

Treatment of Stroke-Like Episodes Requires NO-Precursors, Avoidance of Mitochondrion Toxic Drugs, and Antiepileptics only When Seizures Occur

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LETTER TO THE EDITOR

We were interested to read the article by Mickelsson, *et al.* on a retrospective observational study of the clinical presentation and treatment of 20 stroke-like episodes (SLE) in 12 patients with mitochondrial disorder (MID) due to m.3243A>G, m.8344A>G or W748S variants in POLG1 [Mickelsson, N. *et al.*, 2024]. Ten of the 12 patients had to be admitted to the intensive care unit, 8 received new anti-seizure medication (ASM), and seven of the 12 patients died [Mickelsson, N. *et al.*, 2024]. It was concluded that early recognition of SLE, especially seizures, and prompt treatment are essential to improve the outcome of these patients [Mickelsson, N. *et al.*, 2024]. The study is noteworthy, but several points should be discussed.

The first point relates to the definition of SLE [Mickelsson, N. *et al.*, 2024]. We do not believe that all SLEs manifest with bilateral seizures or impaired consciousness [Mickelsson, N. *et al.*, 2024]. There are several reports of patients with SLE in whom neither focal nor generalized seizures occurred and in whom the EEG recorded during SLE was normal [Dhawan, S. *et al.*, 2024; Salari, M. *et al.*, 2023; Ng, Y. S. *et al.*, 2019]. Therefore, not all patients with SLE require antiepileptic treatment as recommended in a recent consensus statement [Ng, Y. S. *et al.*, 2019]. This is supported by the fact that two of the twelve patients included in the study were not receiving ASM and that in two patients with previous epilepsy, ASM was not altered during SLE [Mickelsson, N. *et al.*, 2024]. Impaired consciousness is also not a constant feature that occurs in every SLE, as required by the SLE definition in the index article [Mickelsson, N. *et al.*, 2024]. Although most SLE is associated with altered consciousness, there are several reports of SLE that do not alter consciousness [Murakami, K. *et al.*, 2023].

The second point is that seven of the 10 patients admitted to the ICU received propofol [Mickelsson, N. *et al.*, 2024]. Propofol is known to be mitochondrial toxic and can cause propofol infusion syndrome when administered as an infusion over a prolonged period of time [Shimizu, J. *et al.*, 2019]. Propofol infusion syndrome is mainly observed in patients with MIDs and can be fatal [Vanlander, A. V. *et al.*, 2012].

The third point is that it was not stated for what reason 10 out of 12 patients with SLE had to be admitted to the ICU [Mickelsson, N. *et al.*, 2024]. Was admission to the ICU due to intractable seizures requiring thiopental anesthesia, respiratory insufficiency due to brainstem involvement, or impaired consciousness with loss of protective reflexes? It is also conceivable that artificial respiration was required in 8 out of 10 patients due to lung infection from aspiration, pulmonary embolism or heart disease.

The fourth point is that the causes of death of the deceased were not specified in detail. Did these patients die from intractable epilepsy, secondary infections, sepsis, cardiac involvement, or due to progression of SLE in terms of size and clinical severity? What were the causes of death at autopsy of these seven patients? Did any of them die from propofol infusion syndrome?

The fifth point is that it is not understandable why only two of the 12 patients received NO precursors such as L-arginine or L-citrulline [Mickelsson, N. *et al.*, 2024]. Although there is limited evidence that NO precursors are truly effective in SLE [Ikawa, M. *et al.*, 2020], they should be administered as long as there is no contraindication or definitive proof of their ineffectiveness.

To summarize, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and

corroborate the study's message. All unanswered questions need to be clarified before readers uncritically accept the conclusions of the study. In patients with SLE requiring ICU admission, ASM should only be administered if these patients have seizures, and propofol or other mitochondrial toxic drugs should be avoided to prevent a risk factor for mortality.

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