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Journal Summary

Advances and challenges in pediatric care: Insights from diverse clinical perspectives

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1. Reassessing febrile seizures: Long-term neurological and psychiatric implications

Source**:** Wang DS, Chung CH, Hsu WF, Chen SJ, Chu DM, Chien WC, Tzeng NS, & Fan HC. (2024). Higher risk of psychiatric disorders in children with febrile seizures: A nationwide cohort study in Taiwan. *Pediatric Neurology*, 154, 26–35. https://doi.org/10.1016/j.pediatrneurol.2024.02.005

Febrile seizures are a prevalent occurrence amongst children aged 6 months–6 years, as evidenced by previous research, such as a Danish study demonstrating a positive correlation between febrile seizures and the overall incidence of psychiatric disorders. In recent years, evolving perspectives on febrile seizures have challenged the notion of their benign prognosis. In this population-based observational study conducted in Taiwan, researchers sought to delve deeper into this association and identify associated risk factors.

Utilising data from the comprehensive Taiwan National Health Insurance Research Database spanning a 15-year period from 2000 to 2015, which covers over 99% of the population, the researchers analysed records of approximately 1,936,512 individuals, accounting for roughly 10% of Taiwan's populace. Following stringent exclusion criteria, the study included 2,464 children diagnosed with febrile seizures as cases, alongside 7,392 controls.

Febrile seizures were examined as the primary exposure, with psychiatric disorders serving as the main outcomes of interest. The retrospective cohort study, encompassing nearly two million children, revealed a noteworthy finding: Children with febrile seizures faced a substantially heightened risk, 4.7 times higher, of developing psychiatric disorders compared to their counterparts without such seizures.

These psychiatric disorders encompassed a spectrum of conditions, including anxiety, depression, bipolar disorder, sleep disorders, substance-related disorders, psychotic disorders, and organic mental disorders, underscoring the breadth of the impact. Of particular significance were comorbidities such as attention-deficit/hyperactivity disorder (ADHD) and intellectual disability, which were identified as significant contributors to psychiatric morbidity amongst children with febrile seizures.

Furthermore, the study highlighted a nuanced risk profile, indicating that children with febrile seizures, particularly those with underlying ADHD, exhibited heightened susceptibility to specific psychiatric morbidities, notably anxiety.

The implications of these findings are profound, emphasising the critical role of vigilance amongst various stakeholders, including parents, clinicians, nurses, and educators, in early detection and intervention. Specifically, the study underscores the importance of considering psychiatric

symptoms in children with febrile seizures and the potential benefits of early referral for appropriate management and support.

2. The retinoid hypothesis: A two-decade review of congenital diaphragmatic hernia

Source: Rivas JF, & Clugston RD. (2024). The aetiology of congenital diaphragmatic hernia: The retinoid hypothesis 20 years later. *Pediatr Res*, 95, 912–921. https://doi.org/10.1038/s41390-023-02905-7

Congenital diaphragmatic hernia (CDH) poses a significant threat to neonatal health, affecting approximately 2–3 in 10,000 births with considerable mortality and long-term morbidity amongst survivors. Despite its clinical significance, the underlying mechanisms of CDH remain elusive. In 2003, Greer *et al*. introduced the retinoid hypothesis, suggesting that aberrant retinoid signalling contributes to abnormal diaphragm development in CDH. Twenty years later, the authors meticulously review the literature, spanning both animal models and human studies, to provide a thorough evaluation of the hypothesis's validity and implications.

CDH presents a complex clinical picture, ranging from isolated defects to more intricate manifestations, such as Bochdalek hernias and Morgagni hernias. Genetic and environmental factors play pivotal roles in CDH aetiology, with up to 40% of cases linked to identifiable genetic causes and various environmental risk factors implicated in disease development.

The retinoid hypothesis posits retinoic acid (RA) signalling disturbances during early gestation as crucial contributors to CDH pathogenesis. RA, a metabolite of dietary Vitamin A, exerts potent developmental regulatory effects, forming the cornerstone of this hypothesis. Since its inception, the retinoid hypothesis has guided significant research efforts, with findings from animal models and human studies providing substantial support.

Over the past two decades, numerous studies have reinforced the association between RA signalling and CDH formation, consolidating the evidence base for the retinoid hypothesis. By synthesising decades of research findings, this review underscores the enduring relevance and significance of the retinoid hypothesis in elucidating the molecular mechanisms underlying CDH development. Furthermore, it highlights the crucial role of RA signalling in diaphragm morphogenesis, offering valuable insights for future investigative endeavours and therapeutic interventions aimed at improving outcomes for affected individuals.

3. Does prednisolone impact recovery in paediatric Bell's palsy? A critical follow-up inquiry

Source: Babl FE, Herd D, Borland ML, Kochar A, Lawton B, Hort J, West A, George S, Oakley E, Wilson CL, Hopper SM, Cheek JA, Hearps S, Mackay MT, Dalziel SR, & Lee KJ. (2024). Facial function in bell palsy in a cohort of children randomised to prednisolone or placebo 12 months after diagnosis. *Pediatric Neurology*, 153, 44–47. https://doi.org/10.1016/j.pediatrneurol.2024.01.011

Inadequate data exists regarding the medium-term recovery of paediatric patients afflicted with Bell palsy or acute idiopathic lower motor neuron facial paralysis. This investigation embarked on a 12-month follow-up study encompassing children aged 6 months–under 18 years, subsequent to their involvement in a randomised trial exploring the effectiveness of prednisolone. Evaluation of facial function employed both the clinician-administered House-Brackmann scale and its modified parent-administered counterpart.

A cohort of 187 children underwent randomisation, with 93 assigned prednisolone and 94 allocated a placebo. At the 6-month juncture, recovery of facial function, as adjudged by the clinician-administered scale, was apparent in 98% (78 out of 80) of the prednisolone cohort and 93% (76 out of 82) of the placebo group. Concurrently, using the modified parent-administered scale, recovery rates stood at 94% (75 out of 80) versus 89% (72 out of 81) at 6 months and 96% (75 out of 78) versus 92% (73 out of 79) at 12 months.

Despite the majority of participants experiencing complete facial function recovery within 6 months, a subset of children exhibited incomplete recovery at the 12-month interval, irrespective of prednisolone administration. These findings underscore the variability in outcomes and underscore the significance of prolonged monitoring in this patient demographic.

4. Does neonatal phototherapy heighten cancer risk in children?

Source: Kuitunen I, Nikkilä A, Kiviranta P, Jääskeläinen J, & Auvinen A. (2024). Risk of childhood neoplasms related to neonatal phototherapy – A systematic review and meta-analysis. *Pediatric Research*, 10.1038/s41390-024-03191-7. Advance online publication. https://doi.org/10.1038/s41390-024-03191-7

According to this systematic review and meta-analysis, children with a history of neonatal phototherapy face a 1.2-–1.6-fold elevated risk of hematopoietic cancers and solid tumours. However, several considerations emerge when interpreting these findings, including limitations in the reporting quality of the primary studies, potential causal pathways and confounding factors.

Some studies suggest that the heightened cancer risk may stem, at least in part, from hyperbilirubinemia rather than phototherapy, a phenomenon known as confounding by indication. This speculation aligns with evidence indicating that cancer incidence amongst children with hyperbilirubinemia, but without phototherapy, falls between

the rates observed in children without hyperbilirubinemia and those subjected to phototherapy.

Initially intending to analyse cancer risk by phototherapy duration and intensity, the researchers found scant reporting on phototherapy duration across most studies. Prematurity, a factor linked to both phototherapy and cancer risk, further complicates the analysis. Notably, while prematurity did not correlate with cancer incidence amongst treated and non-treated premature infants, full-term infants subjected to phototherapy exhibited a slightly elevated risk of hematopoietic cancers.

Comparing their findings to prior meta-analyses, the researchers noted similarities alongside key disparities and concerns. Unlike earlier studies that pooled case-control and cohort data, this review refrained from doing so, thus mitigating heterogeneity in reporting. In addition, while previous analyses lacked sensitivity assessments, this review conducted a more comprehensive evaluation.

Despite its strengths, including adherence to a pre-registered protocol and meticulous analysis, this review is constrained by the limitations of its constituent studies. Many studies exhibited a high risk of bias due to inadequate adjustment for potential confounders. Moreover, the inability to assess mortality or exposure-outcome gradients, coupled with variations in phototherapy practices and incomplete covariate adjustment, underscores the need for further research.

In light of these findings, caution should guide clinical practice. Although neonatal phototherapy appears associated with increased cancer risk, current evidence does not warrant changes in its use. Nonetheless, adherence to guidelines and judicious use of phototherapy are essential to mitigate potential harm. Moving forward, rigorous studies are imperative to deepen our understanding of the relationship between phototherapy and neoplasia and unravel potential causal pathways.

5. Does inhaled salbutamol improve outcomes in preterm infants with chronic lung disease?

Source: Ng G, Bruschettini M, Ibrahim J, & Da Silva O. (2024). Inhaled bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. *The Cochrane Database of Systematic Reviews*, 4(4), CD003214. https://doi.org/10.1002/14651858.CD003214.pub4

Chronic lung disease (CLD) is common amongst preterm infants and is linked to respiratory morbidity. Bronchodilators are often used to alleviate muscle hypertrophy in small airways, potentially improving compliance and reducing airway resistance. Despite their widespread use, it is uncertain whether they lead to better clinical outcomes. This updated Cochrane review aims to evaluate the impact of inhaled bronchodilators on mortality and other complications in preterm infants at risk for or diagnosed with CLD.

Two randomised controlled trials were included in this review, with one providing usable outcome data. The trial, conducted in six neonatal intensive care units, involved 173 infants with a gestational age of <31 weeks. The intervention group received salbutamol for CLD prevention.

The evidence suggests that salbutamol may not significantly affect mortality or CLD at 28 days compared to placebo. However, certainty regarding these outcomes is low due to limited data. The effect of salbutamol on pneumothorax remains uncertain, with no significant differences reported between groups.

No trials evaluated bronchodilator therapy for CLD treatment, highlighting a gap in current research. Future trials should consider including relevant clinical outcomes beyond pulmonary mechanics to better assess the efficacy and safety of bronchodilator agents in preterm infants.

6. Are post-natal corticosteroids safe and effective for preventing bronchopulmonary dysplasia in preterm infants?

Source: Van de Loo M, Van Kaam A, Offringa M, Doyle LW, Cooper C, & Onland W. (2024). Corticosteroids for the prevention and treatment of bronchopulmonary dysplasia: An overview of systematic reviews. The Cochrane Database of Systematic Reviews, 4(4), CD013271. https://doi.org/10.1002/14651858.CD013271.pub2

This Cochrane review delves into the persistent challenge of bronchopulmonary dysplasia (BPD) in pre-mature infants, exploring the potential of post-natal corticosteroid therapy as a solution. Through a meticulous examination of nine systematic reviews, which encompassed a substantial body of evidence comprising 87 randomised controlled trials and involving 9419 preterm infants, the researchers aimed to ascertain both the efficacy and safety of postnatal corticosteroids in this vulnerable population.

The findings offer insights into the nuanced effects of various corticosteroid regimens. Early initiation of systemic dexamethasone or hydrocortisone emerges as a promising intervention, demonstrating a potential reduction in the combined outcome of death or BPD at 36 weeks' post-menstrual age. However, this potential benefit is juxtaposed with notable adverse effects such as cerebral palsy or gastrointestinal perforation, underscoring the need for cautious consideration.

Moreover, late initiation of systemic dexamethasone presents another avenue for intervention, showing efficacy in reducing the risk of death or BPD. Despite its potential benefits, this approach also carries inherent risks, albeit to a lesser extent compared to early initiation.

Inhaled corticosteroids, particularly when initiated early, demonstrate favourable outcomes without apparent adverse

effects, highlighting their potential as a safer alternative. However, further investigation is warranted to elucidate their efficacy in late initiation scenarios.

An intriguing finding emerges regarding endotracheal instillation of corticosteroids with surfactant, showing promise in reducing the risk of death or BPD without evident adverse effects. This novel approach holds potential for clinical application pending further validation through ongoing large-scale trials.

However, amidst these promising findings, the study underscores the need for cautious interpretation and further research, particularly regarding the long-term effects and optimal timing of corticosteroid administration. This nuanced understanding is essential for guiding clinical practice effectively and ensuring the optimal care of preterm infants at risk of BPD.

7. Are there unexplored links between congenital anomalies?

Source: Morris JK, Bergman JE, Barisic I, Wellesley D, Tucker D, Limb E, Addor MC, Cavero-Carbonell C, Dias CM, Draper ES, Echevarría-González-de-Garibay LJ, Gatt M, Klungsøyr K, Lelong N, Luyt K, Materna-Kiryluk A, Nelen V, Neville A, Perthus I, Pierini A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Rouget R, Sayers G, Wertelecki W, Kinsner-Ovaskainen A, & Garne E. (2024). Surveillance of multiple congenital anomalies; searching for new associations. Eur J Hum Genet, 32, 407–412. https://doi.org/10.1038/s41431-023-01502-w

This study scrutinised 1386 unique combinations of dual anomalies co-occurring in individual cases, revealing 31 significant associations, with 20 previously established and 11 novel associations. Amongst these, six pairs of anomalies emerged as new associations, distinct from any known associations or sequences, warranting ongoing surveillance within the EUROCAT framework for potential clustering and trends.

Known associations, delineated based on published literature, included ten pairs associated with limb body wall complex, OEIS complex or VACTERL association. For instance, the association between neural tube defects and omphalocele elucidated three anomaly pairs. In addition, the link between diaphragmatic hernia and pulmonary hypertension explained another pair. Less recognised associations, albeit documented, constituted the remaining three pairs.

Amongst the novel associations, three pairs overlapped, such as severe Congenital heart disease (CHD), Tetralogy of Fallot and common Atrio-ventricular (AV) canal with duodenal atresia, suggesting a potential genetic basis. Notably, the association between encephalocele and an/microphthalmos was scarcely documented in the literature, similar to an/microphthalmos and cleft lip. The association of hydrocephaly and hypoplastic right heart syndrome, predominantly in males with associated renal/genital anomalies, was identified in a few publications, hinting at possible genetic implications or inclusion within VACTERL. Continued surveillance is imperative to monitor these new associations.

Comparable methodologies, such as the co-occurring defect analysis approach, have been employed in prior studies to unveil new associations. However, this study exclusively focused on cases with at least two anomalies, without adjusting for clustering tendencies observed in isolated anomalies. Moreover, the analysis excluded cases with known chromosome or genetic anomalies to spotlight potential novel anomaly clusters rather than reiterating known associations.

The study's strength lies in its extensive EUROCAT dataset, encompassing 32 congenital anomaly registries and over 6.5 million births. Standardised coding methods and stringent data quality monitoring enhance the reliability of findings. Nonetheless, limited access to detailed genetic information for all cases poses a notable limitation.

In essence, while most identified associations corroborate existing literature, the discovery of six new associations underscores the need for continued surveillance, highlighting the evolving landscape of congenital anomalies warranting ongoing investigation within the EUROCAT surveillance system.

8. Navigating uncertainty: Rare disease diagnosis through newborn screening

Source: Raspa M, Kutsa O, Andrews SM, Gwaltney AY, Mallonee E, Creamer A, Han PK, & Biesecker BB. (2024). Uncertainties experienced by parents of children diagnosed with severe combined immunodeficiency through newborn screening. Eur J Hum Genet, 32, 392–398. https://doi.org/10.1038/s41431-023-01345-5

This study sheds light on the uncertainties faced by parents when their child receives a diagnosis through newborn screening. Despite early identification of their child's condition, parents of infants with severe combined immunodeficiency (SCID) encountered various uncertainties about the future. The study findings resonate with prior research on uncertainty in pre-natal or newborn screening diagnoses. For example, parents of infants diagnosed prenatally with congenital heart disease expressed immediate uncertainties post-diagnosis and longer-term uncertainties about prognosis. Similarly, parents of infants screening positive for cystic fibrosis with inconclusive diagnoses also reported uncertainty. In addition, parents of infants identified with Pompe disease through newborn screening faced uncertainties about symptom onset and treatment initiation.

Contrary to expectations from diagnostic odyssey literature, a pre-symptomatic diagnosis through newborn screening did not alleviate uncertainty for parents of children with rare disorders. Instead, uncertainties persisted regarding treatment decisions, outcomes and the long-term course of their child's condition.

A key finding of this study was the dynamic yet persistent nature of uncertainties experienced by parents of children with SCID across their journey. Certain uncertainties were more pronounced at specific stages, whereas others persisted throughout multiple phases. Scientific uncertainties, particularly related to diagnosis and treatment, were prevalent early in the SCID journey, while prognostic uncertainties emerged later, in the post-treatment phase. Personal and practical uncertainties, including logistical, financial and relational aspects, were prominent in the pre-treatment and new normal stages. Existential uncertainties were frequently reported early on but resurfaced in the new normal stage and could persist throughout the child's life. Similar patterns of evolving uncertainty have been observed in other chronic conditions, underscoring the importance of ongoing support for parents throughout their journey.

Parents in this study expressed a range of negative emotional responses to uncertainty, including anxiety, worry, fear, guilt and grief. Managing uncertainty for parents of children with rare genetic conditions such as SCID is a complex process that may culminate in adaptation and acceptance. Hope, optimism, psychosocial support and the provision of information by healthcare providers are vital factors in coping with uncertainty. While this study provides valuable insights, it has limitations. The researchers utilised a convenience sample of predominantly English-speaking mothers recruited through patient advocacy groups, limiting the generalisability of its findings. In addition, the diverse geographic locations and treatment options of participants may have influenced their experiences with uncertainty. Finally, their semi-structured interview approach may have overlooked certain subtypes of uncertainties experienced by parents.

In conclusion, this study underscores the chronic and multifaceted nature of uncertainties in the SCID journey and emphasises the importance of preparing parents for this journey by addressing and assisting them in coping with uncertainty. Healthcare providers, including genetic counsellors, immunologists and transplant specialists, play a pivotal role in supporting parents and providing both informational and emotional support. Leveraging external resources and intrinsic coping mechanisms will aid parents in navigating the road ahead and fostering positive adaptation.

Ethical approval

The Institutional Review Board has waived the ethical approval for this study.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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