Is the *MT-TN* variant m.5703G>A truly causative for myoclonic epilepsy with ragged red fibers syndrome plus?

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To the Editor: With interest we read the article by Fu *et al*[1] about a 35-year-old male patient with late-onset myoclonic epilepsy with ragged red fibers syndrome (MERRF) plus syndrome being attributed to the *MT-TN* variant m.5703G>A. We have the following comments and concerns.

The main shortcoming of the study is that the pathogenicity of the m.5703G>A variant has not been sufficiently confirmed. The authors cite the studies by Moraes *et al* and Vives-Bauza *et al* to underscore that the particular variant was truly pathogenic. However, the investigations carried out to confirm pathogenicity are insufficient. Pathogenicity of mitochondrial DNA (mtDNA) variants can be most accurately assessed by application of the modified Yarham score.[2] The score validates eight items, including number of independent publications, heteroplasmy, segregation of the phenotype with the variant, proven biochemical defect, segregation of the variant with the biochemical defect on single fiber studies, evidence of pathogenicity on cybrid studies or mutant mtDNA steady-state level studies, evolutionary conservation of the nucleotide, and abnormalities on histochemistry.[2] Applying the score to the m.5703G>A variant, a score value of 11 was achieved, indicating that the particular variant was only probably pathogenic. Thus, cybrid or mutant mtDNA steady-state level studies are required to show that the variant is definitively pathogenic.

From valproic acid (VPA) it is well known that it may enhance myoclonus. Additionally, VPA can be mitochondrion-toxic.[3] Thus, we should know why VPA was given to this patient and if it was effective or caused side effects. Patients with MERRF develop cardiac involvement in 18% of the cases. One of the cardiac manifestations in MERRF syndrome is late gadolinium enhancement (LGE), characterized by sub-endocardial, sub-epicardial, patchy, or transmural gadolinium enhancement 7 to 15 minutes after injection of the contrast medium.[4] LGE may occur even in patients with normal echocardiography. Thus, we should be informed if the reported patient underwent cardiac magnetic resonance imaging and if LGE was demonstrated.

The description "abnormalities of the visual pathway" on visually evoked potentials (VEPs) is non-specific and requires further specification. Any lesion along the visual pathways, from the cornea to the visual cortex may result in prolonged latencies or reduced amplitudes of VEPs. Since the pigmentary retinal epithelium is frequently affected in patients with MERRF, manifesting as retinitis pigmentosa, rod and come degeneration, pigmentary shifts, or as optic atrophy, we should be informed about the results of the ophthalmologic investigations in the index case. Since patients with MERRF frequently present with white matter lesions, Leigh-like features, or stroke-like episodes,[5] we should be informed about the findings on cerebral imaging to more accurately interpret the VEPs.

Conflicts of interest

None.

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