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# mtDNA-Variants with Low Heteroplasmy Rate may not be Responsible for Leigh Syndrome

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## Letter to the Editor

In a recent article, Wei et al. reported about a retrospective analysis of 16 patients with late-onset (>2y) Leigh syndrome (LS) [1]. We have the following comments and concerns.

Inclusion criterion 4 is inconclusive [1]. It is not justified to diagnose an abnormal energy metabolism by the presence of an mtDNA mutation. Abnormal energy metabolism can be confirmed only by measuring activities of respiratory chain complexes in the muscle homogenate. How many of the patients undergoing muscle biopsy also had biochemical investigations of respiratory chain complex activities? How many of those undergoing biopsy had polarography? Since 13/16 patients had a mutation in subunits of complex-I, we can expect reduced activity of complex-I on biochemical investigations

It is contradictory to define bilaterally symmetric lesions of the basal ganglia (BG) as inclusion criterion [1] and to include three patients in whom the putamen was only unilaterally involved. How to explain this contradiction?

It is mentioned that 75% of the LS patients carry mutations in nuclear genes, while only 25% carry a mutation in mtDNA located genes [1]. Why were no patients with mutations in nuclear genes included?

Interestingly, 6 of 16 patients had experienced stroke-like episodes (SLEs) according to table 1 [1]. SLEs present with a stroke-like lesion (SLL) on MRI, which is typically hyperintense on DWI and ADC sequences in the acute stage and not confined to any vascular territory. However, in the results section in none of the patients was a SLL described on MRI [1]. How to explain this discrepancy? Did patients with SLLs have multiple MRI investigations and were only MRI investigations reported, which did not show SLLs? Since SLEs are rather a rare phenotypic feature of LS, it would be interesting to learn about the MRI findings in the 6 patients with a SLE. In the method section it is mentioned that only T1, T2, and FLAIR sequences were evaluated [1]. Is this the reason why SLLs were missed and remained undescribed?

Six of 16 patients had seizures, but it remains unclear which type of seizures were found, how frequent they occurred, and how they were treated. Since epilepsy is a prominent feature of LS [2], often determining the outcome of these patients, we should be informed which antiepileptic drugs (AEDs) were given, in particular how many received mitochondrion-toxic AEDs [3] and in how many of the 6 patients seizure control could be achieved. Since some seizures occasionally only respond to a ketogenic diet [4], it should be mentioned how many of the patients with epilepsy and how many of those without seizures were put on a low glycemic/high fat proportion diet.

Three patients were described with general cerebral atrophy according to table 2, but only 2 of these patients had enlarged ventricles [1]. How to explain this discrepancy? Is it conceivable that in the one patient without enlarged ventricles atrophy concerned only the cortex?

Serum lactate was elevated in 11/16 patients. The more sensitive test suggesting a MID compared to resting lactate, is the lactate stress test [5]. How many of the 16 patients with normal resting lactate serum level had in fact lactate elevation during exercise?

Interestingly, 5 of 10 patents had elevated CSF lactate but MRS revealed a lactate peak in 6 patients. Were patients undergoing MRS those who did not have lactate determination in the CSF?

CPEO was described in 5 patients according to table 1, but in the discussion it is mentioned that double vision was the second most frequent manifestation. How to explain this discrepancy?

Heteroplasmy rates were <50% in 5 patients [1]. How to explain that the phenotype was truly attributable to the detected mtDNA variant? Were heteroplasmy rates measured in tissues other than muscle, such as hair follicles, buccal mucosa, muscle, skin fibroblasts, or urinary epithelial cells?

Thirteen of the 16 patients had ataxia but only in 1 patient were abnormalities of the cerebellum described [1]. Was ataxia in the remaining patients attributable to involvement of the spinal cord or to a lesion of the sensory nerves?

Overall, this interesting study has some shortcomings, as outlined above, which limit the interpretation of data and make some of the conclusions questionable.

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