

Influences on genotype/phenotype correlations in mtDNA-related Leigh syndrome are heterogeneous

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Letter to the Editor

With interest we read the article by Wei et al. about 16 patients with late onset (>2y) Leigh syndrome due to mtDNA mutations (MT-ND3, n=7, MT-ND5, n=3, MT-ND6, n=2, MT-ND1, n=1, MT-ATP6, n=2)¹. Clinically, these patients manifested with ataxia, pyramidal tract involvement, dis-turbed cognition, stroke-like episodes, bulbar palsy, failure to thrive, central apnea, ophthalmoparesis, ptosis, dystonia, seizures, optic neuropathy, hypoacusis, myopathy, neuropathy, arrhythmias, and renal insufficiency¹. Presenting manifestations were gait disturbance due to ataxia, hemiplegia or dystonia, seizures, impaired consciousness, double vision, or headache¹. We have the following comments and concerns.

We do not agree with the statements that the study “helps to define the types of clinical and neuroimaging finding in late-onset LS with the mutations of mtDNA” and “sheds light on the identification of genotype–phenotype and genotype–neuroimaging correlations”. In five patients the heteroplasmy rate was below 50%, suggesting that the corresponding mtDNA variant was not causative. To elucidate if mtDNA variants were nonetheless causative it would be helpful to determine heteroplasmy rates not only in lymphocytes but also in hair follicles, muscle cells, skin fibroblasts, buccal mucosa cells, or urinary epithelial cells. Variable heteroplasmy rates between different tissues may impede establishing a strong genotype phenotype correlation.

Interestingly, 6/16 had experienced stroke-like episodes (SLEs) during the disease course. We should be informed how these SLEs manifested clinically, if they disappeared spontaneously or under treatment, or if they recurred. SLEs are known to improve or even regress under therapy with nitric-oxide (NO) precursors, antioxidants, or non-mitochondrion toxic antiepileptic drugs (AEDs)^{2,3}. We should know which of these compounds were given to the six patients with a SLE and if the treatment was beneficial or not.

Interestingly, all 6 patients with a SLE also had seizures. Thus, it is conceivable that seizures were the trigger for the development of a SLE. In this respect it would be helpful to know if seizures occurred prior to the onset of a SLE or during a SLE or if EEGs recorded during the presence of a SLE showed paroxysmal activity in the absence of clinically manifesting seizures.

Mitochondrial disorders (MIDs) due to mtDNA mutations are maternally inherited in 75% of the cases⁴. Thus, it should be mentioned in how many of the 16 patients the family history was positive for a MID and in how many of these patients the mtDNA variant was regarded as sporadic. This information is crucial with regard to genetic counselling and preventing the transmission of the disease.

A shortcoming of the study is that no biochemical investigations were carried out from the muscle homogenate. Since 13/16 patients had mutations in genes encoding subunits of complex-I, we can expect deficiency of complex-I activity in most of the patients.

A further shortcoming of the study is that the current medication of the 16 included patients was not provided. Knowing the current medication is crucial as it may exhibit adverse effects or may improve clinical manifestations and thus may influence the phenotype. This is particularly the case with mitochondrion-toxic AEDs, such as valproic acid, carbamazepine, phenytoin, or phenobarbital⁵. Thus, we should be informed which AEDs the patients with seizures were regularly taking.

Eleven of the 16 patients were put on mitochondrial cocktails but only five remained stable during a minimal follow-up of 1y¹. We would like to know if the dosage of the components of the cocktails was different between those who profited (n=5) and those who did not (n=6). Though the ketogenic diet has been shown beneficial in a number of MID patients⁶, particularly those with mitochondrial epilepsy⁷, none of the included patients obviously received this diet. The ketogenic diet has been shown to be particularly effective in MIDs with complex-I deficiency⁷.

In summary, this study could be more meaningful if heteroplasmy rates from various different tissues would have been provided, if information about the AED regimen and SLE therapeutic regimen would have been mentioned, if the ketogenic diet would have been applied, and if clinical and genetic information about first-degree relatives would have been included.

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