External ophthalmoplegia plus due to the variants m.5669G>A respectively m.5702delA in MT-TN

Abstract:

Pathogenicity of the variants was claimed based on a correlation between mutation load in single muscle fibre’s and reduced expression of mtDNA-encoded subunit MITCO1 in complex-IV and a corresponding reduced COX activity in the same fibbers, which also showed reduced expression of complex-I. However, the Yarham score for assessing the pathogenicity of a mt-tRNA variant was not applied (Yarham, J. W. et al., 2011). Application of the modified Yarham score (Finsterer, J. et al., 2018) yielded the following results: >1 independent report: 0; heteroplasy: 2; disease segregation with the variant: 0; biochemical CI, CII, or CIV defect in muscle homogenate: 0; variant segregation with the biochemical defect in single fibres: 3; mutant mat-tRNA steady state level studies or evidence of pathogenicity on trans-mitochondrial cybrid studies: 0; evidence of normality in cybrid studies: 0; evolutionary conservation of nucleotide: 2; mitochondrial histopathology: 2. Thus, with a scoring result of 9 points the variant has to be classified as only “possibly pathogenic” (Finsterer, J. et al., 2018).

LETTER TO THE EDITOR

With interest we read the article by Visuttijai et al., 2020 about two unrelated patients with progressive external ophthalmoplegia (PEO) due to the variants m.5669G>A (patient-1, 52yo male) and respectively m.5702delA (patient-2, 66yo female) in MT-TN (Visuttijai, K. et al., 2020). It was concluded that these variants are pathogenic and that MT-TN is a hot spot for mutations causing sporadic PEO (Visuttijai, K. et al., 2020). We want to contribute to the following points to the discussion.

PEO may not only manifest in the extra-ocular muscles but also in other organs (PEO plus) (Rossi, M. et al., 2017). Thus, we should know if the two patients were prospectively investigated for multisystem involvement and if abnormalities in tissues other than the extra-ocular muscles were detected. Patients with PEO plus have been reported to manifest, in addition to the extraocular muscles, with dysphagia (Rodríguez-López, C. et al., 2020), dystonia (POLGI variant) (Rossi, M. et al., 2017), dysarthria (Rodríguez-López, C. et al., 2020), epilepsy (Rodríguez-López, C. et al., 2020), vestibular dysfunction (Rossi, M. et al., 2017), and neuropathy (Rodríguez-López, C. et al., 2020). Systolic dysfunction was reported in five patients with PEO plus due to single mtDNA deletions. In a patient with PEO plus carrying a PEO1 variant, acute onset dysphagia has been described. Focal segmental glomerulosclerosis has been found in a 20yo male with PEO plus due to the variant m.3243A>G. Patient-1 obviously did not only manifest in the extraocular muscles but also in the limb muscles as he reacted with exercise intolerance to running for 50m (Visuttijai, K. et al., 2020). Obviously, also patient-2 had myopathy of the limb muscles and dementia. Since patient-1 and patient-2 manifested also in the limb muscles and since patient-2 manifested also in the brain, we do not agree with the notion that the two index patients had pure PEO. Both patients obviously had PEO plus. Missing, however, are the results of cerebral MRI, ophthalmologic and opto-rhino-laryngologist investigations, endocrinologic investigations, nephrologist investigations, and gastrointestinal investigations.

Overall, this interesting study has a number of shortcomings which should be addressed before drawing conclusions as those presented. More evidence for the pathogenicity of the MT-TN variants should be provided and the index patients should be prospectively investigated for subclinical or mildly manifesting multisystem disease (PEO plus).
REFERENCES
1. Finsterer, J. (2020). The phenotypic spectrum of progressive external ophthalmoplegia (PEO) plus is broader than anticipated. *Neurol India 2020*; (in press)