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Stroke in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes is a vasogenic edema and not ischemic

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Abstract

Introduction: there is no common sense how to diagnose and treat stroke-like episodes in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

Aims: to discuss some shortcomings of a previously published paper about a 48yo female with MELAS.

Methods: commentary

Conclusion: the report could be more meaningful if the diagnosis would have been confirmed genetically, if NO-precursors would have been administered for the SLE, if possible, triggers of the SLE would have been discussed, and if the patient would have been prospectively investigated for subclinical or mildly manifesting abnormalities.

Keywords: Mitochondrial; Stroke-like episode; Stroke-like lesion; NO-precursors

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Commentary

Background: diagnosing and treating stroke-like episodes (SLEs) is challenging, as there is a lack of appropriate studies. Since the frequency of patients with a mitochondrial disorder and thus SLEs is increasing, there is a need to unify diagnostic criteria and to offer an effective treatment. In a recent article, Almasi et al. reported about a 48 years old female with MELAS, diagnosed upon the clinical presentation, blood values, and imaging and muscle biopsy findings [1]. Since this study has a number of shortcomings, it is crucial to extensively discuss these points. We have the following comments and concerns.

Aims: the current commentary aims at highlighting and discussing unsolved issues, at stimulating research to meet the unsolved points, and to improve the outcome. There are

a number of shortcomings. Methods: this is a commentary about a previously published female with MELAS. It should help the reader to optimise diagnostic and therapeutic approaches and to deepen the understanding of unsolved issues. Results and discussion: We do not agree with the statement that stroke in MELAS is ischemic [1]. In the acute stage, stroke-like lesions (SLLs) on MRI, the imaging equivalent of a stroke-like episode (SLE), show up as hyperintensity on diffusion weighted imaging (DWI) and as hyperintensity on apparent diffusion coefficient (ADC) maps [2]. Only in the later stages may SLLs convert from a vasogenic edema to non-specific regional abnormalities [2]. How many days after onset of the SLE was the MRI carried out? Did the MRI abnormalities completely resolve with resolution of the clinical manifestations?

As mentioned by the authors, MELAS and mitochondrial disorders (MIDs) in general, are multisystem diseases [3]. The patient obviously manifested with SLEs, seizures, migraine, easy fatigability, lactic acidosis, anemia, and hypoacusis [1]. Were any other of the possible clinical manifestations additionally found, such as short stature, confusion, cognitive impairment, dementia, basal ganglia calcification, ptosis, ophthalmoparesis, visual disturbance, gastro-intestinal problems (vomiting, volvulus), renal insufficiency, or neuropathy [4]? How to explain that the patient had severely elevated serum lactate but respiratory alkalosis? We do not understand why the patient received valproic acid (VPA) after the first seizure. First, a single seizure not necessarily requires treatment with antiepileptic drugs (AEDs) and second it is well established that VPA is mitochondrion-toxic [5]. Even fatalities have been reported due to VPA, particularly in patients carrying POLG1 mutations. Is it conceivable that the first SLE in the described patient was triggered by VPA? Are there other triggers for the SLE conceivable? Why was VPA replaced by levetiracetam? Another therapeutic option for MIDs, particularly mitochondrial epilepsy, is the ketogenic diet. Was the patient put on such a low-glucose and fat-rich diet? Diagnosing MIDs requires documentation of a pathogenic mtDNA or nDNA variant. Was the patient and her first-degree relatives tested for the most common MELAS mutations? In up to one quarter of the MID patients mutations occur spontaneously as de-novo events [6]. Since the parents were clinically unaffected, a de novo mutation is quite likely.

As mentioned by the authors, SLEs are currently best treated with NO-precursors, such as L-arginine or L-citrulline [7]. This is also the recommendation we follow. However, why were no NO-precursors administered in the study of Almasi et al. but instead, mannitol and dexamethasone? From steroids it is known that they may not only have a beneficial but also detrimental effects [8]. Prospective multi-center studies need to be carried to develop the most effective treatment. Conclusions: the study has a number of shortcoming but could be more meaningful if the diagnosis would have been confirmed genetically, if NO-precursors would have been administered for the SLE, if possible triggers of the SLE would have been discussed, and if the patient would have been prospectively investigated for subclinical or mildly manifesting abnormalities.

Author contribution: JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments.

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