Leigh syndrome mimicking Neuromyelitis Optica Spectrum Disorder (NMOSD)

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Abstract:

We report two children with molecularly confirmed mitochondrial disease mimicking Neuromyelitis Optica Spectrum Disorder (NMOSD). The first patient presented at the age of 15 months with acute deterioration following a pyrexial illness with clinical features localising to the brainstem and spinal cord. The second patient presented at 5 years with acute bilateral visual loss. In both cases, MOG and AQP4 antibodies were negative. Both patients died within a year of symptoms onset from respiratory failure. Arriving at an early genetic diagnosis is important for redirection of care and avoiding potentially harmful immunosuppressant therapies.

Introduction:

Leigh syndrome and Leigh-like syndrome are infantile onset mitochondrial encephalopathies associated with bilateral symmetrical lesions in the brain typically affecting deep grey matter and brainstem. Diagnosis of primary mitochondrial disease relies on biochemical assessment of mitochondrial function and molecular genetic analyses of both nuclear and mitochondrial DNA (mtDNA). Acute neurological deterioration is thought to be related to mitochondrial dysfunction causing cellular energy failure, frequently in the context of increased metabolic demands as can occur with intercurrent illnesses[1]. Central nervous system (CNS) inflammation can be seen in some childhood neurodegenerative disease[2.] Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of a central nervous system (CNS) with immune-mediated demyelination, predominantly targeting the optic nerves and the spinal cord and treatment with immunotherapies such as steroids, during the acute episodes of neurological deterioration, may be of benefit[3].

We described two children who presented with rapid neurological deterioration at tertiary paediatric neurology centres with Leigh syndrome, mimicking signs and symptoms of NMOSD. For this case series, parental consents were gained, and medical records were reviewed.

Case 1

A previously healthy 15-month-old Eastern European girl presented with 3 days history of not being able to sit independently following a pyrexial illness. She was the first child of unrelated healthy parents. There was no significant personal or family history. On examination, she had bilateral ophthalmoplegia with left sided nystagmus. She had left sided hemiplegia, central hypotonia, truncal ataxia and swallowing difficulties. Mild developmental delay was noted; she was bottom-shuffling but not able to weight-bear on standing.

Neuroimaging demonstrated bilateral symmetric signal changes in T2-weighted imaging posterior medulla oblongata, dentate nuclei and posterior and central spinal cord **(Figure 1).** Myelin Oligodendrocyte Glycoprotein antibodies (MOG-Ab) and aquaporin-4 antibodies (AQP4-Ab) were negative. Cerebrospinal fluid (CSF) was acellular with normal protein, lactate of 2.4mmol/L and negative oligoclonal bands.

The patient continued to have compensated respiratory acidosis due to hypoventilation with fluctuating lactate levels. Muscle histopathology identified increased lipid deposition and scattered COX negative fibres, with atypical mitochondria on electron microscopy. Mitochondrial respiratory chain enzymology demonstrated low levels of complex I and IV activity. Rapid genetic analysis identified the pathogenic mitochondrial DNA (mtDNA) variant m.8344A>G in the *MTTK* gene at high levels of heteroplasmy (proportion of mutated mtDNA). *MTTK* encodes a mitochondrial tRNA, and hence the mutation impairs synthesis of the mitochondrial complex subunits encoded by the mtDNA genes. She died at 16 months of age from respiratory failure.

Case 2

A previously well 5-year-old girl of Vietnamese origin presented to an ophthalmologist with reduced visual acuity which led to further investigations. She was born following a normal pregnancy and

delivery to unrelated healthy parents. There was no significant family history. Developmentally, her gross motor skills were marginally delayed and there were concerns about poor coordination. Ophthalmological examinations revealed optic nerve pallor with ptosis. She had partial ptosis and bilateral nystagmus in both horizontal and vertical planes. She had poorly coordinated gait and unsteadiness standing on one foot.

Extensive neurological and metabolic investigations included negative MOG and AQP4-Ab. Routine blood tests and infectious screen including CSF study were normal. Nerve conduction studies and electromyography were normal. Neuroimaging showed slender optic nerves with reduced volumes, T2 signal abnormalities in the mid brain and brain stem Diffusion restriction was present in the tegmental lesions along the anterior margins. (Figure 1).

She received empirical intravenous methylprednisolone for 5 days followed by oral prednisolone. She had 3 cycles of plasma exchange. Molecular genetic analysis identified a pathogenic mutation in m.13094T>C within the MT-ND5 mitochondrial DNA (MTND5 gene encodes one of the comple-1 subunits). She had progressive clinical deterioration with ptosis, diplopia, facial diplegia, hand tremor and limb ataxia. She died within 1 year of her presenting illness with a worsening respiratory failure.

Discussion

In this case series, both our patients fulfilled the internationally recognised diagnostic criteria for NMSOD[4] but were diagnosed with mitochondrial disease associated with mutations in complex one. A key challenge is to distinguish between primary and secondary inflammation with active CNS inflammation also reported with mitochondrial dysfunction[2,3].

Both inflammatory and non-inflammatory mimics of NMOSD and other acquired demyelination syndromes (ADS) are important differential diagnoses to be aware of, particularly in paediatrics. The severity of clinical presentation, time to nadir and rate of recovery (or lack of) can be useful clues in the history. Although CSF lactate is a useful biomarker for mitochondrial disorders, normal values do not preclude the diagnosis[7]. Similarly, intrathecal oligoclonal bands can also be seen in the context of secondary inflammation in neurogenetic and neurometabolic disorders[8] and were previously reported in a patient with myelopathy and bilateral optic neuropathy secondary to autosomal recessive biotinidase deficiency[5]. Neuroimaging overlap have also been reported, in retrospective study of 119 children with primary mitochondrial disease, spinal cord involvement was reported in 33 of which 12 had longitudinally extensive transverse myelitis (LETM)[6]. Steroid responsiveness, which is normally a characteristic of ADS has been shown in patients with inherited leukodystrophies including Hypomyelination with brainstem and spinal cord involvement and leg spasticity (HSBL)[2]. In a case series of 14 patients with mitochondrial leukoencephalopathies from India, steroid responsiveness was observed in all patients during the acute attack[3].

To add to this diagnostic complexity, some patients can in fact have dual pathologies such as AQA4-Ab NMOSD in a child with Aicardi-Goutières syndrome[9] and MOG-Ab in a 24-year-old patient with Leber Hereditary Optic Neuropathy (LHON) who subsequently developed longitudinally extensive transverse myelitis[10]. In these cases, there are immunomodulation treatments available which can modify the disease course, resulting in a better prognosis. Our cases had unusual features of brainstem and spinal myelitis and initial investigations covered a wide range of neuro-metabolic and genetic investigations. Their MRI findings fulfilled diagnostic criteria for seronegative NMSOD[4] and negative antibody status added to diagnostic challenges in clinical practice. Both children had a dramatic decline in neurological status and died. Arriving to correct and early diagnosis of mitochondrial diseases is of importance for redirection of care. It would lead to avoidance of potentially harmful and unnecessary immunosuppression therapy. Early and proactive referral to

clinical geneticists and metabolic specialists and consideration of parallel planning can promote better communication with families and improved acceptance of poor prognosis.

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The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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