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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