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Epilepsy in m.3243A>G carriers

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LETTER TO THE EDITOR

We read with interest the article by Chu, *et al*., on a 19-years-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to variant m.3243A>G in *MT-TL1*, which manifested phenotypically with cognitive impairment, visual hallucinations, hypoacusis, epilepsy, stroke-like lesions (SLLs), sensory-motor, axonal neuropathy, "myocarditis", recurrent pneumothorax, and lactic acidosis [Chu, X. *et al*., 2022]. The patient had inherited the variant from his mother, who phenotypically manifested only with ophthalmoparesis [Chu, X. *et al*., 2022]. The study is excellent, but has limitations that are cause for concern and should be discussed.

A limitation of the study is that no heteroplasmy rates of the causative mtDNA variant were reported for any of the affected tissues, neither in the index patient or in his mother [Chu, X. *et al*., 2022]. Knowing the heteroplasmy rates is crucial for assessing the disease progression, the prognosis, and for genetic counselling.

We disagree with the finding that the patient had myelin loss [Chu, X. *et al*., 2022]. The neuropathy was clearly of the axonal type with normal distal latencies, normal nerve conduction velocities, and no conduction blocks [Chu, X. *et al*., 2022]. Although the patient also carried a variant in *IGHMPP2* associated with axonal hereditary neuropathy [Pedurupillay, C. R. *et al*., 2016], it is more likely that the axonal neuropathy was due to variant m.3243A>G previously reported to manifest with neuropathy [Zhou, Y. *et al*., 2018].

A limitation in this respect is that it does not report whether variant c.2011A>G in *IGHMBP2* was homozygous or heterozygous [Chu, X. *et al*., 2022]. Knowledge of the constellation is crucial as hereditary, axonal neuropathy due to mutations in *IGHMBP2* has only been reported in patients homozygous for *IGHMBP2* variants [Pedurupillay, C. R. *et al*., 2016]. For the *IGHMBP2* variant listed in table-5, the authors refer to reference 19, but only 16 references are listed in the reference list.

The patient was admitted for tetany (Chu, X. *et ak*., 2022). However, the serum calcium levels listed in table-2 were normal respectively elevated (Chu, X. *et al*., 2022). We should know how tetany was diagnosed, whether there were typical clinical manifestations, and whether the initial event should be interpreted as a tonic seizure rather than tetany. Particularly, we should know whether tongue biting or urinary leakage occurred during the event and whether creatine-kinase (CK) or lactate were elevated post-ictally.

Another limitation of the study is that no follow-up cerebral magnetic resonance imaging (MRI) was performed. Because SLLs are characterised by dynamic changes in morphology and extent [Finsterer, J. *et al*., 2020], it is crucial to know whether the bilateral cortical lesions shown in figure 1 progressed or regressed during the disease course, and if they regressed, whether a residual lesion, such as laminar cortical necrosis occurred.

Regarding the history of "myocarditis", we should know whether this diagnosis was supported by cardiac MRI with contrast medium or by endo-myocardial biopsy and whether the patient was prospectively investigated for cardiac involvement in MELAS. Cardiac involvement in the form of cardiomyopathy or arrhythmias is common in m.3243A>G carriers [Finsterer, J. *et al*., 2020] and should not be overlooked as they can strongly determine outcome.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. m.3243A>G carriers require thorough work-up of clinically affected and unaffected tissues and close follow-up to assess progression and prognosis, and eventually adjust diagnosis and treatment.

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