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Letter to the Editor

Leigh-Like Features In an M.11778G>A Carrier without LHON

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In a recent article Miyaue *et al.*, reported about a 24yo male with Leber's hereditary optic neuropathy (LHON) due to the variant m.11778G>A which did not manifest in the eyes but only with transient hypoacusis, nystagmus, ataxia, abnormal Romberg signs, and abnormal speech perception (Miyaue, N. *et al.*, 2019). Cerebral MRI at ages 19y, 21y, and 24y showed T2-hyperintensities of the inferior colliculus bilaterally at age 19y, no abnormality at age 21y, and T2-hyperintensities of the vestibular nuclei at age 24y (Miyaue, N. *et al.*, 2019). The mother of the index case carried the same mutation as her son but manifested differentially with subacute visual loss at age 40y (Miyaue, N. *et al.*, 2019). We have the following comments and concerns.

We do not agree with the notion that LHON plus manifests only with central nervous system abnormalities, in addition to the eyes and ears (Miyaue, N. *et al.*, 2019). In addition to eyes, ears, and brain, LHON plus may manifest in the heart with dilated cardiomyopathy, noncompaction, arrhythmias, syncopes, sudden cardiac death, in the peripheral nerves as neuropathy, in the endocrinological organs as diabetes, pituitary adenoma, hypothyroidism, or hyperthyroidism, in the bone marrow as anemia, in the arteries as microangiopathy, or in the kidneys as renal failure (Finsterer, J., & Zarrouk-Mahjoub, S. 2016).

Surprisingly, the patient was treated with steroids although cerebrospinal fluid (CSF) investigations were normal, including autochthonic IgG-production and oligoclonal bands (Miyaue, N. *et al.*, 2019). Which was the rationale for applying steroids in this Leigh-like syndrome of an adolescent? The cases described by Harding *et al.*, may represent an immunological response secondary to the underlying metabolic defect or the described phenotype represents a coincidental simultaneous occurrence of LVHT and multiple sclerosis (Harding, A.E. *et al.*, 1992). From steroids it is well appreciated that they are not only beneficial for mitochondrial disorders (MIDs), but can also have no effect or may induce adverse reactions even with a fatal outcome, as in patients with Kearns-Sayre syndrome (Finsterer, J., & Frank, M. 2015).

Disappearance of the T2-hyperintensity of the inferior colliculi at age 21y suggests that the lesion was rather a vasogenic edema than ischemic in nature. Thus, we should be informed about the characteristics of the lesion on multimodal MRI particularly on diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), and on perfusion weighted images (PWI). A DWI- and ADC-hyperintense lesion with hyperperfusion suggests a stroke-like lesion (SLL), the morphological equivalent of a stroke-like episode (SLE) (Kim, J.H. *et al.*, 2011). Since SLLs may respond to NO-precursors, coenzyme-Q, or steroids, we should be informed if disappearance if the lesion at age 19y is attributable to the application of steroids or if it vanished spontaneously. It would be also interesting to know if the patient ever received L-arginine or coenzyme-Q for cerebral involvement.

Though primary LHON mutations frequently occur in a homoplasmic distribution (Yu-Wai-Man, P., & Chinnery, P.F. 2000), we should be informed about the heteroplasmy rate of the m.11778G>A variant in blood lymphocytes, hair follicles, buccal mucosa cells, skin fibroblasts, muscle cells, and urinary epithelial cells of the index patient. Heteroplasmy rates should not only be provided for the index case but also for the

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mother who carried the same mutation as her son. This is of particular interest since the onset of clinical manifestations was highly variable between son (19y) and mother (40y) (Miyaue, N. *et al.*, 2019). It should be demonstrated if heteroplasmy rates correlated with the phenotype and the age at onset or not.

In summary, the report about the described patient could be more meaningful if the various shortcomings would be addressed. We need to know the heteroplasmy rates, the nature of the cerebral lesions, the effect of steroids, and if there was subclinical affection of organs other than the brain, eyes, and ears. Differences in the age at onset and differences in the clinical presentation between son and mother need to be thoroughly discussed.

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