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MITOCHONDRIAL ENCEPHALOMYOPATHY LACTIC ACIDOSIS AND STROKE-LIKE EPISODES (MELAS) SYNDROME: THE HIGHLY VARIABLE DIAGNOSTIC JOURNEY

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Background Introduction: Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS) syndrome is a rare mitochondrial disorder with neurological manifestations. It is most commonly caused by the m.3243A>G mutation in the mitochondrial gene *MT-TL1*. Patients typically present between two and 20 years-of-age with epilepsy, recurrent headaches, vomiting, hearing/visual impairment and stroke-like episodes.

Objectives We present a case series demonstrating the clinical heterogeneity of MELAS syndrome in children.

Results Case 1 – A 15-year-old male presented with a five-day history of headache and one-day history of vomiting. He had coordination difficulties, short stature, hearing impairment and renal disease. During admission his headaches worsened, and he had episodes of unilateral vision loss and eye deviation with head tilt. Magnetic resonance imaging (MRI) showed bilateral acute infarcts involving parieto-occipital cortices; electroencephalogram (EEG) showed subclinical focal seizures. Mitochondrial genetic sequencing of blood DNA detected m.3243A>G at 58% heteroplasmy.

Case 2 – An eight-year-old female presented with headache, vomiting and focal seizures that responded to intravenous (IV) lorazepam. Convalescent plasma lactate was 2.9mmol/L. MRI showed acute infarct within the medial aspect of the right occipital cortex. Whole genome sequencing (WGS) (reporting threshold 15%) returned no abnormalities. Mitochondrial DNA sequencing from blood, urine and skeletal muscle samples detected a novel *MT-ND1* variant (m.3955G>C) at 13% heteroplasmy in the blood, 46% in urine and 82% in muscle. Significant isolated complex I deficiency was detected on muscle immunohistochemistry.

Case 3 – A 14-year-old female was identified as carrying m.3243A>G (unknown heteroplasmy level) following m.3243A>G identification in her maternal grandmother who presented aged 30 years with diabetes, muscle weakness and hearing/vision loss. She has a six-month history of severe headaches associated with vomiting and preceded by visual disturbances with normal brain MRI.

Case 4 – A six-year-old male, the child of an assisted pregnancy with donor sperm, presented with encephalopathy and seizures. MRI brain showed areas of T2 hyperintensity with subcortical involvement consistent with infarction. Thiamine, riboflavin and coenzyme Q10 were administered. He had a further episode while abroad and was hospitalised, repatriated and died. The m.3252A>G variant was detected at high levels in blood and muscle post-mortem.

Case 5 – A six-year-old female presented with proximal myopathy and lactic acidosis, neurodevelopmental delay, epilepsy and vision loss, and m.3243A>G was detected in the blood. Age 15 years she developed recurrent intestinal pseudo-obstruction and underwent emergency laparotomy and jejunostomy refashioning but deteriorated post-operatively with suspected bowel perforation and intra-abdominal sepsis requiring adhesiolysis and terminal loop ileostomy formation. Post-operatively, brain MRI showed severe generalised cerebral volume loss, secondary to multiple infarcts. She developed multi-organ failure, cardiovascular shock and severe lactic acidosis, and died.

Conclusions Discussion: MELAS syndrome should be considered in children presenting with a range of neurological symptoms. Mitochondrial heteroplasmy and random mitotic segregation contribute to phenotypic variation. Acute encephalopathy with seizures and/or systemic signs should warrant MRI and plasma/CSF lactate analysis. Although precision therapy is lacking, diagnosis through DNA sequencing of various tissue samples improves management, enables cascade screening, and informs family planning decisions of female carriers.

Young People's Health Special Interest Group

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VALPROATE USE IN EPILEPSY: SHOULD OUR DECISION-MAKING BE DIFFERENT FOR ADOLESCENTS?

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Background Sodium valproate is the most effective drug for treating genetic generalised epilepsies. However, MHRA guidance states that 'Valproate should not be used in girls and women of childbearing potential unless other treatments are ineffective or not tolerated' due to teratogenic effects and association with polycystic ovary syndrome. Some of these women and girls will have an idiopathic generalised epilepsy, which will only be well controlled by valproate. They may experience prolonged periods of poor seizure control while being treated with other drugs. Adolescence is a critically sensitive period of biological, social-emotional and cognitive development. Adolescents have different goals and priorities compared to adults. They identify more closely with, and increasingly value the opinions and evaluations of their peers than during other stages of life. Adolescents are hypersensitive to social exclusion and this has been linked with poorer mental health outcomes into adulthood.

Objectives

- Review the current literature around the use of valproate in women and girls
- Review the literature on quality of life (QOL) and mental health (MH) in adolescents and the impact of poor seizure control on this
- Consider the psychosocial impact of delaying or withholding valproate as a treatment option in this population

- Consider models of care which may safely enable shared decision-making in this population

Methods Review of literature with a focus on:

- Literature search of PubMed database focused on the effect of poor seizure control in adolescence on QOL and MH
- Adolescent psychological development, behaviour and goals and how they may impact decision-making in this population
- Strategies to support shared decision-making with high-risk treatments

Results Evidence demonstrates an association between poor seizure control in adolescence and adverse outcomes in MH and QOL.

Uncontrolled seizures cause higher perception of stigma and increase restrictions on participation. They further worsen social exclusion for adolescents.

Evidence suggests the risk of social exclusion by peers outweighs long-term health considerations in adolescence. There is evidence to suggest that adolescents' own confidence in their ability to manage their epilepsy has a role to play in mental health resilience.

Close regulation of isotretinoin in dermatology demonstrates that highly teratogenic drugs can be used safely and effectively in this age group.

Conclusions Women and girls are missing out on optimal treatment of genetic generalised epilepsies due to concerns about potential adverse effects.

The current guidance may place disproportionate emphasis on the risk to a potential unborn child, without due consideration to the impact of poorly controlled seizures on an adolescent girl's psychological and social development. Clinical decision-making currently overlooks factors which are important to adolescents and does not prioritise shared decision-making between adolescent girls and their clinicians. Evidence from developmental psychology, neuroscience and social medicine challenges our current decision-making paradigm.

Restricting access to a medication on the basis of sex without an equally effective substitute is unethical. Clinicians have an obligation to ensure that high quality and effective services are in place to enable women and girls to access valproate safely. Other specialties demonstrate that high-risk medications can be used safely in a well-designed service with informed consent.

British Association of General Paediatrics

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A REGIONAL MULTIDISCIPLINARY TEAM APPROACH FROM THE GENERAL PAEDIATRIC PERSPECTIVE, IN A TERTIARY CENTRE FOR SUSPECTED PIMS-TS

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Background Alder Hey Children's Hospital (AHCH) in North-west England provides regional specialist services and local general paediatric care. Paediatric multisystem inflammatory syndrome temporally associated with Covid-19 (PIMS-TS) is a new disease entity requiring paediatricians from District General Hospitals (DGHs) to seek advice from a number of specialists. During the first/second peak of the pandemic, patients with suspected PIMS-TS were transferred to AHCH under general paediatricians with subspecialist input.

To optimise patient care, during the 3rd peak of the pandemic (January 2021) an efficient virtual multidisciplinary team (MDT) consisting of rheumatology, cardiology, infectious disease and general paediatrics, was created to facilitate discussion of potential PIMS-TS cases. The MDT aimed to coordinate management of patients requiring specialist input, reduce unnecessary transfers whilst ensuring appropriate case management and utilisation of resources.

Daily (including weekends) virtual meetings were held to discuss all active referrals including the patient's lead clinician, with the option of discussion on consecutive days until clinical improvement.

Objectives To analyse the cohort discussed at the MDT (January-March 2021), including demographics, outcomes, and need for transfer to AHCH.

Methods An online referral form using Microsoft SharePoint was distributed to regional DGHs for completion prior to the MDT. Discussion was documented on a database and outcome uploaded to AHCH patient records. These records were reviewed for this study.

Results 35 patients were referred over the 6 week study period. 14 (44%) were female. 21 referrals came from DGHs (66%), the remainder were internal. Age range was 4 months to 17 years; 9.3% <1year, 25% 2–5 years, 40.6% 6–11 years and 25% 12–17 years. At time of discussion, six had a positive covid-19 PCR test and 13 had a confirmed positive household/family contact. PIMS-TS was diagnosed in 7(20%) patients, three of whom were referred from DGHs. One required transfer to AHCH for inotropic support and one for echocardiogram. Two additional transfers to AHCH for surgical opinions were subsequently referred to the MDT. Of the remaining 25 patients (18 from DGHs), four were treated locally for Kawasaki's disease. 19 of 21 (90.5%) DGH referrals to the MDT (majority without PIMS-TS) avoided unnecessary transfer to AHCH for assessment.

Conclusions The daily virtual MDT allowed efficient discussion with exchange of expertise and a collaborative approach from several specialties for suspected PIMS-TS cases across the region. It also enabled continuity across multiple discussions about individual cases. It provided the opportunity to discuss differentials in a new disease entity, empower DGH clinicians to start early treatment of PIMS-TS and recruit where appropriate to the RECOVERY trial. Unnecessary transfers were avoided in 90.5% of external cases. General paediatricians are key valued team members as the spectrum of disease and possible differential is wide. This MDT approach promoted the role of the general paediatrician in caring for these patients. Early treatment with a lower threshold to react and escalate has improved patient care. The use of better IT infrastructure helped bridge the gap of care delivery by geography. Feedback from DGH participants in the MDT was positive.