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In Patients with Juvenile "Stroke", Diabetes, Seizures, and Lactic Acidosis, MELAS Should be considered

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LETTER TO THE EDITOR

We read with interest the article by Camacho-Caballero, *et al*., about a 47 year-old male admitted for a generalised tonic-clonic seizure and a history of diabetes and previous stroke 10 years ago, complicated by structural epilepsy treated with valproic acid (VPA) [Camacho-Caballero, K. *et al*., 2023]. Work-up for elevated serum lactate levels revealed the mtDNA variant m.3243A>G in *MT-TL1* [Camacho-Caballero, K. *et al*., 2023]. Despite administration of L-arginine and replacement of VPA with lamotrigine (LTG), the patient experienced two stroke-like episodes (SLEs) during a two-year follow-up [Camacho-Caballero, K. *et al*., 2023]. The study is impressive, but several points require discussion.

We disagree with the classification of the cerebral lesions shown in figure 1 as ischemic stroke. These abnormalities represent typical stroke-like lesions (SLL), the morphological equivalent of a SLE. SLEs are the phenotypic hallmark of MELAS and occur in the vast majority of these patients [Finsterer, J. 2023]. They are typically located in the temporo-occipital area but can also occur in other locations and are not confined to a vascular territory [Finsterer, J. 2023]. They often initially manifest themselves as seizures, followed by focal or non-specific neurological deficits [Finsterer, J. 2023]. Further arguments against an ischemic stroke are that the patient had no classic cardiovascular risk factors other than diabetes. To further confirm that the lesion shown represents a SLL, it would have been necessary to perform perfusion-weighted imaging (PWI) where the lesion is hyperintense and oxygen extraction fraction (OEF)-MRI, where the lesion is hypointense [Finsterer, J. 2019]. On fluor-deoxy glucose (FDG) positron emission tomography (PET) SLLs typically appear as hypometabolic area [Finsterer, J. 2019]. Hyperintensity on diffusion-weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC) suggest not only ischemia, abscess formation, lymphoma, post-seizures condition, CJD, but also SLL.

A limitation of the study is that heteroplasmy rates in affected an unaffected tissues were not reported. Knowledge of heteroplasmy rates is necessary not only for assessing future disease and outcome, but also for genetic counselling.

Another limitation of the study is that family history was only taken for neurological diseases but mitochondrial disorders (MIDs) can manifest not only in the cerebrum, but also in any other organ or tissue. Since mtDNA variants are transmitted via the maternal line in 75% of cases [Poulton, J. *et al*., 2017], there is a high probability that the causative variant was inherited in the index patient. We should know whether the mother of the index case was examined by a neurologist or genetically tested, and whether other first-degree relatives had multisystem disease suggestive of MID. Particularly in m.3243A>G carriers with low heteroplasmy rates, phenotypic manifestations may be subtle and easily overlooked.

Another limitation is that no information about the first stroke before 10y was provided. We should also know the serum creatine-kinase level at admission, the results of the blood gas analysis, and the HbA1c value.

We disagree that L-arginine is really effective for SLEs. There is no double-blind, placebo-controlled trial that clearly shows that L-arginine has a beneficial effect, neither in either the acute or chronic stages of SLLs.

In conclusion, the excellent study has limitations that should be addressed before drawing final conclusions.

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