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Letter to the Editor

De Novo Mutations M.3243A>G and M.16093T>C Associated With Atypical MIDD Syndrome

Josef Finsterer, MD, PhD

Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

*Corresponding Author
Josef Finsterer, MD, PhD

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In a recent article, Jiang *et al.*, reported about a study of 31 patients with mitochondrial diabetes and deafness (MIDD) syndrome from 10 unrelated families carrying the m.3243A>G variant and two patients also carrying the variant m.16093T>C (Jiang, Z. *et al.*, 2019). We have the following comments and concerns.

We do not agree with the classification of the m.16093T>C variant as pathogenic. This is not only due to the low heteroplasmy rates (<10%) but also due to the low scoring on the modified Yarham score (Finsterer, J. *et al.*, 2018). Item "number of publications" scores 0, item "heteroplasmy" scores 2, item "disease segregation with the variant" scores 2, item "biochemical respiratory chain defect" scores 0, item "variant segregation with biochemical defect in single fiber studies" scores 0, item "evidence of pathogenicity on cybrid studies" scores 0, item "evolutionary conservation of variant" scores 1, and item "histopathological findings" scores 0. This gives a Yarham 5, a figure, which does not even qualify for possible pathogenicity (score: 7-10). Thus, the m.16093T>C variant is benign.

Though 25% of the pathogenic mtDNA variants occur spontaneously and are not inherited (Poulton, J. *et al.*, 2017), it should be discussed if the m.3243A>G variant in family F1957 was missed due to low sensitivity of the applied tests. Sensitivity and specificity of pyrosequencing should be provided.

Though the term "MIDD" suggests a disorder affecting only two organs, it has been previously shown that MIDD is indeed a mitochondrial multiorgan disorder syndrome (MIMODS) (Finsterer, J., & Frank, M. 2017). Manifestations in addition to deafness and diabetes include cerebral abnormalities (cerebellar ataxia, cerebral atrophy, stroke, chorea-ballism, cognitive decline, seizures, migraine, Parkinson syndrome), ocular abnormalities (impaired vision), otologic abnormalities (hypoacusis), endocrine abnormalities (short stature, diabetes, hypoparathyroidism, cerebral calcifications, hypoaldosteronism, Addison disease), cardiac abnormalities (WPW-syndrome, cardiomyopathy), gastro-intestinal abnormalities (pancreatitis, constipation, gastrointestinal pseudoobstruction), renal abnormalities (renal dysfunction), and muscular abnormalities (myopathy, rhabdomyolysis) (Finsterer, J., & Frank, M. 2017). We should be informed about systematic prospective studies about multisystem involvement in MIDD.

In MID patients particularly the heart is affected (Finsterer, J., & Zarrouk-Mahjoub, S. 2018). We thus should be informed if the 31 included patients were prospectively investigated for cardiac involvement by means of echocardiography, long-term ECG recordings, carotid ultrasound, and EEG. Was the family history positive for sudden cardiac death (SCD) in any of the 10 families included?

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White matter lesions (WMLs) are a frequent finding in MIDs. Unfortunately, MRI figures were not provided. We should be informed about the causes of the WMLs. Are they attributable to acquired small vessel disease due to diabetes, arterial hypertension, hyperlipidemia, or smoking? The authors interpret the WMLs as the end stage of an ischemic lesion. Though this is generally possible, it should be discussed if the WMLs represent the end stage of a stroke-like lesion (SLL, metabolic stroke). A SLL is characterised by a cerebral vasogenic edema not confined to a vascular territory. When applying MRI, a SLL manifests as hyperintensity on DWI, ADC, and PWI, and additionally as impaired oxygen extraction from blood on OEF-MRI.

Overall, this interesting study could be more meaningful if the pathogenicity of the variant m.16093T>C was discussed, if the 31 patients were systematically investigated for multisystem disease, and if the cerebral MRIs were provided.

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