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Letter to the Editor

Identification and Characterization of New RNASEH1 Mutations Associated With PEO and Multiple Mtdna Deletions

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In a recent article, Carreno-Gago *et al.*, reported about a 53 years old male with a mitochondrial disorder (MID) due to a novel, homozygous *RNASEH1* variant (Carreño-Gago, L. *et al.*, 2019) secondarily causing multiple mtDNA deletions (Carreño-Gago, L. *et al.*, 2019). We have the following comments and concerns.

There is a need for clarifying if the authors found multiple mtDNA deletions or mtDNA depletion secondary to the *RNASEH1* variant and in the abstract it is indicated that the patient had multiple mtDNA deletion syndrome. The discussion starts with statements about mtDNA depletion, which was not reported in the result section, but mtDNA depletion has to be excluded as the number of mtDNA copies was reported normal (Carreño-Gago, L. *et al.*, 2019). Interestingly, in the discussion the authors mention that neither mtDNA depletion nor multiple mtDNA deletions were detected in the index case (Carreño-Gago, L. *et al.*, 2019). In addition to the mutation load, we should know if the amount of deleted mtDNA differed between more or less affected tissues.

Multiple mtDNA deletions are frequently associated with mitochondrial multiorgan disorder syndrome (MIMOD). Multisystem involvement is frequently subclinical and detection of impairment requires prospective investigations of affected patients. We should know if the index case was investigated for subclinical or mild clinical affection of organs other than the muscle. Of particular interest is the brain, the eyes, the heart, and the endocrine system, as these systems are frequently affected in multiple mtDNA deletion syndrome (Ishikawa, T. *et al.*, 2018; El-Hattab, A.W. *et al.*, 2017). Were there any abnormalities on cerebral MRI, ECG, or echocardiography?

Missing is a report about the results of serum lactate determination at rest or under exercise. Since the index case presented with myopathy and exercise intolerance, it is conceivable that he had elevated serum lactate levels given the absence of cardiac dysfunction. We should know if the lactate stress test (Finsterer, J. 2012) was applied for diagnostic purposes.

Missing is also an extensive family history. It has been reported that there was consanguinity and that the parents were clinically unaffected but this can be assessed only by investigating them. We should be informed if any of the first-degree relatives, including mother and father, were clinically affected and which of them carried the *RNASEH1* variants.

Furthermore, missing is the medication the patient was regularly taking. Certain drugs may contribute to exercise intolerance. Concerning dysphagia, dysarthria, and tongue weakness we should know if they were attributable to affection of the CNS, the supplying nerves, or the smooth respectively tongue muscle.

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Multiple mtDNA deletion syndrome may go along with reduced activity of a single or multiple respiratory chain complexes (Casali, C. *et al.*, 2001). We should know if biochemical investigations were carried out and if activity of any respiratory chain complex was reduced.

Surprisingly, the discussion also mentions that respiratory muscles were affected, which was not stated in the results (Carreño-Gago, L. *et al.*, 2019). It thus should be described how affection of respiratory muscles became evident and if the patient required some sort of ventilatory support.

Overall, this interesting case could profit from clarifying some inconsistencies with regard to mtDNA abnormalities and from providing additional information about the diagnostic work-up for multisystem disease, the family history, biochemical investigations of the muscle, and the medication the index case was regularly taking.

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