CORRESPONDENCE

The metabolic hypothesis is more likely than the epileptogenic hypothesis to explain stroke-like lesions [version 1; peer review: awaiting peer review]

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Abstract
Stroke-like episodes (SLEs) are a hallmark of mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome but occur in other mitochondrial disorders (MIDs) as well. The morphological equivalent of the SLE is the stroke-like lesion (SLL) on magnetic resonance imaging (MRI). The pathophysiology of SLLs is under debate, but several hypotheses have been raised to explain the phenomenon. Of these, the metabolic, epileptogenic, and vascular hypotheses are the most frequently discussed. There are several arguments for and against these hypotheses, but a consensus has not been reached which of them provides the correct explanation. A recent consensus statement generated by a panel of experts applying the Delphi method, favoured the epileptogenic hypothesis and recommended treatment of SLEs with antiepileptic drugs, irrespective if the patient presented with a seizure or epileptiform discharges on electroencephalography (EEG) or not. We disagree with this general procedure and provide the following arguments against the epileptogenic hypothesis: 1. not each SLE is associated with seizures. 2. epileptiform discharges may be absent on EEG during a SLE. 3. SLLs are not restricted to the cortex. 4. antiseizure-drugs (ASDs) may not prevent the progression or recurrence of a SLL. 5. ASDs may terminate seizures but no other phenotypic feature of a SLE. 6. patients already under ASDs are not immune from developing a SLE. 7. SLLs usually last longer than seizures. 8. no animal model supports the epileptogenic hypothesis. The strongest arguments for the metabolic hypothesis are that SLLs are not confined to a vascular territory, that the oxygen-extraction fraction within a SLL is reduced, and that there is hypometabolism within a SLL on FDG-PET. SLLs may respond to antioxidants, NO-precursors, steroids, or the ketogenic diet. ASDs should be applied only if there is clinical or electrophysiological evidence of seizure-activity.

Keywords
mtdna, mitochondrial, stroke-like, epilepsy, stroke-like lesion
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We read with interest the consensus statement by Ng et al. about the pathogenesis and treatment of stroke-like lesions (SLLs). We largely disagree with the consensus paper as it does not consider arguments for alternative pathomechanisms explaining the development of a SLL.

There are several arguments against the epileptogenic hypothesis. First, not all patients with a mitochondrial disorder (MID) who ever experienced a SLL also have an individual history positive for epilepsy. Thus, we disagree with the statement that “seizures are commonly present at the outset of stroke-like episodes (SLEs)”. Second, the electroencephalography during a SLL does not reveal epileptogenic activity in most cases. Third, SLLs are not restricted to the cortex. Though SLLs originate from stressed cortical layers in the majority of cases, there are also extra-cortical locations of SLLs. SLLs have been reported in the thalamus, midbrain, pons, and even the cerebellum. There are even indications that SLLs may develop within the optic nerve. Fourth, anti-seizure drugs (ASDs) may not exhibit a beneficial effect on the dynamics, development, and outcome of a SLL. ASDs may stop seizure activity but may not affect other clinical manifestations of the SLL. Fifth, patients with SLLs may have seizures not time-related to the occurrence of a SLL. Sixth, patients already under ASDs for previous seizures are not be saved from developing a SLL nonetheless. Even if ASDs are given for a SLL, this may not prevent the development of a SLL in another location during the presence of the initial SLL. Seventh, a SLL can last for months, whereas a seizure is usually a limited event unless it is an epileptic state. Eighth, there is no animal model of a MID available in which triggering of seizures induces the development of a SLL.

More plausible than the epileptogenic hypothesis to explain the appearance of a SLL is the metabolic hypothesis. There are several arguments that favour the metabolic over the epileptogenic hypothesis as a pathogenetic model to explain the occurrence of a SLL. First, a MID is a metabolic disorder with a defect in the mitochondrial energy production. Thus, it is conceivable that increased focal oxidative stress cannot be compensated by the already compromised mitochondria and results in a metabolic breakdown, cellular dysfunction, and finally degeneration or apoptosis of neurons, glial cells, endothelial cells, vascular smooth muscle cells, or pericytes. Increased oxidative stress may be due to increased physical or psychological requirements, infections, cerebral ischemia, seizure activity, intoxication, or increased metabolic demand. Second, oxygen-extraction within the SLL is reduced on oxygen-extraction fraction (OEF)-MRI. As with increased oxygen concentrations in venous blood from MID patients, cells within the SLL are no longer capable of utilising oxygen sufficiently. They most likely change their energy metabolism to anaerobic glycolysis or produce ATP within the cytoplasm by means of glycolysis. Third, in the early stages of a SLL, the alterations are predominantly found in cortical areas with particularly high oxidative stress. In accordance with the frequent location of a SLL in the occipito-temporal regions, one of the highest metabolic demands has been found in the occipital cortex. This, is probably attributable to the density of neurons, which is the highest in the occipital cortex. Furthermore, neurons from the visual cortex are exposed to a higher glutaminergic input from dendrites compared to the motor cortex with a high demand to maintain ionic homeostasis after excitatory depolarisation. Fourth, dendrite-rich cortical areas are particularly vulnerable to hypoxia and the density of mitochondria is particularly high in dendrites. Fifth, serum amino acids are decreased at onset of a SLE to increase one day after onset in a single patient. Low levels of serum amino acids suggest that energy during the focal metabolic crisis in the brain is generated via the utilisation of amino acids. Sixth, increased lactate peaks and decreased N-acetylaspartate (NAA)-peaks in m.3243A>G carriers on MR-spectroscopy can be reversed by intravenous L-arginine. Seventh, antioxidants and cofactors can be beneficial in some patients with a SLL as well as steroids which may re-establish the blood-brain barrier disrupted by the metabolic defect.

With regard to epilepsy in MID the panel forgot to discuss the effect of the ketogenic diet (KD). KD may be effective even if conventional ASDs are ineffective and may be even beneficial in epileptic states.

In summary, we agree that seizures may occasionally trigger the development of a SLL but we disagree that this is the general pathophysiology. Much more likely, SLLs result from the primary metabolic defect, which does not allow neurons under stress to meet an increased metabolic demand for whatever reason any longer. Extra-cortical SLLs are no argument against the metabolic hypothesis as high energy demand may not only occur in the cortex but also in other cerebral locations, depending on the current tasks of a network or circuit. High amounts of sensory input may, for example, stress thalamic neurons leading to a SLL there. Understanding the pathophysiology of SLLs is a prerequisite to optimally manage them.

Data availability

Underlying data

No data are associated with this article.

References
