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Letter to Editor

Mitochondrial Epilepsy Requires Specific Therapeutic Management

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Letter to the Editor

With interest we read the review article by Lim and Thomas about the diagnosis and therapeutic management of mitochondrial epilepsies, in particular in *POLG1*-related disease (Alpers-Huttenlocher disease), disease, Leigh syndrome, pyruvate dehydrogenase deficiency, and myoclonic epilepsy with ragged red syndrome (Lim, A., & Thomas, R.H. 2020). We have the following comments and concerns.

We do not agree with the terminology of a SLE as "pathognomonic seizure (Lim, A., & Thomas, R.H. 2020)". The authors seem to be followers of the epileptogenic hypothesis to explain SLEs. The strongest arguments against the epileptogenic hypothesis, however, are that many SLEs do not go along with seizures, that anti-seizure have frequently no effect on SLEs, that no epileptiform activity is recorded on in many patients with a SLE, that stroke-like, the morphological equivalent of a SLE, may also occur in subcortical, even infra-tentorial locations (e.g. thalamus, red nucleus, pons, cerebellum, optic nerve) (Bhatia, K. D. *et al.*, 2020), and that non-ASD drugs can be beneficial for SLEs.

We also do not agree with the statement that epilepsy is rare in other mitochondrial disorders (MIDs), such as neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome, Kearns-Sayre syndrome (KSS), Leber's hereditary optic or non-syndromic MIDs. Particularly, the non-syndromic MIDs, which constitute the biggest group of MIDs and frequently go along with involvement of the brain, manifest frequently, amongst other things, with seizures (Ticci, C. *et al.*, 2020). Among the syndromic MIDs epilepsy has been additionally reported in infantile-onset spino-cerebellar ataxia (IOSCA) and leucoencephalopathy with brain-stem and spinal cord involvement and lactic acidosis (LBSL) (Finsterer, J., & Mahjoub, S. Z. 2012).

The authors do not mention that L-arginine, which is FDA-approved for the indication stroke-like episodes (SLEs), can also exhibit a beneficial effect on SLE-associated seizures (Toribe, Y. *et al.*, 2007). Seizures may be either the trigger or the complication of a SLE and may be intractable to ordinary ASDs. In single cases of intractable epilepsy or even status epilepticus L-arginine has been proven beneficial (Toribe, Y. *et al.*, 2007).

The authors obviously mix up vagal nerve stimulation and epilepsy surgery. Epilepsy surgery does not mean vagal nerve stimulation, as suggested in the review (Lim, A., & Thomas, R.H. 2020). Epilepsy surgery is based on the surgical resection of epileptogenic foci after previous exact identification by invasive EEG recordings in the one third of patients with intractable epilepsy. Neither epilepsy surgery nor

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vagal nerve stimulation has been reported in a patient with a MID.

We do not agree with the conclusion that "there are currently no specific curative treatments for other causes of pediatric mitochondrial epilepsy except from the rare primary coenzyme Q10 A., & Thomas, R.H. 2020). Thiamine-responsive Leigh syndrome due mutations in *SLC19A3* (Savasta, S. *et al.,* 2019). And biotinidase-deficiency due to *BTD* variants should be mentioned. Seizures in these patients may respond to high dose thiamine respectively biotin (Değerliyurt, A. *et al.,* 2019).

The authors do not mention that myoclonic epilepsy in MERRF and other syndromic or non-syndromic MIDs best responds to and (Finsterer, J. *et al.,* 2019; & Finsterer, J. 2019). ASDs such as valproic acid (VPA), or should not be given as first-line treatment (Finsterer, J. *et al.,* 2019).

Missing in the review is a critical discussion of the mitochondrion-toxic effect of various ASDs (Finsterer, J., & Zarrouk Mahjoub, S. 2012). Though the authors mention that VPA is contra-indicated in *POLG1*-related MIDs (Lim, A., & Thomas, R.H. 2020), they do not refer to other potentially mitochondrion-toxic ASDs, such as PB, carbamazepine (CBZ), or (Finsterer, J., & Zarrouk Mahjoub, S. 2012; & Rinalduzzi, S. *et al.,* 2012). TPM may trigger visual impairment in carriers of primary LHON mutations (Rinalduzzi, S. *et al.,* 2012). There is also no mentioning that propofol, often administered for intractable seizures on intensive care units, can exhibit severe side effects in MID patients, such as the propofol-infusion syndrome (Finsterer, J., & Frank, M. 2016; & Vollmer, J. P. *et al.,* 2018).

Finally, it should be mentioned that in MID patients with supra-refractory epileptic state, refractory to benzodiazepines, PHT, propofol, or even thiopental, ketamine may be helpful (Prüss, H., & Holtkamp, M. 2008) and that the ketogenic can be particularly effective in MID patients with refractory epilepsy due to a complex-I deficiency (Paleologou, E. *et al.,* 2017).

Overall, the review has a number of limitations and shortcomings which prohibit drawing conclusions as those presented. Mitochondrial epilepsy should not be treated as epilepsy in non-MID patients but under consideration of the peculiarities of MIDs.

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