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The Clinical Presentation of *POLG*-Related Phenotypes Depends on the Time of Examination As They are Progressive

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LETTER TO THE EDITOR

We read with interest Kadohisha, *et al*., article on a 3-months-old male with a mitochondrial disorder (MID) due to the homozygous variant c.2890C>T in *POLG [Kadohisa, M. et al., 2024]*. The mutation manifested phenotypically as myopathy, encephalopathy, and hepatopathy leading to liver failure *[Kadohisa, M. et al., 2024]*. After liver failure had been judged irreversible based on the clinical deterioration and liver biopsy, the patient underwent living donor liver transplantation (LFLT) with a positive short-term outcome *[Kadohisa, M. et al., 2024]*. The study is excellent, but some points need discussion.

The first point is that the diagnosis myocerebrohepatic spectrum (MCHS) disorder, also known as myo-hepato-cerebral mtDNA depletion syndrome (MDS) has not been confirmed by appropriate testing *[Kadohisa, M. et al., 2024]*. It was claimed that the patient had myopathy, but there is no mention of whether the patient had elevated serum creatine-kinase (CK) or had a muscle biopsy suggestive of mitochondrial myopathy. In addition, it was reported that the patient was able to jump again at the 9 months follow-up. The patient was also described as having developmental delay and dementia but cerebral MRI revealed normal findings *[Kadohisa, M. et al., 2024]*. These discrepancies should be resolved.

A second point is that no sequencing of the mtDNA was performed. It is imperative to study these types of mtDNA alterations because *POLG* variants can cause multiple mtDNA deletions or mtDNA depletion. In this context, we should also know what liver mitochondria looked like. Were the liver mitochondria enlarged or reduced, increased or decreased in number, or did they have abnormal morphology.

A third point is that we disagree with the statement that seizures are uncommon in MCHS *[Kadohisa, M. et al., 2024]*. On the contrary, previous reports have shown that MCHS can be complicated by epilepsy, especially when MCHS progresses to Alpers syndrome or Leigh syndrome *[Scalais, E. et al., 2012]*. A normal EEG, as recorded in the index patient, does not rule out seizures. We also disagree with the statement in the case description that seizures represent a neuromuscular manifestation of *POLG* variants. Seizures should be classified as central nervous system (CNS) manifestations.

A fourth point is that we also disagree with the statement in the conclusion that the patient had no neurological manifestations before transplantation *[Kadohisa, M. et al., 2024]*. On the contrary, the patient was described as having a psychomotor delay and could only speak three-word sentences *[Kadohisa, M. et al., 2024]*. The patient was also diagnosed with myopathy. These discrepancies should be resolved.

A fifth point is that reference limits for blood parameters were not provided *[Kadohisa, M. et al., 2024]*, making it difficult to assess whether a particular value was within or outside the normal range.

In summary, the excellent study has limitations that should be addressed before final conclusions are drawn. Clarifying the weaknesses would strengthen the conclusions and improve the study. In a patient with liver failure and neurological involvement associated with *POLG* variants, LT can limit life and quality of life due to the neurological prognosis and can have serious consequences.

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