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Leigh syndrome can manifest with intracranial calcifications and bleedings ☆,☆☆

Letter to the editor

We read with interest the article by Alemao et al. about 3 patients with Leigh syndrome, who were diagnosed with the disease upon the clinical presentation and the findings on cerebral magnetic resonance imaging (MRI) [1]. In 2 of these patients the diagnosis of Leigh syndrome was genetically confirmed by demonstration of the mtDNA variant m.12622G>A in *MT-ND5* (patient-1) and the variant m.9191T>C in *MT-ATP6*, respectively [1]. The study is appealing but raises concerns that should be discussed.

We disagree with the statement in the discussion that no cerebral calcifications have been reported in patients with Leigh syndrome [1]. In a patient with atypical Leigh syndrome due to a pathogenic *MT-ATP6* variant, basal ganglia calcifications bilaterally have been reported [2]. Intra-cranial calcifications were also reported in a patient with Leigh syndrome due to a mutation in the *ADAR* gene [3]. Several other patients with Leigh syndrome in the literature presented with intra-cranial calcifications. We also disagree that cerebral bleeding does not occur in patients with Leigh syndrome [1]. In a 21-year-old male who succumbed from Leigh syndrome, post-mortem investigations revealed hemorrhages of the corpora mamillaria bilaterally [4].

Because patients with Leigh syndrome often develop lactic acidosis [5], and because lactic acidosis can be documented also in the brain [6], it is crucial that patients with suspected Leigh syndrome also undergo magnetic resonance spectroscopy (MRS) to confirm or disclose a lactate peak or cerebrospinal fluid (CSF) investigations to measure lactate directly in the CSF. Lactate peaks on MRS strongly support the clinical diagnosis of Leigh syndrome. Because Leigh syndrome is commonly associated with lactic acidosis in the blood, it is also crucial to know the blood lactate values.

We disagree with the caption of Figure 6 [1]. Apparent diffusion coefficient (ADC) maps do not show hypointensity as mentioned in the caption on ADC but hyperintensity of the lenticular nucleus, thus suggesting vasogenic edema rather than a cytotoxic edema. There were hypointensities on ADC in the crura cerebri bilaterally but hyperintensities in the lentiform nucleus bilaterally.

We also disagree with the statement in the discussion that a lactate peak can be detected on MRS only in case of severe cerebral lesions. There are patients with a genetically confirmed mitochondrial disorder without structural lesions on MRI but with a lactate peak on MRS [7].

Missing are the heteroplasmy rates of the mtDNA variants in patient 1 and patient 2 [1]. Because heteroplasmy rates can determine the phenotypic expression significantly, it is essential that heteroplasmy rates are determined by quantitative real-time PCR in the most affected tissues.

Because pathogenic mtDNA variants are inherited via the maternal line in 75% of the cases [8], it is crucial to know if the mother or other first-degree relatives were also affected. Missing are the results of electro-encephalography (EEG) recording, as Leigh syndrome is commonly associated with epilepsy. Missing is the genetic confirmation of the diagnosis in patient-3.

We suggest that patients with suspected Leigh syndrome should not only undergo cerebral MRI but also MRS and cerebral CT scans in order to rule out calcifications or bleeding, which may rarely occur in these patients.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Patients with suspected Leigh syndrome require extensive diagnostic work-up including clini-

Abbreviations: ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

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cal, blood/CSF chemical, imaging, bioptical, functional, and genetic studies.

Author contribution

JF: design, literature search, discussion, first draft, critical comments, final approval.

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Josef Finsterer, MD, PhD*
Neurology & Neurophysiology Center, Postfach 20, 1180, Vienna, Austria

Shaundra M. Newstead, PhD
HeatSync Biochemistry Laboratory, 108 W Main St., Mesa, AZ 85201, USA

**Corresponding author.*
E-mail address: fifigs1@yahoo.de (J. Finsterer)

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