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Mitochondrial disorders due to m.3243A>G not meeting diagnostic criteria for MELAS require comprehensive work-up

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We read with interest the article by Lee *et al*. on a 51-year-old female with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to the variant m.3243A>G in *MT-TL1* who was admitted for acute heart failure.[1] The patient's history was positive for pacemaker implantation because of AV-block III at age 27 years, diabetes from age 28 years, thyroid carcinoma, and hypoacusis requiring hearing devices from age 39 years.[1] Renal insufficiency was additionally diagnosed. The patient benefited significantly from guideline-based heart failure therapy.[1] The study is excellent but has limitations that raise concerns and should be discussed.

The main limitation of the study is that the index patient was diagnosed with MELAS without meeting diagnostic criteria for MELAS. MELAS is usually diagnosed according to the Hirano criteria or the Japanese criteria. According to the Hirano criteria, MELAS is diagnosed if there are stroke-like episodes (SLE) < age 40, seizures or dementia, lactic acidosis or ragged-red fibres, normal early development, recurrent headache, and recurrent vomiting.[2] The index patient did not meet any of these criteria. According to the Japanese criteria, the index patient did not meet any of the category-A criteria (headache with vomiting, seizures, hemiplegia, cortical blindness or hemianopsia, and acute cerebral lesion) and only one category-B criteria (lactic acidosis, reduced activity of mitochondrial enzymes, morphological abnormalities of muscle mitochondria, and causative mutation).[3] Rather than with MELAS, the index patient should be diagnosed with a non-syndromic mitochondrial disorder (MID) due to the sporadic variant m.3243A>G phenotypically manifesting with hearing impairment, hypertrophic and dilative cardiomyopathy, AV-block III, diabetes, thyroid cancer, and renal insufficiency manifesting with proteinuria and hyponatriemia.[4]

A second limitation of the study is that heteroplasmy of the m.3243A>G variant was not determined. Although the patient underwent endomyocardial biopsy, heteroplasmy in the tissue clinically most strongly affected was not measured. In clinically affected tissues, heteroplasmy rates of >50% can be expected. Knowing heteroplasmy rates is also crucial for assessing the prognosis and for genetic counselling.

A third limitation of the study is that the patient was not systematically and prospectively investigated for subclinical or mildly manifesting multisystem involvement. Because MIDs are characterized by multi-system involvement, it is crucial that these patients are checked for multi-system involvement. Particularly, cerebral magnetic resonance imaging (MRI), electroencephalography (EEG), lactate stress testing on a bicycle ergometer, needle electromyography (EMG), and muscle biopsy are lacking.

A 4th limitation of the study is that no biochemical investigations of the homogenate of the endo-myocardial biopsy were carried out. Since tRNA variants normally cause a reduction in the function of several respiratory chain complexes, reduced activity of multiple complexes, especially complex-I, is to be expected.[5]

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these limitations would strengthen the conclusions and could improve the study. Carriers of the variant m.3243A>G should undergo extensive diagnostic work-up for multisystem involvement, because affection of organs other than the heart, particularly the brain, can severely determine the outcome and prognosis of these patients.

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Ethics Approval: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data availability

All data are available from the corresponding author.

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