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Letter to the Editor

Leigh Syndrome Due To MTFMT Variants

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In a recent article, Hayhurst *et al.*, reported about a retrospective study of 38 patients carrying a mutation in the methionyl-tRNA formyl-transferase (MTFMT) gene, manifesting phenotypically as Leigh syndrome (Hayhurst, H. *et al.*, 2019). The authors found a later onset and a better outcome of the 38 patients as compared to patients with Leigh syndrome due to mutations in other genes (Hayhurst, H. *et al.*, 2019). We have the following comments and concerns.

According to table 2, the cerebellum was not affected in any of the 38 included patients and ataxia was not a feature of the phenotype in any of the patients (Hayhurst, H. *et al.*, 2019). These findings are unusual since cerebellar ataxia can be a dominant feature of Leigh syndrome (Chourasia, N. *et al.*, 2017). We recommend discussing the absence of ataxia and cerebellar abnormalities on MRI. In this respect, we should know in how many of the four patients with tremor, tremor was attributable to cerebellar involvement.

We do not agree with the notion that ptosis and gaze palsy are "ocular symptoms" as mentioned in the "results" section (Hayhurst, H. *et al.*, 2019). Ptosis and gaze play in Leigh syndrome are usually due to affection of the extra-ocular eye muscles in the metabolic breakdown. Gaze palsy can also result from a CNS lesion or from affection of the cranial nerves supplying the extra-ocular eye muscles. We should know if MRI showed an appropriate lesion that could explain gaze palsy. We also should know how many of the included patients underwent muscle biopsy and if those with gaze palsy or ptosis had myopathy of the skeletal muscles or reduced activity of respiratory chain complexes on biochemical investigations of the muscle homogenate.

One of the patients presented with left-ventricular hypertrabeculation (LVHT), also known as noncompaction. LVHT is a myocardial abnormality of unknown etiology, which is frequently associated with neuromuscular disorder (Finsterer, J., & Stöllberger, C. 2012), in particular mitochondrial disorders (MIDs) (Finsterer, J. 2009), athletism (Caselli, S. *et al.*, 2016), pregnancy (Gati, S. *et al.*, 2014), and Africans (Peters, F. *et al.*, 2012). Since LVHT can be complicated by ventricular arrhythmias, heart failure, stroke/embolism, and sudden cardiac death, we should be informed if the patient with LVHT had a history of any of these complications or developed them during follow-up. Since LVHT can be also acquired (Finsterer, J., & Stöllberger, C. 2012), we should know if the morphology of LVHT changed over time.

Moya-Moya disease was diagnosed in one of the included patients and requires per definition the occlusion or high-grade stenosis of both supra-clinoidal internal carotid arteries (Hayhurst, H. *et al.*, 2019). We should know if this was case in the presented patient with Moya-Moya and if the patient had any cardiovascular risk factors.

Occasionally, patients with Leigh syndrome develop stroke-like episodes (SLEs), which show up as a stroke-like lesion (SLL), on imaging (Finsterer, J. 2019) and manifest phenotypically as hemianopia, hemiparesis, migraine, epilepsy, confusion, or psychiatric disease (Finsterer, J. 2019). Since 1 patient had hemianopia, 10 patients had epilepsy, and 32 motor

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manifestations (Hayhurst, H. *et al.*, 2019), we should know how many of these patients had a history of SLEs and how such patients were managed. Treatment of SLEs is at variance from that of ischemic stroke and includes NO-precursors, antiepileptic drugs (AEDs), antioxidants, and steroids. SLEs have been also reported to occur in the spinal cord (Finsterer, J., & Zarrouk-Mahjoub, S. 2018). Is it conceivable that the T2-hyperintensity at C1-4 in one patient in fact resulted from a SLE of the spinal cord?

Concerning the two patients with Parkinson's disease, did they exhibit abnormalities in the basal ganglia or the substantia nigra? Did these patients respond to L-DOPA, DOPA-agonists, or MAO inhibitors?

Overall, this interesting study could profit from a discussion about the absence of cerebellar involvement, from classification of ptosis and gaze palsy as myopathic, from a more extensive discussion of LVHT and Moya-Moya, and description of the management of patients with Parkinson's disease or SLEs.

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