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Letter to the Editor

Multiple Mtdna Deletions Due To Mitochondrion-Toxicity of Anti-Hepadnaviral Drugs

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In a recent article, Fujii *et al.*, reported about a 68 years old female who received lamivudine (100 mg/d) during 10 years and adefovir (10 mg/d) during 6 years for chronic hepatitis B (Fujii, T. *et al.*, 2019). Since 4 months prior to presentation the patient had developed slowly progressive quadruparesis, being attributed to a secondary mitochondrial myopathy (Fujii, T. *et al.*, 2019). We have the following comments and concerns.

The patient carried multiple mtDNA deletions being attributed to the long-term anti-viral medication (Fujii, T. *et al.*, 2019). Since multiple mtDNA can be also caused by mutations in nDNA-located mitochondrial genes (Rusecka, J. *et al.*, 2018), it is crucial that whole exome sequencing (WES) was carried out to exclude a nuclear genetic cause of the mtDNA variants. Only *POLG1*, *POLG2* and *Twinkle* variants were excluded.

Missing in this respect is a genetic investigation of first degree relatives, in particular the mother. Though single mtDNA deletions occur sporadically in the majority of the cases, they can be maternally inherited in about 4% of the patients. Multiple mtDNA deletions are most frequently autosomally inherited (Poulton, J. *et al.*, 2017).

Morphological abnormalities of mitochondria are best visualised by electron microscopy (ELMI). However, no ELMI studies had been carried in the presented patient. ELMI may not only show increase in number of mitochondria but also increase or decrease in size, abnormal shape, abnormal cristae structure, or deposits of abnormal material. Missing are also biochemical investigations to show which respiratory chain complexes were affected and to which degree their function was impaired by the deletions. Since immune-histology showed reduced COX-activity in ragged-red fibers (RRFs) and non-RRFs, it is likely that biochemical investigations will reveal a complex-IV defect.

Since only a portion of the patients undergoing long-term treatment with anti-hepadnaviral agents develops myopathy, it is conceivable that those developing myopathy are the ones which carry a subclinical muscle defect before initiating the anti-viral treatment. Thus, we should be informed if the presented patient reported muscle symptoms already prior to onset of the anti-viral medication.

We do not agree with the notion that CPEO is a mild mitochondrial disorder (MID). Though CPEO indeed may take a mild course, there are CPEO cases, which manifest not only in the extra-ocular muscles but also in the brain, endocrine organs, the heart, the kidney, or the peripheral nerves (CPEO plus) (Sundaram, C. *et al.*, 2011). Thus, we should be informed if the presented patient was prospectively investigated for involvement of organs other than the extra-ocular muscles or if she manifested clinically with a multisystem disease.

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Though it is not explicitly mentioned that the two anti-viral drugs were given in combination for 6 years, the wording is suggestive of such a regimen. This point is crucial as the combination may have enhanced mitochondrion-toxicity. Though the two compounds were made responsible for myopathy, they were continued. Thus we should be informed about the results of follow-up investigations and the long-term outcome of this patient.

Overall, this interesting case could be more meaningful if results of prospective investigations for multiorgan involvement were provided, if WES was carried out to exclude or confirm the presence of a nDNA located variant, if ELMI and biochemical investigations were carried out, and if the individual and family history was revised for previous muscular complaints or affection of other family members.

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