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【 LETTERS TO THE EDITOR 】

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) due to a m.10158T>C ND3 Mutation with a Normal Muscle Biopsy

Key words: MELAS, stroke-like episodes, MT-ND3

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The Authors reply We greatly appreciate your useful comments on our paper about a case of adult onset mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome in a patient harboring a m.10158T>C mutation in the *MT-ND3* gene (1).

Patient 2 had been diagnosed with idiopathic epilepsy at 25 years of age, and his personal psychiatrist had prescribed a combination of three antiepileptic drugs. We increased the dosage of levetiracetam when he experienced recurrent stroke-like episodes with partial seizures. We agree that carbamazepine should have been discontinued when the patient was revealed to have mitochondrial disease. In our case, it is not known whether carbamazepine acted to enhance seizure-activity. Although a ketogenic diet might have been a therapeutic option (in addition to L-arginine therapy), we did not suggest the adoption of a ketogenic diet to our patients, because we did not have experience with this diet therapy and because there are no reports indicating that a ketogenic diet is effective in the treatment of patients harboring pathogenic mutations of the *MT-ND3* gene. Despite a careful and detailed interview, we could not find any family history suggestive of mitochondrial disease.

In our two cases, the quantification of the mitochondrial DNA heteroplasmy of the biopsied muscles was carried out using a pyrosequence analysis with a mutation-specific pyrosequencing primer, according to the manufacturer's protocol (PyroMark Q24 Qiagen). It is reported that the mutation load varies among specimens, and that it tends to be higher in muscle and lower in blood. However, other specimens were not established (2-6). We did not determine heteroplasmy rates for organs other than the biopsied muscles. However, the variation in the rate of heteroplasmy in the individual organs may reveal new insight into the relationship between genetic heteroplasmy and clinical symptoms.

Unfortunately, we could not measure the respiratory chain activities in the patients' mitochondria. It was previously reported that patients harboring m.10158T>C mutations show isolated complex I deficiency in muscle (2-5). McFarland et al. proposed that mutation loads of >40% cause a complex I defect, with enzyme activity inversely related to the m.10158T>C mutation load (2). However, a recent meta-analysis of patients carrying the m.10191T>C mutation, one of the pathogenic mutations of the *MT-ND3* gene-demonstrated that there was an unclear correlation between the mutation load and Complex I activity in the muscle and liver (7). Thus, it is unclear whether there is a threshold effect or a linear relationship with the mutation load, or if the Complex I activity reflects pathological changes and clinical dysfunction.

The reason why patients who harbor the m.10158T>C mutation do not show muscle weakness or pathological findings suggestive of mitochondrial myopathy in spite of the high rate of heteroplasmy and the low Complex I activity associated with the mutation has not been established. However, the aim of this paper was to recommend mitochondrial DNA analyses using muscle biopsies in patients with suspected stroke-like episodes, even if the muscle pathology has a normal appearance.

The authors state that they have no Conflict of Interest (COI).

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