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Letter to the Editor

Diagnose MELAS and Stroke-Like Episodes in Carriers of m.12315G>A in *MT-TL2* According to Established Criteria

Josef Finsterer
Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

We read with interest the article by Snyder *et al*. about a 5 year-old female with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) due to the variant m.12315G>A in *MT-TL2* [1]. The patient presented phenotypically with developmental regression, stroke-like episodes (SLEs), low L-arginine, low citrulline, low nicotinamide, and low methionine [1]. Despite administration of nicotineamide and N-acetylcysteine, the clinical course was progressive. The study is impressive, but some points require discussion.

We disagree with the diagnosis of MELAS. MELAS is diagnosed according to either the Japanese or Hirano criteria [2, 3]. According to the Hirano criteria, MELAS is diagnosed when SLEs occur before age 40, and there are seizures or dementia, lactic acidosis or ragged-red fibres, normal early development, recurrent headache, or recurrent vomiting [2]. According to the Japanese criteria, MELAS is diagnosed when at least two of the conditions A (headache with vomiting, seizures, hemiplegia, cortical blindness, acute focal lesion on imaging) or at least 2 of the laboratory conditions B (elevated serum or cerebrospinal fluid (CSF) lactate, mitochondrial abnormalities on muscle biopsy, MELAS-related gene mutations) are present [3]. Because the index patient had no seizures associated with SLE and early development was not normal, the Hirano criteria were not met. The index patient also did not meet the Japanese criteria, therefore MELAS cannot be diagnosed.

We also disagree with the description of figure 1. Diffusion weighted imaging (DWI) revealed not only hyperintensity in the temporal cortex bilaterally, but also punctate subcortical lesions on the right side. We also disagree that the lesions on DWI represent cytotoxic oedema. To classify the DWI lesions as cytotoxic oedema, we need to know the results of the apparent diffusion coefficient (ADC) maps. Only if the corresponding area was hypointense on ADC can cytotoxic oedema be diagnosed. Furthermore, right-sided hyperintensity on DWI has no counterpart on T2. Does the right-sided lesion represent an acute ischemic stroke or an early stage stroke-like lesion (SLL)? What were the clinical manifestations of the right-sided lesion? Was this a second SLL? How did this lesion develop at follow-up?

A limitation is that the mother, who suffered from bipolar disorder, was not clinically examined [1]. Although she tested negative for the variant of the index patient in blood, it is conceivable that she transmitted the variant to her child, but the mutation did not occur in the blood lymphocytes because they were not phenotypically affected. Therefore, we should know whether the mother's clinical neurologic examination, cerebral MRI, spectroscopy, and electroencephalography (EEG) were all normal. We should also know whether first-degree relatives other than the mother were clinically affected. It would also be interesting to know whether tissues other than blood have been examined for heteroplasmy rates of the causative *MT-TL2* variant.

A second limitation is that no EEG was recorded during the SLE corresponding to the left-sided SLL. Since a pathophysiological hypothesis of SLLs is that they are the consequence of cortical seizure activity [4], it is mandatory to record serial EEGs in patients with SLE.

A third limitation is that the patient was not prospectively evaluated for multisystem involvement in the disease. Because mitochondrial disorders usually manifest phenotypically as a multisystem disease, either from the onset or with disease progression, it is crucial to evaluate these patients for impairment of other organs.

In summary, MELAS should be diagnosed only if the Hirano or Japanese criteria are met. SLLs should only be diagnosed if the imaging criteria for diagnosing SLLs are met. To assess whether the causative variant was inherited from the mother or occurred sporadically, it is important to clinically and genetically examine the mother and other first-degree relatives.

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Statement of Ethics: a) The study was approved by the institutional review board (responsible: Finsterer J.) at the 4th November 2022. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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