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Letter to the Editor

The Successful Treatment of Mitochondrial Epilepsy Requires the Application of the Entire Antiepileptic Regimen

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Letter to the Editor

We read with interest the review by Na *et al*. on the therapeutic management of mitochondrial epilepsy (mtE) [1]. The article is noteworthy, but several points deserve discussion.

First, the therapeutic options for treating mtE are more diverse than discussed in the review. They lack the use of vagus nerve stimulation, as tested in MERRF patients [2], transcranial direct current stimulation (DCS) [3], glucocorticoids [4], ketamine [5], NO precursors, and antioxidants.

Second, stroke-like episodes (SLE) were not considered as a cause of seizures [1]. SLE is the main feature of MELAS but can also occur in other mitochondrial diseases (MID) [6]. SLE is thought to be triggered by seizures, as they usually originate in the cortex or are complicated by focal or generalized seizures. In SLE-associated seizures, not only antiepileptic drugs (ASMs) but also NO precursors (L-arginine, L-citrulline) and antioxidants can be helpful [6].

The third point is that the CNS manifestations of MID are more diverse than discussed in the review [1]. In addition to epilepsy, developmental delay/regression, migraine, pyramidal tract/extrapyramidal anomalies, MIDs can also manifest as SLE, pituitary dysfunction (short stature, hypothyroidism, hypogonadism, hypocorticism), cerebral atrophy, sleep disturbances, optic atrophy, central sleep apnea syndrome, central respiratory dysfunction, failure to thrive, dysphagia, and CNS disorders secondary to cardiac involvement in MIDs (e.g., cardiomyopathy, heart failure, arrhythmias) [7].

The fourth point is that some of the ASMs can be dangerous for MIDs [8]. In particular, valproic acid (VPA) is known to cause acute liver failure in MID patients due to POLG1 mutations [8]. But glucocorticoids can also be fatal, especially in patients with Kearns-Sayre syndrome.

The fifth point is that the treatment of status epilepticus (SE) and supra-refractory SE (SRSE) has not been specifically addressed [1]. SE and SRSE are common complications of MTE, especially in patients with Leigh syndrome. SE and SRSE can be frequent causes of death, especially in patients with early-onset Leigh syndrome. Because the topic has serious clinical implications, it is important to discuss it in a review on the treatment of MTE. In this context, it is missing to mention that not only VPA and benzodiazepines can be used for this indication, but also other ASMs available for intravenous administration, such as levetiracetam, lacosamide, phosphenytoin, ketamine, phenobarbital, or brexanolone.

The sixth point is that dietary measures should be taken not only in refractory epilepsy, but generally in all forms of MTE. Ketogenic therapy should only be discontinued in case of intolerance.

The seventh point is that MIDs can manifest with lactic acidosis in the brain, especially in MELAS. Since lactic acidosis can trigger seizures, measures to reduce lactate in the CSF or brain parenchyma are essential. Lactate-lowering measures include avoiding lactate-increasing medications (e.g., biguanides, reverse transcriptase inhibitors, zivodine, stavodine, linezolid, propofol, sorafenib) and using lactate-lowering medications (reduction of physical activity, fluid intake, oxygen therapy, etc.).

The treatment of mtE is more diverse than described. Since MIDs often manifest with SE or SRSE, these seizure types must be given special consideration.

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