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Letter to the Editor

mtDNA depletion due to FBXL4 variants requires quantification for assessing genotype / phenotype correlations

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With interest we read the article by Ballout *et al.*, about a 9 months old female born to consanguineous parents with multiorgan, encephalo-myopathic mitochondrial depletion syndrome (MDS) due to the mutation c.1303C>T in *FBXL4* (Ballout, R.A. *et al.*, 2019). Clinical manifestations included developmental delay, generalised hypotonia, facial dysmorphism, microcephaly, fronto-temporal cerebral atrophy, anemia, leukopenia, and lactic acidosis (Ballout, R.A. *et al.*, 2019). The study raises the following comments and concerns.

The index patient was diagnosed with a mitochondrial disorder (MID) due to mtDNA depletion. However, in the results section it is not mentioned to which degree the amount of mtDNA was depleted in various tissues of the index case. We thus should be informed how mtDNA depletion was determined, about the amount of depleted mtDNA, and if this amount was different between various tissues.

Though the presented variant followed an autosomal recessive trait of inheritance in a family with a high rate of consanguinity, it is unusual that the family history was negative for MIDs (Ballout, R.A. *et al.*, 2019). Since MIDs can manifest subclinically or with only discrete clinical manifestations, we should be informed if all first-degree relatives were systematically screened for subclinical or mildly manifesting MID and if the variant segregates with the disease through the family.

MIDs are frequently multisystem disorders affecting the brain, eyes, ears, endocrine system, heart, lungs, liver, pancreas, and intestines, kidneys, bone marrow, cartilage, immune cells, muscle, peripheral nerves, or skin (Finsterer, J. *et al.*, 2018). Thus we should be informed if the index case was systematically investigated not only for cerebral, ophthalmologic, otologic, cardiac disease, and gastrointestinal disease, but also for involvement of organs / tissues as described above. Anemia and leukopenia are typical phenotypic features of a MID. Thus we should know if the authors regarded them as hematological manifestations of the disease or if other causes of anemia, were evident. Since epilepsy is a frequent manifestation of MIDs (Finsterer, J., & Carvalho, E.H.T. 2017), we should be informed if the index case ever developed seizures and if EEG recording showed presence or absence of epileptiform discharges.

The index patient was reported to have developed dropped head syndrome. It should be mentioned if dropped head was due to generalised hypotonia or if there was muscle weakness or atrophy of the neck extensor muscles (Drain, J.P. *et al.*, 2019). In this respect it is also crucial to know if the index patient had undergone needle electromyography, muscle biopsy and immune-histological and biochemical investigations to confirm the mitochondrial nature of dropped head syndrome. Dropped head can be a manifestation of a MID (Finsterer, J. 2004). Since the patient was reported to have had mild lactic acidosis we also should know if there was elevated lactate in the cerebro-spinal fluid (CSF), either by direct

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measurement of lactate in the CSF or by MR-spectroscopy.

Overall, this interesting case could be more meaningful, if the amount of mtDNA depletion was presented, if first-degree family members were systematically screened for subclinical or mildly manifesting MID, if the index case was systematically and prospectively investigated for multisystem disease, if EEGs were recorded, if the nature of the dropped head was clarified, and if cerebral lactate was measured.

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