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Letter to the Editor

Treating metabolic stroke is currently unsupported by evidence

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We read with interest the review article by Orsucci *et al*. about the pathophysiology, clinical presentation, and treatment of stroke-like episodes (SLEs), the clinical equivalent of cerebral stroke-like lesions (SLLs), also known as metabolic stroke, and mainly occurring in primary (genetic) mitochondrial disorders (MIDs) [1]. It was concluded that no etio-pathophysiological therapies are currently available for SLLs and that gene therapy seems to be a promising strategy [1]. The study is appealing but raises concerns that need to be discussed.

We do not agree that SLLs are generally triggered by epileptic seizures [1]. There are patients who have neither seizures nor an electroencephalogram (EEG) with epileptiform discharges, but still develop SLLs [2]. In a recent study of 88 patients with MELAS and 23 patients with a *POLG-1* variant, all of whom had developed SLLs, motor seizures, occipital seizures, or status epilepticus were found in only 63%, 52%, and 22% of the MELAS patients respectively [2]. Epileptic discharges were only recorded in 55% of MELAS patients [2]. These findings support the fact that there are MID patients without seizures or epileptic activity before, during, or after the onset of a SLL. Even in those who have developed seizures or who have recorded epileptiform discharges, it is unclear whether the seizure is the chicken or the egg of SLLs. Of course, seizures can be the cause of oxidative stress in cortical areas, which triggers SLLs, but there are several other causes of oxidative stress as well. Physical over-activity and emotional stress as well as infections or focal metabolic stress can be responsible for the development of SLLs.

A further argument against seizures being the exclusive trigger of SLLs is that SLLs occur not only in cortical areas but also in subcortical regions or even in the cerebellum [3]. The morphology of a cerebellar SLL is just as incongruent with a vascular territory as in supra-tentorial SLLs [3]. The cerebellum is not usually considered a source of seizure activity.

We disagree with the recommendation to generally treat an evolving SLL with intravenous anti-seizure drugs (ASDs) such as phenytoin or phenobarbital [1]. It is known that these compounds can be toxic to mitochondria and possibly trigger oxidative stress and thus worsen the clinical appearance of a SLL [4]. Accordingly, mitochondrion-toxic ASDs such as carbamazepin, valproic acid, phenytoin, or phenobarbital should not be used as drugs of first choice.

The review does not discuss dietary measures to prevent metabolic stress in patients with a MID. Changes in the daily requirement profile, lifestyle changes, and dietary changes toward an anaplerotic diet can reduce lactic acidosis, a potential trigger of SLLs [5]. The review makes no recommendations for the treatment of SLLs that are not associated with seizures.

Cerebral edema accompanying a SLL is not a common feature and may be caused by inadequate attempts at therapy [6]. Treatment of SLLs by craniotomy should be avoided, if possible, in order not to further increase the oxidative stress of a patient with an ongoing SLL.

Overall, the interesting review has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could enhance the study. Up to now, neither a uniform trigger of SLLs nor a uniform treatment of SLLs has been identified.

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