related to aberrant nucleic acid processing or sensing, with subsequent chronically enhanced activation of type I interferon signaling [1]. While the neurological phenotype of AGS is broad, the disease most frequently presents as an early-onset acute encephalitis, in some cases after several months of completely normal development. The encephalopathic period usually lasts several months, characterized by significant neurological irritability and a loss of previously acquired skills. Notably, the acute disease phase is often, albeit not always, followed by clinical stabilization with no apparent further disease progression, and with the acquisition of new, even if limited, milestones in some patients [2]. Mutations in *ADAR1* represent a special case, sometimes presenting with the subacute onset of bilateral striatal necrosis and severe dystonia [3].

Marie-Louise Frémond and Marie Hully contributed equally to this work.

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[Intervention Review]

Patient education interventions for the management of inflammatory bowel disease

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ABSTRACT

Background

Inflammatory bowel disease (IBD) is a life-long condition for which currently there is no cure. Patient educational interventions deliver structured information to their recipients. Evidence suggests patient education can have positive effects in other chronic diseases.

Objectives

To identify the different types of educational interventions, how they are delivered, and to determine their effectiveness and safety in people with IBD.

Search methods

On 27 November 2022, we searched CENTRAL, Embase, MEDLINE, ClinicalTrials.gov, and WHO ICTRP with no limitations to language, date, document type, or publication status. Any type of formal or informal educational intervention, lasting for any time, that had content focused directly on knowledge about IBD or skills needed for direct management of IBD or its symptoms was included. Delivery methods included face-to-face or remote educational sessions, workshops, guided study via the use of printed or online materials, the use of mobile applications, or any other method that delivers information to patients.

Selection criteria

All published, unpublished and ongoing randomised control trials (RCTs) that compare educational interventions targeted at people with IBD to any other type of intervention or no intervention.

Data collection and analysis

Two review authors independently conducted data extraction and risk of bias assessment of the included studies. We analysed data using Review Manager Web. We expressed dichotomous and continuous outcomes as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs). We assessed the certainty of the evidence using GRADE methodology.

Main results

We included 14 studies with a total of 2708 randomised participants, aged 11 to 75 years. Two studies examined populations who all had ulcerative colitis (UC); the remaining studies examined a mix of IBD patients (UC and Crohn's disease). Studies considered a range of disease

^{68}Ga-DOTATATE PET in Restaging and Response to Therapy in Neuroblastoma: A Case Series and a Mini Review

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^{68}Ga-DOTATATE PET/CT is widely used for the evaluation of neuroendocrine tumors. Some reports exist on its use in the management of neuroblastoma. Building on the prior reports as well as our previous experience in using this technique for initial staging, we propose to describe its practical benefits in restaging and response to therapy. We describe different aspects including supply logistics, preparation, spatial resolution, and other practical applications. **Methods:** We reviewed the medical records for 8 patients who were evaluated with ^{68}Ga-DOTATATE PET/CT at our institution over 2 y. A note was made of the patient and disease characteristics and the indication for PET imaging, and the results were retrospectively analyzed for feasibility, logistics, radiation exposure, and utility in answering the clinical question. **Results:** Eight children (5 girls and 3 boys; age range, 4–60 mo; median age, 30 mo) diagnosed with neuroblastoma were imaged with ^{68}Ga-DOTATATE PET/CT and 5 with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT/CT over 2 y. Three ^{68}Ga-DOTATATE PET scans were done for staging, 10 for response evaluation, and 2 for restaging. ^{68}Ga-DOTATATE PET accurately identified neuroblastoma lesions suspected or seen on anatomic imaging. It has been shown to be more specific and more sensitive than ^{123}I-MIBG and at times also MRI. It had better spatial and contrast resolution than ^{123}I-MIBG. ^{68}Ga-DOTATATE PET was better than ^{123}I-MIBG SPECT/CT, CT, and MRI in the detection of early progression and viable tumor delineation for response assessment, as well as in target volume definition for external-beam radiotherapy and proton-beam radiotherapy. ^{68}Ga-DOTATATE PET was also better at assessing bony and bone marrow disease changes with time. **Conclusion:** ^{68}Ga-DOTATATE PET/CT offers added value and a superior edge to other imaging modalities in restaging and response assessment in neuroblastoma patients. Further multicenter evaluations in larger cohorts are needed.

Key Words: neuroblastoma; DOTATATE; ^{123}I-MIBG; restaging

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Neuroblastoma is the most common extracranial malignant solid tumor in children, accounting for 8%–10% of all pediatric malignancies (*1,2*). It usually develops in a paraspinal location in the chest or abdomen, originating from embryonal neural crest cells (*3*). It has a wide spectrum of presentation that depends on the biologic characteristics of the tumor. On one end of the spectrum is stage 4S disease, which is primarily a disease of infants that either resolves spontaneously or is exquisitely sensitive to minimal treatment. On the other end of the spectrum is highly aggressive neuroblastoma, which involves many organ systems, is often resistant to multimodality treatment, and is associated with poor outcomes. Diversity of clinical presentation and behavior reflects the biologic characteristics of the tumor. Insights into the biologic features of the tumor have led to improved understanding of its clinical behavior. These include amplification of the MYCN (v-myc avian myelocytomatosis virus–related oncogene, neuroblastoma-derived), deletion of chromosome 1p, or other segmental or numeric chromosomal abnormalities.

The first neuroblastoma staging system, the International Neuroblastoma Staging System, was developed in the late 1980s and was later modified as risk groups were defined. The International Neuroblastoma Risk Group Task Force developed the International Neuroblastoma Risk Group Staging System for presurgical staging. This system relies on clinical criteria and image-defined risk factors (*4,5*).

Anatomic imaging modalities such as CT and MRI are essential for evaluating abdominal neuroblastoma masses. Nuclear medicine imaging modalities, such as ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) planar whole-body scintigraphy, are used to characterize primary tumors and detect distant metastatic sites including lymph nodes, bones, bone marrow, and soft tissues. Historically, ^{123}I-MIBG has been used with 2-dimensional planar imaging for initial staging and follow-up. Somatostatin receptor imaging with SPECT octreotide scanning was later introduced to evaluate about 10% of non–^{123}I-MIBG-avid neuroblastoma cases (*6–8*). In the early 21st century, hybrid 3-dimensional SPECT/CT scanners have come into routine use in clinical practice for the evaluation and staging of neuroblastoma patients, compared with 2-dimensional planar imaging.

In the late 1990s, ^{18}F-FDG PET was shown to be a valuable tool to demonstrate the heterogeneity of disease in neuroblastoma patients and non–^{123}I-MIBG-avid disease and proved to be a good prognostic indicator (*9*). Over the last 25–30 years, new radiotracers compatible with PET scanners

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LETTER TO THE EDITOR

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Care with child development and André Bullinger's special look at prematurity

Cuidados com o desenvolvimento infantil e o olhar especial de André Bullinger sobre a prematuridade

Jacques Sizun[a,*], Pierre Kuhn[b], Charlotte Tscherning[c]

To the Editor,

We read with great interest the article "Care with child development and André Bullinger's special look at prematurity" published in one of the latest issues of the Revista Paulista de Pediatria[1]. Authors rightly highlighted the impact of early environment on preterm infants' neurobehavioral development and the need for early intervention aimed at optimizing this development. Additionally, they highlighted the importance of parental presence in the NICU.

The article is presented as a review of the literature in the PubMed, SciELO and Cairn databases. Unfortunately, the design of this review is not described, in particular the criteria for selecting articles, data extraction and synthesis of the results. This absence of a rigorous method explains the authors' conclusions: "The Bullinger Approach (shows) … promising results for the prevention of neurodevelopmental disabilities, especially those related to orality". The claim that the practice of "this approach can prevent neuromotor, language, eating and parent-infant relationship disorders in preterm infants" is not scientifically demonstrated and is pure speculation. No randomized clinical trial has been conducted to assess the impact of the Bullinger Approach. The specific techniques used in this program (asymmetrical positioning, contrasting checkerboard visual stimulation) have not been assessed for their impact.

Conversely, the other two programs described in this review are based on robust scientific data.

According to meta-analyses, the Kangaroo Mother Care is associated with an increase in breastfeeding rate in preterm babies[2], a decrease in length of hospital stay[3], and a reduction in mortality mainly in resource-limited settings[3]. Additionally, a randomized controlled study demonstrated a positive impact at adult age on IQ and attention scores[4].

Meta-analyses demonstrated that the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) is effective in improving preterm infants' neurobehavioral and neurological development at two weeks of Corrected Age (CA)[5], significantly reduces the length of hospital stay[6], and increases the psychomotor development index at 9- and 12-months CA[6]. A randomized controlled study showed promising results at school age[7]. The large preterm birth cohort study (in France, 2011) Epipage 2 demonstrated that NIDCAP implementation significantly influenced the Kangaroo Mother Care initiation during the first week of age in preterm newborns compared with no training or with Bullinger Approach[8].

Other early intervention programs such as Close Collaboration with parents[9] or Family Integrated Care[10] have been thoroughly evaluated and are not cited in this review emphasizing its lack of completeness.

As for medical treatments, the early non-pharmacological interventions in high-risk newborns need to be based on an evidence-based approach. This is important for the choice of the interventions, for the training of professionals as well as for information to parents.

We strongly recommend that randomized trials be conducted to assess the impact of the Bullinger Approach.

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Journal of
Cardiothoracic Surgery

RESEARCH Open Access

Endovascular treatment of a traumatic thoracic pseudo-aneurysm in a pediatric patient: a case report with review of literature

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Abstract

Blunt aortic injury (BAI) as a result of thoracic trauma is a rare entity in the adult and pediatric population. The endovascular approach has been the preferred method of management over operative repair in adults. However, data on pediatrics is limited to case reports and case series with no long-term follow-up. There are no current guidelines for management in the pediatric population. We are reporting a successful repair of a traumatic thoracic aortic aneurysm in a 13 year old boy with covered stents, with a review of relevant literature.

Keywords Aortic injury, Pseudo-aneurysm, TEVAR, Blunt thoracic injury

Introduction

Traumatic vascular injury in general and thoracic aortic injury in specific is relatively rare in children and adolescents compared to the adult population [1]. The mechanism of injury in such cases is most often blunt rather than penetrating trauma. Heckman et al. reports an incidence of < 1% for blunt traumatic aortic injury (BTAI) in the pediatric population using the data from US National Trauma Database [2]. A slightly higher incidence in the range of 1.5–2% is reported in adults [3]. The presence of such injury reflects on the severity of the mechanism and the possibility of other associated life-threatening injuries. Data from the National Pediatric Trauma Registry reports an overall mortality of 15% for children with blunt thoracic injury. The pediatric population is anatomically predisposed to thoracic injury. One of the reasons is the increased compliance of the chest wall due to incomplete rib ossification and a cartilaginous chest wall [4]. In addition, because of a relatively small volume to body surface area, children are at higher risk for injuries to multiple organs after blunt trauma [5–7].

The current society of vascular surgery classification grades aortic injury as minimal aortic injury (MAI) and significant aortic injury (SAI) based on the absence or presence of external aortic wall deformity, respectively [8]. MAI and SAI are further divided into four types ranging from Type I which is Intimal tear or flap to type IV which is open rupture. While there have been multiple studies evaluating the efficacy and success of conservative management of MAI, most of the cases of SAI have to undergo either endovascular or operative repair [9]. Below is a case report of a successful repair of traumatic thoracic aortic aneurysm in a 13 year old boy with covered stents, and a review of the literature for similar cases.

Case report

A previously healthy 13-year-old boy was brought to hospital following a motor vehicle accident. He was a front-seat passenger and was unrestrained. Speed at the time of impact was not known. At the time of presentation, he was alert and oriented with a Glascow-Coma Scale (GCS)

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ORIGINAL ARTICLE

AACPDM

Collagenase treatment decreases muscle stiffness in cerebral palsy: A preclinical ex vivo biomechanical analysis of hip adductor muscle fiber bundles

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Funding information
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Abstract

Aim: To determine the dose–response relationship of collagenase *Clostridium histolyticum* (CCH) on collagen content and the change in muscle fiber bundle stiffness after ex vivo treatment of adductor longus biopsies with CCH in children with cerebral palsy (CP).

Method: Biopsy samples of adductor longus from children with CP (classified in Gross Motor Function Classification System levels IV and V) were treated with 0 U/mL, 200 U/mL, 350 U/mL, or 500 U/mL CCH; percentage collagen reduction was measured to determine the dose–response. Peak and steady-state stresses were determined at 1%, 2.5%, 5%, and 7.5% strain increments; Young's modulus was calculated.

Results: Eleven patients were enrolled (nine males, two females, mean age at surgery 6 years 5 months; range: 2–16 years). A linear CCH dose–response relationship was determined. Peak and steady-state stress generation increased linearly at 5.9/2.3mN/mm^2, 12.4/5.3mN/mm^2, 22.2/9.7mN/mm^2, and 33.3/15.5mN/mm^2 at each percentage strain increment respectively. After CCH treatment, peak and steady-state stress generation decreased to 3.2/1.2mN/mm^2, 6.5/2.9mN/mm^2, 12.2/5.7mN/mm^2, and 15.4/7.7mN/mm^2 respectively ($p < 0.004$). Young's modulus decreased from 205 kPa to 100 kPa after CCH ($p = 0.003$).

Interpretation: This preclinical ex vivo study provides proof of concept for the use of collagenase to decrease muscle stiffness in individuals with CP.

Cerebral palsy (CP) describes 'a group of permanent disorders of the development of movement and posture, causing activity limitation' attributed to an insult to the developing brain, with musculoskeletal deficits that are progressive with growth.[1] Spastic CP is associated with a velocity-dependent increase in muscle stiffness that precedes the development of fixed muscle contracture, that is, a permanent shortening of the muscle tendon unit.[2,3] In younger children with CP, surgical lengthening carries a high risk of recurrent contractures.[4] Intramuscular injections of botulinum neurotoxin A (BoNT-A) have been used as an alternative to surgery, decreasing spasticity by blocking acetylcholine release at the neuromuscular junction. Paradoxically, a study reported that BoNT-A injection caused significant muscle atrophy, replacing contractile material with fibrous and fatty tissue.[5] Although injections of BoNT-A were effective in preventing contractures in the hereditary spastic mouse model, this has never been replicated in children with CP.[6] Hence, there is a pressing need to identify an effective nonsurgical alternative for the treatment of CP muscle contracture.

Smith et al. reported that stiffness of muscle fiber bundles in children with CP was associated with increased collagen in the extracellular matrix (ECM) rather than from the fibers themselves.[7] They hypothesized that the upregulation

This original article is commented on by Chambers on pages 1548–1549 of this issue.

Abbreviations: BoNT-A, botulinum neurotoxin A; CCH, collagenase *Clostridium histolyticum*; ECM, extracellular matrix; HBSS, Hanks' Balanced Salt Solution; TDC, typically developing control.

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Research Letter

Research Letter

Middle East respiratory syndrome coronavirus and the 2022 world cup football tournament in Qatar

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Key words: MERS-CoV, mass gatherings, FIFA 2022, coronavirus

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a zoonotic virus, which causes a respiratory illness in animals and humans. It can be transmitted from animals to humans and humans to humans, with case fatality rates of up to 35%.[1] There is a significant potential for MERS-CoV to be transmitted during mass gathering events. Most cases have been reported from the Arabian peninsula and frequently linked to contact with dromedary camels, but human-to-human transmission can also occur, especially in the health care settings.[1] The potential for MERS-CoV transmission during mass gatherings is an ongoing concern. However, MERS-CoV infection has rarely been reported in pilgrims returning from Hajj, one of the largest annual mass gathering events in Saudi Arabia.[2,3]

Sporting events are also large mass gathering events, which may facilitate the transmission of infectious diseases such as MERS-CoV. Between 20 November and 18 December 2022, Qatar hosted the 2022 FIFA World Cup (WC-2022) football tournament, which attracted more than 1.4 million visitors.[4] Hypothetical concerns were recently raised about the potential for MERS-CoV transmission during the WC-2022 and a concurrent camel pageant championship.[5] The Ministry of Public Health (MOPH) in Qatar maintains a robust monitoring, testing and contact tracing program for MERS-CoV in accordance with the World Health Organization (WHO) guidelines.

In preparation for the FIFA WC, random respiratory samples from 200 camel workers and 100 camels were tested and were negative for MERS-CoV. For the current report, we reviewed all human MERS-CoV tests conducted in Qatar during 2022, including the duration of the WC-2022 (20 November to 18 December 2022).

During the WC-2022, rapid medical evaluation units were set up at each of the eight stadia where matches were held as well as multiple 'fan zones', which were publicly accessible areas hosting multiple activities (e.g. concerts, live-match broadcast on large screens, etc.) throughout the duration of the WC-2022. The National Ambulance Service deployed mobile teams throughout the country where visitors and fans were housed. All services were linked to the national network of primary health care centres and major secondary and tertiary care hospitals for any potential transfers or urgent or emergency care. These services were available and accessible to all visitors. All medical services were supported by the Ministry of Public Health Qatar and

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CASE REPORT Open Access

The diagnostic value of DMSA scan in differentiating functional pseudo-tumors from malignancies in scarred kidneys: case series and literature review

Enas Hussein Mohammed[1*], Ahmad Kaddourah[1,2], Noor Al Khori[3] and Mehdi Djekidel[4]

Abstract

Background The terms "renal regenerating nodule" and "nodular compensatory hypertrophy" are used in the literature to describe functioning pseudo-tumors (FPT) in the setting of an extensively scarred kidney. FPTs are usually discovered incidentally during routine renal imaging. Differentiating these FPTs from renal neoplasms is critical but can be challenging in the setting of chronic kidney disease (CKD) given the limitations related to using contrast-based imaging.

Case summaries We report a pediatric case series of 5 CKD patients, with history of urinary tract infections, in which tumor-like lesions evolved in scarred kidneys and were incidentally discovered on routine renal imaging. These were diagnosed as FPT by utilizing dimercaptosuccinic acid (DMSA) imaging and showed stable size and appearance upon follow-up with ultrasound and MRI.

Conclusion FPTs can be picked up on routine imaging of pediatric patients with CKD. Although larger cohort studies are needed to confirm these conclusions, our case series supports the evidence that DMSA scan showing uptake at the site of the mass can be a useful tool to suggest the diagnosis of FPTs in children with kidney scarring, and that SPECT DMSA scan adds more precision in picking up and accurately localizing FPTs compared to planar DMSA.

Keywords Renal regenerating nodule$_1$, Renal pseudo-tumor$_2$, Chronic kidney disease$_3$, Dimercaptosuccinic acid scan, DMSA$_4$, Single photon emission computed tomography, SPECT$_5$, case series$_6$

Background

Urinary tract infections (UTIs) in children can be severe enough to cause renal scarring and chronic kidney disease (CKD). Classically, the mature kidney is considered to have limited cellular regenerative capacity [1, 2]. However, this concept has been challenged by many studies in which biological evidence was introduced suggesting the ability of the kidneys to endogenously regenerate [1, 3–6]. There are a few reports describing the development of parenchymal functioning tumor-like masses in scarred kidneys. [7–10]. Although some reports describe these functioning pseudo-tumors (FPT) as "regenerating nodules", their nature and whether they are newly regenerated renal tissue

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MINIREVIEWS

Tyrosine kinase inhibitors and human epidermal growth factor receptor-2 positive breast cancer

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Abstract

The body of evidence investigating human epidermal growth factor receptor-2 (HER2) directed therapy in patients with breast cancer (BC) has been growing within the last decade. Recently, the use of tyrosine kinase inhibitors (TKIs) has been of particular interest in the treatment of human malignancies. This literature commentary is intended to highlight the most recent findings associated with the widely-studied TKI agents and their clinical significance in improving the outcomes of HER2 positive BC.

Key Words: Human epidermal growth factor receptor-2 positive breast cancer; Tyrosine kinase inhibitors; Lapatinib; Pyrotinib; Tucatinib; Trastuzumab

Core Tip: Newly published randomized controlled trials within the past two years have provided compelling evidence on the use of tyrosine kinase inhibitors (TKIs) such as Lapatinib, Pyrotinib, Neratinib, Tucatinib, Ruxolitinib, and Afatinib. Several of these agents were found to offer better outcomes in terms of progression-free survival when combined with other agents. While some TKIs, namely Lapatinib, and Neratinib, are supported with a large amount of data than others, the medical literature still lacks substantial evidence to draw a clinical conclusion that could modify/add to the present recommendations in human epidermal growth factor receptor-2 positive breast cancer treatment guidelines.

BRIEF REPORT

Rare Antagonistic Leptin Variants and Severe, Early-Onset Obesity

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SUMMARY

Hormone absence or inactivity is common in congenital disease, but hormone antagonism remains controversial. Here, we characterize two novel homozygous leptin variants that yielded antagonistic proteins in two unrelated children with intense hyperphagia, severe obesity, and high circulating levels of leptin. Both variants bind to the leptin receptor but trigger marginal, if any, signaling. In the presence of nonvariant leptin, the variants act as competitive antagonists. Thus, treatment with recombinant leptin was initiated at high doses, which were gradually lowered. Both patients eventually attained near-normal weight. Antidrug antibodies developed in the patients, although they had no apparent effect on efficacy. No severe adverse events were observed. (Funded by the German Research Foundation and others.)

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Drs. Funcke, Moepps, and Roos and Drs. Fischer-Posovszky and Wabitsch contributed equally to this article.

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Leptin serves as a signal of energy sufficiency in the brain, where a critically low level of the hormone triggers behavioral, metabolic, and endocrine responses that aim at restoring and preserving energy reserves.[1] Leptin acts by binding to the long isoform of the leptin receptor (LEPRb),[2] eliciting various signaling events, including phosphorylation of signal transducer and activator of transcription 3 (STAT3).[2]

Congenital leptin deficiency and dysfunction are rare, autosomal recessive forms of severe, early-onset obesity caused by changes in the leptin gene (*LEP*; gene identification number, 3952).[3-6] To date, 21 distinct variants have been described (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[7] Most of the variants cause defects in production or secretion and result in complete hormone deficiency,[3,4,7] although a few variants result in impaired receptor binding and hormone dysfunction.[5,6] Intense hyperphagia and impaired satiety develop in affected persons, leading to rapid weight gain and severe obesity with hyperinsulinemia, hyperglycemia, dyslipidemia, and hepatic steatosis.[7] These persons generally have hypogonadotropic hypogonadism, delayed pubertal development, and recurrent severe infections.[7] The disease can be treated efficiently with recombinant leptin.[8]

THE JOURNAL OF PEDIATRICS • www.jpeds.com COMMENTARY

Patent Ductus Arteriosus in Premature Infants: Clinical Trials and Equipoise

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Persistent patency of the ductus arteriosus is common in premature infants, yet patent ductus arteriosus (PDA) management varies widely. In observational studies, PDA is associated with prolonged assisted ventilation, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy, renal impairment, and mortality.[1-7] These associations led many clinicians to treat a PDA in all preterm infants. However randomized controlled trials (RCTs) of PDA treatment have failed to demonstrate significant reductions in clinically important outcomes. As an example, prophylactic indomethacin trials (for reducing IVH) demonstrate that indomethacin reduces incidence of symptomatic PDA, need for ligation, and IVH, but has no effect on BPD, NEC, long-term neurodevelopmental impairment (NDI) or death.[1,8] Thus, it is unclear if PDA is part of the causal pathway for development of these morbidities.

One of the explanations for the lack of effect from PDA treatment is that there is no standardized definition of a hemodynamically significant PDA (hsPDA). This may lead to a wide range of "symptomatic" PDA included in the trials, including PDAs that would likely close on their own without intervention.[9-11] If trials enriched their populations with PDAs with greater hemodynamic effects, there may be greater clinical benefit to treatment of the PDA. Current "gold standard" definitions of hemodynamic significance are based on echocardiographic measures including PDA diameter ≥1.5 mm, left atrium: aortic root ratio ≥1.4:1, and other flow and velocity parameters.[12,13] As these measurements alone do not provide detail on end organ effect, several scoring systems have been proposed to incorporate both echocardiographic and clinical criteria in the definition of hsPDA.[10,14] Other research has focused on biomarkers such as natriuretic peptides[12,13] or incorporation of novel technologies such as near infrared spectroscopy.[15] A standardized definition of hsPDA is one way to narrow the population of trial participants to discover if there is a cohort of preterm infants at high risk of morbidity without PDA treatment. This, in combination with a consensus on clinically relevant outcome measures, would allow for better cross comparison between RCTs.

Management of PDA varies widely in clinical practice. Some sites and clinicians aggressively manage PDAs, administering prophylactic indomethacin (to reduce IVH, with the added effect of reducing hsPDA), frequently screening for PDA, and administering medications to close the PDA. Other sites and clinicians are conservative and do not even look for PDA with echocardiograms and essentially ignore it. These clinicians note that while incidence of PDA is higher with lower gestational age and birth weight, spontaneous closure still occurs at some point.[9,16-20] Indeed, the neonatal field has become more conservative over time, with decreasing rates of PDA diagnosis, medical treatment, and ligation over the past decade.[11,21] This leads to challenges in conducting trials because of lack of clinician equipoise, with providers often practicing in the extremes of either aggressive treatment or no treatment whatsoever, unwilling to have their patients randomized to either arm of a trial.

Well-designed trials to evaluate the long-term impact of PDA interventions are needed. Despite years of rigorous study, the optimal method and timing of ductal closure or other management of PDA in preterm neonates remains unclear. At its most basic interpretation, equipoise refers to the point at which "there is insufficient scientific evidence to clearly state the superiority of an intervention" and is often considered to be an ethical prerequisite to conducting RCTs.[22] When interpreted on the individual level, equipoise is highly problematic for the clinician scientist who, in their role as a physician, has a duty to offer treatment recommendations and preferences to patients, but as an investigator must be equally confident of study treatment options.

BPD	Bronchopulmonary dysplasia
hsPDA	Hemodynamically significant patent ductus arteriosus
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NRN	Neonatal Research Network
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDA	Patent ductus arteriosus
RCTs	Randomized controlled trials

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Below- versus above-elbow cast treatment of displaced distal forearm fractures in children: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives: Distal forearm fractures are the most common pediatric fractures. This study aimed to investigate the effectiveness of below-elbow cast treatment for displaced distal forearm fractures in children compared to above-elbow cast through meta-analysis of randomized controlled trials.

Methods: Several databases from January 1, 2000 until October 1, 2021 were searched for randomized controlled trials that assessed below versus above-elbow cast treatment of displaced distal forearm fractures in pediatric patients. The main meta-analysis comparison was based on the relative risk of loss of fracture reduction between children undergoing below versus above-elbow cast treatment. Other outcome measures including re-manipulation and cast-related complications were also investigated.

Results: Nine studies were eligible of the 156 articles identified, with a total of 1049 children. Analysis was undertaken for all included studies with a sensitivity analysis conducted for studies with high quality. In the sensitivity analysis, the relative risks of loss of fracture reduction (relative risk = 0.6, 95% confidence interval = 0.38, 0.96) and re-manipulation (relative risk = 0.3, 95% confidence interval = 0.19, 0.48) between the below and above-elbow cast groups were in favor of below-elbow cast and statistically significant. Cast-related complications were in favor of below-elbow cast but did not attain statistical significance (relative risk = 0.45, 95% confidence interval = 0.05, 3.99). Loss of fracture reduction was noted in 28.9% of patients treated with above-elbow cast and 21.5% in below-elbow cast. Re-manipulation was attempted in 48.1% versus 53.8% of children who lost fracture reduction in the below-elbow cast and above-elbow cast groups, respectively.

Conclusion: Below-elbow cast treatment was favored, with statistical significance, in terms of loss of fracture reduction and re-manipulation, and was not associated with a higher risk of cast-related complications. The accumulative evidence currently does not support above-elbow cast treatment and below-elbow cast treatment should be the mainstay for displaced distal forearm fractures in children.

Level of evidence: Level I, meta-analysis of therapeutic level I studies.

Keywords: Displaced distal forearm fractures, pediatrics, cast, randomized controlled trial, meta-analysis

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Case Series

Case Series

Experience of the Sudanese doctors in surgery of conjoined twins

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Abstract

Surgical separation of conjoined twins remains one of the most unique and rewarding experiences in the field of pediatric surgery, bearing in mind that this decision is their best chance of survival. These are the first reported cases of successfully separating omphalopagus conjoined twins by the liver in Sudan. After an emergency cesarean section, 62-day-old term-conjoined twins were referred to our pediatric surgery center. Examination revealed well-appearing twins fused from the xiphoid to the umbilicus; imaging confirmed a fused liver with a separate portal and caval structures, necessitating surgical separation and closure, which was done successfully on subsequent hours with well tolerance and recovery discharged on day 21. The second case involved 21-day-old term-conjoined female twins who were fused from the xiphoid to the umbilicus and shared the same cord, as well as complete fusion of the liver with separate other vital organs. They were successfully separated and recovered well.

INTRODUCTION

Throughout history, the separation of conjoined twins has remained one of the most difficult challenges in the field of pediatric surgery, owing to the technical and ethical complexity of the procedure, which is extremely risky and life-threatening in the majority of cases [1]. This complexity mainly depends on the position of the fusion and the shared internal organs involved [1, 2]. The most common forms are thoracopagus, omphalopagus, pyopagus, isciopagus and craniopagus [3].

The incidence varies between one in 50 000 and one in 20 000 live births with female commonality [3, 4]. The diagnosis can be made from 12 weeks gestation through prenatal ultrasonography, while at 20 weeks the anatomy and extent of the conjoined area can be identified [4].

Even though these twins appear theoretically divisible, any attempt to separate them may result in severe hemorrhage and hypovolemic shock, especially if done early in life. These are infrequent in the ischiopagus and pyopagus varieties [1].

Herein we report the first two cases in Sudan of Omphalopagus twins conjoined by the liver referred to our pediatric surgery center, separated successfully by our multidisciplinary team led by pediatric surgeons with a good outcome.

CASE 1

A 62 days old, term-conjoined female twins were referred by ambulance to the pediatric-center police hospital, Sudan.

The mother was a 21-year-old female with a family history of multiple pregnancies, para three delivered uneventfully vaginally with a good outcome. Her pregnancy passed well with good antenatal care and early use of tonics, on 30 weeks the abdominal ultrasound revealed monochronic conjoined twins. At 40 weeks gestation, an emergency cesarian section was done due to labor pain, outcome was full-term, monochromic conjoined twins, cephalic, cried immediately and passed urine and meconium within 1st 24 h. On examination, both babies appeared well, not pale or jaundiced and not distressed, and weighed 2.4 kg for each one. They were fused from the xiphoid to the umbilicus with the used area covered by skin, and shared the same umbilical cord. Abdominal Computed tomography revealed a fusion of the

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Acute paediatric asthma treatment in the prehospital setting: a retrospective observational study

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ABSTRACT

Objectives To describe the incidence of and patterns of 'escalated care' (care in addition to standard treatment with systemic corticosteroids and inhaled bronchodilators) for children receiving prehospital treatment for asthma.

Design Retrospective observational study.

Setting State-wide ambulance service data (Ambulance Victoria in Victoria, Australia, population 6.5 million)

Participants Children aged 1–17 years and given a final diagnosis of asthma by the treating paramedics and/or treated with inhaled bronchodilators from 1 July 2019 to 30 June 2020.

Primary and secondary outcome measures We classified 'escalation of care' as parenteral administration of epinephrine, or provision of respiratory support. We compared clinical, demographic and treatments administered between those receiving and not receiving escalation of care.

Results Paramedics attended 1572 children with acute exacerbations of asthma during the 1 year study period. Of these, 22 (1.4%) had escalated care, all receiving parenteral epinephrine. Patients with escalated care were more likely to be older, had previously required hospital admission for asthma and had severe respiratory distress at initial assessment.

Of 1307 children with respiratory status data available, at arrival to hospital, the respiratory status of children had improved overall (normal/mild respiratory distress at initial assessment 847 (64.8%), normal/mild respiratory distress at hospital arrival 1142 (87.4%), p<0.0001).

Conclusions Most children with acute exacerbations of asthma did not receive escalated therapy during their pre-hospital treatment from ambulance paramedics. Most patients were treated with inhaled bronchodilators only and clinically improved by the time they arrived in hospital.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Highly generalisable, with the use of a comprehensive electronic state-wide ambulance database.
⇒ Most ambulance cases were concentrated in metropolitan regions; this may limit generalisability to rural and regional settings.
⇒ Bias was minimised by direct download from electronic medical record, rather than abstraction by reviewers.
⇒ It is possible that a small number of critically ill cases were misclassified due to an ambulance diagnosis other than asthma.

INTRODUCTION

Asthma is a frequent reason for children to attend the emergency department (ED),[1 2] and one of the most common reasons for paediatric hospitalisation after an ED visit.[3] In the USA, the rate of paediatric ED visits for asthma increased by 13.3% between 2001 and 2010,[4] while in the UK, it is estimated that a child is admitted to hospital with an asthma attack every 20 min.[5]

Most children with asthma have mild or moderate exacerbations, and respond to first-line treatment with inhaled bronchodilator therapy and systemic steroids.[6–9] However, some children with severe asthma require more intensive therapies including intravenous medications, endotracheal intubation and/or admission to intensive care.[9–11] Management of acute severe asthma is complicated by a number of problems, including a large number of treatment options, wide variation in self-reported and actual physician practice,[12–15] and a weak evidence base.[16 17]

Early initiation of therapy in the prehospital setting may abort an asthma attack and prevent further escalation on arrival to the ED. This in turn may prevent the need for more invasive treatment and potential complications or side effects of medications used in escalation. The introduction of a new treatment protocol emphasising early use of systemic corticosteroids in a large Emergency Medical Services system was associated with reduced rates of hospitalisation, less need for critical care and shortened hospital length of stay.[18] Systemic corticosteroid administration has been the subject of successful improvement projects in the prehospital setting.[19] However, a separate study identified high rates of paramedic non-compliance with

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REVIEW ARTICLE

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A review of rapid food safety testing: using lateral flow assay platform to detect foodborne pathogens

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ABSTRACT

The detrimental impact of foodborne pathogens on human health makes food safety a major concern at all levels of production. Conventional methods to detect foodborne pathogens, such as live culture, high-performance liquid chromatography, and molecular techniques, are relatively tedious, time-consuming, laborious, and expensive, which hinders their use for on-site applications. Recurrent outbreaks of foodborne illness have heightened the demand for rapid and simple technologies for detection of foodborne pathogens. Recently, Lateral flow assays (LFA) have drawn attention because of their ability to detect pathogens rapidly, cheaply, and on-site. Here, we reviewed the latest developments in LFAs to detect various foodborne pathogens in food samples, giving special attention to how reporters and labels have improved LFA performance. We also discussed different approaches to improve LFA sensitivity and specificity. Most importantly, due to the lack of studies on LFAs for the detection of viral foodborne pathogens in food samples, we summarized our recent research on developing LFAs for the detection of viral foodborne pathogens. Finally, we highlighted the main challenges for further development of LFA platforms. In summary, with continuing improvements, LFAs may soon offer excellent performance at point-of-care that is competitive with laboratory techniques while retaining a rapid format.

KEYWORDS

lateral flow assay; LFA; food safety; foodborne pathogens; sensitivity

Introduction

In the last decade, outbreaks of foodborne diseases from various food sources have raised public awareness of food safety (Karp et al. 2015). According to the World Health Organization (WHO 2022), around 600 million individuals – almost 1 in 10 people worldwide– acquire foodborne infections after eating contaminated food each year. In addition, nearly 420,000 individuals die yearly from diarrheal disorders (WHO 2022). A substantial number of these fatalities were avoidable through early detection of pathogens in food and water (WHO 2022, 2016). Unfortunately, children under five years of age carry 40% of the foodborne disease burden, with 125,000 deaths yearly (WHO 2022). The symptoms of foodborne diseases range from simple gastroenteritis to potentially catastrophic neurologic, hepatic, and renal complications (Fung, Wang, and Menon 2018). The majority of foodborne diseases are attributed to bacteria (*Campylobacter spp., Salmonella spp., Staphylococcus aureus (S. aureus), Vibrio cholera (V. cholera), Escherichia coli (E.coli) O157:H7, Clostridium perfringens*, and *Listeria monocytogenes (L. monocytogenes))*, viruses (Norovirus, Hepatitis E, Hepatitis A, Rotavirus, Adenoviruses, Sapoviruses, and Astroviruses), and protozoa (*Cryptosporidium* spp., *Cyclospora spp.*, and *Toxoplasma* spp.) (Bintsis 2017; Adley and Ryan 2016).

Foodborne diseases impede socioeconomic development by straining healthcare systems and harming national economies, tourism, and international food trade. Around $110 billion is lost annually in productivity and medical expensesas a result of contaminated food with foodborne pathogens in low-income and middle-income countries (WHO 2022, 2016). In addition, globalization of trade has increased the risk of the transnational spread of foodborne diseases in the current scenario. Although they were once limited to

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POSITION STATEMENT Open Access

Real-world evidence in achondroplasia: considerations for a standardized data set

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Abstract

Background Collection of real-world evidence (RWE) is important in achondroplasia. Development of a prospective, shared, international resource that follows the principles of findability, accessibility, interoperability, and reuse of digital assets, and that captures long-term, high-quality data, would improve understanding of the natural history of achondroplasia, quality of life, and related outcomes.

Methods The Europe, Middle East, and Africa (EMEA) Achondroplasia Steering Committee comprises a multidisciplinary team of 17 clinical experts and 3 advocacy organization representatives. The committee undertook an exercise to identify essential data elements for a standardized prospective registry to study the natural history of achondroplasia and related outcomes.

Results A range of RWE on achondroplasia is being collected at EMEA centres. Whereas commonalities exist, the data elements, methods used to collect and store them, and frequency of collection vary. The topics considered most important for collection were auxological measures, sleep studies, quality of life, and neurological manifestations. Data considered essential for a prospective registry were grouped into six categories: demographics; diagnosis and patient measurements; medical issues; investigations and surgical events; medications; and outcomes possibly associated with achondroplasia treatments.

Conclusions Long-term, high-quality data are needed for this rare, multifaceted condition. Establishing registries that collect predefined data elements across age spans will provide contemporaneous prospective and longitudinal information and will be useful to improve clinical decision-making and management. It should be feasible to collect a minimum dataset with the flexibility to include country-specific criteria and pool data across countries to examine clinical outcomes associated with achondroplasia and different therapeutic approaches.

Keywords Achondroplasia, Registry, Real-world data, Real-world evidence, Growth, Quality of life, Registry, Rare disease

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cancers

MDPI

Article

Kidney Cancer Diagnosis and Surgery Selection by Machine Learning from CT Scans Combined with Clinical Metadata

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Simple Summary: Diagnosis is the most important step in treating and managing kidney cancer, requiring accurate identification, localization, and classification of tumor regions. The selection of appropriate surgical procedures for malignant cases is further based on tumor volume and relative severity. In recent years, machine-learning-based approaches have been proposed to localize, quantify, and stratify kidney tumors using contrast-enhanced computed tomography (CT) images. However, previous studies have largely neglected the integration of patient metadata with clinical images to better diagnose and guide surgical interventions. In the current study, we developed a combined clinical and image-based approach to classify kidney cancers using a publicly available dataset. We show that the inclusion of clinical features alongside medical images improves the performance of kidney tumor classification. We further used clinical data together with a machine-learning approach to predict the expected surgical procedure employed in individual kidney cancer patients. In addition to cancer stage and tumor volume, some surprisingly common demographic features were revealed to be key determinants of the surgical procedure later selected for nephrectomy.

Abstract: Kidney cancers are one of the most common malignancies worldwide. Accurate diagnosis is a critical step in the management of kidney cancer patients and is influenced by multiple factors including tumor size or volume, cancer types and stages, etc. For malignant tumors, partial or radical surgery of the kidney might be required, but for clinicians, the basis for making this decision is often unclear. Partial nephrectomy could result in patient death due to cancer if kidney removal was necessary, whereas radical nephrectomy in less severe cases could resign patients to lifelong dialysis or need for future transplantation without sufficient cause. Using machine learning to consider clinical data alongside computed tomography images could potentially help resolve some of these surgical ambiguities, by enabling a more robust classification of kidney cancers and selection of optimal surgical approaches. In this study, we used the publicly available KiTS dataset of contrast-enhanced CT images and corresponding patient metadata to differentiate four major classes of kidney cancer: clear cell (ccRCC), chromophobe (chRCC), papillary (pRCC) renal cell carcinoma, and oncocytoma (ONC). We rationalized these data to overcome the high field of view (FoV), extract tumor regions of interest (ROIs), classify patients using deep machine-learning models, and extract/post-process CT image features for combination with clinical data. Regardless of marked data imbalance, our combined approach achieved a high level of performance (85.66% accuracy, 84.18% precision, 85.66% recall, and 84.92% F1-score). When selecting surgical procedures for malignant tumors (RCC), our method proved even more reliable (90.63% accuracy, 90.83% precision, 90.61% recall, and 90.50% F1-score). Using feature ranking, we confirmed that tumor volume and cancer stage are the most relevant clinical features for predicting surgical procedures. Once fully mature, the approach we propose could be used to assist surgeons in performing nephrectomies by guiding the choices of optimal procedures in individual patients with kidney cancer.

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Review

Managing Labour in Women with COVID-19

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Abstract: Since first reported in December 2019 in Wuhan, China, COVID-19 caused by Severe Acute Respiratory Syndrome (SARS) Corona virus2 (SARS CoV-2) quickly spread to become a pandemic that has caused significant morbidity and mortality. The rapidity of the spread of the virus and the high mortality at the outset threatened to overwhelm health systems worldwide, and, indeed, this significantly impacted maternal health, especially since there was minimal experience to draw from. Experience with Covid 19 has grown exponentially as the unique needs of pregnant and labouring women with COVID-19 infection have become more evident. Managing COVID-19 parturients requires a multidisciplinary team consisting of anaesthesiologists, obstetricians, neonatologists, nursing staff, critical care staff, infectious disease and infection control experts. There should be a clear policy on triaging patients depending on the severity of their condition and the stage of labour. Those at high risk of respiratory failure should be managed in a tertiary referral centre with facilities for intensive care and assisted respiration. Staff and patients in delivery suites and operating rooms should be protected by enforcing infection protection principles such as offering dedicated rooms and theatres to SARS CoV-2 positive patients and using personal protective equipment. All hospital staff must be trained in infection control measures which should be updated regularly. Breastfeeding and care of the new-born must be part of the healthcare package offered to COVID-19 parturient mothers.

Keywords: COVID-19; antenatal care; labour; anaesthesia; analgesia; pregnant labouring women delivery and breastfeeding

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1. Introduction

In December 2019, the world learned of the first case of a patient infected with atypical pneumonia caused by the 2019 novel coronal virus (severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2) in Wuhan, China [1]. The infection spread rapidly, and by mid-March 2020, more than 190 countries had reported cases prompting the WHO to declare it a pandemic. In February 2020, the World Health Organization designated the disease as COVID-19, which stands for coronavirus disease 2019 [1,2]. Over half a billion COVID-19 infections worldwide and over 6 million deaths have so far been reported [2].

As is typical with viruses in this genre, mutations frequently lead to the emergence of new strains. There are currently five strains of the SARS-CoV-2 virus that are of concern: the Alpha, Beta, Gamma, Delta and Omicron variants [3]. These variants have specific traits, including increased transmissibility and a tendency to cause more severe disease for some. While the Delta and Alpha variants seem to be associated with more severe disease, the Omicron variant is associated with less severe illness but is more infectious. Globally as of May 2023, WHO is currently monitoring two variants of interest (VOIs),

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In vitro and in vivo study on fine-grained Mg–Zn–RE–Zr alloy as a biodegradeable orthopedic implant produced by friction stir processing

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ABSTRACT

Magnesium alloys containing biocompatible components show tremendous promise for applications as temporary biomedical devices. However, to ensure their safe use as biodegradeable implants, it is essential to control their corrosion rates. In concentrated Mg alloys, a microgalvanic coupling between the α-Mg matrix and secondary precipitates exists which results in increased corrosion rate. To address this challenge, we engineered the microstructure of a biodegradable Mg–Zn–RE–Zr alloy by friction stir processing (FSP), improving its corrosion resistance and mechanical properties simultaneously. The FS processed alloy with refined grains and broken and uniformly distributed secondary precipitates showed a relatively uniform corrosion morphology accompanied with the formation of a stable passive layer on the alloy surface. In vivo corrosion evaluation of the processed alloy in a small animal model showed that the material was well-tolerated with no signs of inflammation or harmful by-products. Remarkably, the processed alloy supported bone until it healed till eight weeks with a low in vivo corrosion rate of 0.7 mm/year. Moreover, we analyzed blood and histology of the critical organs such as liver and kidney, which showed normal functionality and consistent ion and enzyme levels, throughout the 12-week study period. These results demonstrate that the processed Mg–Zn–RE–Zr alloy offers promising potential for osseointegration in bone tissue healing while also exhibiting controlled biodegradability due to its engineered microstructure. The results from the present study will have profound benefit for bone fracture management, particularly in pediatric and elderly patients.

1. Introduction

Bone fracture management involves fixation using an implant to support bone/tissue healing followed by its removal [1,2]. Permanent implants made from titanium, stainless steel and cobalt-chromium have been commonly used in orthopedic surgeries [3]. Patients can benefit from biodegradable implants by avoiding secondary removal surgery, reducing pain, physical discomfort, and cost savings [4,5]. Essential requirements for biodegradable bone implant material include biocompatibility with living tissues, mechanical integrity over its intended service life and controlled degradation coupled with non-toxic byproducts [5]. Amongst different biodegradable metals, Mg alloys have been found to possess optimal mechanical properties that are closet to bones and good biocompatibility [6–8]. Consequently, Mg based alloys have been extensively researched for biodegradable implant application [6–14].

Mg alloys utilization as implants is impeded by their comparatively high corrosion rates. Mg has a low electrode potential of −2.372 V [15] against normal hydrogen electrode, making it extremely active in aqueous media containing chloride ions, such as human body physiological conditions. Although $Mg(OH)_2$ formed during exposure to aqueous media can act as a passive surface film [16,17], Mg exhibits

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Clinical Review

The Impact of the COVID-19 Pandemic on the Physical and Mental Health of School-Aged Children

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Abstract

Description

The SARS-CoV-2 (COVID-19) pandemic caused a deleterious impact on global health. School-aged children were significantly impacted by the pandemic. These impacts may be attributed to the fact that this age group is at a vulnerable developmental stage and is susceptible to profound effects. We conducted a thorough literature review using PubMed, Medline, and Science Direct electronic database searches between 2020-2022. We retrieved 757 studies, 25 of which were included in our review. We considered the impact of the COVID-19 pandemic on the physical and mental health of school-aged children (5-18 years), and the results were analyzed and included in our narrative review. Reduced physical activity and low health-related quality of life were observed in school-aged children during the pandemic in comparison to pre-pandemic. Factors such as age, fears/stress, mood states, socio-economic status, pre-COVID sedentary time, and activity levels were attributed to reduced physical activity. Depression and anxiety were the most common symptoms noted. Absenteeism, substance abuse, sleep disorders, and eating disorders were also increased. The negative influence of increased screen time, restricted physical activity, and social isolation were also considered and discussed. The COVID-19 pandemic has acted as a physical, mental, and social contagion for children. Interventions to promote physical and mental health need to be initiated in homes, schools, communities, and countries.

Keywords

COVID-19; pandemics; pediatrics; psychological distress; psychological resilience; adolescent; child; psychological adaptation; mental health

Introduction

The SARS-CoV-2 (COVID-19) pandemic caused a pernicious impact on global health. All age groups of people were stricken by the pandemic in one form or another. The pandemic had a harmful effect on physical, social, and mental health in many ways[1] and few were spared from the deleterious outcomes of the pandemic. School-aged children were also significantly impacted during this period. The depths of these impacts may be attributed to the fact that this age group is at a vulnerable developmental stage causing profound effects. In addition, home isolation, restricted physical activities, limited social interaction, and financial recession made the situation worse for school-aged groups. Initially, schools were closed, and later, online teaching methods were introduced to reduce the transmission of disease between children. These unanticipated changes in the teaching schedules and methodology, the fear of the disease, and the disease itself affected children substantially.[1-4] These changes brought about a negative influence on the physical activities of the children which in turn gradually impacted their mental and psycho-social health.[5-7]

In Persian Gulf countries with a high prevalence of overweight and obese school-aged children, the effects of the SARS-CoV-2 pandemic might have been even more detrimental.[8-10] In the World Health Organization (WHO) report on obesity and overweight in 2018, more than

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CLINICAL RESEARCH

Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK)

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Introduction: Continuous renal replacement therapy (CRRT) is used for the symptomatic management of acute kidney injury (AKI) and fluid overload (FO). Contemporary reports on pediatric CRRT are small and single center in design. Large international studies evaluating CRRT practice and outcomes are lacking. Herein, we describe the design of a multinational collaborative.

Methods: The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) is an international collaborative of pediatric specialists whose mission is to improve short- and long-term outcomes of children treated with CRRT. The aims of this multicenter retrospective study are to describe the epidemiology, liberation patterns, association of fluid balance and timing of CRRT initiation, and CRRT prescription with outcomes.

Results: We included children ($n = 996$, 0–25 years) admitted to an intensive care unit (ICU) and treated with CRRT for AKI or FO at 32 centers (in 7 countries) from 2018 to 2021. Demographics and clinical characteristics before CRRT initiation, during the first 7 days of both CRRT, and liberation were collected. Outcomes include the following: (i) major adverse kidney events at 90 days (mortality, dialysis dependence, and persistent kidney dysfunction), and (ii) functional outcomes (functional stats scale).

Conclusion: The retrospective WE-ROCK study represents the largest international registry of children receiving CRRT for AKI or FO. It will serve as a broad and invaluable resource for the field of pediatric critical care nephrology that will improve our understanding of practice heterogeneity and the association of CRRT with clinical and patient-centered outcomes. This will generate preliminary data for future interventional trials in this area.

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KEYWORDS: acute kidney injury; continuous renal replacement therapy; database; fluid overload; pediatric; WE-ROCK

In recent years, our understanding of AKI and the pathologic state of FO in critically ill children and young adults has increased exponentially. Fluid balance (FB) is the difference between total input and output and is often expressed as "daily or cumulative" over a defined duration of time. The 26th Pediatric Acute Disease Quality Initiative defined FO as a pathologic state of FB associated with clinically observable events.[1]

AKI and pathologic FO have been shown to occur commonly among critically ill children and young

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[11]The members of the WE-ROCK Investigators are listed in the Appendix.

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TRANSFUSION

Patient and specimen identification in a tertiary care pediatric hospital: Barcodes do not scan themselves

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Abstract

Background: Despite the safety improvements linked to the use of barcodes for patient and specimen identification, patient misidentification remains a leading cause of transfusion-associated reactions including fatalities. A wealth of evidence supports the use of barcodes in general, but there is less published evidence of real-world barcode compliance. This project investigates barcode scanning compliance for patient and specimen identification at a tertiary care pediatric/maternity hospital.

Study Design and Methods: Transfusion laboratory specimen collection noncompliance events between January 1, 2019, and December 31, 2019 were retrieved from the hospital laboratory information system. Data were analyzed including stratification of collections by collector role and collection event. A survey of blood collectors was conducted.

Results: Collection compliance for 6285 blood typing specimens was evaluated. Full barcode scanning identification of both patient and specimen was utilized in only 33.6% of total collections. The remaining two thirds of collections were overridden by the blood collector: no barcode scanning occurred in 31.3%, while the specimen accession label was scanned but not the patient armband in 32.3% of total collections. There were significant differences between phlebotomists and nurses, with more phlebotomists performing the full scanning and specimen scanning only, while more nurses obtained specimens without patient or specimen scanning ($p < .001$). Blood collectors identified hardware challenges and training gaps as key contributors to barcode noncompliance.

Abbreviations: DMAIC, define, measure, analyze, improve, and control; PAID, positive accession identification; PPID, positive patient identification.

Eileen R. A. McBride and Jason C. Ford contributed equally to the manuscript.

VISUAL DIAGNOSIS

Gastrointestinal Complications in Infants with Congenital Diaphragmatic Hernia

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CASE 1

A term male infant, with prenatally diagnosed left-sided congenital diaphragmatic hernia (CDH), presents at 36 hours after birth with hypothermia, increased inflammatory markers, and intrathoracic bowel dilatation.

Prenatal and Birth Histories

- The infant is born to a 33-year-old gravida 3 para 2 woman with diabetes, hypothyroidism, and preeclampsia.
- Prenatal ultrasonography revealed a left-sided CDH at 22 weeks' gestation.
- Fetal magnetic resonance imaging (MRI) at 28 weeks' gestation showed herniation of the stomach and bowel, with an observed-to-expected total fetal lung volume (O/E TFLV) ratio of 0.34.
- Horseshoe kidney was also identified prenatally with ultrasonography and confirmed with fetal MRI.
- Amniocentesis revealed XY karyotype.
- Estimated gestational age was 37 weeks.
- Following spontaneous labor, the infant was born by vacuum-assisted vaginal delivery; maternal magnesium sulfate was provided prior to delivery because of maternal preeclampsia. There were no maternal risk factors for sepsis.
- The infant was intubated in the delivery room at 3 minutes of age with a 3.5-mm uncuffed endotracheal tube (ETT), and a large nasogastric tube (NGT) was inserted to decompress the intrathoracic bowel.
- Apgar scores were 7 and 8 at 1 and 5 minutes, respectively.

Presentation

In the NICU, the infant initially had a stable cardiorespiratory course. His first chest radiograph (CXR) (Fig 1) showed normal bowel occupying the left hemithorax. A CDH repair was planned after 72 hours of age upon optimization of clinical status.

However, at 36 hours of age, the infant developed hypothermia and an increase in inflammatory markers, which prompted initiation of antibiotics (penicillin and gentamicin). A repeat CXR (Fig 2) showed dilation of the intrathoracic bowel.

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CLINICAL RESEARCH ARTICLE

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Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study

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Abstract

Introduction/Aims: NURTURE (NCT02386553) is an open-label study of nusinersen in children (two *SMN2* copies, $n = 15$; three *SMN2* copies, $n = 10$) who initiated treatment in the presymptomatic stage of spinal muscular atrophy (SMA). A prior analysis after ~3 y showed benefits on survival, respiratory outcomes, motor milestone achievement, and a favorable safety profile. An additional 2 y of follow-up (data cut: February 15, 2021) are reported.

Methods: The primary endpoint is time to death or respiratory intervention (≥6 h/day continuously for ≥7 days or tracheostomy). Secondary outcomes include overall survival, motor function, and safety.

Results: Median age of children was 4.9 (3.8–5.5) y at last visit. No children have discontinued the study or treatment. All were alive. No additional children utilized

Abbreviations: 6MWT, 6-Minute Walk Test; AE, adverse event; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurologic Examination, Section 2; PASA, Parent Assessment of Swallowing Ability; pNF-H, phosphorylated neurofilament-heavy chain; PT, physical therapist; SAE, serious adverse event; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, survival motor neuron 1; *SMN2*, survival motor neuron 2; WHO, World Health Organization.

Prior Presentation: Part of these data were previously presented at the 2022 Muscular Dystrophy Association—Clinical and Scientific Conference, Nashville, TN, USA, March 13–16, 2022; European Paediatric Neurology Society—14th Congress, Glasgow, UK, April 28–May 2, 2022; Cure SMA–2022 Annual Conference, Anaheim, CA, USA, June 15–17, 2022; SMA Europe–3rd International Scientific Congress on Spinal Muscular Atrophy, Barcelona, Spain, October 21–23, 2022; and 2023 Muscular Dystrophy Association—Clinical and Scientific Conference, Dallas, TX, USA, March 19–22, 2023.

For affiliations refer to page 168

PLOS ONE

RESEARCH ARTICLE

Corneal confocal microscopy demonstrates sensory nerve loss in children with autism spectrum disorder

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Data Availability Statement: The data used for statistical analysis in this study is available at (https://figshare.com/articles/dataset/ASD/21836214).

Abstract

Autism spectrum disorder (ASD) is a developmental disorder characterized by difficulty in communication and interaction with others. Postmortem studies have shown cerebral neuronal loss and neuroimaging studies show neuronal loss in the amygdala, cerebellum and inter-hemispheric regions of the brain. Recent studies have shown altered tactile discrimination and allodynia on the face, mouth, hands and feet and intraepidermal nerve fiber loss in the legs of subjects with ASD. Fifteen children with ASD (age: 12.00 ± 3.55 years) and twenty age-matched healthy controls (age: 12.83 ± 1.91 years) underwent corneal confocal microscopy (CCM) and quantification of corneal nerve fiber morphology. Corneal nerve fibre density (fibers/mm^2) (28.61 ± 5.74 vs. 40.42 ± 8.95, $p = 0.000$), corneal nerve fibre length (mm/mm^2) (16.61 ± 3.26 vs. 21.44 ± 4.44, $p = 0.001$), corneal nerve branch density (branches/mm^2) (43.68 ± 22.71 vs. 62.39 ± 21.58, $p = 0.018$) and corneal nerve fibre tortuosity (0.037 ± 0.023 vs. 0.074 ± 0.017, $p = 0.000$) were significantly lower and inferior whorl length (mm/mm^2) (21.06 ± 6.12 vs. 23.43 ± 3.95, $p = 0.255$) was comparable in children with ASD compared to controls. CCM identifies central corneal nerve fiber loss in children with ASD. These findings, urge the need for larger longitudinal studies to determine the utility of CCM as an imaging biomarker for neuronal loss in different subtypes of ASD and in relation to disease progression.

Introduction

Autism Spectrum Disorder (ASD) is a complex and heterogenous neurodevelopmental brain disorder affecting 1–2% of children worldwide [1, 2]. It is characterized by an impairment in social communication and restricted/repetitive behaviour attributed to altered levels of neurotransmitters and neuro-axonal development [3]. Most research has focused on brain-centric mechanisms with little attention to peripheral nerve involvement. However, studies have reported abnormal peripheral sensory responses in multiple domains [4–6] in relation to ASD severity [7]. This is now recognized in the autism diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V, as hyper/hypo reactivity to sensory stimuli [8].

Cureus

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Advancing Artificial Intelligence for Clinical Knowledge Retrieval: A Case Study Using ChatGPT-4 and Link Retrieval Plug-In to Analyze Diabetic Ketoacidosis Guidelines

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Abstract

Introduction

This case study aimed to enhance the traceability and retrieval accuracy of ChatGPT-4 in medical text by employing a step-by-step systematic approach. The focus was on retrieving clinical answers from three international guidelines on diabetic ketoacidosis (DKA).

Methods

A systematic methodology was developed to guide the retrieval process. One question was asked per guideline to ensure accuracy and maintain referencing. ChatGPT-4 was utilized to retrieve answers, and the 'Link Reader' plug-in was integrated to facilitate direct access to webpages containing the guidelines. Subsequently, ChatGPT-4 was employed to compile answers while providing citations to the sources. This process was iterated 30 times per question to ensure consistency. In this report, we present our observations regarding the retrieval accuracy, consistency of responses, and the challenges encountered during the process.

Results

Integrating ChatGPT-4 with the 'Link Reader' plug-in demonstrated notable traceability and retrieval accuracy benefits. The AI model successfully provided relevant and accurate clinical answers based on the analyzed guidelines. Despite occasional challenges with webpage access and minor memory drift, the overall performance of the integrated system was promising. The compilation of the answers was also impressive and held significant promise for further trials.

Conclusion

The findings of this case study contribute to the utilization of AI text-generation models as valuable tools for medical professionals and researchers. The systematic approach employed in this case study and the integration of the 'Link Reader' plug-in offer a framework for automating medical text synthesis, asking one question at a time before compilation from different sources, which has led to improving AI models' traceability and retrieval accuracy. Further advancements and refinement of AI models and integration with other software utilities hold promise for enhancing the utility and applicability of AI-generated recommendations in medicine and scientific academia. These advancements have the potential to drive significant improvements in everyday medical practice.

Categories: Endocrinology/Diabetes/Metabolism, Family/General Practice, Healthcare Technology
Keywords: clinical decision tool, clinical decision support system, clinical decision support, chatgpt, large language model, generative ai, artificial intelligence in medicine, chatgpt-4

Introduction

Remarkable advancements in artificial intelligence and language processing capabilities have propelled AI text generative models, such as ChatGPT, to new heights of performance [1-4]. These models have demonstrated exceptional abilities in providing excellent answers, thanks to their extensive training on diverse corpora during pre-training. However, incorporating these models into scientific academia, particularly medicine, presents challenges and limitations that must be addressed critically [4].

One significant challenge arises from the need for more incorporation of proper citations within the generated text [4]. Linking information to specific sources is crucial for establishing credibility and upholding the integrity of academic writing. Additionally, these models can occasionally generate non-factual information, referred to as "hallucinations" [5], which undermine the reliability and trustworthiness of the generated content. Furthermore, there may be instances where the generated answers lack

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POSITION STATEMENT Open Access

European Achondroplasia Forum guiding principles for the detection and management of foramen magnum stenosis

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Abstract

Foramen magnum stenosis is a serious, and potentially life-threatening complication of achondroplasia. The foramen magnum is smaller in infants with achondroplasia, compared with the general population, and both restricted growth in the first 2 years and premature closure of skull plate synchondroses can contribute to narrowing. Narrowing of the foramen magnum can lead to compression of the brainstem and spinal cord, and result in sleep apnoea and sudden death. There is a lack of clarity in the literature on the timing of regular monitoring for foramen magnum stenosis, which assessments should be carried out and when regular screening should be ceased. The European Achondroplasia Forum (EAF) is a group of clinicians and patient advocates, representative of the achondroplasia community. Members of the EAF Steering Committee were invited to submit suggestions for guiding principles for the detection and management of foramen magnum stenosis, which were collated and discussed at an open workshop. Each principle was scrutinised for content and wording, and anonymous voting held to pass the principle and vote on the level of agreement. A total of six guiding principles were developed which incorporate routine clinical monitoring of infants and young children, timing of routine MRI screening, referral of suspected foramen magnum stenosis to a neurosurgeon, the combination of assessments to inform the decision to decompress the foramen magnum, joint decision making to proceed with decompression, and management of older children in whom previously undetected foramen magnum stenosis is identified. All principles achieved the ≥ 75% majority needed to pass (range 89–100%), with high levels of agreement (range 7.6–8.9). By developing guiding principles for the detection and management of foramen magnum stenosis, the EAF aim to enable infants and young children to receive optimal monitoring for this potentially life-threatening complication.

Keywords Achondroplasia, European Achondroplasia Forum, Foramen Magnum Stenosis, Guiding principles, Detection, Management, Recommendations

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Effects of previous infection, vaccination, and hybrid immunity against symptomatic Alpha, Beta, and Delta SARS-CoV-2 infections: an observational study

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Summary

Background Protection against SARS-CoV-2 symptomatic infection and severe COVID-19 of previous infection, mRNA two-dose vaccination, mRNA three-dose vaccination, and hybrid immunity of previous infection and vaccination were investigated in Qatar for the Alpha, Beta, and Delta variants.

Methods Six national, matched, test-negative, case-control studies were conducted between January 18 and December 18, 2021 on a sample of 239,120 PCR-positive tests and 6,103,365 PCR-negative tests.

Findings Effectiveness of previous infection against Alpha, Beta, and Delta reinfection was 89.5% (95% CI: 85.5–92.3%), 87.9% (95% CI: 85.4–89.9%), and 90.0% (95% CI: 86.7–92.5%), respectively. Effectiveness of two-dose BNT162b2 vaccination against Alpha, Beta, and Delta infection was 90.5% (95% CI, 83.9–94.4%), 80.5% (95% CI: 79.0–82.0%), and 58.1% (95% CI: 54.6–61.3%), respectively. Effectiveness of three-dose BNT162b2 vaccination against Delta infection was 91.7% (95% CI: 87.1–94.7%). Effectiveness of hybrid immunity of previous infection and two-dose BNT162b2 vaccination was 97.4% (95% CI: 95.4–98.5%) against Beta infection and 94.5% (95% CI: 92.8–95.8%) against Delta infection. Effectiveness of previous infection and three-dose BNT162b2 vaccination was 98.1% (95% CI: 85.7–99.7%) against Delta infection. All five forms of immunity had >90% protection against severe, critical, or fatal COVID-19 regardless of variant. Similar effectiveness estimates were observed for mRNA-1273. A mathematical model accurately predicted hybrid immunity protection by assuming that the individual effects of previous infection and vaccination acted independently.

Interpretation Hybrid immunity, offering the strongest protection, was mathematically predicted by assuming that the immunities obtained from previous infection and vaccination act independently, without synergy or redundancy.

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Full Length Article

Bivalirudin or heparin for systemic anticoagulation during pediatric extracorporeal membrane oxygenation: Multicenter retrospective study

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ABSTRACT

Background: The objective of this study is to evaluate the outcomes of unfractionated heparin (UFH) compared to bivalirudin anticoagulation in pediatric ExtraCorporeal Membrane Oxygenation (ECMO).
Methods: A multicenter retrospective study, that included pediatric patients <18 years of age, who were supported on ECMO between June 2017 and May 2020. Patients treated with UFH were matched 2:1 by age and type of ECMO support to the bivalirudin group.
Results: The bivalirudin group (75 patients) were matched to 150 patients treated with UFH. Baseline characteristics and comorbidities of the two groups were similar. Veno-Arterial ECMO was the most common mode (141/225 [63 %]) followed by extracorporeal cardiopulmonary resuscitation (48/225 [21 %]). Bivalirudin treatment was associated with lower odds of bleeding events (aOR 0.23, 95%CI 0.12–0.45, $p < 0.001$) and lower odds of thrombotic events (aOR 0.48, 95%CI 0.23–0.98, $p = 0.045$). Patients who received bivalirudin had lesser odds for transfusion with fresh frozen plasma, and platelets (aOR 0.26, CI 0.12–0.57, $p \leq 0.001$ and aOR 0.28, CI 0.15–0.53, $p < 0.001$, respectively). After adjusting for the type of ECMO support and adjusting for age, bivalirudin was associated with a decrease in hospital mortality by 50 % compared to the UFH group (aOR 0.50, 95% CI 0.27–0.93, $p = 0.028$). Similarly, for neurological disability at time of discharge, bivalirudin was associated with higher odds of intact neurological outcomes compared to UFH (OR 1.99 [95%CI 1.13–3.51], $p = 0.017$).
Conclusions: This study demonstrated that effective anticoagulation can be achieved with bivalirudin, which was associated with lesser odds of bleeding events and utilization of blood products. Bivalirudin, in comparison with UFH, was associated with greater odds of hospital survival and intact neurological function at the time of discharge. A prospective randomized trial is required to validate the results of this study.

1. Background

Extracorporeal membrane oxygenation (ECMO) is a form of advanced life support that is frequently deployed for patients with cardiac and/or respiratory failure refractory to conventional medical therapies. Despite technologic advancements in circuit and material design, including flow parameters and surface coatings, ECMO continues to necessitate systemic anticoagulation to prevent thromboembolic complications. Hemorrhagic and thrombotic complications are frequent events in ECMO and are associated with 28 %- 40 % decrease in survival [1,2]. Unfractionated Heparin (UFH) has been the mainstay of systemic anticoagulation in ECMO for decades due to a

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Urinary tract infections in children from the Gulf Cooperation Council countries: a literature review (2011–2022)

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Urinary tract infections (UTIs) are common healthcare-associated and community-acquired bacterial infections in children. Data on pediatric UTIs in the Gulf Cooperation Council (GCC) region (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates) have not been collated. Our aim is to review the published literature on the risk factors, etiology, antimicrobial susceptibility, and treatment of pediatric (aged <18 years) UTIs from healthcare and community settings in the GCC countries.

KEYWORDS

urinary tract infection, pediatric, Gulf Cooperation Council (GCC), antimicrobial susceptibility, antimicrobial resistance

1. Introduction

Urinary tract infections (UTIs) are common in children (1–3). Up to 11% of children have had a UTI by 16 years of age, with higher infection rates in girls than boys (4–7). The diagnosis, prevalence and risk factors for UTIs may be stratified by patient sex or age, or the presence of underlying anatomical anomalies [such as vesicoureteral reflux (VUR)] that can lead to the recurrence of infection (1, 8). Awareness of the current risk factors for pediatric UTIs and factors contributing to recurrent UTIs can improve the clinical outcome of children with UTIs.

Uropathogenic *Escherichia coli* accounts for 80%–90% of pediatric UTIs (9). Resistance to common antibiotics used to treat UTIs, such as ampicillin and trimethoprim-sulfamethoxazole, is high among *E. coli* urinary isolates from children in the Gulf Cooperation Council (GCC) region [Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE)] (10). Furthermore, isolates producing extended-

Abbreviations
3GC, third-generation cephalosporin; CA, community-acquired; CA-UTI, community-acquired urinary tract infection; CFU, colony forming units; CRE, carbapenem-resistant Enterobacterales; ESBL, extended-spectrum β-lactamase; HA, hospital-acquired; HA-UTI, hospital-acquired UTI; IV, intravenous; MCUG, micturating cystourethrogram; SPIDS, Saudi Pediatric Infectious Diseases Society; UAE, United Arab Emirates; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

Population immunity of natural infection, primary-series vaccination, and booster vaccination in Qatar during the COVID-19 pandemic: an observational study

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Summary

Background Waning of natural infection protection and vaccine protection highlight the need to evaluate changes in population immunity over time. Population immunity of previous SARS-CoV-2 infection or of COVID-19 vaccination are defined, respectively, as the overall protection against reinfection or against breakthrough infection at a given point in time in a given population.

Methods We estimated these population immunities in Qatar's population between July 1, 2020 and November 30, 2022, to discern generic features of the epidemiology of SARS-CoV-2. Effectiveness of previous infection, mRNA primary-series vaccination, and mRNA booster (third-dose) vaccination in preventing infection were estimated, month by month, using matched, test-negative, case–control studies.

Findings Previous-infection effectiveness against reinfection was strong before emergence of Omicron, but declined with time after a wave and rebounded after a new wave. Effectiveness dropped after Omicron emergence from 88.3% (95% CI: 84.8–91.0%) in November 2021 to 51.0% (95% CI: 48.3–53.6%) in December 2021. Primary-series effectiveness against infection was 84.0% (95% CI: 83.0–85.0%) in April 2021, soon after introduction of vaccination, before waning gradually to 52.7% (95% CI: 46.5–58.2%) by November 2021. Effectiveness declined linearly by ~1 percentage point every 5 days. After Omicron emergence, effectiveness dropped from 52.7% (95% CI: 46.5–58.2%) in November 2021 to negligible levels in December 2021. Booster effectiveness dropped after Omicron emergence from 83.0% (95% CI: 65.6–91.6%) in November 2021 to 32.9% (95% CI: 26.7–38.5%) in December 2021, and continued to decline thereafter. Effectiveness of previous infection and vaccination against severe, critical, or fatal COVID-19 were generally >80% throughout the study duration.

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Original Article

Value of radiomics in differentiating synchronous double primary lung adenocarcinomas from intrapulmonary metastasis

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Background: Distinguishing synchronous double primary lung adenocarcinoma (SDPLA) from intrapulmonary metastasis (IPM) of lung cancer has significant therapeutic and prognostic values. This study aimed to develop and validate a CT-based radiomics model to differentiate SDPLA from IPM.

Methods: A total of 153 patients (93 SDPLA and 60 IPM) with 306 pathologically confirmed lesions were retrospectively studied. CT morphological features were also recorded. Region of interest (ROI) segmentation was performed semiautomatically, and 1,037 radiomics features were extracted from every segmented lesion The differences of radiomics features were defined as the relative net difference in radiomics features between the two lesions on CT. Those low reliable (ICC <0.75) and redundant (r>0.9) features were excluded by intraclass correlation coefficients (ICC) and Pearson's correlation. Multivariate logistic regression (LR) algorithm was used to establish the classification model according to the selected features. The radiomics model was based on the four most contributing differences of radiomics features. Clinical-CT model and MixModel were based on selected clinical and CT features only and the combination of clinical-CT and Rad-score, respectively.

Results: In both the training and testing cohorts, the area under the curves (AUCs) of the radiomics model were larger than those of the clinical-CT model (0.944 *vs.* 0.793 and 0.886 *vs.* 0.735 on training and testing cohorts, respectively), and statistically significant differences between the two models in the testing set were found (P<0.001). Meanwhile, three radiologists had sensitivities of 84.2%, 63.9%, and 68.4%, and specificities of 76.9%, 69.2%, and 76.9% in differentiating 19 SDPLA cases from 13 cases of IPM in the testing set. Compared with the performance of the three radiologists, the radiomics model showed better accuracy to the patients in both the training and testing cohorts. Among the three models, the radiomics model showed the best net benefits.

Conclusions: The differences of radiomics features showed excellent diagnostic performance for preoperative differentiation between synchronous double primary lung adenocarcinoma from interpulmonary metastasis, superior to the clinical model and decisions made by radiologists.

PLOS ONE

RESEARCH ARTICLE

Unsupervised anomaly appraisal of cleft faces using a StyleGAN2-based model adaptation technique

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Competing interests: The authors have declared that no competing interests exist.

Abstract

A novel machine learning framework that is able to consistently detect, localize, and measure the severity of human congenital cleft lip anomalies is introduced. The ultimate goal is to fill an important clinical void: to provide an objective and clinically feasible method of gauging baseline facial deformity and the change obtained through reconstructive surgical intervention. The proposed method first employs the StyleGAN2 generative adversarial network with model adaptation to produce a normalized transformation of 125 faces, and then uses a pixel-wise subtraction approach to assess the difference between all baseline images and their normalized counterparts (a proxy for severity of deformity). The pipeline of the proposed framework consists of the following steps: image preprocessing, face normalization, color transformation, heat-map generation, morphological erosion, and abnormality scoring. Heatmaps that finely discern anatomic anomalies visually corroborate the generated scores. The proposed framework is validated through computer simulations as well as by comparison of machine-generated versus human ratings of facial images. The anomaly scores yielded by the proposed computer model correlate closely with human ratings, with a calculated Pearson's r score of 0.89. The proposed pixel-wise measurement technique is shown to more closely mirror human ratings of cleft faces than two other existing, state-of-the-art image quality metrics (Learned Perceptual Image Patch Similarity and Structural Similarity Index). The proposed model may represent a new standard for objective, automated, and real-time clinical measurement of faces affected by congenital cleft deformity.

1 Introduction

Cleft lip with or without associated cleft palate (CL +/- CP) is one of the most common major congenital anomalies. The National Birth Defects Prevention Network 2017 Congenital Malformations Surveillance Report, which studied the United States birth cohort between 2010–2014, reported CL +/- CP prevalence at 1 in 1000 live births [1]. Surgical management

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BMC Musculoskeletal Disorders

RESEARCH Open Access

Metabolic syndrome and the likelihood of knee pain and functional disability: evidence from a large middle eastern population-based study

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Abstract

Objectives Metabolic Syndrome (MetS) has been associated with knee osteoarthritis (KOA) in animal studies, but epidemiologic evidence of the association remains controversial. We investigated the association between MetS and knee pain and functional disability, the hallmarks of KOA, in a Middle Eastern population with high reported MetS rates.

Methods A population-based study of adult individuals was conducted between 01/2016 and 03/2019. Data collected included age, sex, blood pressure, body mass index (BMI), waist circumference (WC), and comprehensive metabolic panel blood tests. Knee symptoms were assessed using The Western Ontario and McMaster Arthritis index (WOMAC) The Adult Treatment Panel III criteria was applied to determine if participants had MetS. Multivariable regression was used to determine the association of MetS, and its components, with the WOMAC total and subscale scores.

Results Of 6,000 participants enrolled, 15.5% had MetS. The multivariate regression demonstrated that participants with MetS had significantly higher WOMAC total and subscale scores after adjusting for demographic variables; however, these associations were not significant after adjusting for BMI. Multivariate regression examining the association between MetS components and the WOMAC scores showed sex-based significant differences with WOMAC scores; however, the differences were not larger than the minimally clinical important differences.

Conclusions This study demonstrated that after adjustment for BMI, neither MetS nor its individual parameters were associated with worse knee symptoms. As such, the association between MetS and worse knee symptoms requires further study.

Keywords Metabolic, Syndrome, Knee, Pain, Dysfunction

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Rapid Communication

Rapid Communication

Bivalent mRNA-1273.214 vaccine effectiveness against SARS-CoV-2 omicron XBB* infections

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Key words: Hybrid immunity, natural infection, waning vaccine effectiveness, asymptomatic infection, Qatar, variant-containing COVID-19 vaccines

In October of 2022, Qatar introduced COVID-19 bivalent vaccination for persons ≥ 12 years using the 50-μg mRNA-1273.214 vaccine combining SARS-CoV-2 ancestral and omicron BA.1 strains.[1] We estimated this vaccine's effectiveness against SARS-CoV-2 infection.

Using Qatar's national SARS-CoV-2 databases, we conducted a matched, retrospective, cohort study to compare infection incidence in the national cohort of persons who received the vaccine (bivalent cohort) to that in the national cohort of Qatar residents whose last vaccination was ≥6 months before follow-up start (no-recent-vaccination cohort; Supplementary Appendix 1). The 6-month cut-off was chosen because of negligible effectiveness of first-generation vaccines against omicron infection ≥ 6 months after vaccination.[2]

Incidence of infection was defined as the first SARS-CoV-2 PCR-positive or rapid-antigen-positive test after the start of follow-up, regardless of symptoms. Cohorts were balanced on observed confounders through exact matching. Follow-up started 7 days after the person in the bivalent cohort received their vaccine dose. Associations were estimated using Cox proportional-hazards models adjusted for the matching factors and testing rate.

During follow-up, 65 infections were recorded in the bivalent cohort and 406 in the no-recent-vaccination cohort. Cumulative incidence was 0.80% (95% CI: 0.61–1.07%) in the bivalent cohort and 1.00% (95% CI: 0.89–1.11%) in the no-recent-vaccination cohort, 150 days after follow-up start (Figure 1A). Incidence was dominated by omicron XBB* subvariants including XBB, XBB.1, XBB.1.5, XBB.1.9.1, XBB.1.9.2, XBB.1.16 and XBB.2.3.

Adjusted hazard ratio comparing infection incidence in the bivalent cohort to that in the no-recent-vaccination cohort was 0.75 (95% CI: 0.57–0.97; Figure 1B). Bivalent vaccine effectiveness was 25.2% (95% CI: 2.6–42.6%). Effectiveness was 21.5%

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Outcome analysis of staged preputial graft technique for primary proximal hypospadias with and without post-operative vacuum physiotherapy

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Keywords
Proximal hypospadias; Severe chordee; Outcome; Staged repair; Vacuum physiotherapy

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Summary

Purpose
Management of proximal hypospadias remains challenging. We assessed the results of staged preputial graft repairs (SPG) for proximal hypospadias and hypothesize that post-operative vacuum physiotherapy (VP) improves graft suppleness and overall outcomes.

Materials and methods
Retrospective analysis of n = 71 patients with proximal hypospadias and severe ventral penile curvature (PC) of ≥50° after degloving. PC was corrected using ventral transverse incisions of the tunica albuginea (VTITA) without applying a tourniquet, taking care to avoid injuring the underlying erectile tissue. The ventral raw area at the penile shaft, including VTITA, were covered with either divided and partially mobilized urethral plate, or with the inner preputial graft itself. During the second stage, a tunica vaginalis flap was often used to cover the tubularized neourethra. Outcomes and post-op complications were assessed after each stage, comparing patients who received vacuum physiotherapy (VP+, n = 49) with those who did not (VP-, n = 22).

Results
Mean PC was 66°, average follow-up duration was 13.01 months, and overall complication rate was 22.5%. Only 6 of 49 VP + patients experienced complications (12.24%; 4 fistulas; 2 urethral strictures) and no recurrence of PC after second stage was observed in this group. VP- patients displayed a significantly higher rate of complications, with 10 of 22 cases (45.45%) exhibiting fistula development (n = 5) and glans dehiscence (n = 5). Recurrence of mild PC after first-stage repair was comparable between patient groups (12% VP+, 18% VP-) and easily corrected by simple graft tubularization or dorsal plication during second-stage repair.

Conclusions
Staged repair using VTITA is effective for correcting proximal hypospadias with severe chordee. VP appears to promote and expedite graft suppleness and significantly improves patient outcomes.

Summary figure 1

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Examining Feasibility, Acceptability, and Preliminary Outcomes of a Culturally Adapted Evidence-Based Postpartum Depression Preventive Intervention for Women in Doha, Qatar: Protocol for a Randomized Controlled Trial

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Abstract

Background

Postpartum depression and anxiety are the 2 most common perinatal mental health disorders, with prevalence rates higher among women living in the Middle East than in most Western countries. The negative outcomes associated with postpartum depression and anxiety are profound and include less responsive parenting and compromised infant and young child development.

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ORIGINAL ARTICLE

Fostering research in pediatric interventional radiology: needs assessment and suggestions for support

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Abstract

Background Due to the rarity of pediatric diseases, collaborative research is the key to maximizing the impact of research studies. A research needs assessment survey was created to support initiatives to foster pediatric interventional radiology research.

Objective To assess the status of pediatric interventional radiology research, identify perceived barriers, obtain community input on areas of research/education/support, and create metrics for evaluating changes/responses to programmatic initiatives.

Materials and methods A survey link was sent to approximately 275 members of the Society for Pediatric Interventional Radiology (SPIR) between May and October 2020. Data was collected using a web-based interface. Data collected included practice setting, clinical role, research experience, research barriers, and suggestions for future initiatives.

Results Fifty-nine surveys were analyzed with a staff physician survey response rate of 28% (56/198). A wide range of practice sizes from 15 countries were represented. Respondents were predominantly staff physicians (95%; 56/59) with an average of 11 years (range: 1–25 years) of clinical experience working at academic or freestanding children's hospitals. A total of 100% (59/59) had research experience, and 70% (41/58) had published research with a mean of 30 peer-reviewed publications (range: 1–200). For job security, 56% (33/59) of respondents were expected or required to publish, but only 19% (11/58) had research support staff, and 42% (25/59) had protected research time, but of those, 36% (9/25) got the time "sometimes or never." Lack of support staff, established collaborative processes, and education were identified as top barriers to performing research.

Conclusions The needs assessment survey demonstrated active research output despite several identified barriers. There is a widespread interest within the pediatric interventional radiology community for collaborative research.

Keywords Child · Interventional radiology · Needs assessment · Pediatric · Respondents · Societies · Survey

Background

Pediatric interventional radiology is an evolving specialty. Increasing numbers of children are undergoing minimally invasive interventions as more institutions provide pediatric interventional radiology services and a wider scope of procedures is offered. There are large variations in the size, organizational structure, and staffing of pediatric interventional radiology practices.

Critical assessment of interventional radiology procedures and their outcomes is essential to provide the best patient care possible. As diseases within the pediatric population are often rare, it is difficult for a single site to recruit an adequate number of patients to perform properly powered, impactful, clinical research studies. The creation of multi-institutional collaborative research groups has had a major impact on health outcomes in other clinical specialties [1, 2]. The introduction of organized collaborative research in pediatric interventional radiology would require a variety of supportive strategies to effectively gather data from multiple sites with varying resources.

Extended author information available on the last page of the article

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BMC Pediatrics

RESEARCH Open Access

Prevalence and determinants of school bullying in Qatar: a cross-sectional study

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Abstract

Background School bullying is a wide-spread phenomenon that manifests in various forms. It has both short-term and long-term devastating consequences on physical, mental and social wellbeing. The Middle East and North Africa (MENA) region, including Qatar, has a relatively high prevalence of school bullying. This research aims at identifying the prevalence of bullying, particularly unsafe environments were bullying takes place, and its attributes at schools in Qatar.

Methods In a cross-sectional study, 980 students from 10 schools in Qatar completed an anonymous self-completion standardized questionnaire to assess the different aspects of bullying from school students' point of view.

Results The prevalence of bullying victimization and perpetration was found to be 41.0% and 31.7% among school students in Qatar, respectively. Classroom (67.5%) and hallways (64.8%) were the most frequently indicated environments of bullying whereas library was the least indicated one (28.3%). Verbal bullying was the most used type of bullying by students. Overall, students in Qatar believe that bullying is considerably a significant issue at their schools, yet schools are safe place for them to be in. Gender, age, ethnicity, school grade and years living in Qatar showed significant differences among the students.

Conclusion School bullying is a serious, yet a manageable global problem. Our findings re-demonstrated the alarming high prevalence of school bullying in Qatar, highlighted student related and school related factors which have implications for future multidimensional action and research and recommended measures to foster safety at school.

Keywords Bullying, Schools, Qatar

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Review article

Recommendations for use of adhesives on hospitalized newborns: A systematic review of the literature

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ABSTRACT

Background: The skin is the largest organ in the human body. It provides multiple barrier functions, tactile or defensive, and acts as a mediator allowing for the attachment of vital monitoring devices with medical adhesives. Adhesives consist of several layers with varying compositions and properties. We aimed to provide recommendations for their use in the care of hospitalized neonates on the basis of a systematic literature review.
Methods: We searched PubMed for English or French articles published before May 29, 2020, using the keywords "adhesive," "tape,", "skin," and "neonat*." Recommendations were developed after review by a multidisciplinary group including 15 professionals and parent representatives.
Results: We identified 295 studies, and from 30 eligible studies we developed six recommendations according to four perspectives: assessment of the skin condition to improve the methods of application of the different adhesives and their removal; use of adhesives as a platform; and discouraging the regular use of semi-permeable dressings to compensate for the immaturity of the skin barrier.
Conclusion: Skin lesions are common for hospitalized neonates. Use of adhesives may increase the occurrence of such lesions. Adhesives should be subject to good clinical practice guidelines. Health professionals caring for newborns should know the tools for screening and preventing skin lesions.

1. Introduction

The skin is the largest organ of the human body. It provides multiple barrier functions, tactile or defensive [1–3]. The skin acts as a mediator allowing for the attachment of vital monitoring devices and serves as a barrier to the access of other organs, for example, the veins and pleura. It develops throughout pregnancy, reaching maturity close to that of a full-term newborn at about 34–35 gestational weeks.

The stratum corneum, which provides the skin barrier effect, develops during the last trimester of pregnancy. The stratum corneum is less developed when birth takes place prematurely, since the degree of skin maturation is correlated with gestational age. In extremely preterm infants, the thinness of the stratum corneum leads to great dysfunction of the barrier effect of the skin (loss of heat and fluids by evaporation, fluid and electrolyte disturbance, infection, skin lesions). The dermal and epidermal layers are linked by fibrils that ensure their cohesion. In premature newborns, the fibrils are weaker and less numerous [1].

The maturation of the skin barrier continues over time [4]. Air exposure accelerates this maturation. In premature infants born at 23–25 weeks of gestation, the barrier function of the skin is considered mature when they reach 30–32 weeks of age. Therefore, an assessment of skin maturation must take into account the term of birth but also postnatal age. The most commonly used measures to assess and monitor the function of the stratum corneum are transepidermal water loss (TEWL) and pH [5].

Skin lesions are among the most frequent iatrogenic accidents in newborns [6]. Some risk factors of skin lesions have been identified: low birth weight, low gestational age, length of hospital stay, presence of a central venous or arterial line, mechanical ventilation, and noninvasive ventilation [7]. Skin lesions can have various origins: burns (chemical or contact), ulcerations or necrosis at pressure points (support points), and extravasation of infusion fluids. They can also be linked to the adhesives themselves, owing to the fragility of the junction between the epidermis and dermis. Indeed, the bond between the adhesive and epidermis can be stronger than that

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Epidemiology of combined immunodeficiencies affecting cellular and humoral immunity– a multicentric retrospective cohort study from the Arabian Peninsula

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ABSTRACT

Aims: To understand the characteristics of combined immunodeficiency disorders that affect cellular and humoral immunity (CID) in the Arabian Peninsula.
Methods: Retrospective study of 236 patients with CID from the region were enrolled from 2004 to 2022.
Results: 236 patients were included with a majority being profound CID. Among patients with a family history of CID, the ages at onset and diagnosis, and the delay in diagnosis were lower compared to those with no family history of CID, but this did not affect time to transplant. HSCT was performed for 51.27% of the patients with median time from diagnosis to HSCT of 6.36 months. On multivariate analysis, patients who underwent early transplant had increased odds of having CD3 count ≤1000 cell/μl, diagnosed by screening or erythroderma.
Conclusion: There is a delay in diagnosis and treatment of CID in our region. Establishing newborn screening programs and HSCT units in our region are the urgent need.

1. Introduction

Combined immunodeficiency disorders that affect cellular and humoral immunity (CID) are a group of single gene defects that result in a wide range of clinical manifestations and account for a significant burden of morbidity and mortality [1]. The incidence of CID is reported to vary from 1:100,000 to 1:5000 live births worldwide, depending on rates of consanguinity and the effects of underlying genetic mutations in the population of interest [2]. However, this could still be considered a likely underrepresentation of the incidence as many patients with CID are missed due to misdiagnosis of an atypical presentation, early death, and lack of well-maintained national registries that keep track of CID incidence [2,3].

The crux of CID management lies in the early diagnosis and swift initiation of therapy, thereby increasing the survival rate [4]. Therefore, a genetic diagnosis helps initiate curative interventions for CIDs, such as Hematopoietic Stem Cell Transplantation (HSCT), enzyme replacement, or gene therapy [3]. With the advancement in molecular techniques such as Next Generation DNA Sequencing, whole genome sequencing, and whole exome sequencing, identifying such gene defects with a short turnaround time has made early specific diagnosis possible [2]. However, a strong clinical suspicion is needed so the treating physician can initiate the work-up and early management plan. Although neonatal screening for severe combined immunodeficiency (SCID) that identifies defective T-cell generation through quantification of T-cell receptor excision circles (TRECs) is available in many places, it neither identifies

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Two-Year Outcomes After Minimally Invasive Surfactant Therapy in Preterm Infants
Follow-Up of the OPTIMIST-A Randomized Clinical Trial

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IMPORTANCE The long-term effects of surfactant administration via a thin catheter (minimally invasive surfactant therapy [MIST]) in preterm infants with respiratory distress syndrome remain to be definitively clarified.

OBJECTIVE To examine the effect of MIST on death or neurodevelopmental disability (NDD) at 2 years' corrected age.

DESIGN, SETTING, AND PARTICIPANTS Follow-up study of a randomized clinical trial with blinding of clinicians and outcome assessors conducted in 33 tertiary-level neonatal intensive care units in 11 countries. The trial included 486 infants with a gestational age of 25 to 28 weeks supported with continuous positive airway pressure (CPAP). Collection of follow-up data at 2 years' corrected age was completed on December 9, 2022.

INTERVENTIONS Infants assigned to MIST (n = 242) received exogenous surfactant (200 mg/kg poractant alfa) via a thin catheter; those assigned to the control group (n = 244) received sham treatment.

MAIN OUTCOMES AND MEASURES The key secondary outcome of death or moderate to severe NDD was assessed at 2 years' corrected age. Other secondary outcomes included components of this composite outcome, as well as hospitalizations for respiratory illness and parent-reported wheezing or breathing difficulty in the first 2 years.

RESULTS Among the 486 infants randomized, 453 had follow-up data available (median gestation, 27.3 weeks; 228 females [50.3%]); data on the key secondary outcome were available in 434 infants. Death or NDD occurred in 78 infants (36.3%) in the MIST group and 79 (36.1%) in the control group (risk difference, 0% [95% CI, −7.6% to 7.7%]; relative risk [RR], 1.0 [95% CI, 0.81-1.24]); components of this outcome did not differ significantly between groups. Secondary respiratory outcomes favored the MIST group. Hospitalization with respiratory illness occurred in 49 infants (25.1%) in the MIST group vs 78 (38.2%) in the control group (RR, 0.66 [95% CI, 0.54-0.81]) and parent-reported wheezing or breathing difficulty in 73 (40.6%) vs 104 (53.6%), respectively (RR, 0.76 [95% CI, 0.63-0.90]).

CONCLUSIONS AND RELEVANCE In this follow-up study of a randomized clinical trial of preterm infants with respiratory distress syndrome supported with CPAP, MIST compared with sham treatment did not reduce the incidence of death or NDD by 2 years of age. However, infants who received MIST had lower rates of adverse respiratory outcomes during their first 2 years of life.

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Visual Abstract

Supplemental content

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Group Information: The OPTIMIST-A Trial Investigators appear in Supplement 4.

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ASSISTED REPRODUCTION TECHNOLOGIES

Low E-visibility of embryologists on fertility clinic websites: a web-based cross-sectional study

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Abstract

Purpose This study assessed the visibility of embryologists on fertility clinic websites among Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA) member clinics.

Methods During a 1-month interval (March 2022), all Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA) member fertility clinic websites were evaluated. The professional representation of the primary care team was examined including specialties, the presence of headshots, and biographies.

Results A total of 446 fertility clinic websites were scanned in the search. The embryology team has the least common professional identification by their names (53.58%) compared to gynecology clinicians (96.21%, $p<0.001$) and nurses (55.58%, $p<0.001$). This trend also applies to other types of professional identifiers, such as headshots and biographies. Professional headshots of embryologists (50.34%) were less prominent than those of gynecology clinicians (93.51%, $p<0.001$). A similar trend was observed in the biographies of the embryology team (47.20%) compared to gynecology clinicians (95.08%, $p<0.001$).

Conclusion The present study revealed that embryologists have low professional visibility on fertility clinic websites. Fertility clinics may prioritize enhancing the online visibility of their embryology laboratory team. This approach could potentially enhance the recognition of their team, foster transparency, and provide accessible information about the skills and expertise of healthcare professionals involved in the treatment process.

Keywords Fertility · Website · Embryologist · E-visibility · Society for Assisted Reproductive Technology (SART) · Human Fertilisation and Embryology Authority (HFEA)

Introduction

The deep-rooted relationship between technology and modern society has led to a paradigm shift in several sectors, including healthcare. In the field of reproductive health, the integration of technology and medicine has transformed the way patients seek and access specialist care and reproductive health information [1]. A significant proportion of patients nowadays are internet-savvy and prefer consulting fertility clinic websites as their primary source of information, with almost 28.1% of prospective patients relying on such websites [2]. As a result, initiatives have been taken to evaluate and rate the quality of these websites, with guidelines from professional societies and regulatory authorities emphasizing the need for transparency, evidence-based practices, and updated information for patients [3, 4]. While it is essential for

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Short- and longer-term all-cause mortality among SARS-CoV-2-infected individuals and the pull-forward phenomenon in Qatar: a national cohort study ☆

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ABSTRACT

Objectives: We assessed short-, medium-, and long-term all-cause mortality risks after a primary SARS-CoV-2 infection.

Methods: A national, matched, retrospective cohort study was conducted in Qatar to assess risk of all-cause mortality in the national SARS-CoV-2 primary infection cohort compared with the national infection-naïve cohort. Associations were estimated using Cox proportional-hazards regression models. Analyses were stratified by vaccination status and clinical vulnerability status.

Results: Among unvaccinated persons, within 90 days after primary infection, the adjusted hazard ratio (aHR) comparing mortality incidence in the primary-infection cohort with the infection-naïve cohort was 1.19 (95% confidence interval 1.02-1.39). aHR was 1.34 (1.11-1.63) in persons more clinically vulnerable to severe COVID-19 and 0.94 (0.72-1.24) in those less clinically vulnerable. Beyond 90 days after primary infection, aHR was 0.50 (0.37-0.68); aHR was 0.41 (0.28-0.58) at 3-7 months and 0.76 (0.46-1.26) at ≥8 months. The aHR was 0.37 (0.25-0.54) in more clinically vulnerable persons and 0.77 (0.48-1.24) in

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ORIGINAL ARTICLE
Cosmetic

Impact of Surgical Rejuvenation on Visual Processing and Character Attribution of Faces

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Background: This study considers observers' reflexive responses to the rejuvenated face, and how instinctive responses relate to subjective judgment. We investigated observers' reflexive perception of faces both pre and post surgical intervention during the early stages of visual processing. Subjective character attribution for all test images was also assessed by the same observers.

Method: Forty frontal facial images of 20 patients portraying the pre- and post-operative high superficial musculoaponeurotic system facelift along with variable concomitant procedures were studied. Nineteen lookzone regions were mapped post hoc onto each image. Forty observers examined the images, whereas an eye-tracking camera recorded their eye movements. Visual fixation data were recorded and analyzed. Observers also rated each image on the basis of five elemental positive character attributes.

Results: A statistically coherent but nonsignificant ($P > 0.05$) trend was identified with the surgical intervention resulting in greater attention being paid to the central triangle region of the face with reduction in attention to the facial periphery. Facial rejuvenation significantly increased the subjective character ratings of all five positively valenced attributes tested. Average age estimate of the photos decreased significantly from 54 to 48.6 years (true average age of 57.4 years).

Conclusions: We provide data illustrating both reflexive and subjective responses to facial rejuvenation. Observers reported a more favorable impression of the treated faces and evaluated them as being younger than their true age. A trend was detected for increased visual fixation of the central facial region following rejuvenation. Interpretation of these findings and indication for further research is provided.
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INTRODUCTION

First impressions are largely determined by physical appearance and can contribute to a lasting positive perception in general.[1,2] Multiple studies have considered patient satisfaction following facial rejuvenation surgery and generally report favorable outcomes and an overall enhancement of youthful appearance.[3,4] However, few studies have evaluated observer impressions of patient appearance following such rejuvenative intervention. It is understood that observer impressions are formed rapidly, with initial visual processing of a face beginning within 170 milliseconds of exposure, and facial recognition estimated to occur as early as 300 milliseconds.[5–8] Tracking an observer's eye movements during facial inspection provides information about particular structural areas of reflexive interest or attraction. Accordingly, eye-tracking is a research modality that can highlight for patients and their providers areas of the face that are subconsciously considered of interest to others.[5–9] During rhytidectomy and related facial rejuvenation procedures, various areas of the face are targeted for improvement: forehead rhytids, brow position and contour, redundant eyelid skin, eyelid position and canthal angulation, glabellar lines, deepening of the nasolabial folds, jowls,

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Urologist validation of an artificial intelligence-based tool for automated estimation of penile curvature

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Summary

Introduction
Severity of penile curvature (PC) is commonly used to select the optimal surgical intervention for hypospadias, either alone or in conjunction with other phenotypic characteristics. Despite this, current literature on the accuracy and precision of different PC measurement techniques in hypospadias patients remains limited.

Purpose
Assess the feasibility and validity of an artificial intelligence (AI)-based model for automatic measurement of PC.

Material and methods
Seven 3D-printed penile models with variable degrees of ventral PC were used to evaluate and compare interobserver agreement in estimation of penile curvatures using various measurement techniques (including visual inspection, goniometer, manual estimation via a mobile application, and an AI-based angle estimation app. In addition, each participant was required to complete a questionnaire about their background and experience.

Results
Thirty-five clinical practitioners participated in the study, including pediatric urologists, pediatric surgeons, and urologists. For each PC assessment method, time required, mean absolute error (MAE), and inter-rater agreement were assessed. For goniometer-based measurement, the lowest MAE achieved was derived from a model featuring 86° PC. When using either UVI (unaid visual inspection), mobile apps, or AI-based measurement, MAE was lowest when assessing a model with 88° PC, indicating that high-grade cases can be quantified more reliably. Indeed, MAE was highest when PC angle ranged between 40° and 58° for all the investigated measurement tools. In fact, among these methodologies, AI-based assessment achieved the lowest MAE and highest level of inter-class correlation, with an average measurement time of only 22 s.

Conclusion
AI-based PC measurement models are more practical and consistent than the alternative curvature assessment tools already available. The AI method described in this study could help surgeons and hypospadiology researchers to measure PC more accurately.

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Procedural sedation programme minimising adverse events: a 3-year experience from a tertiary paediatric emergency department

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ABSTRACT

Introduction A well-developed procedural sedation programme in the paediatric emergency department can minimise adverse events. We examined how adherence to current best evidence ensures safe delivery of paediatric sedation in a newly established tertiary paediatric hospital.

Methods Our sedation service uses a robust provider training and privileging system, standardised policy and procedures and rigorous data collection all within an evidence-based clinical governance process. We examined sedation data from the first 3 years of operation.

Results From July 2018 to May 2022, ketamine was used in 3388 of the 3405 sedations. The mean age of sedated children was 5.5 years (range 6 months to 17.8 years) and common indications were closed reduction of fractures and laceration repairs. A total of 148 (4.37%, 95% CI 3.68% to 5.06%) adverse events were documented, including 88 (2.59%, 95% CI 2.06% to 3.13%) cases of vomiting, 50 (1.48%, 95% CI 1.07% to 1.88%) cases related to airway and breathing with 40 (1.18%, 95% CI 0.82% to 1.54%) cases of oxygen desaturation, 6 (0.18%, 95% CI 0.04% to 0.32%) cases of laryngospasm, 4 (0.12%, 95% CI 0% to 0.23%) cases of apnoea.

Conclusion This study presents a large single-centre dataset on the use of intravenous ketamine in paediatric procedural sedation. Adhering to international standards and benchmarks for provider skills and training, drug administration and monitoring facilities, with a strict clinical governance process, optimizes patient safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Procedural sedation using intravenous ketamine is used regularly in paediatric emergency departments for short procedures, but can be associated with serious adverse events.
⇒ These adverse events are often related to unsafe practices and are preventable in many instances.

WHAT THIS STUDY ADDS

⇒ We present a case series of over 3400 procedural sedation interventions where adverse events were significantly lower than those quoted in the literature.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By adhering to international standards and benchmarks for provider skills and training, drug administration and monitoring facilities, with a strict clinical governance process, patient safety can be optimised.

INTRODUCTION

Injuries are among the most common reasons for paediatric emergency visits[1] and may often require procedural sedation. Provision of procedural sedation in the emergency department (ED) by non-anaesthetists can improve patient experience and enhance resource management, but serious untoward incidents can occur.[2–5] These adverse events are often related to unsafe practices and may be preventable.[6] The emerging body of sedation literature emphasises standards and benchmarks for provider skills/numbers and training, drug administration and monitoring facilities.[7–13] As one of the largest tertiary paediatric hospitals in the Middle East, Sidra Medicine has developed an integrated operational framework. Procedural sedation outside the operating rooms is governed by the Procedural Sedation Committee, chaired by Anaesthesia and

vice chaired by Emergency Medicine. As a newly opened hospital, great efforts were made to ensure the development of a standardised process of oversight, education and training, care delivery and documentation of all procedural sedations. The committee was struck in 2016 with a view to ensure a long-term vision and plan with regard to safe sedation in the hospital, using expertise from both the Emergency Medicine and Anaesthesia to develop the high standard required by the hospital. The committee is a multidisciplinary group, with stakeholders all having a voice in the development of policy and procedure. This arrangement we feel is somewhat unique, especially in the Middle East. Policy and procedures developed have since been reviewed and confirmed in two separate Joint Commission International (JCI) hospital accreditation processes, meeting standards for safe sedation across specialties and professions. The committee governs procedural sedation practice outside the operating theatres, when being provided by non-anaesthesiologists. The ED is the largest provider of sedations in the hospital, with much fewer numbers in paediatric intensive care unit and neonatal intensive care unit. Currently, ward/

CORONAVIRUS

History of primary-series and booster vaccination and protection against Omicron reinfection

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Laboratory evidence suggests a possibility of immune imprinting for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We investigated the differences in the incidence of SARS-CoV-2 reinfection in a cohort of persons who had a primary Omicron infection, but different vaccination histories using matched, national, retrospective, cohort studies. Adjusted hazard ratio for reinfection incidence, factoring adjustment for differences in testing rate, was 0.43 [95% confidence interval (CI): 0.39 to 0.49] comparing history of two-dose vaccination to no vaccination, 1.47 (95% CI: 1.23 to 1.76) comparing history of three-dose vaccination to two-dose vaccination, and 0.57 (95% CI: 0.48 to 0.68) comparing history of three-dose vaccination to no vaccination. Divergence in cumulative incidence curves increased markedly when the incidence was dominated by BA.4/BA.5 and BA.2.75* Omicron subvariants. The history of primary-series vaccination enhanced immune protection against Omicron reinfection, but history of booster vaccination compromised protection against Omicron reinfection. These findings do not undermine the public health utility of booster vaccination.

INTRODUCTION

Three years into the coronavirus disease 2019 (COVID-19) pandemic, the global population carries heterogeneous immune histories derived from various exposures to infection, viral variants, and vaccination (*1*). Laboratory evidence suggests the possibility of immune imprinting, a negative impact of vaccination on subsequent protective immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced by vaccination or infection, or a combination of both (*1*–*4*). Epidemiological evidence for immune imprinting in immune histories related to infection was recently investigated, but no evidence was found for imprinting compromising protection against B.1.1.529 (Omicron) subvariants (*5*). A pre-Omicron infection followed by an Omicron reinfection enhanced protection against a second Omicron reinfection (*5*).

We investigated epidemiological evidence for imprinting in immune histories related to vaccination using matched, retrospective cohort studies conducted on the total population of Qatar from the onset of the Omicron wave on 19 December 2021 (*6*) through 15 September 2022. We compared the incidence of SARS-CoV-2 reinfection in the national cohort of individuals who had a primary documented Omicron infection after primary-series (two-dose) vaccination (designated as the two-dose cohort) to that in the national cohort of individuals with a documented primary Omicron infection, but no vaccination history (designated as the unvaccinated cohort). Analogously, we also compared reinfection incidence in those who had a documented primary Omicron infection after booster (third dose) vaccination (designated as the three-dose cohort) to each of the two-dose and unvaccinated cohorts.

These immune histories were investigated because of specific immunological scenarios observed in immunological laboratory data (*1*) because of their pervasiveness in the global population and because of their potential relevance to the protection of bivalent booster vaccination that is being scaled up in different countries.

A documented primary Omicron infection was defined as the first record of a SARS-CoV-2–positive polymerase chain reaction (PCR) or rapid antigen test after the onset of the Omicron wave in Qatar on 19 December 2021 (*6*) in an individual that had no record of a prior pre-Omicron infection. SARS-CoV-2 reinfection was defined, per the conventional definition in the literature, as a documented infection ≥90 days after an earlier infection, to avoid misclassifying prolonged SARS-CoV-2 positivity as reinfection if a shorter time interval is used (*6*–*8*). Matched pairs were followed from 90 days after the primary Omicron infection to record the incidence of SARS-CoV-2 reinfection.

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Diabetology & Metabolic Syndrome

RESEARCH Open Access

The effectiveness of blood glucose and blood ketone measurement in identifying significant acidosis in diabetic ketoacidosis patients

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Abstract

Background Patients with diabetic ketoacidosis (DKA), a potentially fatal complication of type 1 diabetes, have hyperglycemia, ketonemia and metabolic acidosis. Blood glucose and blood ketone results are often used to triage patients with suspected DKA. This study aimed to establish how effective blood glucose and blood ketone (beta-hydroxybutyrate, BOHB) measurements are in identifying patients with significant acidosis and sought to validate existing diagnostic BOHB thresholds.

Methods Initial Emergency Department results on 161 presumptive DKA episodes in 95 patients (42 F, 53 M, age range 14–89 years) containing a complete dataset of D (glucose), K (BOHB) and A (Bicarbonate [HCO_3] and pH) results.

Results Blood glucose correlated poorly with BOHB ($r = 0.28$ $p = 0.0003$), pH ($r = -0.25$, $p = 0.002$) and HCO_3 ($r = -0.17$, $p = 0.04$). BOHB, though better, was still limited in predicting pH ($r = -0.44$, $p < 0.0001$) and HCO_3 ($r = -0.49$, $p < 0.0001$). A HCO_3 of 18mmol/L equated to a BOHB concentration of 4.3mmol/L, whilst a HCO_3 of 15mmol/L equated to a BOHB of 4.7mmol/L. Of the 133 of 161 events with $HCO_3 < 18$mmol/L, 22 were not hyperglycemic (> 13.9mmol/L, n = 8), ketonemic (≤ 3mmol/L, n = 9) or either (n = 5).

Conclusions The commonly employed BOHB diagnostic cutoff of 3mmol/L could not be verified. Since acid-base status was poorly predicted by both glucose and BOHB, this highlights that, regardless of their results, pH and/or HCO_3 should also be tested in any patient suspected of DKA.

Keywords Diabetic ketoacidosis, beta-hydroxybutyrate, Ketones, Bicarbonate, Acid-base status, pH

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WILEY

IMAGES IN EMERGENCY MEDICINE

Gastrointestional

Upper abdominal mass in children

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1 | PATIENT PRESENTATION

We present 2 pediatric cases with abdominal mass. The first case was a 12-year-old girl who presented with upper abdominal pain for 1 week with intermittent episodes of vomiting non-bloody, non-bilious in nature but no diarrhea and no fever. Abdominal examination showed a firm mass in the left upper quadrant. X-ray of the abdomen showed distended gastric viscus with inspissated content with transition zone at the pylorus raising the suspicion of bezoar (Figure 1). The patient was taken to the operating room and the big mass of hair was removed with open laparoscopy (Figure 2). The second case was a 7-year-old with a history of recurrent upper abdominal pain for a few months with no vomiting, fever, or diarrhea. She had a history of eating foreign objects (hair and pencil erasers). Abdominal examination suggested a firm mass in the epigastric area. X-ray of the abdomen was inconclusive. Computed tomography (CT) of the abdomen and pelvis with contrast was obtained, which showed bezoar in the gastric cavity (Figure 3). The patient was taken for open laparoscopy and a mass of hair was extracted (Figure 4). In both cases, psychiatric evaluation and follow-up was arranged.

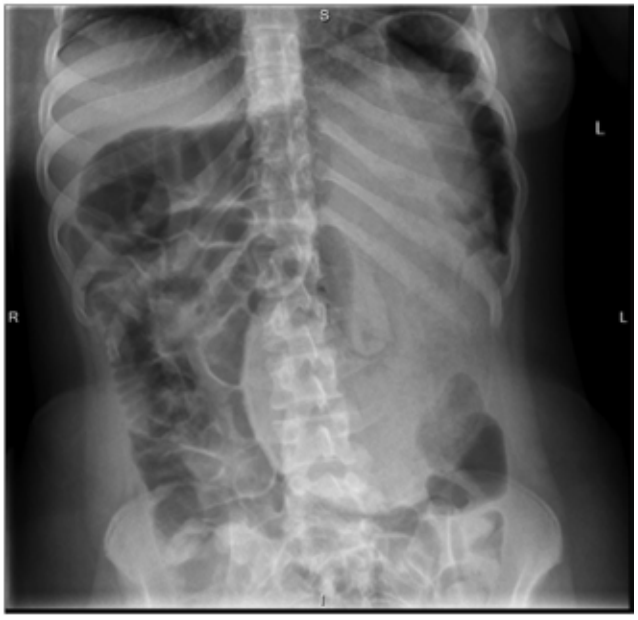

FIGURE 1 X-ray of the abdomen in case 1.

2 | DIAGNOSIS

2.1 | Gastric trichobezoar

Trichobezoar is a mass of ingested hair (mostly patient's own hair) that accumulates in the gastrointestinal tract, mostly in the gastric mucosa. In some cases, gastric bezoars extend into the small intestine and are called Rapunzel syndrome.[1] Trichobezoars are rare in children. Gastrointestinal trichobezoar usually present with signs and symptoms, such as abdominal pain, vomiting, and abdominal mass; whereas, in some cases, they manifest as small bowel obstruction, gastric perforation, intussusception, and bleeding per rectum.[2] Trichobezoars are diagnosed with imaging (CT scan) and endoscopy. The

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Harnessing Artificial Intelligence: Strategies for Mental Health Nurses in Optimizing Psychiatric Patient Care

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ABSTRACT

This narrative review explores the transformative impact of Artificial Intelligence (AI) on mental health nursing, particularly in enhancing psychiatric patient care. AI technologies present new strategies for early detection, risk assessment, and improving treatment adherence in mental health. They also facilitate remote patient monitoring, bridge geographical gaps, and support clinical decision-making. The evolution of virtual mental health assistants and AI-enhanced therapeutic interventions are also discussed. These technological advancements reshape the nurse-patient interactions while ensuring personalized, efficient, and high-quality care. The review also addresses AI's ethical and responsible use in mental health nursing, emphasizing patient privacy, data security, and the balance between human interaction and AI tools. As AI applications in mental health care continue to evolve, this review encourages continued innovation while advocating for responsible implementation, thereby optimally leveraging the potential of AI in mental health nursing.

Abbreviations: AI: Artificial Intelligence; ML: Machine Learning; DL: Deep Learning; NLP: Natural Language Processing; RPM: Remote Patient Monitoring; CBT: Cognitive Behavioral Therapy; CCBT: Computerized Cognitive Behavioral Therapy; PTSD: Post-Traumatic Stress Disorder; EHRs: Electronic Health Records; SVM: Support Vector Machines; VR: Virtual Reality; WHO: World Health Organization; FDA: Food and Drug Administration; MHN: Mental Health Nursing; AIHTs: AI health technologies; ADNI: Alzheimer's Disease Neuroimaging Initiative; EHRs: Electronic Health Records

Introduction

Mental health nursing, a specialized field within the broader nursing profession, plays a pivotal role in managing, treating, and caring for patients with various psychiatric disorders (Kumar et al., 2020). It is a profession that requires empathy, patience, and excellent communication skills, coupled with in-depth knowledge about mental health disorders and the most effective therapeutic interventions. However, the landscape of mental health care is rapidly changing with the advent of Artificial Intelligence (AI). AI is becoming increasingly integrated into healthcare, providing tools and systems that can help predict, diagnose, and treat illnesses more effectively and efficiently (Nashwan, 2023; Nashwan et al., 2023). AI has multiple means to achieve human-like performance; it attracts much interest in the medical landscape, including predictive medicine, patient diagnostics studies, clinical decisions, risk predictions, and support with exceptional outcomes (Albahri et al., 2023). In mental health nursing, AI has the potential to revolutionize patient care by enhancing diagnostic accuracy, optimizing treatment plans, providing personalized care, and reducing the burden on healthcare professionals (Bajwa et al., 2021). AI's potential to improve psychiatric patient care is massive. By utilizing algorithms that learn and adapt over time, AI can identify subtle changes in a patient's behavior or speech patterns that might indicate a change in their mental health status. This allows for earlier intervention and possibly prevents a major mental health crisis.

AI can also assist in treatment planning by analyzing data from various sources to predict the most effective interventions for a specific patient (Davenport & Kalakota, 2019). This review aims to discuss strategies for mental health nurses (MHNs) to harness the power of AI in optimizing psychiatric patient care. Integrating AI in mental health nursing will require a shift in how nurses approach patient care and developing strategies to effectively implement this change is paramount. This includes training and education about AI, ethical considerations, and collaboration with AI

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Implementation of Supportive Care Program to Decrease CLABSI in a Middle East Pediatric Hematology and Oncology Inpatient Unit

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Affiliations + expand

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Abstract

Background: Central venous catheters (CVCs) support the administration of chemotherapy and other medications, blood products, fluids, and nutrient infusions, and reduce the need for peripheral blood sampling in children with cancer. CVC use is also associated with the risk of central-line-associated bloodstream infection (CLABSI). Despite the implementation of CLABSI care bundles, CLABSI prevention remains challenging. **Method:** This project implemented supportive preventive care interventions to decrease CLABSI in pediatric hematology/oncology patients in a tertiary hospital in the Middle East region. Interventions included bathing or skin care once daily, oral care twice daily, and ambulating patients three times daily. Parent and staff education materials were developed. The project moniker was Step 1-2-3, inspired by successful implementations of such measures in a U.S. cohort showing reduced CLABSI rates. The project used a mixed methods approach. We report outcomes through August 2022. **Results:** Pre-project (12/2019-05/2020) five CLABSIs occurred in the inpatient unit. Following the implementation of Step 1-2-3, Pediatric Oncology achieved 492 CLABSI-free days. Six CLABSIs then occurred over a short period of time between October 2021 and January 2022, which was associated with high levels of patient acuity and staff sick leave. The inpatient ward remained CLABSI-free from January 9, 2022, through August 2022. **Discussion:** Extended periods of CLABSI-free care in a pediatric hematology/oncology unit are achievable. A variety of factors contribute to the sustainability of being CLABSI-free. Data collection and analysis are important factors which aided in our understanding of our own CLABSI events.

Keywords: CLABSI; Middle East; pediatric cancer; quality improvement; supportive care.

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Research Article

Prevalence of Sleep-Disordered Breathing in Prader–Willi Syndrome

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Introduction. Sleep-disordered breathing (SDB) is common in patients with Prader–Willi Syndrome (PWS). However, the prevalence of SDB varies widely between studies. Early identification of SDB and factors contributing to its incidence is essential, particularly when considering growth hormone (GH) therapy. *Objectives.* The aims of the study were to describe the prevalence and phenotypes of sleep-disordered breathing (SDB) in patients with Prader–Willi syndrome (PWS) and to determine the effects of age, gender, symptoms, GH therapy and body mass index on SDB severity. *Methods.* This study was a retrospective chart review of all patients with genetically confirmed Prader–Willi syndrome who underwent diagnostic overnight polysomnography (PSG) in the sleep laboratory at Sidra Medicine. Clinical and PSG data of enrolled patients were collected. *Results.* We identified 20 patients (nine males, eleven females) with PWS who had overnight sleep polysomnography (PSG) at a median age (IQR) of 5.83 (2.7–12) years. The median apnea-hypopnea index (AHI) was 8.55 (IQR 5.8–16.9) events/hour. The median REM-AHI was 27.8 (IQR 15–50.6) events/hour. The median obstructive apnea-hypopnea index (OAHI) was 7.29 (IQR 1.8–13.5) events/hour. The median central apnea-hypopnea index (CAHI) was 1.77 (IQR 0.6–4.1) events/hour. Nineteen patients (95%) demonstrated SDB by polysomnography (PSG) based on AHI ≥1.5 events/hour. Nine patients (45%) were diagnosed with obstructive sleep apnea (OSA). Three patients (15%) were diagnosed with central sleep apnea (CSA). Seven patients (35%) were diagnosed with mixed sleep apnea. No correlations were observed between AHI and age, gender, BMI, symptoms, or GH therapy. However, REM-AHI was significantly correlated with BMI ($P = 0.031$). *Conclusion.* This study shows a high prevalence of SDB among our patients with PWS. Obstructive sleep apnea was the predominant phenotype. BMI was the only predictor for high REM-AHI. Further studies of large cohorts are warranted to define SDB in PWS and design the appropriate treatment.

1. Introduction

Prader–Willi syndrome (PWS) is a rare genetic disorder characterized by the absence of the expression of the paternally inherited genes in chromosome 15 q11–13 region [1]. The estimated prevalence of PWS is one in 10,000–25,000 live births [2]. Patients with PWS can have multisystem abnormalities that include neurodevelopmental delay, growth retardation, endocrine and metabolic disturbances, and behavioral disorders that vary with age. During infancy, the main clinical features of PWS include hypotonia, feeding difficulties, and poor growth. Patients develop hyperphagia from childhood and onward due to hypothalamic dysfunction and consequent morbid obesity. Other manifestations include hypogonadism, psychomotor delay, hypothyroidism, and short stature [1, 2].

Sleep-related breathing disorders (SDBs) are common and potentially serious complications of PWS that can affect patients at any age. Multiple studies have reported a high prevalence of SDB among individuals with PWS ranging between 44 and 100%, compared to a prevalence of 2-3% in the general population [1–3]. Craniofacial dysmorphology affecting upper airway size, adenotonsillar hypertrophy, obesity, hypotonia, chest wall deformities, and defective

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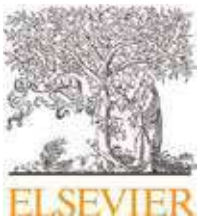

Contents lists available at ScienceDirect

Data in Brief

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Data Article

Large-scale annotation dataset for fetal head biometry in ultrasound images

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Dataset link: Large-Scale Annotation Dataset for Fetal Head Biometry in Ultrasound Images (Original data)

Keywords:
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Data annotation
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ABSTRACT

This dataset features a collection of 3832 high-resolution ultrasound images, each with dimensions of 959×661 pixels, focused on Fetal heads. The images highlight specific anatomical regions: the brain, cavum septum pellucidum (CSP), and lateral ventricles (LV). The dataset was assembled under the Creative Commons Attribution 4.0 International license, using previously anonymized and de-identified images to maintain ethical standards. Each image is complemented by a CSV file detailing pixel size in millimeters (mm). For enhanced compatibility and usability, the dataset is available in 11 universally accepted formats, including Cityscapes, YOLO, CVAT, Datumaro, COCO, TFRecord, PASCAL, LabelMe, Segmentation mask, OpenImage, and ICDAR. This broad range of formats ensures adaptability for various computer vision tasks, such as classification, segmentation, and object detection. It is also compatible with multiple medical imaging software and deep learning frameworks. The reliability of the annotations is verified through a two-step validation process involving a Senior Attending Physician and a Radiologic Technologist. The Intraclass Correlation Coefficients (ICC) and Jaccard similarity indices (JS) are utilized to quantify inter-rater agreement. The dataset exhibits high annotation reliability, with ICC values averaging at 0.859 and 0.889, and JS values

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Seroprevalence of hepatitis E virus (HEV) among male craft and manual workers in Qatar (2020–2021)

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ABSTRACT

Background: The rapid growth of Qatar in the last two decades has attracted a large influx of immigrant craft and manual workers (CMWs) seeking employment in jobs associated with food handling, domestic service, and construction. Nearly 60 % of Qatar's population are expatriates CMWs, including many from hyperendemic countries for HEV. Thus, estimating the seroprevalence of HEV in Qatar and understanding its epidemiology is essential for public health efforts to control HEV transmission in Qatar.

Methods: Blood samples from 2670 CMWs were collected between 2020 and 2021. All samples were tested for HEV-IgG antibodies. Positive HEV-IgG samples were tested for HEV-IgM antibodies, and those positives were also tested for viral antigens using an HEV-Ag ELISA kit and HEV-RNA by RT-PCR to confirm current HEV infections.

Results: The seroprevalence of HEV-IgG was 27.3 % (729/2670; 95 % CI: 25.6–29.0). Of those HEV-IgG positive, 8.23 % (60/729; 95 % CI: 6.30–10.5) were HEV-IgM positive. Of the IgM-positive samples, 2 were HEV-RNA positive (3.39 %; 95 % CI: 0.40–11.7), and 1 was HEV-Ag positive (1.69 %; 95 % CI: 0.04–9.09). In addition, HEV-IgG seroprevalence was associated with age and nationality, with the highest seroprevalence in participants from Egypt (IgG 60.0 %;

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Transcatheter Closure of Superior Sinus Venosus Defects

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Abstract

Superior sinus venosus defect is a communication between the right and left atrium located above the upper margin of the oval fossa, immediately inferior to the junction of the superior vena cava and the right atrium. It is systematically associated with partial anomalous pulmonary venous drainage, especially of the right upper pulmonary vein. Surgical repair has been the gold standard approach to close that defect. Introduced in 2014, percutaneous closure has gradually become a safe and effective alternative to surgery in carefully selected patients, although worldwide experience remains limited. This article provides an appraisal of the patients' selection process and a step-by-step description of the procedure as well as a comprehensive review of its outcomes.

Keywords: 3-dimensional technology; congenital heart disease; multimodal fusion imaging; sinus venosus defect; transcatheter closure.

Case Reports › BMJ Case Rep. 2023 Nov 9;16(11):e256232. doi: 10.1136/bcr-2023-256232.

Omental infarction in an overweight child: conservative treatment is a safe approach

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Affiliations + expand

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Abstract

A previously healthy but overweight (body mass index (BMI) of 24.4) adolescent boy presented with fever and significant right-sided abdominal pain. An abdominal ultrasound scan revealed an omental infarction (OI), which was treated conservatively. OI has been described in overweight teenage children with abdominal trauma but can be missed if not considered. A missed diagnosis could result in an unnecessary laparotomy or laparoscopic surgery. Although CT is the gold standard for diagnosis, ultrasonography is an effective approach to identifying OI in children. The benefits of early diagnosis of OI by abdominal ultrasound include a shorter hospital stay and a reduction in unnecessary investigations and surgery.

Keywords: Emergency medicine; Paediatrics (drugs and medicines); Trauma.

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Pediatric Blood & Cancer

RESEARCH ARTICLE

Prognostic impact of pre-referral tumor resection in unilateral Wilms tumor: A single-institute experience from a lower middle-income country

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Abstract

Introduction: The objectives of this study were to evaluate the prognostic impact of pre-referral surgical resection of Wilms tumor (WT) performed at non-oncology centers, and to strategize an improved care plan for this very curable pediatric tumor.

Methods: In this study conducted in a large pediatric cancer center in Pakistan, we retrospectively reviewed the electronic medical records (EMR) of 149 patients with unilateral WT from September 2008 to August 2017. Based on treatment approach, patients were categorized into two groups: (i) pre-referral tumor resection (PTR: $n = 75$), and (ii) post-neoadjuvant chemo nephrectomy (PCN: $n = 74$).

Results: The proportion of metastatic disease in PTR and PCN groups was 33.3% and 35.1%, respectively. In the PTR subset, median time to admission after PTR was 5 weeks (mean 11, SEM 2.8, range: 2–202) weeks, with 53.3% ($n = 40$) presenting more than 4 weeks after PTR. Twenty patients had no cross-sectional imaging prior to PTR and underwent surgery after abdominal ultrasound only. On baseline imaging at our center, 58.7% ($n = 44$) of the PTR group had radiologically evaluable disease (four metastases only, 19 local residual tumor only, 21 both localized tumor and visible metastases). Disease staging was uncertain in 23 patients because of no or inadequate histology specimens and/or lymph node sampling in patients with no evaluable disease. Statistically significant differences were recorded for the two subsets regarding tumor volume, extent and nodularity, renal vein and renal sinus involvement, lymph node status, tumor rupture and histopathologic features, and tumor stage, with a 10-year event-free survival (EFS) for PCN and PTR of 74.3% and 50.7%, respectively ($p < .001$). In the PTR group, EFS for those presenting within 4 weeks and later was 91.4% versus 15.0%, respectively ($p < .0001$).

Conclusion: Suboptimal pre-referral surgical intervention results in poor survival outcomes in unilateral WT. Our findings highlight the need for a comprehensive action plan for educating healthcare professionals engaged in WT diagnosis and referral process.

Abbreviations: COG, Children's Oncology Group; EFS, event-free survival; IPSO, International Society of Pediatric Surgical Oncology; LMIC, low- and middle-income countries; OS, overall survival; PCN, post-neoadjuvant chemo nephrectomy; PSPO, Pakistan Society of Pediatric Oncology; PTR, pre-referral tumor resection; RTSG, Renal Tumour Study Group; SIOP, Societe Internationale d'oncologie pediatrique; SKMCH, Shaukat Khanum Memorial Cancer Hospital and Research Center; WT, Wilms tumor.

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Core outcomes and factors influencing the experience of care for children with severe acute exacerbations of asthma: a qualitative study

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ABSTRACT

Objective To identify the outcomes considered important, and factors influencing the patient experience, for parents and caregivers of children presenting to hospital with a severe acute exacerbation of asthma. This work contributes to the outcome-identification process in developing a core outcome set (COS) for future clinical trials in children with severe acute asthma.

Design A qualitative study involving semistructured interviews with parents and caregivers of children who presented to hospital with a severe acute exacerbation of asthma.

Setting Hospitals in 12 countries associated with the global Pediatric Emergency Research Networks, including high-income and middle-income countries. Interviews were conducted face-to-face, by teleconference/video-call, or by phone.

Findings Overall, there were 54 interviews with parents and caregivers; 2 interviews also involved the child. Hospital length of stay, intensive care unit or high-dependency unit (HDU) admission, and treatment costs were highlighted as important outcomes influencing the patient and family experience. Other potential clinical trial outcomes included work of breathing, speed of recovery and side effects. In addition, the patient and family experience was impacted by decision-making leading up to seeking hospital care, transit to hospital, waiting times and the use of intravenous treatment. Satisfaction of care was related to communication with clinicians and frequent reassessment.

Conclusions This study provides insight into the outcomes that parents and caregivers believe to be the most important to be considered in the process of developing a COS for the treatment of acute severe exacerbations of asthma.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Management of acute severe asthma in children is based on weak evidence and inconsistent outcome measures. There is a need to develop a globally relevant core outcome set (COS) to ensure robust future research.

⇒ Qualitative interviews are increasingly used as part of COS development, however, often concentrate on participants from high-income countries.

WHAT THIS STUDY ADDS

⇒ This study highlights the outcomes that parents and caregivers of children with acute severe exacerbations of asthma from a broad range of countries consider important to include in a COS.

⇒ The study also provides information about the factors which influence the patient and family experience in children with an acute exacerbation of asthma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study was part of the process of developing a COS for use in trials and other studies for the treatment of acute severe exacerbations of asthma in children worldwide.

INTRODUCTION

Management of acute severe asthma exacerbations in children in the emergency department (ED) is complicated by a variety of possible treatment options,[1] significant variation in practice,[2 3] and little evidence to support the use of one particular medication over another.[1] The Paediatric Emergency Research Networks (PERN) asthma working group was formed in 2017. It aims to gather the input of patients, families and clinicians

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RESEARCH Open Access

An expanded clinical spectrum of hypoinsulinaemic hypoketotic hypoglycaemia

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Abstract

Background Hypoketotic hypoglycaemia with suppressed plasma fatty acids and detectable insulin suggests congenital hyperinsulinism (CHI). Severe hypoketotic hypoglycaemia mimicking hyperinsulinism but without detectable insulin has recently been described in syndromic individuals with mosaic genetic activation of post-receptor insulin signalling. We set out to expand understanding of this entity focusing on metabolic phenotypes.

Methods Metabolic profiling, candidate gene and exome sequencing were performed in six infants with hypoketotic, hypoinsulinaemic hypoglycaemia, with or without syndromic features. Additional signalling studies were carried out in dermal fibroblasts from two individuals.

Results Two infants had no syndromic features. One was mistakenly diagnosed with CHI. One had mild features of megalencephaly-capillary malformation-polymicrogyria (MCAP) syndrome, one had non-specific macrosomia, and two had complex syndromes. All required intensive treatment to maintain euglycaemia, with CHI-directed therapies being ineffective. Pathogenic *PIK3CA* variants were found in two individuals – *de novo* germline c.323G>A (p.Arg108His) in one non-syndromic infant and postzygotic mosaic c.2740G>A (p.Gly914Arg) in the infant with MCAP. No causal variants were proven in the other individuals despite extensive investigation, although rare variants in mTORC components were identified in one. No increased PI3K signalling in fibroblasts of two individuals was seen.

Conclusions We expand the spectrum of PI3K-related hypoinsulinaemic hypoketotic hypoglycaemia. We demonstrate that pathogenic germline variants activating post-insulin-receptor signalling may cause non-syndromic hypoinsulinaemic hypoketotic hypoglycaemia closely resembling CHI. This distinct biochemical footprint should be sought and differentiated from CHI in infantile hypoglycaemia. To facilitate adoption of this differential diagnosis, we propose the term "pseudohyperinsulinism".

Keywords Hypoinsulinemic hypoglycaemia, PI3K, Pseudohyperinsulinism, Insulin signalling

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Quantification of vesicoureteral reflux using machine learning

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Keywords
Voiding cystourethrogram (VCUG); Vesicoureteral reflux (VUR); Machine learning; Feature extraction

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Summary

Introduction
The radiographic grading of voiding cystourethrogram (VCUG) images is often used to determine the clinical course and appropriate treatment in patients with vesicoureteral reflux (VUR). However, image-based evaluation of VUR remains highly subjective, so we developed a supervised machine learning model to automatically and objectively grade VCUG data.

Study design
A total of 113 VCUG images were gathered from public sources to compile the dataset for this study. For each image, VUR severity was graded by four pediatric radiologists and three pediatric urologists (low severity scored 1—3; high severity 4—5). Ground truth for each image was assigned based on the grade diagnosed by a majority of the expert assessors. Nine features were extracted from each VCUG image, then six machine learning models were trained, validated, and tested using 'leave-one-out' cross-validation. All features were compared and contrasted, with the highest-ranked then being used to train the final models.

Results
F1-score is a metric that is often used to indicate performance accuracy of machine learning models. When using the highest-ranked VCUG image features, F1-scores for the support vector machine (SVM) and multi-layer perceptron (MLP) classifiers were 90.27 % and 91.14 %, respectively, indicating a high level of accuracy. When using all features combined, F1 scores were 89.37 % for SVM and 90.27 % for MLP.

Discussion
These findings indicate that a distorted pattern of renal calyces is an accurate predictor of high-grade VUR. Machine learning protocols can be enhanced in future to improve objective grading of VUR.

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Kawarabi: Administrative Structuring of a Multicenter Research Collaborative to Study Kawasaki Disease in the Arab Countries

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Abstract

Kawasaki disease (KD), the leading cause of acquired heart disease in children in developed countries, merits conducting detailed studies in Arab countries. We introduce Kawarabi, as a multicenter research collaborative effort dedicated to improving diagnosis, care, and outcome of children and adults with KD in the Arab world. During the COVID-19 pandemic, there emerged a new multisystem inflammatory syndrome in children; a disease similar to KD. This highlighted the challenges that Arab physicians face in diagnosing and managing children with KD and KD-like illnesses. Kawarabi brings together experts in North America and Arab nations to study this family of diseases in a not-for-profit, voluntary scientific collaborative setting. Bylaws addressing the vision, objectives, structure, and governance of Kawarabi were established, and vetted by the 45 organizing members in 2021. An initial scientific publication showed evidence of a decreased level of awareness of the disease in the general population, as well as the lack of access to resources available for physicians caring for children with KD in Arab countries. Kawarabi has since held several educational webinars and an inaugural yearly meeting. The groundwork for future initiatives targeted at increasing awareness and understanding of the management and the long-term outcomes of children with KD in the region was established. Data on KD in the Arab world are lacking. Kawarabi is a multicenter research collaborative organization that has the unique resources, diversified ethnic makeup, and energy, to accomplish significant advances in our understanding and management of KD and its variants.

Keywords: Arab; Kawasaki disease; multicenter collaborative.

[Intervention Review]

Infliximab for medical induction of remission in Crohn's disease

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ABSTRACT

Background

Infliximab is a monoclonal antibody that binds and neutralises tumour necrosis factor-alpha (TNF-α), which is present in high levels in the blood serum, mucosa and stool of people with Crohn's disease.

Objectives

To evaluate the benefits and harms of infliximab alone or in combination with another agent for induction of remission in Crohn's disease compared to placebo or active medical therapies.

Search methods

On 31 August 2021 and 4 March 2023, we searched CENTRAL, MEDLINE, Embase, ClinicalTrials.gov and World Health Organization ICTRP.

Selection criteria

Randomised control trials (RCTs) comparing infliximab alone or in combination with another agent to placebo or another active comparator in adults with active Crohn's disease.

Data collection and analysis

Pairs of review authors independently selected studies and conducted data extraction and risk of bias assessment. We expressed outcomes as risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). We assessed the certainty of the evidence using GRADE.

Our primary outcomes were clinical remission, clinical response and withdrawals due to adverse events. Our secondary outcomes were endoscopic remission, histological remission, endoscopic response, and serious and total adverse events.

Main results

The search identified 10 RCTs with 1101 participants. They were conducted between 1999 and 2019, and 7/10 RCTs included biologically naive participants. All but one RCT, which did not provide information, were multicentre and funded by pharmaceutical companies, and their authors declared conflicts. The age of the participants ranged from 26 to 65 years. Results were based on one study unless otherwise stated.

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ORIGINAL ARTICLE

WILEY

SARS-CoV-2 infection and effects of age, sex, comorbidity, and vaccination among older individuals: A national cohort study

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Abstract

Background: We investigated the contribution of age, coexisting medical conditions, sex, and vaccination to incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and of severe, critical, or fatal COVID-19 in older adults since pandemic onset.

Methods: A national retrospective cohort study was conducted in the population of Qatar aged ≥50 years between February 5, 2020 and June 15, 2023. Adjusted hazard

Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Efficacy and Safety of Remdesivir in Hospitalized Pediatric COVID-19: A Retrospective Case-Controlled Study

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Introduction: While most children experience mild coronavirus disease 2019 (COVID-19) infections, a minority of cases progress to severe or critical illness. This study aimed to assess the efficacy and safety of Remdesivir (RDV) therapy in children with moderate to severe COVID-19, enhancing clinical decision-making and expanding our understanding of antiviral treatments for pediatric patients.

Methods: The study included 60 patients, 38 receiving RDV treatment and 22 serving as the control group. Data was collected retrospectively from January 2021 to January 2022 through electronic hospital records.

Results: Regarding the main clinical symptoms reported, most patients experienced Upper Respiratory Tract Infections (93.3%), indicating respiratory involvement. Additional symptoms included Central Nervous System (11.7%) and Gastrointestinal (10.0%). Among the 38 cases in the RDV group included in the study, the adverse effects associated with using RDV: Hypoalbuminemia in 19 cases (50.0%) and anemia in 18 cases (47.4%), making them the most common adverse effects. Only one case in the RDV group experienced non-RDV-related death with a different clinical diagnosis. The results showed that RDV treatment was well-tolerated in pediatric patients, with no significant differences in hospital stay and oxygen treatment compared to the control group with P values (0.2, 0.18), respectively.

Conclusion: The outcomes indicate that Remdesivir may represent a safe and therapeutic choice for children with coronavirus disease 2019 (COVID-19).

Keywords: COVID-19, remdesivir, RDV, efficacy, safety, SARS-CoV-2

Introduction

The pathogenic agent SARS-CoV-2, belonging to the novel coronavirus 2 family, exerts its predominant effects on the respiratory tract, eliciting the onset of a complex and potentially life-threatening condition known as severe acute respiratory syndrome.[1] The disease exhibits a spectrum of clinical presentations, from mild and asymptomatic manifestations to severe cases characterized by hypoxemia, ultimately culminating in respiratory failure and mortality.[2] However, in the case of children, COVID-19 disease predominantly presents in a mild form and can often be managed with supportive care alone. Only a small proportion of children experience severe or critical illness, necessitating assisted ventilation and admission to the intensive care unit during the infection.[3]

In the quest for treating coronavirus disease 2019 (COVID-19) effectively, the main focus lies in utilizing extensively studied randomized trials and well-established medications.[4–8] Antivirals with inhibitory effects on protease and nucleotide or nucleoside analogs targeting viral RNA synthesis have been repurposed for the management of coronavirus

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Evaluation of Immulex *S. pneumoniae* Omni test for the direct detection of *S. pneumoniae* from positive blood cultures

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ABSTRACT

Rapid and early identification of *Streptococcus pneumoniae* from positive blood cultures is crucial for the management of patients with bloodstream infections (BSI). Many identification systems in microbiology laboratories have difficulty differentiating *S. pneumoniae* from other closely related species in the *Streptococcus mitis* group. To overcome this limitation, we developed a rapid workflow in our laboratory combining direct MALDI-TOF MS identification with the Immulex *S. pneumoniae* Omni test (SSI Diagnostica, Denmark) for rapid detection of *S. pneumoniae* directly from positive blood cultures. The workflow was evaluated using 51 *Streptococcus* isolates. Compared to conventional biochemical testing, our new workflow demonstrates 100 % specificity and sensitivity for the detection and differentiation of *S. pneumoniae* from other closely related species. Our new workflow is accurate, cost-effective, and can easily be implemented in microbiology laboratories that already perform direct MALDI-TOF identification from positive blood cultures to improve the management of patients with invasive pneumococcal disease.

Importance: Invasive pneumococcal disease remains a major public health problem worldwide. Reducing the time to identify *Streptococcus pneumoniae* in positive blood cultures allows patients to be treated sooner with more targeted and effective antibiotics. We evaluated a two-step protocol where positive blood cultures are first tested directly by MALDI-TOF MS and any samples containing *Streptococcus* species are tested by Immulex *S. pneumoniae* Omni test to both detect and differentiate *S. pneumoniae* from other closely related *Streptococcus* species. Our study results showed 100 % sensitivity and specificity, and a much faster turn-around time than conventional methods.

1. Introduction

Streptococcus pneumoniae is a major cause of severe infections such as community-acquired pneumonia (CAP), bacteremia, and meningitis worldwide in young children and elderly [1,2]. The incidence of invasive pneumococcal infections is tracked by the Centers

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Father's perceptions and care involvement for their very preterm infants at French neonatal intensive care units

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Objectives: We aimed to evaluate (1) fathers' perceptions and care involvement for their very premature infants and their views of the hospitalization period based on parental reports and (2) their evolution over time.

Methods: We used an online parental survey to assess answers from parents of very preterm infants who were successfully discharged from French neonatal units. We analysed answers from February 2014 to January 2019 to an anonymous internet-based survey from the GREEN committee of the French Neonatal Society. Responses were compared for period 1 (P1, 1998 to 2013) and period 2 (P2, 2014 to 2019).

Results: We analyzed 2,483 surveys, 124 (5%) from fathers and 2,359 (95%) from mothers. At birth, 1,845 (80%) fathers were present in the hospital, but only 879 (38%) were near the mother. The presence of fathers in the NICU increased from P1 to P2 (34.5% vs. 43.1%, $p = 0.03$). Nearly two thirds of fathers accompanied their infants during transfer to the NICU (1,204 fathers, 60.6%). Fathers and mothers had similar perceptions regarding relationships with caregivers and skin-to-skin contact with their infants. However, more fathers than mothers felt welcome in the NICU and in care involvement regarding requests for their wishes when they met their infant (79% vs. 60%, $p = 0.02$) and in the presentation of the NICU (91% vs. 76%; $p = 0.03$). Mothers and fathers significantly differed in the caring procedures they performed ($p = 0.01$), procedures they did not perform but wanted to perform ($p < 0.001$), and procedures they did not perform and did not want to perform ($p < 0.01$).

Conclusion: Most fathers were present at the births of their very preterm infants, but fewer fathers were near the mother at this time. Less than two thirds of fathers

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Surfactant and neonatal hemodynamics during the postnatal transition

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ABSTRACT

Surfactant replacement therapy (SRT) has revolutionized the management of respiratory distress syndrome (RDS) in premature infants, leading to improved survival rates and decreased morbidity. SRT may, however, be associated with hemodynamic changes, which can have both positive and negative effects on the immature cardiovascular system, during the transitional adaptation from fetal to extrauterine environment. However, there is a relative paucity of evidence in this domain, with most of them derived from small heterogeneous observational studies providing conflicting results.

In this review, we will discuss the hemodynamic changes that occur with surfactant administration during this vulnerable period, focusing on available evidence regarding changes in pulmonary and systemic blood flow, cerebral circulation and their clinical implications.

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1. Introduction

Respiratory distress syndrome (RDS) in preterm neonates is caused by surfactant deficiency, which leads to decreased lung compliance, increased airway resistance and impaired gas exchange, resulting in hypoxemia and hypercapnia [1]. These alterations in pulmonary function can also affect the hemodynamics, potentially leading to cardiac dysfunction and poor perfusion [2].

Surfactant replacement therapy (SRT) is the cornerstone in the treatment of RDS and has revolutionized outcomes in preterm neonates. Not only is surfactant used in management of RDS, but can also be used for post surfactant slump, or the worsening respiratory failure owing to progressive atelectasis in extremely premature infants previously treated with surfactant [3]. Surfactant is also utilized in term infants with meconium aspiration syndrome [4] and/or pulmonary hypertension [5,6] to treat lung disease. SRT has also been used to manage secondary surfactant inactivation noted in other aspiration syndromes like milk, blood or bile into the lungs and in the setting of congenital pneumonia [2,7]. The administration of surfactant, a complex mixture of phospholipids and proteins that coats the alveolar surface, has been shown to improve oxygenation and decrease the need for mechanical ventilation [8].

Knowledge of the interdependence of the heart and lungs is essential for practicing clinicians; specifically, the hemodynamic consequences of ventilation strategies and respiratory consequences of cardiovascular disease ("cardiac lung disease") are important considerations. The hemodynamic effects of both surfactant deficiency and SRT are accentuated during the critical period of transitional adaptation from fetal circulation to extra uterine life [9]. The transitional circulation refers to the time from birth to complete circulatory adaptation, whereby the circulation transforms from the fetal to neonatal phenotype, the duration of which can vary from a few hours to days [10]. Appropriate physiology based cardiorespiratory management is extremely crucial during this period as the fragile cerebral vasculature is highly susceptible to changes in systemic and pulmonary blood flow, partly due to the

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Systematic Review

A Meta-Analysis of the Global Stillbirth Rates during the COVID-19 Pandemic

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Abstract: COVID-19 has been shown to have variable adverse effects on pregnancy. Reported data on stillbirth rates during the pandemic have, however, been inconsistent—some reporting a rise and others no change. Knowing the precise impact of COVID-19 on stillbirths should help with the planning and delivery of antenatal care. Our aim was, therefore, to undertake a meta-analysis to determine the impact of COVID-19 on the stillbirth rate. Databases searched included PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science, with no language restriction. Publications with stillbirth data on women with COVID-19, comparing stillbirth rates in COVID-19 and non-COVID-19 women, as well as comparisons before and during the pandemic, were included. Two independent reviewers extracted data separately and then compared them to ensure the accuracy of extraction and synthesis. Where data were incomplete, authors were contacted for additional information, which was included if provided. The main outcome measures were (1) stillbirth (SB) rate in pregnant women with COVID-19, (2) stillbirth rates in pregnant women with and without COVID-19 during the same period, and (3) population stillbirth rates in pre-pandemic and pandemic periods. A total of 29 studies were included in the meta-analysis; from 17 of these, the SB rate was 7 per 1000 in women with COVID-19. This rate was much higher (34/1000) in low- and middle-income countries. The odds ratio of stillbirth in COVID-19 compared to non-COVID-19 pregnant women was 1.89. However, there was no significant difference in population SB between the pre-pandemic and pandemic periods. Stillbirths are an ongoing global concern, and there is evidence that the rate has increased during the COVID-19 pandemic, but mostly in low- and middle-income countries. A major factor for this is possibly access to healthcare during the pandemic. Attention should be focused on education and the provision of high-quality maternity care, such as face-to-face consultation (taking all the preventative precautions) or remote appointments where appropriate.

Keywords: SARS; COVID-19; stillbirth; meta-analysis; pre- and post-pandemic

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1. Introduction

The global burden of stillbirth(SB) continues [1], with an estimated two million every year. COVID-19 has an adverse effect on pregnancies [2,3], but there have been conflicting reports on increasing SB rates during the pandemic [4–7].

A population study from two Philadelphia Hospitals in the USA [8] did not detect any stillbirth changes with COVID-19, but a study from Nepal [9] showed a higher rate of

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Plate Objective Scoring Tool (POST) in distal hypospadias: Correlation with post-repair complications

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Summary

Objectives
The Plate Objective Scoring Tool (POST) accurately reflects configuration of the urethral plate in distal hypospadias. Here we assessed whether POST score also correlates with patient risk of complications after surgical repair.

Methods
Data were obtained prospectively from pre-pubertal boys who underwent primary hypospadias repair between January 2020 and February 2023. Both POST and Glans—Urethral Meatus—Shaft (GMS) scores were determined in triplicate by three independent reviewers before evaluating correlation with complications after surgery.

Results
POST ratios were strongly correlated with incidence of post-repair complications in n = 121 patients. Mean POST score was 1.10 (range 0.5—1.62) and average GMS value was 5.29 ± 1.36 (median G = 2, M = 2, S = 1). Bivariate correlation analysis indicated that POST score can accurately predict risk of complications after surgery (Pearson correlation coefficient r = 0.821 [0.724—0.918], 95 % CI). A POST threshold of 1.2 provided the highest specificity for risk of post-operative complications, which occurred in 4.4 % of patients with POST score ≥1.2 (2/45 cases), compared with 25 % among patients with POST score <1.2 (19/76 cases).

Conclusions
This study confirms that POST index can be used as a surrogate marker of urethral plate quality and accurately predicts the outcome of distal hypospadias repair. Objective scoring of POST revealed that low ratios were significantly associated with high risk of postoperative complications. In future, this approach could be used to stratify patients and better identify cases that require close follow-up care.

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Practice of Epidemiology

Estimating protection afforded by prior infection in preventing reinfection: applying the test-negative study design

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Abstract

The COVID-19 pandemic has highlighted the need to use infection testing databases to rapidly estimate effectiveness of prior infection in preventing reinfection (PE_S) by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. Mathematical modeling was used to demonstrate a theoretical foundation for applicability of the test-negative, case–control study design to derive PE_S. Apart from the very early phase of an epidemic, the difference between the test-negative estimate for PE_S and true value of PE_S was minimal and became negligible as the epidemic progressed. The test-negative design provided robust estimation of PE_S and its waning. Assuming that only 25% of prior infections are documented, misclassification of prior infection status underestimated PE_S, but the underestimate was considerable only when > 50% of the population was ever infected. Misclassification of latent infection, misclassification of current active infection, and scale-up of vaccination all resulted in negligible bias in estimated PE_S. The test-negative design was applied to national-level testing data in Qatar to estimate PE_S for SARS-CoV-2. PE_S against SARS-CoV-2 Alpha and Beta variants was estimated at 97.0% (95% CI, 93.6-98.6) and 85.5% (95% CI, 82.4-88.1), respectively. These estimates were validated using a cohort study design. The test-negative design offers a feasible, robust method to estimate protection from prior infection in preventing reinfection.

Key words: reinfection; test-negative design; effectiveness; mathematical model; SARS-CoV-2; COVID-19.

Introduction

Estimating effectiveness of prior infection in preventing reinfection (PE_S) is essential to understanding the epidemiology of a given infection. Various studies estimated PE_S for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.[1-9] However, there are challenges in estimating PE_S using conventional epidemiologic study designs. Such designs require extensive, complete electronic health records to be feasible. Vaccination scale-up makes it difficult to disentangle immunity induced by prior infection from that induced by vaccination.

Even when it is feasible to apply conventional designs, estimates can be prone to strong bias, due to misclassification of prior infection status, since many prior infections are not documented.[10-12] Effects of this bias increase with increased

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REVIEW ARTICLE

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Expert opinion on management of moderate-to-severe atopic dermatitis in Qatar

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ABSTRACT

Atopic dermatitis (AD), a chronic-relapsing inflammatory skin disorder, manifests with intense itching and eczematous lesions impairing quality of life. A heterogeneous population, and regional clinical practices for treating AD warrant the development of guidelines in Qatar. Therefore, guidelines for the management of moderate-to-severe AD in Qatar have been developed and discussed. Experts, including dermatologists and immunologists, used the Delphi technique for developing guidelines. Consensus was defined as ≥75% agreement or disagreement. AD is highly prevalent in primary and tertiary dermatology centers. AD-associated foot eczema and psoriasiform eczema are more frequent in Qatar than in Europe or USA. SCORing Atopic Dermatitis Index quantifies disease severity and itch. Dermatology Life Quality Index assesses the quality of life. Atopic Dermatitis Control Tool assesses long-term disease control. Moderate-severe AD benefits from new topicals like Janus-kinase-inhibitors or PDE4-inhibitors combined with phototherapy. Currently approved systemic agents are dupilumab, baricitinib, abrocitinib, and upadacitinib. New anti-IL-13 and anti-IL-31 therapies will soon be available. Patient education, allergy testing, and comorbidity consideration are critical in the management of AD. The expert panel established a comprehensive and pragmatic approach to managing moderate-to-severe AD, thereby assisting clinical decision-making for healthcare professionals in Qatar.

Abbreviations: AD: Atopic dermatitis; ADCT: Atopic Dermatitis Control Tool; CSA: cyclosporine A; DLQI: Dermatology Life Quality Index; EADV: European Academy of Dermatology and Venereology; EASI: Eczema Area and Severity Index; FDA: Food and Drug Administration or EMA - European Medicines Agency; IGA: Investigator Global Assessment; JAK-inhibitors: Janus-kinase; MENA: Middle East and North Africa; PRAC: Pharmacovigilance Review Assessment Committee; QoL: quality of life; TGCS: Topical glucocorticosteroids; TPE: therapeutic patient education

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Atopic dermatitis; consensus; biologics; dupilumab; JAK-inhibitor; treatment

Introduction

Atopic dermatitis (AD) is an inflammatory dermatological disease characterized by intense itching and recurrent eczematous lesions (1). It typically begins during infancy and gradually recurs or may persist to adolescence/adulthood with intermittent flare-ups and remissions (2); however, a bimodal model with a second peak in middle-aged and older adults is not uncommon (3). The disease can vary from mild-to-moderate to severe, necessitating different treatment regimens (4).

The global prevalence rate of AD ranges from 2.7 to 20.1% in children and 2.1 to 4.9% in adults (5,6). Over the last 30 years, its prevalence surged 2- to 3-folds worldwide. In developed countries, the prevalence rate of AD is 1–3% in the older age groups, being slightly higher in elderly males (7,8). In the Middle East and North Africa (MENA) region, the prevalence of AD appears to have significantly increased, although exact epidemiological data is limited, and the design of the studies varies. The estimated prevalence rate of AD in MENA varies from 2.1% to 23.3% across countries and age groups (9). A high prevalence of 30% has been found in a recent retrospective, cross-sectional study of 4521 patients from Qatar. The prevalence was found to be higher among boys (31.42%) than among girls (28.81%). The Qatari population demonstrated a greater prevalence of AD (34.4%) than the population that was non-Qatari. The prevalence was highest in children aged 6 months to one year (41.79%), followed by 8–12 years of age (32.8%), and was the least among 5–8 year olds (23.05%) (10). Arid climatic conditions worsen AD due to heat, low humidity contributing to dryness of the skin (9). In general, the epigenetic factors modulating AD in the population of MENA are poorly studied. Additionally, regional and ethnic diversity, as well as endotype specificities, may contribute to the varying prevalence, phenotypes, and therapy responses to AD globally, including MENA (9,11).

AD presents debilitating clinical symptoms and has several allergic comorbidities like allergic conjunctivitis, allergic rhinitis, food allergy, allergic asthma, nasal polyposis, along with bacterial,

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ORIGINAL ARTICLE

WILEY

Single-center review on safety of biodegradable airway stenting in pediatric population

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None

Abstract

Background: Tracheobronchomalacia (TBM) and airway stenosis are recognized etiologies of airway obstruction among children. Their management is often challenging, requiring multiple interventions and prolonged respiratory support with associated long-term morbidity. Metallic or silicone stents have been used with mixed success and high complication rates. More recently biodegradable Ella stents (BES) provided an attractive interventional option.

Objectives: We report our experience in the treatment of TBM and vascular airway compression using BES. We deliberately downsized them to minimize intraluminal granulation tissue formation.

Materials and Methods: Retrospective study over an 8-year period between November 2012 and December 2020 of pediatric patients with severe airway obstruction requiring airway stenting for extubation failure, malacic death spells, recurrent chest infections, or lung collapse.

Results: Thirty-three patients (5 tracheal and 28 bronchial diseases) required 55 BES during the study period. The smallest patient weighed 1.8 kg. Median age of patient at first stent implantation was 13.1 months (IQR 4.9–58.3). The majority of the bronchial stents were in the left main bronchus (93%), of which 57% for vascular compression. Repeat stents were used in 19 patients (57.7%), with a range of two to four times. We did not experience erosion, infection, or obstructive granuloma needing removal by forceps or lasering. Three stent grid occluded with secretions needing bronchoscopic lavage. Stent migration occurred in three patients.

Conclusions: BES holds promise as a treatment option with low rate of adverse effects for a specific subset of pediatric patients with airway malacia or vascular compression. Further studies are warranted.

KEYWORDS

airway stents, biodegradable, pediatric, review, safety, tracheobronchomalacia, vascular compression

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STANDARD ARTICLE

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Juvenile idiopathic epilepsy in Egyptian Arabian foals, a potential animal model of self-limited epilepsy in children

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Abstract

Background: Juvenile idiopathic epilepsy (JIE) is categorized as a generalized epilepsy. Epilepsy classification entails electrocortical characterization and localization of epileptic discharges (ED) using electroencephalography (EEG).

Hypothesis/Objectives: Characterize epilepsy in Egyptian Arabian foals with JIE using EEG.

Animals: Sixty-nine foals (JIE, 48; controls, 21).

Methods: Retrospective study. Inclusion criteria consisted of Egyptian Arabian foals: (1) JIE group diagnosed based on witnessed or recorded seizures, and neurological and EEG findings, and (2) control group of healthy nonepileptic age-matched foals. Clinical data were obtained in 48 foals. Electroencephalography with photic stimulation was performed under standing sedation in 37 JIE foals and 21 controls.

Results: Abnormalities on EEG were found in 95% of epileptic foals (35 of 37) and in 3 of 21 control asymptomatic foals with affected siblings. Focal ED were detected predominantly in the central vertex with diffusion into the centroparietal or frontocentral regions (n = 35). Generalization of ED occurred in 14 JIE foals. Epileptic discharges commonly were seen during wakefulness (n = 27/37 JIE foals) and sedated sleep (n = 35/37 JIE foals; 3/21 controls). Photic stimulation triggered focal central ED in 15 of 21 JIE foals.

Conclusions and Clinical Importance: Juvenile idiopathic epilepsy has a focal onset of ED at the central vertex with spread resulting in clinical generalized tonic-clonic seizures with facial motor activity and loss of consciousness. Electroencephalography with photic stimulation contributes to accurate phenotyping of epilepsy. Foals with

Abbreviations: BRE, benign rolandic epilepsy; ED, epileptic discharges; EEG, electroencephalogram; EEG, electroencephalography; IED, interictal epileptic discharges; IPS, intermittent photic stimulation; JIE, juvenile idiopathic epilepsy; PD, photic driving; PPR, photoparoxysmal response; PS, photic stimulation; SeLECTs, self-limited epilepsy with centrotemporal spikes; SWS, slow wave sleep.

Monica Aleman and Ruba Benini contributed equally as first authors.

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Estimating age and gender from electrocardiogram signals: A comprehensive review of the past decade

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ABSTRACT

Twelve lead electrocardiogram signals capture unique fingerprints about the body's biological processes and electrical activity of heart muscles. Machine learning and deep learning-based models can learn the embedded patterns in the electrocardiogram to estimate complex metrics such as age and gender that depend on multiple aspects of human physiology. ECG estimated age with respect to the chronological age reflects the overall well-being of the cardiovascular system, with significant positive deviations indicating an aged cardiovascular system and a higher likelihood of cardiovascular mortality. Several conventional, machine learning, and deep learning-based methods have been proposed to estimate age from electronic health records, health surveys, and ECG data. This manuscript comprehensively reviews the methodologies proposed for ECG-based age and gender estimation over the last decade. Specifically, the review highlights that elevated ECG age is associated with atherosclerotic cardiovascular disease, abnormal peripheral endothelial dysfunction, and high mortality, among many other cardiovascular disorders. Furthermore, the survey presents overarching observations and insights across methods for age and gender estimation. This paper also presents several essential methodological improvements and clinical applications of ECG-estimated age and gender to encourage further improvements of the state-of-the-art methodologies.

1. Introduction

Electrocardiogram (ECG) is a medical test that measures the heart's electrical activity. One of the observable and measurable outcomes of the depolarization and repolarization of the atrial and ventricular chambers of the heart is the generation of electrical impulses. These electrical changes (i.e., voltages) are captured by electrodes placed on the surface of the human body, which sampled over time generate a voltage versus time plot of the ECG signal. The changes in the different ECG parameters (e.g., PR interval, QRS complex) allow electrophysiologists to detect electrical abnormalities and diagnose cardiovascular diseases (CVDs). On the other hand, imaging-based techniques, such as Ultrasound (i.e., Echocardiography), Computed Tomography (i.e., CT), and Magnetic Resonance Imaging (MRI) [1], provide a visual perspective with morphological and hemodynamic evaluation of different chambers of the human heart allowing prediction of different CVDs. The imaging-based methodologies are employed in healthcare facilities by skilled professionals and are not patient-friendly because of their high cost, radiation exposure, injection of contrast enhancement compounds, and long acquisition time. ECG is preferred over other heart monitoring techniques because of its high patient safety, low cost, non-invasive nature, and wide availability (i.e., accessibility in small clinics, outpatient departments, and even embedded in wearable devices).

Conventionally, ECG signals are studied by electrophysiologists by examining morphological features and ECG parameters. The observations are correlated with the established ECG standards for different age groups to detect heart abnormalities. However, patients with the same CVDs may present notable differences in their ECG parameters. Also, two different heart diseases may manifest with roughly similar ECG patterns, subject to the patient's lifestyle, age, and other medical conditions [2]. Furthermore, ECG captured from the same patient may exhibit individual variability. To elaborate, a slight movement of electrodes or change in ECG capturing equipment introduces low-frequency interference (i.e., baseline drift) and alters the magnitude of the electrical voltages captured by the electrodes [3]. Therefore, analysis of ECG

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Histopathology

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Teratoma-associated and so-called pure Wilms tumour of the ovary represent two separate tumour types with distinct molecular features

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Teratoma-associated and so-called pure Wilms tumour of the ovary represent two separate tumour types with distinct molecular features

Aims: Ovarian Wilms tumour (WT)/nephroblastoma is an extremely rare neoplasm that has been reported to occur in pure form or as a component of a teratomatous neoplasm. We hypothesized that teratoma-associated and pure ovarian WT may represent different tumour types with diverging molecular backgrounds. To test this hypothesis, we comprehensively characterized a series of five tumours originally diagnosed as ovarian WT.

Methods and Results: The five cases comprised three teratoma-associated (two mature and one immature) and two pure WTs. Two of the teratoma-associated WTs consisted of small nodular arrangements of "glandular"/epithelial structures, while the third consisted of both an epithelial and a diffuse spindle cell/blastemal component. The pure WTs consisted of "glandular" structures, which were positive for sex cord markers (including inhibin and SF1) together with a rhabdomyosarcomatous component. The two pure WTs harboured *DICER1* pathogenic variants (PVs), while the three associated with teratomas were *DICER1* wildtype. Panel-based DNA sequencing of

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RESEARCH PAPER

Factors associated with immediate postoperative pulmonary complications after Appendectomies under general anesthesia: A retrospective analysis

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ABSTRACT

Background: Postoperative pulmonary complications (PPC) include any complication that affects the respiratory system after anesthesia and surgery and are a significant cause of postoperative mortality and morbidity.

Objectives: To describe the risk factors for immediate postoperative pulmonary complications after appendectomy under general anesthesia and to determine if rapid sequence induction decreases the risk.

Design and Setting: A retrospective analysis of perioperative medical records of patients who underwent appendectomy under general anesthesia over a year, from January 1st, 2014, to December 31st, 2014, at Hamad General Hospital, Doha, Qatar, was done.

Results: Of the 1005 patients who met the inclusion criteria, 27 (3.7%) had PPC. The incidence of PPC had a significant positive association with diabetes mellitus (DM), bronchial asthma (BA), number of intubation attempts, laparoscopic approach, and longer surgeries (>2 h). Hypertension, recent or ongoing upper respiratory tract infections, and smoking were not associated with an increased risk of PPC. Non-rapid sequence intubation (RSI) was not associated with an increased risk of PPC compared with RSI.

Conclusions: The incidence of immediate PPC in ASA 1 and 2 appendectomy patients aged between 15 and 50 is significant. There is an increased risk among asthmatics, diabetics, and those with difficult airways. The RSI technique does not offer protection.

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PICS/AEPC/APPCS/CSANZ/SCAI/SOLACI: Expert Consensus Statement on Cardiac Catheterization for Pediatric Patients and Adults With Congenital Heart Disease

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Affiliations + expand

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No abstract available

Keywords: adult congenital heart disease; cardiac catheterization; cardiac catheterization standards; congenital heart disease; quality and outcomes; resource limited environments.

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Life-Saving Treatments for Spinal Muscular Atrophy: Global Access and Availability

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Abstract

Background and objectives: Spinal muscular atrophy (SMA) is a neurodegenerative disorder manifesting with progressive muscle weakness and atrophy. SMA type 1 used to be fatal within the first 2 years of life, but is now treatable with therapies targeting splicing modification and gene replacement. Nusinersen, risdiplam, and onasemnogene abeparvovec-xioi improve survival, motor strength, endurance, and ability to thrive, allowing many patients to potentially attain a normal life; all have been recently approved by major regulatory agencies. Although these therapies have revolutionized the world of SMA, they are associated with a high economic burden, and access to these therapies is limited in some countries. The primary objective of this study was to compare the availability and implementation of treatment of SMA from different regions of the world.

Methods: In this qualitative study, we surveyed health care providers from 21 countries regarding their experiences caring for patients with SMA. The main outcome measures were provider survey responses on newborn screening, drug availability/access, barriers to treatment, and related questions.

Results: Twenty-four providers from 21 countries with decades of experience (mean 26 years) in treating patients with SMA responded to the survey. Nusinersen was the most available therapy for SMA. Our survey showed that while genetic testing is usually available, newborn screening is still unavailable in many countries. The provider-reported treatment cost also varied between countries, and economic burden was a major barrier in treating patients with SMA.

Discussion: Overall, this survey highlights the global inequality in managing patients with SMA. The spread of newborn screening is essential in ensuring improved access to care for patients with SMA. With the advancement of neurotherapeutics, more genetic diseases will soon be treatable, and addressing the global inequality in clinical care will require novel approaches to mitigate such inequality in the future.

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ORIGINAL PAPER

An Eastern Europe and Middle East multinational expert Delphi consensus study on the prevention, diagnosis, and treatment of developmental dysplasia of the hip before walking age

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Abstract

Purpose The incidence of developmental dysplasia of the hip (DDH) is higher in Eastern Europeans and Middle Easterners. This study aimed to establish consensus among experts in this geographical area on the management of DDH before walking age.

Methods Fourteen experienced orthopedic surgeons agreed to participate in a four-round online consensus panel by the Delphi method. The questionnaire included 31 statements concerning the prevention, diagnosis, and treatment of DDH before walking age.

Results Consensus was established for 26 (84%) of 31 statements. Hip ultrasonography is the proper diagnostic tool under six months in DDH; universal newborn hip screening between three and six weeks is necessary; positive family history, breech presentation, female gender, and postnatal swaddling are the most important risk factors; Ortolani, Barlow tests, and limitation of abduction are the most important clinical findings; Pavlik harness is the first bracing preference; some Graf type IIa hips and all Graf type IIb and worse hips need abduction bracing treatment; the uppermost age limit for closed and open reductions is 12 months and 12–24 months, respectively; anatomic reduction is essential in closed and open reductions, postoperative MRI or CT is not always indicated; anterior approach open reduction is better than medial approach open reduction; forceful reduction and extreme positioning of the hips (> 60° hip abduction) are the two significant risk factors for osteonecrosis of the femoral head.

Conclusion The findings of the present study may be useful for clinicians because a practical reference, based on the opinions of the multinational expert panel, but may not be applicable to all settings is provided.

Keywords Developmental dysplasia of the hip · Prevention · Diagnosis · Treatment · Consensus study

Introduction

Developmental dysplasia of the hip (DDH) can lead to significant functional disabilities if the diagnosis is delayed, the hip is left untreated, or the treatment is inadequate [1]. However, discussions are still ongoing, and no universally accepted consensus exists on several aspects of DDH like prevention strategies, exact aetiology, proper diagnostic tools, and ideal treatment methods in various types of hip pathologies in different age groups. The results of several cross-sectional surveys revealed great variations in the daily practices of clinicians concerning the diagnosis and treatment of DDH [2–7]. On the other hand, expert consensus studies aim to develop guidelines for different aspects of several disorders. The results of consensus studies related to the prevention, diagnosis, and treatment of DDH before walking age can be considered valuable to provide a practical reference for clinicians, but the number of such national or multinational paediatric orthopaedics or interdisciplinary studies is limited [8–12].

The incidence of DDH is higher in Caucasians, particularly in Eastern Europeans and in Indo-Mediterraneans, particularly in the Middle Easterners [13]. Therefore, we

Extended author information available on the last page of the article

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ORIGINAL ARTICLE

WILEY

The MiniMed 780G automated insulin delivery system adapts to substantial changes in daily routine: Lessons from real world users during Ramadan

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Funding information
Medtronic International Trading Sàrl

Abstract

Aim: To report on the effectiveness and safety of the MiniMed 780G automated insulin delivery system in real-world users during the month of Ramadan.

Materials and Methods: CareLink Personal data were extracted from MiniMed 780G system users from the Gulf region. Users were included if they had ≥10 days of sensor glucose data during the month of Ramadan 2022 as well as in the month before and after. For the main analysis, continuous glucose monitoring endpoints were aggregated per month and were reported by time of day (daytime: 05.31-18.00 h,

genes

MDPI

Case Report

A Complex Intrachromosomal Rearrangement Disrupting *IRF6* in a Family with Popliteal Pterygium and Van der Woude Syndromes

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Abstract: Clefts of the lip and/or palate (CL/P) are considered the most common form of congenital anomalies occurring either in isolation or in association with other clinical features. Van der woude syndrome (VWS) is associated with about 2% of all CL/P cases and is further characterized by having lower lip pits. Popliteal pterygium syndrome (PPS) is a more severe form of VWS, normally characterized by orofacial clefts, lower lip pits, skin webbing, skeletal anomalies and syndactyly of toes and fingers. Both syndromes are inherited in an autosomal dominant manner, usually caused by heterozygous mutations in the Interferon Regulatory Factor 6 (*IRF6*) gene. Here we report the case of a two-generation family where the index presented with popliteal pterygium syndrome while both the father and sister had clinical features of van der woude syndrome, but without any point mutations detected by re-sequencing of known gene panels or microarray testing. Using whole genome sequencing (WGS) followed by local de novo assembly, we discover and validate a copy-neutral, 429 kb complex intra-chromosomal rearrangement in the long arm of chromosome 1, disrupting the *IRF6* gene. This variant is copy-neutral, novel against publicly available databases, and segregates in the family in an autosomal dominant pattern. This finding suggests that missing heritability in rare diseases may be due to complex genomic rearrangements that can be resolved by WGS and de novo assembly, helping deliver answers to patients where no genetic etiology was identified by other means.

Keywords: popliteal pterygium syndrome; 1q32; *IRF6* gene; Cleft palate; cleft lip; syndactyly; intrachromosomal rearrangements; whole-genome sequencing

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1. Introduction

Orofacial clefts (OFC), specifically, clefts of the lip and/or the palate (CL/P), are among the most common form of congenital craniofacial anomalies affecting about 1 in 500 to 1 in 2500 births depending on the population [1,2]. The majority of cleft lip and palate cases occur as a non-syndromic isolated phenotype with complex disease etiology, while about 30% of cases are syndromic occurring in association with other mendelian phenotypes [1,2]. Previous studies have shown that both genetic and environmental factors contribute to the cause of orofacial clefts making it difficult to identify the main etiology in many cases; however, it was also shown that many of the syndromic cases of CL/P were due to chromosomal abnormalities and/or monogenic causes [3].

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CELLULAR THERAPIES

TRANSFUSION

Albumin-based solution is the ideal post-thawing suspension medium for cord blood hematopoietic stem cells: A stability and proliferative evaluation

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Abstract

Background: Cryopreservation and thawing protocols represent key factors for the efficacy of cellular therapy products, such as hematopoietic stem cells (HSCs). While the HSC cryopreservation has already been standardized, the thawing procedures have been poorly studied. This study aimed to evaluate the thawing and washing protocol of cord blood (CB) derived HSCs or the HPC(CB), by selecting the optimal thawing solution and determining CD34+ cells' stability over time.

Study Design and Methods: Seven cryopreserved CB products were thawed, washed, and resuspended in three different solutions (10% Dextran40 in NaCl equally prepared with 5% human albumin; 5% human albumin in PBS/EDTA; and normal saline) and stored at 4°C (±2°C). Mononuclear cell (MNC) count, CD45+/CD34+ cell enumeration, and cell viability were tested at 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 h. The protocol with the selected solution was further validated on additional 10 CB samples. The above parameters and the colony-forming unit (CFU) assay were analyzed at time points 0, 2, 4, 6, and 8 h.

Results and Discussion: The results showed that the 5% human albumin was the most suitable thawing solution. MNCs were stable up to 4 h ($p = 0.009$), viable CD45+ cells were unstable even at 2 h ($p = 0.013$), and viable CD34+ cells were stable until 6 h ($p = 0.019$). The CFU assay proved the proliferative potential up to 8 h, although significantly decreased after 4 h ($p = 0.013$), and correlated with the viable CD34+ cell counts. We demonstrated that the post-thawed and washed HPC(CB) using 5% human albumin is stable for up to 4 h.

Abbreviations: 7AAD, 7-aminoactinomycin D; AABB, association for the advancement of blood & biotherapies; BFU-E, burst-forming unit-erythroid; BM, bone marrow; CAR-T, chimeric antigen receptor T-cells; CB, cord blood; CFU-GEMM, CFU-granulocyte-erythrocyte-monocyte-megakaryocyte; CFU-GM, CFU-granulocyte-macrophage; CPD, citrate phosphate dextrose; CTP, cell Therapy Products; CFU, colony-forming unit; DMSO, dimethyl sulfoxide; DPBS, dulbecco's phosphate-buffered saline; FITC, fluorescein isothiocyanate; HES, hydroxyethyl starch; HPC(CB), cord blood-derived HSCs; HSC, hematopoietic stem cells; LN_2, liquid nitrogen; MNC, mononuclear cell; NaCl or NS, sodium chloride or normal saline; PB, peripheral blood; PE, phycoerythrin; QC, quality control; RT, room temperature; TS, thawing solution.

Associations between HLA class II alleles and IgE sensitization to allergens in the Qatar Biobank cohort

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Background: Allergic disorders are the consequence of IgE sensitization to allergens. Population studies have shown that certain human leukocyte antigen (HLA) alleles are associated with increased or decreased risk of developing allergy.
Objective: We aimed to characterize the relationship between HLA class II allelic diversity and IgE sensitization in an understudied Arab population.
Methods: We explored associations between IgE sensitization to 7 allergen mixes and mesquite (comprising 41 food or aeroallergens) and 45 common classical HLA class II alleles in a well-defined cohort of 797 individuals representing the general adult population of Qatari nationals and long-term residents. To do so, we performed HLA calling from whole genome sequencing data at 2-field resolution using 2 independent algorithms. We then applied 3 different regression models to assess either each allergen mix independently, in the context of IgE sensitization to other allergens tested, or polysensitization.
Results: More than half (n = 447) of the study participants showed IgE sensitization to at least 1 allergen, most of them (n = 400) to aeroallergens (Phadiatop). We identified statistically significant negative and positive associations with 24 HLA class II alleles. These have been reported to confer risk or protection from variety of diseases; however, only a few have previously been associated with allergy in other populations.
Conclusions: Our study reveals several new risk and protective genetic markers for allergen-specific IgE sensitization. This is a first and essential step toward a better understanding of the origins of allergic diseases in this understudied population.
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Key words: *Allergens, association study, IgE sensitization, Qatar Biobank*

Allergic IgE sensitization is a prerequisite and first step in the development of clinical type 1 hypersensitivity/allergic disorders.[1] Such sensitization is characterized by allergen-specific IgE in the serum or plasma, or an immediate weal and flare reaction on skin prick testing that exceeds clinically defined thresholds. IgE-associated allergy affects approximately a third of the human population and comprises a spectrum of immune disorders of varying severity, including allergic rhinitis and conjunctivitis (ie, hay fever), allergic asthma, atopic dermatitis, food allergy, oral allergy syndrome, acute urticaria/angioedema, and anaphylaxis (eg, to medications, venoms).[2,3]

Despite its prevalence, the underlying pathophysiology, mechanisms, and contributing factors of IgE-associated allergy are incompletely understood.[3] At the molecular level, primary allergic sensitization is characterized by allergen exposure and human leukocyte antigen (HLA) class II–dependent presentation of allergen-derived peptides by antigen presenting cells to naive T lymphocytes, followed by loss of tolerance of these cells to otherwise benign antigens followed by their differentiation into T_H2 cells. These allergen-specific T_H2 cells then promote B-cell activation, differentiation, and class switching, resulting in the production of allergen-specific IgE.[3] Upon reexposure of sensitized individuals to the allergen, which may occur at any age, allergen binding to these IgE antibodies can then lead to more aggressive and rapid histamine-mediated responses, which underpin the clinical manifestations of an allergic response through the activation of basophils and tissue-resident mast cells.[4] While this host defence mechanism has evolved to protect against parasitic infections and venoms of arthropods, other invertebrates, or vertebrates,[5,6] in modern-day human life, seemingly maladaptive IgE-mediated immune responses to otherwise benign allergens have become more prevalent, negatively affecting human health and quality of life. A variety of factors have been postulated to explain the recent increase in prevalence of allergic diseases, including urbanization and pollution, the hygiene hypothesis, different dietary exposure/habits, altered early life feeding, and changes in the microbiome.[7]

Given the critical role of the HLA class II glycoproteins in primary allergic sensitization and the high level of genetic diversity of these genes among the human population,[8] it is not surprising that associations between certain HLA types and responsiveness toward allergens were identified even before the completion of the Human Genome Project.[9,10] Nonetheless, previous genetic association studies have predominantly been conducted in populations of European ancestry, while studies in other populations are still significantly underpowered.[11] Here, we leveraged data from 800 adults in the Qatar Biobank (QBB) cohort study. This population-based long-term study aims to collect high-quality biological samples and curated data to

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An integrated tumor, immune and microbiome atlas of colon cancer

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The lack of multi-omics cancer datasets with extensive follow-up information hinders the identification of accurate biomarkers of clinical outcome. In this cohort study, we performed comprehensive genomic analyses on fresh-frozen samples from 348 patients affected by primary colon cancer, encompassing RNA, whole-exome, deep T cell receptor and 16S bacterial rRNA gene sequencing on tumor and matched healthy colon tissue, complemented with tumor whole-genome sequencing for further microbiome characterization. A type 1 helper T cell, cytotoxic, gene expression signature, called Immunologic Constant of Rejection, captured the presence of clonally expanded, tumor-enriched T cell clones and outperformed conventional prognostic molecular biomarkers, such as the consensus molecular subtype and the microsatellite instability classifications. Quantification of genetic immunoediting, defined as a lower number of neoantigens than expected, further refined its prognostic value. We identified a microbiome signature, driven by *Ruminococcus bromii*, associated with a favorable outcome. By combining microbiome signature and Immunologic Constant of Rejection, we developed and validated a composite score (mICRoScore), which identifies a group of patients with excellent survival probability. The publicly available multi-omics dataset provides a resource for better understanding colon cancer biology that could facilitate the discovery of personalized therapeutic approaches.

Although there has been a substantial amount of research conducted on biomarkers for primary colon cancer, the current clinical guidelines in the USA and Europe (including the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines) only rely on the tumor-node-metastasis staging and the detection of DNA mismatch repair (MMR) deficiency or microsatellite instability (MSI), in addition to standard clinicopathological variables, to determine treatment recommendations[1,2]. MSI is caused by somatic or germline

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REVIEW Open Access

Maternal microbiota and gestational diabetes: impact on infant health

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Abstract

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that has been associated with an increased risk of obesity and diabetes in the offspring. Pregnancy is accompanied by tightly regulated changes in the endocrine, metabolic, immune, and microbial systems, and deviations from these changes can alter the mother's metabolism resulting in adverse pregnancy outcomes and a negative impact on the health of her infant. Maternal microbiomes are significant drivers of mother and child health outcomes, and many microbial metabolites are likely to influence the host health. This review discusses the current understanding of how the microbiota and microbial metabolites may contribute to the development of GDM and how GDM-associated changes in the maternal microbiome can affect infant's health. We also describe microbiota-based interventions that aim to improve metabolic health and outline future directions for precision medicine research in this emerging field.

Keywords Microbiome, GDM, Neonatal health, 16S rRNA

Introduction

Pregnancy is a complex process that is influenced by a variety of interconnected molecular and cellular mechanisms [1]. During pregnancy, there are many physiological changes that occur, including hormonal, immunological, microbial, and metabolic changes, which are all tightly regulated to help maintain homeostasis and ensure the delivery of a healthy infant [1, 2]. However, if these physiological changes are disrupted, various pregnancy-related complications can occur leading to negative consequences for both the mother and her baby [3]. There has been increasing interest in studying the role of microbiota in reproductive health and associated changes during pregnancy and newborn life.

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Indigenous microbial communities, also known as the microbiota, form intricate ecosystems that are uniquely adapted to the constantly fluctuating physiology of their hosts [4]. Three-quarters of an individual's microbiome can be traced back to their mother, with the infant being exposed to vaginal microbes as they pass through the birth canal [5]. Additionally, maternal oral [6], fecal [7, 8], skin [9] and placental [10] microbiota can also contribute to the seeding and colonization of the infant microbiome. Breastmilk plays a role in the maturation and nourishment of the infant microbiome after birth [11]. Microbiome imbalance (also known as dysbiosis) may affect the mother's metabolic profile, contribute to pregnancy complications, and impact neonatal health [12].

Gestational diabetes mellitus (GDM) is defined as an abnormal glucose intolerance during pregnancy [13]. It has been linked to numerous adverse maternal and neonatal outcomes, such as cesarean section delivery, preeclampsia, large birth weight, shoulder dystocia, and hypoglycemia in newborns [13]. The prevalence of GDM is increasing and it affects a significant percentage of pregnancies [13]. Research has shown that the maternal microbiome may be altered in GDM pregnancies in

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Understanding the Genetics of Early-Onset Obesity in a Cohort of Children From Qatar

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Abstract

Context

Monogenic obesity is a rare form of obesity due to pathogenic variants in genes implicated in the leptin–melanocortin signaling pathway and accounts for around 5% of severe early-onset obesity. Mutations in the genes encoding the MC4R, leptin, and leptin receptor are commonly reported in various populations to cause monogenic obesity. Determining the genetic cause has important clinical benefits as novel therapeutic interventions are now available for some forms of monogenic obesity.

Objective

To unravel the genetic causes of early-onset obesity in the population of Qatar.

Methods

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Genome Medicine

RESEARCH Open Access

Genomic architecture of autism spectrum disorder in Qatar: The BARAKA-Qatar Study

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Abstract

Background Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired social and communication skills, restricted interests, and repetitive behaviors. The prevalence of ASD among children in Qatar was recently estimated to be 1.1%, though the genetic architecture underlying ASD both in Qatar and the greater Middle East has been largely unexplored. Here, we describe the first genomic data release from the BARAKA-Qatar Study—a nationwide program building a broadly consented biorepository of individuals with ASD and their families available for sample and data sharing and multi-omics research.

Methods In this first release, we present a comprehensive analysis of whole-genome sequencing (WGS) data of the first 100 families (372 individuals), investigating the genetic architecture, including single-nucleotide variants (SNVs), copy number variants (CNVs), tandem repeat expansions (TREs), as well as mitochondrial DNA variants (mtDNA) segregating with ASD in local families.

Results Overall, we identify potentially pathogenic variants in known genes or regions in 27 out of 100 families (27%), of which 11 variants (40.7%) were classified as pathogenic or likely-pathogenic based on American College of Medical Genetics (ACMG) guidelines. Dominant variants, including de novo and inherited, contributed to 15 (55.6%) of these families, consisting of SNVs/indels (66.7%), CNVs (13.3%), TREs (13.3%), and mtDNA variants (6.7%). Moreover, homozygous variants were found in 7 families (25.9%), with a sixfold increase in homozygous burden in consanguineous versus non-consanguineous families (13.6% and 1.8%, respectively). Furthermore, 28 novel ASD candidate genes were identified in 20 families, 23 of which had recurrent hits in MSSNG and SSC cohorts.

Conclusions This study illustrates the value of ASD studies in under-represented populations and the importance of WGS as a comprehensive tool for establishing a molecular diagnosis for families with ASD. Moreover, it uncovers a significant role for recessive variation in ASD architecture in consanguineous settings and provides a unique resource of Middle Eastern genomes for future research to the global ASD community.

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biomedicines

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Review

Obesity-Associated Non-T2 Mechanisms in Obese Asthmatic Individuals

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Abstract: Obesity and asthma are two common health issues that have shown increased prevalence in recent years and have become a significant socioeconomic burden worldwide. Obesity increases asthma incidence and severity. Obese asthmatic individuals often experience increased exacerbation rates, enhanced airway remodeling, and reduced response to standard corticosteroid therapy. Recent studies indicate that obesity-associated non-T2 factors such as mechanical stress, hyperinsulinemia, systemic inflammation, adipose tissue mediators, metabolic dysregulation, microbiome dysbiosis, and high-fat-diet are responsible for increased asthma symptoms and reduced therapeutic response in obese asthmatic individuals. This manuscript reviews the recent findings highlighting the role of obesity-associated factors that contribute to airway hyper-reactivity, airway inflammation and remodeling, and immune cell dysfunction, consequently contributing to worsening asthma symptoms. Furthermore, the review also discusses the possible future therapies that might play a role in reducing asthma symptoms by diminishing the impact of obesity-associated non-T2 factors.

Keywords: obesity; asthma; hyperinsulinemia; microbiome

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1. Introduction

Asthma is one of the most prevalent non-communicable lung diseases that impact both pediatric and adult populations globally. An international study reported that approximately 300 million people worldwide are affected by asthma, with around 1000 asthma-related deaths every day [1]. Asthma is characterized by airway limitation due to a combination of pathophysiological events, including airway obstruction, hyper-reactivity, inflammation, increased mucus production, and airway remodeling [2].

The prevalence of obesity is increasing at an alarming rate worldwide. Extensive studies over the last two decades have shown that increased adiposity is linked to the risk of asthma incidence in children [3–6]. A recent meta-analysis revealed that obesity can increase the likelihood of asthma by 50% in children [7]. Another study based on the data from the Taiwan Children's Health Study informed that an increase in adiposity before the age of 6 years is linked to an enhanced risk of childhood asthma, while adiposity gain in the prepubertal stage predicts asthma in young adulthood [8]. Individuals who are obese and suffer from asthma often face a more severe manifestation of exacerbations and a diminished quality of life than their normal-weight counterparts diagnosed with asthma [9]. This disparity is further highlighted by obese asthmatic patients' reduced responsiveness to conventional asthma treatments. Such limited effectiveness not only undermines these individuals' wellbeing and health prospects but also imposes an additional societal burden. This situation underscores the imperative for tailored, effective intervention strategies for obese individuals with asthma, ensuring improved and equitable health outcomes for all asthma patients [9,10].

metabolites

MDPI

Protocol

Sphingolipids in Childhood Asthma and Obesity (SOAP Study): A Protocol of a Cross-Sectional Study

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Abstract: Asthma and obesity are two of the most common chronic conditions in children and adolescents. There is increasing evidence that sphingolipid metabolism is altered in childhood asthma and is linked to airway hyperreactivity. Dysregulated sphingolipid metabolism is also reported in obesity. However, the functional link between sphingolipid metabolism, asthma, and obesity is not completely understood. This paper describes the protocol of an ongoing study on sphingolipids that aims to examine the pathophysiology of sphingolipids in childhood asthma and obesity. In addition, this study aims to explore the novel biomarkers through a comprehensive multi-omics approach including genomics, genome-wide DNA methylation, RNA-Seq, microRNA (miRNA) profiling, lipidomics, metabolomics, and cytokine profiling. This is a cross-sectional study aiming to recruit 440 children from different groups: children with asthma and normal weight (n = 100), asthma with overweight or obesity (n = 100), overweight or obesity (n = 100), normal weight (n = 70), and siblings of asthmatic children with normal weight, overweight, or obesity (n = 70). These participants will be recruited from the pediatric pulmonology, pediatric endocrinology, and general pediatric outpatient clinics at Sidra Medicine, Doha, Qatar. Information will be obtained from self-reported questionnaires on asthma, quality of life, food frequency (FFQ), and a 3-day food diary that are completed by the children and their parents. Clinical measurements will include anthropometry, blood pressure, biochemistry, bioelectrical impedance, and pulmonary function tests. Blood samples will be obtained for sphingolipid analysis, serine palmitoyltransferase (SPT) assay, whole-genome sequencing (WGS), genome-wide DNA methylation study, RNA-Seq, miRNA profiling, metabolomics, lipidomics, and cytokine analysis. Group comparisons of continuous outcome variables will be carried out by a one-way analysis of variance or the Kruskal–Wallis test using an appropriate pairwise multiple comparison test. The chi-squared test or a Fisher's exact test will be used to test the associations between categorical variables. Finally, multivariate analysis will be carried out to integrate the clinical data with multi-omics data. This study will help us to understand the role of dysregulated sphingolipid metabolism in obesity and asthma. In addition, the multi-omics data from the study

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Article

Functional Characterization of Novel *MC4R* Variants Identified in Two Unrelated Patients with Morbid Obesity in Qatar

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Abstract: The leptin–melanocortin pathway is pivotal in appetite and energy homeostasis. Pathogenic variants in genes involved in this pathway lead to severe early-onset monogenic obesity (MO). The *MC4R* gene plays a central role in leptin–melanocortin signaling, and heterozygous variants in this gene are the most common cause of MO. A targeted gene panel consisting of 52 obesity-related genes was used to screen for variants associated with obesity. Variants were analyzed and filtered to identify potential disease-causing activity and validated using Sanger sequencing. We identified two novel heterozygous variants, c.253A>G p.Ser85Gly and c.802T>C p.Tyr268His, in the *MC4R* gene in two unrelated patients with morbid obesity and evaluated the functional impact of these variants. The impact of the variants on the *MC4R* gene was assessed using in silico prediction tools and molecular dynamics simulation. To further study the pathogenicity of the identified variants, GT1-7 cells were transfected with plasmid DNA encoding either wild-type or mutant *MC4R* variants. The effects of allelic variations in the *MC4R* gene on cAMP synthesis, *MC4R* protein level, and activation of PKA, ERB, and CREB signaling pathways in both stimulated and unstimulated α-MSH paradigms were determined for their functional implications. In silico analysis suggested that the variants destabilized the *MC4R* structure and affected the overall dynamics of the *MC4R* protein, possibly leading to intracellular receptor retention. In vitro analysis of the functional impact of these variants showed a significant reduction in cell surface receptor expression and impaired extracellular ligand binding activity, leading to reduced cAMP production. Our analysis shows that the variants do not affect total protein expression; however, they are predicted to affect the post-translational localization of the *MC4R* protein to the cell surface and impair downstream signaling cascades such as PKA, ERK, and CREB signaling pathways. This finding might help our patients to benefit from the novel therapeutic advances for monogenic forms of obesity.

Keywords: *MC4R*; monogenic obesity; severe obesity; childhood obesity; Qatar

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1. Introduction

Obesity is a complex condition caused by genetic, lifestyle, and environmental factors, which has become a significant health problem worldwide [1]. Monogenic obesity due to single-gene pathogenic variants in the leptin–melanocortin pathway, an essential energy homeostasis pathway, accounts for 6% of the total cases of severe early-onset obesity [2]. The melanocortin-4 receptor (*MC4R*) gene is a crucial component in this pathway and is

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Validation of plasma protein glycation and oxidation biomarkers for the diagnosis of autism

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Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder in children. It is currently diagnosed by behaviour-based assessments made by observation and interview. In 2018 we reported a discovery study of a blood biomarker diagnostic test for ASD based on a combination of four plasma protein glycation and oxidation adducts. The test had 88% accuracy in children 5–12 years old. Herein, we present an international multicenter clinical validation study ($N = 478$) with application of similar biomarkers to a wider age range of 1.5–12 years old children. Three hundred and eleven children with ASD (247 male, 64 female; age 5.2 ± 3.0 years) and 167 children with typical development (94 male, 73 female; 4.9 ± 2.4 years) were recruited for this study at Sidra Medicine and Hamad Medical Corporation hospitals, Qatar, and Hospital Regional Universitario de Málaga, Spain. For subjects 5–12 years old, the diagnostic algorithm with features, advanced glycation endproducts (AGEs)—N^{ϵ}-carboxymethyl-lysine (CML), N^{ω}-carboxymethylarginine (CMA) and 3-deoxyglucosone-derived hydroimidazolone (3DG-H), and oxidative damage marker, *o,o'*-dityrosine (DT), age and gender had accuracy 83% (CI 79 – 89%), sensitivity 94% (CI 90–98%), specificity 67% (CI 57–76%) and area-under-the-curve of receiver operating characteristic plot (AUROC) 0.87 (CI 0.84–0.90). Inclusion of additional plasma protein glycation and oxidation adducts increased the specificity to 74%. An algorithm with 12 plasma protein glycation and oxidation adduct features was optimum for children of 1.5–12 years old: accuracy 74% (CI 70–79%), sensitivity 75% (CI 63–87%), specificity 74% (CI 58–90%) and AUROC 0.79 (CI 0.74–0.84). We conclude that ASD diagnosis may be supported using an algorithm with features of plasma protein CML, CMA, 3DG-H and DT in 5–12 years-old children, and an algorithm with additional features applicable for ASD screening in younger children. ASD severity, as assessed by ADOS-2 score, correlated positively with plasma protein glycation adducts derived from methylglyoxal, hydroimidazolone MG-H1 and N^{ϵ}(1-carboxyethyl)lysine (CEL). The successful validation herein may indicate that the algorithm modifiable features are mechanistic risk markers linking ASD to increased lipid peroxidation, neuronal plasticity and proteotoxic stress.

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INTRODUCTION

Autism Spectrum Disorders (ASD) is a prenatal disorder which originates in the first trimester of pregnancy and affects 78 million people worldwide [1, 2]. It has high heritability [3], which may reflect genetic vulnerability to shared environmental exposures [4]. Major concerns for subjects with suspected ASD, their parents, and carers are timely access to clinical diagnosis. Guidelines for diagnosis of ASD recommend involvement of a multidisciplinary team of child and adolescent psychiatrists, child neurologists, developmental-behavioural paediatricians, or child psychologists. ASD diagnosis is based on assessments in structured observations, interviews and examinations, medical/developmental review, and assessment instruments. It is currently standardized to the Diagnostic and Statistical Manual of Mental Disorders-5 criteria (DSM-5) with recommended duration of the diagnostic procedure of 3–6 months [5]. Due to a global shortage of specialists trained to assess suspected children using these established criteria, and the growing prevalence of the condition, diagnosis is often preceded by a long delay, in some cases greater than one year, from first referral to expert team evaluation [2].

There is an unmet clinical need for diagnostic techniques based on biomarkers which corroborate well with diagnosis of ASD by experts in child development [2]. The consensus report by the American Psychiatric Association (APA) Work Group on Neuroimaging Markers of Psychiatric Disorders proposed that a promising biomarker-based test for diagnosis of ASD should meet threshold classification criteria of at least 80% specificity and sensitivity [6]. A recent systematic review found no biomarker for diagnosis of ASD meeting these criteria with evidence from two or more independent studies in agreement [7].

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