POLG1-related Mitochondrial Disorder with MNGIE- and Leigh-like Features

Sir,

With interest we read the article by Huang *et al*. about a 49-year-old Chinese male who developed progressive gastro-intestinal dysmotility with diarrhoea and abdominal pain since age 42 years, ptosis, double vision, and progressive quadruparesis since age 48y, and ophthalmoparesis since age 49y being attributed to the compound heterozygous mutations c. 3643+1G>A and c.2396C>A in *POLG1*.[1] Further work-up revealed diverticulosis, gastro-duodenal distension, mixed polyneuropathy, elevated cerebrospinal fluid (CSF) protein, and myopathy.[1] We have the following comments and concerns.

We agree that there are some similarities between classical MNGIE syndrome and the index case but there are also a number of dissimilarities, which should be stressed. Similarities with MNGIE include, gastro-intestinal dysmotility, polyneuropathy, chronic progressive external ophthalmoplegia, and cachexia.[2] Other typical manifestations of MNGIE,

such as onset before age 20 years, short stature, pigmentary retinopathy, leukoencephalopathy, cerebellar manifestations, and hypoacusis,[2] were not present in the index patient. Phenotypic features that are unusual for MNGIE but were found in the index patient include the bilaterally symmetric thalamic and basal ganglia lesions, diverticulosis, quadruparesis, and elevated CSF protein.

We disagree with the description of the cerebral MRI. The index patient not only had mild periventricular white matter lesions (WMLs) but also bilateral basal ganglia and thalamic lesions as shown on FLAIR and T2-weighted images in Figure 1. MRI findings are atypical for MNGIE, which is usually associated with severe confluent and extensive supra-tentorial WMLs but not with basal ganglia or thalamic lesions.[3] Thus, the MRI findings rather suggest Leigh- or Leigh-like syndrome than MNGIE.

Nothing is reported about blood chemical values, why we should be informed if mitochondrial myopathy also manifested with creatine-kinase elevation or elevated serum lactate or pyruvate.

Since *POLG1* mutations are frequently associated with epilepsy[4] we should know if the individual history was positive for seizures, and if electroencephalography recordings ever revealed epileptiform discharges.

We should also be informed if CSF lactate was elevated and if the MR-spectroscopy showed a lactate peak.

Missing in the report is the effect of the compound heterozygous *POLG1* mutation on the mtDNA. *POLG1* mutations may secondarily lead to multiple mtDNA deletions,[5] or mtDNA depletion[6] an effect that usually worsens the phenotype.

Missing is also a biochemical investigation of the muscle homogenate. We should know if the activity of any of the respiratory chain complexes was reduced.

Application of steroids in mitochondrial disorder can be beneficial, without an effect, or detrimental.[7] Thus steroids should be given with caution irrespective of the underlying mutation.

In conclusion, this interesting case report could profit from discussing the similarities and dissimilarities between MNGIE and *POLG1*-related MIDs, from investigating the effect of the POLG1 variants on mtDNA, from revising the interpretation of the MRI findings, and from providing results about the biochemical investigations of the muscle.

Author contribution

Josef Finsterer: design, literature search, discussion, first draft, critical comments.

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Conflicts of interest

There are no conflicts of interest.

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