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Letter to the Editor

Leigh-Like Syndrome Due To the COX4/1 Variant C.454C>A

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In a recent article, Pillai *et al.*, reported about two male siblings, aged 3y (patient-1) and 11y (patient-2), who presented with a Leigh-like syndrome (LLS) due to the novel homozygous variant c.454C>A in *COX4/1* (Pillai, N. R. *et al.*, 2019). The two siblings were born to consanguineous parents who each carried the *COX4/1* variant in the heterozygous form. We have the following comments and concerns.

We do not agree with the statement that ETC-analysis of the muscle homogenate supports the pathogenicity of the *COX4/1* variant (Pillai, N. R. *et al.*, 2019). ETC-analysis not only revealed reduced complex-IV activity but also reduced complex-I (27%) and complex-II (50%) activities. These results are not indicative of an isolated complex-IV defect and thus do not support the statement.

Furthermore, describing patient-2 as "not having any dysmorphic features" is misleading given the fact that the patient had microcephaly according to table 1 (Pillai, N. R. *et al.*, 2019).

We also do not agree with the statement that clinical manifestations of COX-deficiency range from lactic acidosis to myopathy (Pillai, N. R. *et al.*, 2019). There are a number of reports showing that COX-deficiency can manifest as severe, multisystem disease (Pitceathly, R. D. *et al.*, 2013; Campos, Y. *et al.*, 2001).

A shortcoming of the study is that patient-2 received topiramate (TPM) and valproic acid (VPA) for epilepsy (Pillai, N. R. *et al.*, 2019). From VPA it is well-known that it is mitochondrion-toxic (Finsterer, J., & Zarrouk Mahjoub, S. 2012), particularly in patients carrying *POLG1* mutations, where it can be even fatal (Uusimaa, J. *et al.*, 2008). It should be discussed if progression of the phenotype was at least partially attributable to intake of VPA.

Patient-2 was also treated with ACTH for hypsarrhythmia (Pillai, N. R. *et al.*, 2019). From steroids it is well-known that they may have a beneficial, detrimental, or no effect in mitochondrial disorders (MIDs) (Finsterer, J., & Frank, M. 2015). Is it conceivable that progression of the disease was enhanced by administration of ACTH?

A further shortcoming of the study is that both siblings were not cardiologically investigated. Cardiologic investigations are crucial as the heart can be affected in LLS and determined the outcome (Papadopoulou, L. C. *et al.*, 1999). Concerning the scheduled echocardiography, it has to be stressed that echocardiography may be insufficient for assessing cardiac involvement. Particularly, for documentation of myocardial fibrosis and noncompaction, cardiac MRI is the investigation of choice. Myocardial fibrosis can be elegantly seen upon the presence of late gadolinium enhancement (LGE) (Cardona, A. *et al.*, 2019). Myocardial fibrosis may predict the occurrence of ventricular arrhythmias (Centurión, O. A. *et al.*, 2019). Additionally, long-term ECG recordings are crucial for assessing the outcome of LLS.

Patient-1 presented with hypoplasia of toes 2-5 bilaterally (Pillai, N. R. *et al.*, 2019), which has not been reported earlier. Only brachydactylia of the hands has been reported in a 72y female with suspected MID (Finsterer, J., & Strobl, W. 2012). We should be

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informed how COX-deficiency can cause hypoplasia of toes.

In patient-1 elevated cerebro-spinal fluid (CSF) lactate was reported (Pillai, N. R. *et al.*, 2019). We should know the results of MR-spectroscopy (MRS), particularly if elevated CSF lactate manifested as lactate peak on MRS.

Since both parents carried the mutation in the heterozygous form, we should know if they manifested clinically or not.

Phenotypic expression of *COX4/1* variants is highly heterogeneous (Pillai, N. R. *et al.*, 2019). Thus, we should know if haplotype or mtDNA polymorphisms other than *MDN1* contributed to the marked phenotypic heterogeneity.

Overall, this interesting study could be more meaningful by providing results of the work-up for cardiac involvement, by clarifying some inconsistences, and by discussing possible explanations for features uncommon in MIDs.

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