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Letter to the Editor

High Heteroplasmy of the Variant in MT-TW in Single Muscle Fibers without Myopathy

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With interest we read the article by Nesti *et al.*, about a 40 years old female with multisystem disease including hypoacusis, hypothyroidism, diabetes, ovarian failure, retinopathy, dilated cardiomyopathy, and renal insufficiency, being attributed to the variant m.5522G>A in *MT-TW* (Nesti, C. *et al.*, 2019). We have the following comments and concerns.

We do not agree that the variant m.5522G>A was definitively pathogenic. When applying the modified Yarham score (Finsterer, J. *et al.*, 2018), a value of 10 could be calculated (at least two independent reports: 2; heteroplasmy: 2; segregation with variant: 0; biochemical defect in complexes I, III, or IV: 2; variant segregation in single fiber studies: 3; pathogenicity of variant in cybrid studies: 0; evolutionary conservation: 0; strong histopathological evidence: 1) score (Finsterer, J. *et al.*, 2018). Thus, the pathogenicity of the variant has to be classified as possibly pathogenic (7-10 points).

A further shortcoming of the study is that first degree relatives were not systematically investigated for mildly manifesting or subclinical mitochondrial disorder (MID). Since 75% of the pathogenic mtDNA variants are transmitted via a maternally trait of inheritance (Poulton, J. *et al.*, 2017), we should be informed if the mother was clinically affected or not. Particularly we should know if she had undergone a neurologic, cardiologic, ophthalmologic, oto-rhino-laryngologic examination to exclude subclinical involvement in the disease. The barely detectable heteroplasmy rate in her blood lymphocytes or urinary epithelial cells suggests that she was clinically unaffected.

Concerning liver cirrhosis we should be informed if this was due to heart failure and congestion of the liver or if there were hepatopathy prior to the onset of heart failure or another cause like hepatitis after developing heart failure that could explain liver cirrhosis. We should also know in this respect if the patient was scheduled for liver transplantation or if liver cirrhosis was compensated at the last follow-up.

We should also be informed if ovarian failure was diagnosed upon the history (amenorrhoea, hypomenorrhoea) or if hormone levels were abnormally reduced. In this respect we should know if endocrine abnormalities were attributable to pituitary insufficiency (Yasui, M. *et al.*, 1993) and if the pituitary gland was normal on imaging and functional studies or not.

There is a strong discrepancy between the high heteroplasmy rates of the variant in single muscle fibers and the absence of clinical manifestations in the muscle. There was obviously no muscle weakness, no wasting, no fasciculations, and needle electromyography was normal. Creatine-kinase values were normal as well (Nesti, C. *et al.*, 2019). Additionally, the total heteroplasmy rate in muscle was only 40%. The authors should provide an explanation for this discrepancy.

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We should also know the indication for implantation of an implantable cardioverter defibrillator (ICD). Was this due to severe intractable heart failure or due to malignant ventricular arrhythmias on long-term ECG recordings? Since MIDs are frequently associated with left ventricular hypertrabeculation (LVHT) (Finsterer, J. 2009) and since LVHT is complicated by ventricular arrhythmias, heart failure, and embolism, we should be informed if echocardiography or cardiac MRI was indicative of LVHT and if the history was positive for cardio-embolic events.

Overall, this interesting case could be more meaningful if there was more strong confirmation of the pathogenicity of the accused variant, if first-degree relatives were systematically investigated for the phenotype, if the discrepancy between high heteroplasmy rates in single fibers and the absence of clinical manifestations in the skeletal muscle was explained, and if the pituitary gland was investigated to explain the multiple endocrine abnormalities.

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