# Caution When Using Valproate for Seizures in POLG1 Carriers

**Fatal hepatopathy in POLG1 carriers suggests the use of valproic acid.**

We read with interest the article by Muthusamy *et al*.[1] about a 20-year-old female with a mitochondrial disorder (MID) due to the variant c.2243G>C in *POLG1* clinically manifesting with initially focal seizures that after temporary suppression progressed to generalized seizures, status epilepticus, refractory status epilepticus, super-refractory status epilepticus, and ultimately death. In addition, she developed liver failure with the progression of the disease.[1] The study is appealing but carries limitations that raise concerns and should be discussed.

A limitation of the study is that the entire medications the patient received from the onset of seizures were not reported. Of particular interest is whether the patient ever received valproic acid or any other mitochondrion-toxic antiepileptic drug (AED) that could explain refractoriness to the AED treatment. From valproic acid, it is well-known that it is liver toxic and was even made responsible for several fatalities in *POLG1* carriers.[2,3] From carbamazepine, phenobarbital, and phenytoin, it is also known that they can be mitochondrion-toxic and can cause severe side effects.[4]

Another limitation of the study is that the patient did not undergo an autopsy. Of particular interest would be to explore the nature of progressive diffusion-weighted imaging (DWI) hyperintensities. It would be interesting to know whether they were interpreted as stroke-like lesions, seizure-related, or due to a direct toxic effect of the AED treatment. Missing in this respect is the classification of the DWI hyperintensities as cytotoxic or vasogenic edema. We should know if apparent diffusion coefficient (ADC) maps were hyperintense (vasogenic edema) or hypointense (cytotoxic edema).

Another limitation is that it was not reported whether the *POLG1* variant was inherited or sporadic. Knowing the origin of the variant is crucial, particularly for genetic counseling.

There is also no mention of the effect of the *POLG1* variant on mitochondrial DNA (mtDNA).[1] Because *POLG1* mutations secondarily cause mtDNA depletion, and single or multiple mtDNA deletions,[5] it is essential to examine mtDNA by Southern blot, three primer competitive polymerase chain reaction (PCR), or sequencing.

There is no mention of whether the index patient manifested clinically also in organs other than the brain. *POLG1*-related disorders are commonly multisystem diseases,[6] which manifest particularly in the central nervous system, endocrine organs, heart, liver, nerves, and muscles. We should know if any of these organs in addition to the brain were prospectively investigated for being affected by the mutation intra vitam or at autopsy.

Regarding the cause of crossed cerebellar diaschisis, it could be also due to loss of cerebrovascular autoregulation or decreased metabolism in the non-ischemic hemisphere due to the release of vasoactive metabolites.[7]

There is no mention of the presumed cause of death.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. In *POLG1* carriers, manifesting with epilepsy application of valproic acid should be absolutely avoided because of its potentially fatal hepatotoxic effect in these patients. The AED management in *POLG1*-carriers should generally not include mitochondrion-toxic AEDs, if possible.

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## Conflicts of interest

There are no conflicts of interest.

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