

## Valproic acid for myoclonic epilepsy in *POLG1* carriers can be fatal

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With interest we read the article by Tarka *et al.* about the autopsy findings of an 8-year-old female with mitochondrial disorder (MID) due to the compound heterozygous variants c.2243G>C and c.2542G>A in *POLG1* [1]. The patient manifested clinically with mental retardation, developmental regression, and myoclonic epilepsy, for which she received valproic acid (VPA) [1]. Neuropathological studies after death from acute pancreatitis and liver failure revealed bilaterally symmetric degenerative lesions of the accessory olivary nuclei in addition to typical features of Alpers-Huttenlocher disease (AHD) [1]. It was concluded that pancreatitis prior to liver failure is unusual [1]. The study is appealing but raises comments and concerns.

The main shortcoming is that the patient received VPA. It is well known that VPA can cause acute liver failure in patients carrying *POLG1* variants [2]. In some of these patients the outcome was even fatal [3]. Thus, VPA is contraindicated in patients carrying *POLG1* variants. Missing in this respect is the dosage of VPA, seizure frequency, compliance, quality of seizure control, and the VPA serum levels.

Since *POLG1* carriers may manifest with hepatopathy even in the absence of VPA, we should know if liver parameters were ever elevated prior to the application of VPA and if abdominal ultrasound ever detected liver enlargement, fatty infiltration, cysts, or fibrosis prior to starting VPA. Did the patient suf-

fer from a coagulation disorder or from hypo-proteinemia?

Since *POLG1* may cause secondary mtDNA damage [4], we should know if there was a secondary mtDNA point mutation, mtDNA deletion/duplication, or if there was mtDNA depletion. Secondary damage may strongly determine the phenotype and thus the outcome of *POLG1* carriers.

We do not agree with the diagnosis of AHD. AHD is diagnosed upon the triad: mtDNA depletion, resistant epilepsy, and liver failure triggered by VPA [3]. However, the index patient met only 1 criterion. We do not agree with the statement that pancreatitis as a side effect of VPA is “extremely rare” [1]. On the contrary, pancreatitis is well appreciated as an adverse reaction to VPA [5].

Though the MRI of the brain was reported as normal, we should know which modalities were applied. Of particular interest is diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), perfusion weighted imaging (PWI,) and oxygen-extraction fraction (OEF) sequences. Furthermore, we should know if magnetic resonance spectroscopy (MRS) or direct measurement of cerebro-spinal fluid (CSF) lactate was ever carried out to see if there was lactic acidosis in the brain or not. Since the patient developed epilepsy, we should know if a neurodevelopmental defect was excluded as the cause of epilepsy by application of an epilepsy protocol according to

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the ILAE for the work-up of the etiology by means of imaging.

Missing is if the patient was a mono- or di-zygotic twin. Missing is the information if the parents were consanguineous or non-consanguineous. Missing are clinical and genetic investigations of the parents and other first-degree relatives. Missing is a discussion about the phenotypic heterogeneity of *POLG1* variants, which may not only cause syndromic MID, but also non-syndromic MID, as in the presented case.

Overall, the interesting study has a number of limitations which should be met before drawing conclusions as those presented. Details about the family history and epilepsy are required and the results of clinical and genetic work-up of first-degree relatives are required. The effect of the *POLG1* variants on mtDNA should be detailed. Details about cerebral imaging studies should be provided.

## Disclosure

The author declares no conflict of interest.

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