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LETTER TO THE EDITOR

Adult-onset MELAS syndrome in a 51-year-old woman without typical clinical manifestations: a case report

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We sincerely appreciate the insightful comments on our work 'Adult-onset MELAS syndrome in a 51-year-old woman without typical clinical manifestations'.[1]

Dr. Finsterer has pointed out several limitations and concerns about the diagnosis of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome for the case we reported[2]: (i) not meeting clinical diagnostic criteria previously suggested[3,4]; (ii) no further investigation for subclinical multisystem involvement; (iii) no determination of heteroplasmy for the m.3243A > G variant; (iv) no biochemical investigations of the endomyocardial biopsy (EMB).

First, we conceptually agree with Dr. Finsterer's points of view. As noted in the discussion section, the patient had no symptoms or signs indicative of classical MELAS syndrome, so it was questionable whether the patient could be diagnosed with MELAS syndrome based on identifying the m.3243 A > G variant of *MT-TL1*. According to Dr. Finsterer, in this context, the patient should be classified into non-syndromic mitochondrial disorder (MID) resulting from the sporadic m.3243 A > G variant. The index patient had exhibited multi-systemic manifestations as she had developed hearing loss, diabetes, short stature, and cardiac problems, including atrioventricular block and left ventricular systolic dysfunction with increasing age, as seen in m.3243A > G variant carriers. MELAS syndrome has been perceived as representative of m.3243A > G variant-related disease because historically m.3243A > G variant was discovered through MELAS syndrome.[5] However, because it has been noted that m.3243A > G variant carriers exhibit a wide range of clinical phenotypes,[6] distinguishing MELAS syndrome from non-syndromic MID may be considered a historical concept in clinical practice. As Dr. Finsterer pointed out, the patient in our case report was hard to be diagnosed with MELAS syndrome according to the classical view, however, based on the advanced genetic diagnostics, the patient could be diagnosed with m.3243A > G variant-related disease to which MELAS syndrome belongs. Since the patient in our case report already had various symptoms or signs suggestive of multi-systemic involvements, we did not perform further investigation, such as electromyography or muscle biopsy. However, we fully agree with Dr. Finsterer that the involvement of central nervous system should be monitored closely in the future.

As the exact mechanism for variability of clinical phenotypes in patients with m.3243 A > G variant-related diseases are not yet understood, for now, those patients are classified based on symptoms. Future advances in molecular biology diagnostics may allow a more refined classification of m.3243A > G variant carriers. We would like to introduce this case because we successfully diagnosed MID by active application of EMB and genetic testing in a patient with the gradual development of symptoms over 24 years. Through a comprehensive retrospective review of the patient's various clinical manifestations, we could conclude that those were related to m.3243 A > G variant.

We thank Dr. Finsterer and readers for their interest and kind advice for our work. We hope this work can help readers understand the clinical variability of m.3243 A > G variant-related disease.

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