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LETTER TO THE EDITOR

Stroke-like lesions should not be mixed up with ischemic stroke in MELAS with cardioembolic risk

We read with interest the article by Salari et al. on a 34-year-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome who had reportedly suffered from recurrent, ischemic, cardioembolic strokes.[1] The patient presented phenotypically with cognitive decline, epilepsy, "stroke," myopathy, and lactic acidosis.[1] During the clarification of the ischemic strokes, a patent foramen ovale (PFO) and thrombi in the left atrial appendage (LAA) were found.[1] It was concluded that the index patient is the first with MELAS and a PFO and the first with a progressive pattern of ischemic lesions.[1] The study is excellent but has limitations that should be discussed.

The major limitation of the study is that the MELAS diagnosis was not genetically confirmed.[1] Although the patient had manifestations of mitochondrial disorder (MID), presented cerebral lactic acidosis and a muscle biopsy showing ragged-red fibers (abnormal mitochondrial on Gomori trichrome stain),[1] detecting a causative mutation would strongly support the diagnosis. Knowledge of the genetic cause is also crucial for assessing the patient's course and outcome and for genetic counseling. According to the Japanese MELAS diagnostic criteria, proof of a pathogenic genetic defect is a prerequisite for diagnosing MELAS.[2]

A second limitation of the study is that the cerebral lesions presented in figure 1 at ages 27, 28, and 34 years, may not necessarily correspond to ischemic lesions but could also represent stroke-like lesions (SLLs), the morphological equivalent of a stroke-like episode (SLE) at various stages. SLEs are the hallmark of MELAS and manifest with characteristic clinical and imaging peculiarities. Arguments for SLLs are that previous lesions had resolved at follow-up and that cerebral lactic acidosis was present.[1] FLAIR images are not sufficient to differentiate between ischemic stroke and SLLs in the acute stage.[3] Other modalities must be shown, such as diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), perfusion-weighted imaging (PWI), oxygen-extraction fraction (OEF), and magnetic resonance spectroscopy (MRS) to confirm or exclude ischemia or SLLs. SLLs are characterized on multimodal MRI by hyperintensity at T2/FLAIR, DWI, PWI, and hypointensity at OEF.[3] MRS shows a lactate peak and a SLL does not conform to vascular territory and initially expands, then regresses after reaching a nadir, finally ending as white matter lesion, cyst, atrophy, cortical laminar necrosis, or the toenail sign.[3] Thrombi in the left atrial appendage (LAA) do not necessarily mean that a cardio-embolism has occurred. Ischemic stroke in the acute stage is characterized by DWI hyperintensity and ADC hypointensity confined to a vascular territory. In the chronic stage, differentiation from other chronic lesions is usually not possible.

A third limitation is that neither the mother nor the father of the index patient has been clinically evaluated by a neurologist or has undergone instrumental examination or genetic testing. As MELAS due to mtDNA variants is transmitted maternally in 75% of cases,[4] it is imperative that first-degree relatives, particularly the mother, are evaluated clinically and genetically. Even when first-degree relatives appear clinically normal at first glance, they may have mild or subclinical manifestations of the disease that could be detected by a physician familiar with MIDs.[5] For this reason, family screening is mandatory.

We disagree with the statement in the abstract that the index patient "is the first reported case of MELAS with PFO".[1] Several other MELAS patients with a PFO have been reported.[6] For example, PFO has been reported in a 41 year-old male with MELAS due to the variant m.3243A > G in *MT-TL1*.[6]

No mention is made of what treatment the patient received for the three "ischemic" strokes. Has he ever had thrombolysis or thrombectomy? What secondary prophylaxis was given? There is also no mention of what antiseizure drugs (ASDs) the index patient was receiving. Knowledge of the ASDs is critical as some of them can be mitochondrion toxic such as barbiturates, phenytoin, carbamazepine, valproic acid, or zonisamide.[7]

We disagree with the assumption that MELAS is the most common MID.[1] The most common MIDs are the

non-syndromic MIDs (those which do not fit to any mitochondrial syndrome), which often go undetected. We also disagree with the assumption that MELAS is always maternally transmitted. Since MELAS can also be due to variants in *POLG1*,[8] inheritance can also be autosomal dominant or recessive.

Overall, the interesting study has limitations which challenge the results and their interpretation. Addressing these limitations could further strengthen and reinforce the statement of the study. There are no "unique features" in this case report. The patient most likely had three SLEs and was at increased risk of cardioembolism. The ischemic nature of the reported brain lesions has not been convincingly documented.

KEYWORDS

MELAS, multimodal MRI, stroke, stroke-like episode, stroke-like lesion

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Josef Finsterer: Conceptualization; data curation; formal analysis; writing – original draft.

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