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Letter to the Editor

Mitochondrial epilepsy is not confined to syndromic mitochondrial disorders and not each stroke-like episode is seizure-triggered

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We read with interest the review article by Loprione *et al*. on epilepsy in mitochondrial disorders (MIDs) [1]. It was concluded that seizures and status epilepticus are one of the most frequent symptoms of MIDs, occurring in 20-50% of them, that patients with specific genotypes are more at risk of developing seizures than others, and that the management and treatment of mitochondrial epilepsy needs to be personalized [1]. The study attracts attention, but has limitations that are cause for concerns and should be discussed.

We disagree with the notion that epilepsy is the most common cerebral nervous system (CNS) clinical feature of primary mitochondrial disorders (MIDs) [1]. More common than epilepsy are, for example, headache, cognitive impairment, or ataxia. Seizures may be more common in the pediatric MID population as compared to adult MIDs.

We also disagree with the statement that "status epilepticus usually coexists with stroke-like episodes (SLEs)" [1]. Epilepsy in MIDs can occur together with or without SLEs. MID patients can manifest with a number of structural lesions other than stroke-like lesions (SLLs), the morphological equivalent of a SLE. These include atrophy, cysts, calcifications, neoplasms, white or grey matter lesions, bleeding, iron deposits, or edema.

We also disagree with the notion that syndromic MIDs, such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome, myoclonic epilepsy with ragged red fibers (MERRF) syndrome, POLG-related disorders, and Leigh syndrome are the MIDs in which epilepsy most commonly occurs [1]. MIDs most commonly manifesting with epilepsy are the non-syndromic MIDs. They constitute the majority of primary MIDs and are often undetected for years.

We disagree that "SLEs are generally regarded as manifestations of prolonged and aberrant ictal activity" and "associated with status epilepticus" [1]. What triggers SLLs is so far unknown but there are a number of MID patients manifesting with SLEs who never experienced a seizure and in whom the electroencephalogram (EEG) never showed epileptiform discharges. Therefore, it cannot be concluded that seizures generally trigger SLEs [1].

Propofol should be avoided if possible in patients with a MID. Although it may have a beneficial effect on prolonged seizures or status epilepticus in some MIDs, it also can have side effects, such as the propofol infusion syndrome, which can unmask a previously unknown MID and can be lethal in some cases [2].

Missing in the review is a critical discussion of mitochondrion-toxicity of several anti-seizure drugs (ASDs). These include particularly phenobarbital, carbamazepine, phenytoin, valproic acid, and topiramate [3]. In single patients with *POLG1* variants, valproic acid can be even fatal [4].

Overall, the review by Loprione *et al*. has several limitations that call the results and their interpretation into question. Addressing these issues would strengthen the conclusions and could improve the status of the study. Mitochondrial epilepsy is more common in non-syndromic than syndromic MIDs and SLEs are not only triggered by seizures but several other factors as well. When treating mitochondrial epilepsy the mitochondrion-toxic potential of some ASDs should be considered.

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