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Letter to the Editor

POLG1 Variants May Not Only Manifest As MNGIE-Like but Also As Leigh-Like Phenotype

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In a recent article, Huang *et al.*, reported about a 49yo Chinese male with multisystem mitochondrial disorder (MID) manifesting with gastrointestinal compromise (gastro-intestinal dysmotility), leukoencephalopathy, ptosis, and axonal, sensorimotor neuropathy (Huang, H. *et al.*, 2019). Mitochondrial neuro-gastro-intestinal encephalopathy (MNGIE) was suspected but surprisingly a novel *POLG1* variant was detected upon WES (Huang, H. *et al.*, 2019). We have the following comments and concerns.

We do not agree with the classification of the case as MNGIE-like. Leukoencephalopathy in MNGIE is usually much more severe and usually the entire white matter is hyperintens on T2-weighted MRI images (Çoban, G. *et al.*, 2013). Another argument against MNGIE is that the patient manifested gastroinestinally only with diarrhoea, episodic abdominal pain, and diverticulosis (Huang, H. *et al.*, 2019). Gastro-intestinal compromise in MNGIE usually dominates the phenotype and is much more severe and includes satiety (fullness) after eating only a small portion, dysphagia, post-prandial nausea and vomiting, diarrhoea, and intestinal blockage (Filosto, M. *et al.*, 2018). Gastro-intestinal problems lead to extreme weight loss and muscle wasting (cachexia) (Filosto, M. *et al.*, 2018). Diverticulosis is a frequent gastrointestinal manifestation of MIDs (Finsterer, J., & Frank, M. 2017). Another feature which does not fit with the MNGIE phenotype are the symmetric thalamic T2-hyperintensities shown in figure 1. This feature rather suggests a Leigh-like phenotype than MNGIE. A further argument against MNGIE is the late onset of the disease. Though MNGIE may occasionally start in adulthood it most frequently has its onset in the second or third decade of life (Filosto, M. *et al.*, 2018).

We also do not agree with the notion that the index patient is the first to present with MNGIE and leukoencephalopathy and to carry a *POLG1* variant. Leukoencephalopathy in a MNGIE-like phenotype due to a *POLG1* variant has been also reported by Yasuda *et al.*,. in 2019 (Yasuda, K. *et al.*, 2019). Yasuda *et al.*,. also claimed to have reported the first patient with a MNGIE-like phenotype including leukoencephalopathy due to a *POLG1* variant (Yasuda, K. *et al.*, 2019).

Cerebrospinal fluid (CSF) investigations in *POLG1* carriers may show elevated cerebral lactate (De Vries, M. C. *et al.*, 2008). We should be informed if CSF lactate was elevated also in the index patient or if MR-spectroscopy revealed a lactate peak.

POLG1 mutation carriers frequently present with epilepsy (Scalais, E. *et al.*, 2012). Thus, we should know if the index patient ever developed seizures or had a history of pediatric epilepsy. We should also know if epileptiform discharges were ever recorded on electroencephalography (EEG).

At least epilepsy has been shown to respond favourably to ketogenic diet (KD) (Martikainen, M. H. *et al.*, 2012). We should know if the KD was ever applied in the index patient and if he responded favourably to KD.

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Because of the markedly elevated CSF protein the index patient was initially misdiagnosed as inflammatory demyelinating polyneuropathy (CIDP) (Huang, H. *et al.,* 2019). CIDP is a chronic, demyelinating neuropathy but the index patient had axonal neuropathy. We should know why nonetheless CIDP was assumed. Another feature of CIDP is the occurrence of conduction blocks (Dyck, P. J. B., & Tracy, J. A. 2018, June). We should be informed if any conduction blocks were recorded and if there was slowing of the conduction velocity in any of the investigated nerves. It should be also mentioned if anti-ganglioside antibodies were ever elevated.

Overall, this interesting case could be more meaningful if it was re-classified as adult Leigh-like syndrome or as mitochondrial multiorgan disorder syndrome (MIMODS) due to a *POLG1* variant, if entire results of CSF investigations were presented, if the KD was applied to see if there was any beneficial effect on the clinical manifestations, and if results of EEG recordings were reported.

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