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**Letter to the Editor**

# Stroke-like lesions in MELAS are not caused by regional vasospasms of cerebral arteries

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We read with interest the article by Zhao *et al*. about three patients (patient-1 (32yo male), patient-2 (57yo female), patient-3 (22yo female)) with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to the variant m.3243A>G, in whom stroke-like lesions (SLLs) were attributed to reversible focal, vasoconstriction as demonstrated by magnetic resonance angiography (MRA) [1]. The study is appealing but raises concerns that should be discussed.

We disagree with the notion that SLLs, the morphological equivalent of stroke-like episodes (SLEs) on cerebral imaging, are due to transient, focal cerebral vasoconstriction. Several arguments support the view that SLLs are not caused by cerebral vasculopathy. First, SLLs are not confined to a vascular territory [2]. Second, the morphological appearance and dynamics of SLLs on MRI is at variance from ischemic stroke [2]. Third, vasoconstriction may be present in the absence of a SLL [1]. Fourth, autopsy of MELAS patients with a SLL does not show necrosis as in ischemic stroke [3, 4]. Fifth, Ischemic lesions usually remain visible on imaging whereas SLLs usually disappear.

Concerning patient-1, there is a discrepancy between vasospasm in the right middle cerebral artery (MCA) (figure 1, panel D) and the SLL (figure 1, panel C), which involves the right posterior lobe. Since the occipital lobe is supplied by the posterior cerebral artery (PCA), vasospasms of the right MCA cannot be responsible for the SLL in an occipito-temporal distribution. A further argument against a causal relation between vasospasms and the SLL in patient-1 is the discrepancy between the size of the SLL and the location of the vasospasm in the M1 segment of the MCA [1]. Vasospasm of the M1 segment suggests that the entire MCA territory should be affected but not only a small portion of the supply area as shown in patient-1.

We also disagree with the notion that macro-angiopathy in MELAS is not well recognised as expressed in the introduction [1]. On the contrary, it is well known that MELAS can be associated with rupture of the aorta, dissection of the carotid arteries, ectasia of large arteries, and aneurysm formation [5]. There is also increasing evidence that MELAS can be associated with atherosclerosis [6] either due to classical risk factors such as diabetes, arterial hypertension, or hyperlipidemia, which are more prevalent among MELAS patients compared to the "healthy" population, or due to the underlying genetic defect [6].

An explanation for segmental, cerebral artery vasospasms in MELAS could be the scenario that vasospasms are a secondary phenomenon triggered by the SLLs. There is ample evidence that SLLs are characterised by hyperperfusion in the acute stage and hypo-perfusion in the subacute stage [7]. Therefore, vasospasms could be responsible for hypo-perfusion as seen on perfusion weighted imaging in subacute SLLs [2]. It is also conceivable that vasospasms represent areas of focal sympathetic over-activity. We also should not exclude that the MRA findings were misinterpreted and rather represent artefacts than a true pathology. This is why presumed vasospasms on MRA should be confirmed by conventional digital subtraction angiography (DSA) immediately after the MRA. DSA is more sensitive for assessing the vessel diameter and for documenting the dynamics of the lumen width.

Missing is the MRA of the second SLL in patient-3 [1]. Though vasospasms were described in the right MCA and right PCA, this finding is not documented in figure-3.

Missing are the results of the electroencephalography (EEG) investigations [1]. Since SLLs can be triggered by seizures, it is crucial to know if any of the three patients had seizures prior to onset of the SLEs and if any of the EEGs revealed epileptiform discharges.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. There is no evidence for the assumption that SLLs in MELAS are due to reversible vasospasms of intracerebral arteries.

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