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Reply to letter to the editor☆,☆☆

Dear Sir,

This letter is in response to the letter by Dr Josef Finsterer, and we appreciate his interest in our case report detailing the diagnosis and treatment of a patient with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome [1].

In his letter, Dr Finsterer expresses several concerns with our report. In particular, the lack of evidence of heteroplasmy rates of affected tissues, mtDNA copy number, and satisfactory imagings of stroke-like episodes could challenge our diagnosis and interpretation. Indeed, knowledge of heteroplasmy rates would significantly help us understand the clinical variability and outcome, as well as deliver better genetic counseling to our patient [2,3]. Unfortunately, molecular genetic studies to identify this index, along with the more state-of-the-art neuroimaging that could better visualize stroke-like lesions such as FDG-PET and MR-spectroscopy, are currently unavailable at our institution. You and others have advanced our understanding of features of metabolic stroke in mitochondrial diseases, reporting that these are highly dynamic and vary with time [4]. We believe that a key strength of our study was the acquisition of a series of our patient's neuroimages spanning 7 years. In the acute stage, her lesions were hyperintense on T2/FLAIR, hypointense on ADC maps, and did not conform to any vascular territories on DWI. These lesions also originated in the left occipital-parietal cortical region due to focal metabolic breakdown and remained stable for 5 years, before they became hyperintense on ADC maps and co-existed with a new lesion in the right occipital-parietal cortical region. Her final MRI showed that the mentioned lesions atrophied, suggesting that neuronal and glial damages have reached the threshold of irreversible cell death. Having said that, the patient was not admitted to our institution when she first presented her symptoms, hence we acknowledge that the corresponding images were not of the best quality.

Dr Finsterer also commented that the patient's CSF profile was not entirely normal as lactate was elevated, to which we agree, and on her medications and treatment, to which we are grateful and would like to mention herein. After the patient was correctly diagnosed with MELAS, we started her on an oral mixture of coenzyme Q10, thiamine, folic acid, acetyl L-carnitine, and arginine. Anti-epileptic drugs with high mitochondrion-toxic profile, such as valproic acid, carbamazepine, phenytoin, or phenobarbital, were avoided [5]. Instead, topiramate and levetiracetam were chosen to control the patient's migraine and epilepsy. Additionally, her disease progress is being assessed with neurological examinations, disability rating scale (the Modified Rankin Score), and several neuropsychological tests that evaluate memory, executive and visuospatial functions every 3-6 months.

Finally, per Dr Finsterer's suggestion, we would like to briefly mention the epidemiology of mitochondrial disorders. Once considered rare, there is growing consensus that they actually represent the most common inherited errors of metabolism [6]. A recent and comprehensive analysis of 666 participants with mitochondrial disorders in North America reported Leigh syndrome and MELAS to be the first and second most frequent classical syndromes (seen in 97 and 71 individuals, respectively) [7]. Skladal et al. reported the minimum birth prevalence of primary mitochondrial disorders to be 6.2 cases per 100,000 births in Australia, and as high as 58.6 cases per 100,000 in those with Lebanese origin [8]. In addition, more than 3000 neonatal cord blood samples from the UK were examined and at least 1 in 200 healthy born children carried a pathogenic mitochondrial DNA mutation, among which the most common was m.3243A>G [9], also seen in our patient. There are relatively few reports about Asian populations, with 1 study in Taiwan reported that 0.1% (1 in 1017) of their screened newborns in a tertiary hospital carried a homoplasmic mitochondrial mutation [10]. Taken together, these data suggest that mitochondrial disorders are fairly common. Despite this, we ultimately agree with Dr Finsterer that these conditions are frequently overlooked and patients are often only diagnosed years after they develop symptoms.

Respectfully

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