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Leigh Syndrome is Different from NMOSD

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LETTER TO THE EDITOR

The study by Kim, *et al*., [2023] is excellent but has limitations.

We disagree that the two patients had evidence of neuromyelitis optica spectrum disorder (NMOSD). Arguments against NMOSD are that the disease was progressive, patient-1 was unresponsive to steroids, there was no enhancement of cerebral or spinal lesions, the lesions in patient-1 were symmetric, both patients had supratentorial lesions, both patients had lactic acidosis, patient-2 had no spinal cord involvement, both had developmental delay, and specific antibodies or OCBs were negative in both patients. In addition, ptosis and ophthalmoplegia are rare features in NMOSD but common in MIDs.

The heteroplasmy rate in patient-1 was described as "high" [Kim, N. N. *et al*., 2023]. We should know the exact number. No heteroplasmy was reported in patient-2. Knowing the heteroplasmy rates in different tissues is crucial as it ultimately allows for prediction of disease progression and outcome. They are also important for genetic counselling. Near homoplasy could explain why patient-1's phenotype resembled that of Leigh syndrome and not MERRF syndrome, which is the classic phenotype in m.8344A>G carriers and characterised by epilepsy, myoclonus, or myopathy in addition to the described phenotype. m.8344A>G carriers with Leigh syndrome and near homoplasmy have been previously reported [Russo, S. N. *et al*., 2021].

It is not understandable why patient-2 was treated with methyl-prednisolone [Kim, N. N. *et al*., 2023]. It is known that steroids worsen the phenotype of MIDs and can even be fatal in individual cases [Finsterer, J. *et al*., 2015]. Has patient-2 developed side effects to glucocorticoids?

Spinal cord involvement in MIDs is not uncommon. There are even syndromic MIDs in which the spinal cord is exclusively or predominantly affected, such as leukoencephalopathy with brainstem and spinal cord involvement and lactic acidosis (LBSL), which is due to variants in *DARS2*. In addition, spinal cord involvement is common in pediatric MIDs, which can mimic demyelinating disease [Alves, C.A.P.F. *et al*., 2021].

MIDs due to mtDNA variants are transmitted maternally in 75% of cases [Poulton, J. *et al*., 2017]. Therefore, it is imperative that the mother has been clinically and genetically examined.

A limitation is that both patients were not prospectively evaluated for multisystem involvement. Since MIDs are usually multisystem diseases, either present already at the onset of the disease or developing into a multisystem disease over time, it is important that these patients are evaluated for them. Of particular interest is whether or not the heart was affected, as cardiac disease can greatly affect the outcome of MIDs.

A second limitation is that magnetic resonance spectroscopy (MRS) had not been performed. Since CSF lactate was increased, it is conceivable that the MRS of the affected brain regions show lactate peaks, which speaks strongly against NMOSD.

A third limitation is that the effect of contrast medium on cerebral and spinal MRI has not been reported. Primary or secondary inflammatory demyelination can be documented by enhancement of cerebral or spinal lesions, and spinal lesions in NMNSD usually enhance.

The diagnosis of NMOSD should not only be based on diagnostic criteria, but also on the individual clinical picture and the assessment of the treating physician, as well as the careful exclusion of all eligible differential diagnoses.

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