

## Letter to the Editor

## Is Levetiracetam And Clonazepam Truly The Treatment of Choice For Myoclonus In MERRF?

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Josef Finsterer, MD, PhD**Keywords:** mitochondrial, mtDNA, deletion, multisystem, cardiac involvement.

In a recent article, Su *et al.*, reported about the anti-seizure drug (ASD) treatment of 17 patients with genetically confirmed MERRF syndrome (Su, L. J. *et al.*, 2018). It was found that monotherapy with LEV, CZP, VPA, or TPM was less effective than combination therapies of these 4 ASDs (Su, L. J. *et al.*, 2018). The most effective ASD combination was that of LEV and CZP, resulting in a beneficial effect in 12/17 patients (Su, L. J. *et al.*, 2018). We have the following comments and concerns.

Response to ASD treatment of myoclonic epilepsy in MERRF patients may not only depend on the stage of the disease and the phenotype, but also on the heteroplasmy rate of the m.8344A>G variant. Thus, we should be informed which heteroplasmy rates were found in the 17 included patients, and in which tissues heteroplasmy rates were determined. Heteroplasmy rates may strongly vary between hair follicles, skin fibroblasts, muscle cells, blood lymphocytes, buccal mucosa cells, or urinary epithelial cells.

Interestingly, 2 of the four patients with progressive disease after 4 months of monotherapy were on VPA (Su, L. J. *et al.*, 2018). From VPA it is well known that it can be mitochondrion-toxic, particularly in patients carrying *POLG1* mutations (Finsterer, J., & Zarrouk Mahjoub, S. 2012). VPA has been even made responsible for fatalities among patients with a mitochondrial disorder (MID) (Hynynen, J. *et al.*, 2014). VPA in these patients was particularly liver toxic (Hynynen, J. *et al.*, 2014). It should be discussed if deterioration of myoclonic epilepsy in 2 of the 17 patients is actually attributable to

VPA toxicity rather than ineffectivity of VPA or the natural disease course.

MERRF is a clinically defined disorder, diagnosed if the four canonical features myoclonus, generalised epilepsy, ataxia, and myopathy are present (Finsterer, J. *et al.*, 2018). Though all 17 patients presented with myocloni, only 7 had generalised tonic clonic seizures, only 14 patients had ataxia, and muscle biopsy was carried out in only 11 patients (Su, L. J. *et al.*, 2018). Furthermore, the results of muscle biopsy in the 11 patients were not reported. Assuming that muscle biopsy showed ragged-red mitochondrial myopathy in all of them, only 3/17 presented with all four canonical phenotypic features. This surprising finding should be explained. Variable heteroplasmy rates could be an explanation.

In addition to the four canonical features, cognitive decline and myopathy, MERRF patients may present with migraine, psychiatric disease, stroke-like episodes, respiratory insufficiency, neuropathy, ptosis, ophthalmoparesis, optic atrophy, pigmentary retinopathy, hypoacusis, arrhythmias, cardiomyopathy, dysphagia, vomiting, gastrointestinal dysmotility, diabetes, hypothyroidism, short stature, and lipomatosis (Finsterer, J. *et al.*, 2018). This is why we should be informed if any of these additional phenotypic presentations were present in any of the 17 included patients.

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Article History

Received: 12.09.2019

Accepted: 28.09.2019

Published: 10.10.2019

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Missing in this study is also the family history. Since 75% of the MIDs associated with mtDNA variants are maternally transmitted (Poulton, J. *et al.*, 2017), we should be informed in how many of the 17 cases the family history was positive for the disease. It is conceivable that the frequency of epilepsy and myocloni is different between sporadic and inherited cases.

A further shortcoming is that drugs other than ASDs were not mentioned. Since ASDs may interfere with other drugs leading to enhancement or attenuation of the ASD effect, we should know which drugs the 17 patients were taking in addition to ASDs.

In summary, this interesting study could profit from provision of heteroplasmy rates, a more comprehensive description of the phenotype, from a detailed family history, and from mentioning all drugs the included patients were regularly taking.

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