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Letter to the Editor

Similar phenotype of Leigh syndrome due to m.10197G>A but variable heteroplasmy in mother and child

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We eagerly read the article by Wei *et al*. about a 19 years-old male with Leigh syndrome due to the variant m.10197G>A who manifested with spinal cord involvement [1]. His mother carried the variant as well and manifested with a similar phenotype as her son, except for spinal cord involvement [1]. Heteroplasmy rates in blood and urinary sediment were 68 and 93% respectively in the index patient and 19 and 61% respectively in the mother [1]. The study is appealing but raises concerns which require discussion.

We disagree with the notion that Leigh syndrome in the index patient had an adult onset [1]. Diplopia started at age 14 and cerebral MRI at that time revealed symmetric lesions in the thalami, midbrain, and pons [1]. These lesions, most likely had developed already before age 14 and were most likely subclinical until age 14. Therefore, the onset was either already in infancy or childhood but definitively not in adulthood.

It is not comprehensible why the index patient was treated with methyl-prednisolone at age 14 and again at age 19 [1]. We should know if antibodies against acetyl-choline receptors or anti-MUSK antibodies were elevated and if repetitive nerve stimulation disclosed an abnormal decremental response at that time. We should also be informed if the cerebral lesions detected at age 14 were misinterpreted as multiple sclerosis. Did visually-evoked potentials at age 14 show prolonged p100 latencies? At age 19 it was already evident that the patient had a mitochondrial disorder. Mitochondrial disorders usually do not benefit from steroids but might get even worse under steroids [2].

A limitation of the study is that the cerebro-spinal fluid (CSF) was not investigated for lactate and that no magnetic resonance spectroscopy (MRS) had been carried out. Leigh syndrome is usually associated with elevated lactate in the CSF and MRS usually shows a lactate peak. Elevation of CSF lactate is likely since serum lactate was elevated in the index patient [1].

Aggravating weakness is described at age 19 but it is not mentioned at which age muscle weakness started. At age 18 the patient was still able to carry out normal daily activities. Therefore, muscle weakness must have been between age 18 and age 19.

At age 18 the patient complained about clumsiness of hands [1]. However, clinical neurologic exam at age 19 did not disclose any sensory disturbances. This discrepancy should be solved. We should know if the patient ever underwent nerve conduction studies and if sensory nerve conduction or sensory nerve action potentials of the ulnar or median nerves were reduced.

Since the patient had quadrispasticity and a broad-based gait already at age 19 on clinical exam, it is not comprehensible how the patient could have developed spastic gait at age 20 and 21. The patient should have presented with spastic gait already at age 19.

Severity of the phenotype was obviously similar in the index patient and his mother. However, heteroplasmy rate of the m.10197G>A variant was lower in the mother than her son. Readers should be informed how these discrepancy can be explained.

Spinal cord involvement is not uncommon in Leigh syndrome and has been repeatedly reported [3, 4].

Overall, the interesting study has several limitations which challenge the results and their interpretation. Clarifying these weaknesses would strengthen the conclusions and could improve the study.

Declarations

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