



Microbleeds within Mitochondrial Stroke-Like Lesion Rather Result from Their Vulnerability Than from Microangiopathy

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LETTER TO THE
EDITOR

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ABSTRACT

MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episode) is one of the most common syndromic mitochondrial disorders (MID) and is due to the variant m.3243A>G in MT-TL1 in approximately 80% of cases. MELAS is a multisystem disorder with stroke-like episodes (SLEs) as a pathognomonic feature. The morphological correlate of SLEs in cerebral imaging are stroke-like lesions (SLLs). SLLs present on cerebral MRI with a T2, FLAIR, DWI, and PWI-hyperintense and OEF-hypointense lesion that is not confined to a vascular territory and extends to a nadir before disappearing or terminating as a structural lesion. Occasionally, these features are accompanied by microbleeds within the SLL, usually along the cortex. These microbleeds are thought to result from laminar cortical necrosis, and end-stage of a SLL or seizures, a common manifestation of SLEs.

KEY WORDS:

MELAS, stroke-like lesion, microbleeds, laminar cortical necrosis

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LETTER TO THE EDITOR

We eagerly read the article by Martens et al. about a 35-year-old male with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome due to the variant m.3243A>G whose cerebral magnetic resonance imaging (MRI) showed microbleeds within stroke-like lesions (SLLs) [1]. It was concluded that microhemorrhages can present on MRI in (sub)acute MELAS lesions and may reflect mitochondrial microangiopathy [1]. The study is appealing but raises concerns that require discussion.

We disagree with the statement that the index case is “the first report of a case of juxtacortical microhemorrhages in MELAS” [1]. In a study of 14 SLLs, the morphological equivalent of a stroke-like episode (SLE) on MRI, in six patients with MELAS, T1-weighted images showed hyperintense cortical signals compatible with laminar cortical necrosis (LCN) during the subacute stage of the SLE [2], and fat-suppression MRI confirmed intracortical gyral hemorrhage in one SLE [2]. Petechial gyral microhemorrhages were also pathologically confirmed on the autopsy of another patient [2]. In seven of nine SLEs, focal cortical hyperperfusion was seen in single photon emission computed tomography (SPECT) studies [2]. In nine of eleven episodes, focal epileptiform discharges were recorded on electroencephalography (EEG) in the acute stage of the SLLs [2]. Small bleeding within a SLL has been also reported in a 56-year-old female with MELAS in whom the history was negative for arterial hypertension or coagulopathy [3]. There are also reports of hemorrhagic transformation of SLLs in MELAS patients [4].

We also disagree with the statement that ‘microhemorrhages can present on MRI in (sub) acute MELAS lesions and may reflect mitochondrial microangiopathy’ [1]. Although some of the MELAS patients may manifest with diabetes, hyperlipidemia, or arterial hypertension, microangiopathy is rather unlikely

the cause of bleeding within a SLL. First, most MELAS patients do not manifest with radiological evidence of microangiopathy on MRI. Second, bleeding does not occur in cerebral areas outside a SLL. Third, MELAS patients are commonly young, suggesting that microangiopathy is not present in these patients. Fourth, microbleeds were absent on the initial MRI and were only seen on follow-up MRI, suggesting that the vulnerability of a SLL but not microangiopathy was responsible for the bleedings. More likely than from microangiopathy, bleeding within SLLs results from LCN or seizure activity. Seizures can be complicated by microbleeds [4]. There is also evidence that LCN can be complicated by bleeding. Because SLLs are commonly associated with LCN, it can be speculated that focal cortical necrosis favors the development of bleeding.

Overall, the interesting study has limitations that challenge the results and their interpretation. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Microbleeds within the SLLs of MELAS patients are more likely to result from seizures or LCN than from microangiopathy.

Declarations

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Ethics Approval: Was in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent to Participate: Was obtained from the patient.

Consent for Publication: Was obtained from the patient.

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Code Availability: Not applicable.

Author Contribution: Josef Finsterer: design, literature search, discussion, first draft, critical comments, final approval.

REPLY BY THE AUTHORS

DEAR EDITOR,

We thank the responding authors for their interest and comments.

Please note that we do not claim to be the first to demonstrate microhemorrhages in MELAS in general, but that, to our knowledge, we demonstrate an imaging pattern on MRI that has not been described before in patients with MELAS. For clarity, we refer to 'microhemorrhages' from an imaging point of view, that is, punctate foci on susceptibility weighted imaging (SWI).

The provided references by the responding authors refer to petechial hemorrhage in cortical laminar necrosis or macroscopic hemorrhage. On the available T1-weighted imaging (time-of-flight-sequence [5]) that was performed on all our scans, no cortical hyperintensity was present during any stage of the MELAS lesions to suggest cortical LCN. In addition, none of the abnormalities on SWI showed any diffuse, gyriform pattern as has been reported in cortical laminar necrosis [6]. Indeed, also subcortical foci of susceptibility have been described in cortical laminar necrosis [6], as well as in other conditions like status epilepticus, and therefore other etiology cannot be excluded [7].

The responding authors state that 'microbleeds . . . were only seen on follow-up on MRI, suggesting that the vulnerability of a stroke-like lesion but not microangiopathy was responsible for the bleedings.' This

is inaccurate, since we also reported microhemorrhages in an acute lesion. Furthermore, the time of appearance of the abnormalities on SWI is not by itself equal to the time of onset of the specific underlying pathological process, as there may be a threshold of vessel injury to overcome before microhemorrhages develop and because blood products may need time to become apparent on SWI.

As the imaging pattern that we report shows similarities to cerebral amyloid angiopathy, we hypothesize (not conclude) that this could reflect mitochondrial microangiopathy. The angiopathy theory, in addition to the cytopathy theory, is one of the two major theories for the development of MELAS-lesions and suggests that MELAS lesions are the result of abnormal mitochondrial endothelial function that impairs autoregulation [8]. In fact, angiopathy has been reported to be a frequent finding at autopsy in patients with MELAS [9]. In addition, even in case mitochondrial dysfunction is not the culprit pathophysiological process in MELAS, it could make vessels more susceptible to other types of injury with aging. Interestingly, there is supportive evidence that mitochondrial dysfunction plays a role in cerebral amyloid angiopathy [10].

We hope further research may provide more insights on the true incidence and etiology of the demonstrated abnormalities.

Sincerely,
Dr. Benjamin Verhaaren, MD PhD

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