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Letter to the Editor

Optimising Management of Mitochondrial Epilepsy Requires Longitudinal Studies

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With interest we read the article by Ticci *et al.*, about a cross-sectional survey of Italian patients with a mitochondrial disorder (MID) and epilepsy (MID-E) (Ticci, C. *et al.*, 2020). Among 1467 MID patients 10% had epilepsy (Ticci, C. *et al.*, 2020). It was concluded that "a better definition of epilepsy in MIDs may foster the diagnostic workup, management, and treatment of patients" (Ticci, C. *et al.*, 2020). The study has a number of shortcomings.

The main shortcoming is its retrospective and cross-sectional design. To assess the course of epilepsy and treatment it is crucial to include longitudinal follow-up data.

The number of MID-E patients in the text and table-1 are discordant. The results mention "clinical and genetic data" were obtained from 98 MID-E patients but in table-1 100 patients are listed (Ticci, C. *et al.*, 2020). Which is the true figure? Since only 100 respectively 98 of the 147 MID-E patients were diagnosed genetically, we should know how the other 47/49 patients were diagnosed.

A further discrepancy is evident in table-3. Eleven patients carrying the variant m.3243A>G had generalised seizures at onset but further down 21/41 of these patients had generalised seizures at onset. This discrepancy is evident also for patients carrying other variants (Ticci, C. *et al.*, 2020).

Discrepant is also that only 10% of the entire cohort had MID-E but epilepsy was the presenting manifestation in 50% of the cases.

It is unclear why the phenotypic features "failure to thrive" and "short stature" were evaluated together. Concerning the differentiation between "cerebellar signs" and "tremor" (Ticci, C. *et al.*, 2020), tremor can be a cerebellar sign as well. We should know how tremor was assessed as non-cerebellar and if patients with tremor also had other manifestations of extra-pyramidal involvement (26 had a movement disorder).

Since stroke-like lesions (SLLs) are frequently associated with seizures (Finsterer, J., & Wakil, S. M. 2016), we should know in how many MID-E patients seizures occurred in association with SLLs. Since 23.1% had stroke-like episodes (SLEs), the clinical correlate of a SLL (Finsterer, J. 2019), a high rate of SLL-associated seizures can be expected.

Since many MID patients receive cocktails mixed of antioxidants, cofactors, and lactate-lowering agents, and since some of them may also have a

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beneficial effect on epilepsy (Chandra, S. R. *ET AL.*, 2015) we should know each patient's "cocktail" therapy. Since the effect of anti-seizure drugs (ASDs) depends also on the further co-medication it is crucial to know it.

Concerning seizure-types in table-2 it is not comprehensible why among the 7 patients with a single seizure altogether 10 patients were listed. We should know if the 3 patients with "motor" seizures belong to the group of patients with generalised seizures.

From a number of ASDs it is known that they are potentially mitochondrion-toxic (Finsterer, J. 2017). These include valproic acid (VPA), carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), and topiramate (TPM) (Chandra, S. R. *et al.*, 2015; & Finsterer, J. 2017). We should know if the poor response to ASDs in early-onset MID-E under VPA, CBZ, and PHT in figure-2 was attributable to this toxicity.

Missing is a differentiation between MID-E patients on a single, two or more ASDs.

Overall, the study has a number of inconsistencies and shortcomings which need to be addressed before final conclusions can be drawn. There is no need for a new definition of mitochondrial epilepsy but a need for thorough work-up of MID-E patients.

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