CORRESPONDENCE

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

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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

Open Peer Review

Reviewer Status
Invited Reviewers
1
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Any reports and responses or comments on the article can be found at the end of the article.
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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 mitochondrial disorder (MID) available in which triggering of seizures induces the development of a SLL.

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.

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


Open Peer Review

Current Peer Review Status:  

Version 1

Reviewer Report 14 April 2020

https://doi.org/10.21956/wellcomeopenres.17283.r38255

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Finsterer provides an alternative proposal to the recently published consensus statement on diagnosis and management of stroke-like episodes related to mitochondrial disorders, in which seizures are highlighted as a core aspect of stroke-like episodes which should be targeted through therapeutics. The author outlines several lines of evidence pointing to an alternative metabolic hypothesis, in which seizures can be a consequence but are not the root cause of neuronal injury. The arguments are convincing and provide a framework for a more rational and well rounded pathophysiology of stroke like episodes, and provides the basis for possible changes to the published consensus statement.

Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epilepsy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
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Thank you for these valuable comments

**Competing Interests:** No competing interests were disclosed.