The metabolic hypothesis is more likely than the epileptogenic hypothesis to explain stroke-like lesions [version 2; peer review: 2 approved]

Josef Finsterer
Krankenanstalt Rudolfsstiftung, Messerli Institute, Vienna, 1180, Austria

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 SLL. 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
Corresponding author: Josef Finsterer (fipaps@yahoo.de)

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The seventh argument in favour of the metabolic hypothesis was discarded.

Any further responses from the reviewers can be found at the end of the article

Correspondence

We read with interest the consensus statement by Ng et al. about the pathogenesis and treatment of stroke-like lesions (SLLs). We disagree with the consensus paper in the point that 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, the statement that “seizures are commonly present at the onset of stroke-like episodes (SLEs)” is not comprehensible. Second, the electroencephalography (EEG) during a SLE does not reveal epileptogenic activity in most cases, irrespective if the patient experienced a seizure or not. 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 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 extension, development, and outcome of a SLL. ASDs may stop seizure activity but may not affect morphology, extension, or dynamics of a SLL or its other clinical manifestations. Fifth, patients with SLLs may have seizures timely-unrelated to the occurrence of a SLL. Sixth, patients already under ASDs for previous seizures may not be saved from developing a SLL nonetheless. Even if ASDs are given for a SLL, this may not prevent the development of a second or third SLL in the same or another location. 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 in favour of the metabolic 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. Functionally impaired mitochondria may not be resistant against increased oxidative stress resulting 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 suggesting that impaired mitochondria can no longer utilise oxygen properly. 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, 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 may be decreased at onset of a SLE to increase shortly afterwards again. Low levels of serum amino acids suggest that energy during the focal, cerebral, metabolic crisis is generated by 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. Generally, the NO-precursor L-arginine seems to exhibit a beneficial effect on the extension, progression, duration, and outcome of a SLL, why it has been approved by the FDA as a treatment of SLLs.

In summary, we agree that seizures may occasionally trigger the development of a SLL but we disagree that this is the general pathophysiology. Other triggers should, as outlined above, be considered as well. SLLs may develop in response to stress as neurons carrying mutated mitochondria are no longer capable to meet an increased metabolic demand. 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 or cerebellar 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
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Mirian C.H. Janssen  
Amalia Children’s Hospital, Department of Pediatrics, Radboud Center for Mitochondrial Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

No new additional comments

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Metabolic disease in adults, Mitochondrial disease, MELAS

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.

Version 1

Reviewer Report 19 June 2020

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Mirian C.H. Janssen
Amalia Children’s Hospital, Department of Pediatrics, Radboud Center for Mitochondrial Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

The author comments on the recently published European consensus on management of stroke like episodes.

The goal of the consensus was not to elaborate extensively on the pathomechanism of SLLs. In the
The goal of the consensus was not to elaborate extensively on the pathomechanism of SLLs. In the introduction it is described that underlying mechanism of stroke-like episodes remains unclear. The vascular theory is explained and also the theory of neuronal hyper-excitability. It is emphasized that there are controversies surrounding the mechanisms. The recommendations are derived from the consensus approach, based on clinical experience from the leading mitochondrial clinical services of several European countries and the appraisal of current literature. They acknowledge that the majority of the recommendations are not evidence-based due to the inherent challenges of conducting clinical trials in rare diseases.

The author states that the metabolic hypothesis is more likely to explain SLL than the epileptogenic hypothesis and puts several arguments against the epileptic theory like “patients with SLLs may have seizures not time-related to the occurrence of a SLL”, “patients already under ASDs for previous seizures are not be saved from developing a SLL nonetheless, even if ASDs are given for a SLL” and there is no animal model of a MID available in which triggering of seizures induces the development of a SLL.

These arguments are not convincing against the epileptic theory nor pro the metabolic theory. The argument “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”, has not been proven at all. These are suggestions which have not been proven in a proper clinical trial. That is also the case for the ketogenic diet.

Although the metabolic theory sounds plausible, the author has no valid data to substantiate this theory, it is only based on anecdotal case reports. For this reason I find the article not suitable for indexing. A more proper critical appraisal on evidence concerning the metabolic theory would be valuable.

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

Are any opinions stated well-argued, clear and cogent?
No

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
No

Is the conclusion balanced and justified on the basis of the presented arguments?
No

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

**Reviewer Expertise:** Metabolic disease in adults, Mitochondrial disease, MELAS.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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Joe Finsterer, Messerli Institute, Vienna, Austria
The author comments on the recently published European consensus on management of stroke-like episodes. The goal of the consensus was not to elaborate extensively on the pathomechanism of SLLs. In the introduction it is described that underlying mechanism of stroke-like episodes remains unclear. The vascular theory is explained and also the theory of neuronal hyper-excitability. It is emphasized that there are controversies surrounding the mechanisms. The recommendations are derived from the consensus approach, based on clinical experience from the leading mitochondrial clinical services of several European countries and the appraisal of current literature. They acknowledge that the majority of the recommendations are not evidence-based due to the inherent challenges of conducting clinical trials in rare diseases.

If the recommendations of the consensus group are not evidence-based, as indicated by Prof. Janssen, they have a similar strength as other expert opinions.

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The argument “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”, has not been proven at all. These are suggestions which have not been proven in a proper clinical trial. That is also the case for the ketogenic diet. We agree, that the evidence for antioxidants, steroids, and the ketogenic diet (KD) is low. Only a few clinical and experimental studies are available that gave promising results with these compounds [Frey et al. Biochim Biophys Acta Mol Basis Dis 2017, Steriade et al. Pediatr Neurol 2014, Haefeli et al, PlosOne 2011]. However, NO-precursors (eg. L-arginine), and not antioxidants, steroids, and the KD are the most widely proposed treatment for SLLs. For supporting NO-precursors, controlled studies are available [Rodan et al. PlosOne 2015, Koga et al. J Neurol 2018, El-Hattab et al, Mol Genet Metab 2016].

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We do not agree that only case reports are available for arguing in favour of the metabolic hypothesis. There are a few case-control, observational, and prospective clinical trials [Rodan et al. PlosOne 2015, Koga et al. J Neurol 2018, El-Hattab et al, Mol Genet Metab 2016, Sudo et al. Brain Development 2014] and experimental trials [Desquiret-Demas et al. Biochim Biophys Acta 2012] available. Furthermore, case reports do not mean no evidence, just lower evidence than randomised, controlled studies. Since no very high level studies are currently available, a critical appraisal of the metabolic theory can rely only on the currently available data and these are the few observational, controlled studies, case reports, and expert opinions.
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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**Author Response 18 Apr 2020**

**josef finsterer,** Messerli Institute, Vienna, Austria

Thank you for these valuable comments
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