Beneficiality of combined levetiracetam, clonazepam for myoclonus in MERRF requires further confirmation

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To the Editor: With interest, we read the article by Su *et al*[1] about the antiepileptic drug (AED) treatment of 17 patients with genetically confirmed myoclonic epilepsy with ragged-red fibers (MERRF) syndrome. It was found that monotherapy with either levetiracetam (LEV), clonazepam (CZP), valproic acid (VPA), or topiramate (TPM) was less effective than combination therapies of these 4 AEDs[1]. The most effective AED combination was that of LEV and CZP, resulting in a beneficial effect in 12/17 patients.[1] We have the following comments and concerns.

Response to AED 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 4 patients with progressive disease after 4 months of monotherapy were on VPA.[1] From VPA it is well known that it can be mitochondrion toxic, particularly in patients carrying *POLG1* mutations.[2] VPA has been even made responsible for fatalities among patients with a mitochondrial disorder (MID).[3] VPA in these patients was particularly liver toxic.[3] It should be discussed if the 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 4 canonical features myoclonus, generalized epilepsy, ataxia, and myopathy are present.[4] Though all 17 patients presented with myocloni, only 7 had generalized tonic-clonic seizures, only 14 patients had ataxia, and muscle biopsy was carried out in only 11 patients.[1] Furthermore, the results of the 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 4 canonical phenotypic features. This surprising finding should be explained. Variable heteroplasmy rates could be an explanation.

In addition to the 4 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.[4] This is why we should be informed if any of these additional phenotypic presentations were present in any of the 17 included patients.

Missing in this study is also the family history. Since 75% of the MIDs associated with mitochondrial DNA (mtDNA) variants are maternally transmitted,[5] 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 AEDs were not mentioned. Since AEDs may interfere with other drugs leading to enhancement or attenuation of the AED effect, we should know, which drugs the 17 patients were taking in addition to AEDs.

In summary, this interesting study could profit from the 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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Author's Reply: On behalf of the authors of the article titled "Antimyoclonic Effect of Levetiracetam and Clonazepam Combined Treatment on Myoclonic Epilepsy with Ragged-Red Fiber Syndrome with m.8344A > G Mutation" We appreciate Prof. Josef Finstererfor his careful reading and priceless comments on our paper.[1] All patients in the paper are sporadic cases, and their DNA were obtained from the muscle. We noticed the existence of heteroplasmy of mitochondrial DNA and m.8344A > G.[6] It is a good comment for our next research, but we did not detect the heteroplasmy rates in this paper. The presenting symptoms and signs of patients were recorded in the article, and no other abnormalities were found. Michelangelo Mancuso found that the great majority did not have full-blown myoclonic epilepsy with ragged-red fibers (MERRF) syndrome by analyzing 321 patients with m.8344A > G mutation.[6] In all patients, myoclonus, muscle weakness and ataxia appeared in 35% to 45% of patients; generalized seizures and hearing loss showed in 25% to 34.9%.[6] Here, our cases were diagnosed by clinical manifestations, muscle biopsy, and genetic findings. Our cases are consistent with the study. Valproic acid (VPA) was used in 2 patients as the initial treatment, which is related to the initial wrong diagnosis. We considered that the patients with progressive disease (PD) conditions were related to mitochondrial toxicity of VPA.[7,8] After all, we did not find obvious liver dysfunction according to the case records. Some patients were prescribed B vitamins and idebenone irregularly except for antiepileptic drugs (AEDs) in our patients. The heterogeneity of mitochondrial genes is too complicated. The clinical heterogeneity of our patients should be related to genetic heterogeneity. The reader's suggestions make a lot of sense for our further work and research. We will make further improvements and thank the readers for their suggestions.

Conflicts of interest

None.

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