Movement Disorders
CLINICAL PRACTICE

Reply to: Double Trouble from *POLG1* and *CLCN1* Variants with Intrafamilial Phenotypic Heterogeneity

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We thank Dr. Finsterer for his comments[1] and his interest in our case report.[2] We are happy to respond to the points he raised.

Although the deceased daughter suffered from therapy-resistant epileptic seizures, neither the father nor the son ever had seizures. Moreover, neither of them had myoclonus, so there was no indication for additional diagnostic workup with a view to myoclonic epilepsy.

The clinical signs were described as "twitching" by the affected father and son. This was initially considered to be myoclonus, but was then identified as myotonia both on clinical grounds and needle electromyogram showing myotonic discharges.

We refrained from performing a muscle biopsy because neither the father nor son stated continuous muscle pain and neither had muscle weakness. The diagnosis was confirmed by genetic testing and could explain the clinical phenotype, therefore we felt further invasive diagnostic procedures including muscle biopsy were not warranted, particularly because no therapeutic consequences were expected.

We also did not specifically investigate mitochondrial DNA depletion or multiple mitochondrial DNA deletions because an unequivocal diagnosis of mitochondrial disorders was already made based on the clinical findings and detection of the *POLG1* variant. Theoretically, knowledge of the amount of mitochondrial DNA might be interesting, but the focuses of our study were clinical phenotyping and raising awareness of the presence of multiple genetically defined disorders in a single family.

Although the mother, who carries a different mutation than her husband and her living children, was asymptomatic and did not have any clinical signs, the daughter albeit asymptomatic did indeed have mild ptosis as a possible sign of the mutation in the *POLG1* gene, but did not show any other abnormal clinical signs. The question of why family members with the same mutation are differently affected (brother and sister) and why the mother did not show any signs despite a pathogenic mutation in the *POLG1* gene is very relevant indeed. It raises the important issue of reduced penetrance. On an individual basis, it is currently impossible to decide why one mutation carrier of a potentially pathogenic mutation develops symptoms and signs, whereas another with an identical mutation does not. Finding answers for this conundrum requires studies of large groups of clinically and genetically well-defined populations and multinational cooperation as, for instance, is currently realized within the Research Unit "Protect Move" (http://protect-move.de) dedicated to investigating reduced penetrance in genetically determined Parkinson's disease.

Both patients receive regular cardiac investigations including echocardiogram because of the increased risk of cardiac complications in both disorders. Also, the father is now treated with lamotrigine,[3] whereas the son takes mexiletine licensed for the treatment of myotonia in Germany requiring cardiac follow-up. Both patients benefited from their therapy.

Lastly, it is correct that *POLG1* variants can cause a variety of syndromes, including Leigh syndrome; MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes); MERRF (myoclonic epilepsy with ragged-red fibers); MEMSA (myoclonic epilepsy myopathy sensory ataxia); SANDO (sensory ataxic neuropathy, dysarthria, ophthalmoparesis); and CPEO (chronic progressive external ophthalmoplegia syndrome), which was not mentioned in our article because of space limitations.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: Approval of an institutional review board was not required for this work. Written consent for publication was obtained from the patients. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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