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Letter to the Editor

Supposed Late Onset of MELAS Often Turns Out to be a Classical Early Beginning

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With interest we read the article by Diao *et al*. on a 61 year-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome with onset at the age of 61 [1]. The initial clinical manifestation was migraine-like headache in the context of a stroke-like episode (SLE) followed by right-sided hemiparesis including the face, hemianopia to the left, hallucinations, emotional instability, and lethargy [1]. Despite administration of ATP, coenzyme-Q, and L-arginine, the patient experienced a second SLE about two months later on the contralateral side, clinically manifesting with focal seizure and left-sided hemiparesis [1]. He recovered incompletely under lamotrigine, coenzyme-Q, and L-arginine [1]. The study is compelling, but has limitations that are cause of concerns and should be discussed.

We are not convinced that onset of MELAS was late in the index patient [1]. The strongest argument for an earlier onset than presumed is that the patient had generally reduced tendon reflexes. Except for acute neuropathy or myopathy, reduced tendon reflexes usually exist for longer. Therefore, it is quite likely that the patient had pre-existing neuropathy or myopathy with an onset long before the age of 61. Did the patient ever complain about easy fatigability, muscle cramps, exercise intolerance, or sensory disturbances before the age of 61? Was creatine-kinase (CK) or lactate ever elevated prior to the age of 61? Another argument against late-onset MELAS is that SLEs are rarely the initial manifestation of MELAS. Other indications for an earlier onset than presumed are short stature, facial dysmorphism, hypoacusis, early-onset cataract, cardiac disease, or hypothyroidism.

A shortcoming of the study in this respect is that the patient was not prospectively examined for subclinical or clinically manifesting multisystem disease. MELAS usually manifests as a multi-organ disease affecting not only the brain or the muscles but also the eyes, ears, endocrine system, heart, intestines, immune system, bones, skin, kidneys, and nerves [2]. Therefore, it is critical that MELAS patients are systematically screened for multisystem involvement since early diagnosis and treatment of multisystem disease can improve their outcome.

Electroencephalography (EEG) recordings after the first SLE showed high and low amplitude sharp slow-wave activity across both hemispheres. This finding, along with elevated creatine-kinase and post-ictal lethargy suggest that the first SLE was triggered by or accompanied by seizures. We should know why anti-seizure medication was not started after the first EEG and whether the individual history was positive for seizures or syncope. An argument for seizures as a trigger of the first SLE is that the patient presented with lethargy, instability, and hallucinations during the first SLE [1].

It would have been interesting to know the results of the biochemical examination of the muscle homogenate. Biochemical examinations allow to assess whether function of respiratory chain complexes I to IV is within normal limits or reduced due to reduced amounts of tRNA(Leu). In MELAS reduction of multiple respiratory chain complexes can be documented.

There is no mention whether or not first-degree relatives were examined clinically or genetically. Knowing whether the variant m.3243A>G occurred sporadically or was inherited is crucial for genetic counselling.

A further limitation of the study is that the results of multimodal MRI were only incompletely reported. We should know the results of apparent diffusion coefficient (ADC) maps, perfusion-weighted imaging (PWI), susceptibility-weighted imaging (SWI), and oxygen-extraction fraction (OEF) MRI. Stroke-like lesions (SLLs) show up as hyperintensity not only on DWI but also on T2/FLAIR, PWI, and OEF.

It would have been interesting to know the heteroplasmy rate not only in blood lymphocytes, where it was relatively low. The low heteroplasmy rate suggests that the variant m.3243A>G was not causative. Determining heteroplasmy rates in tissues other than lymphocytes, such as muscle, urinary epithelial cells, skin fibroblasts, hair follicles, or buccal mucosa cells, could help

establish the variant m.3243A>G as causative. If muscle is still available for heteroplasmy testing, higher rates than in blood are to be expected.

A limitation of the study is that no reference limits were reported and that there is no mention of hight, hearing, vision, thyroid function, deformities, and the current medication.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Before classifying MELAS as late onset, subclinical or mildly manifesting long-term abnormalities need to be ruled out.

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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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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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