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Letter to the Editor

The Presence of the m.3243A>G Variant in a Heteroplasmic State does not Necessarily Indicate MELAS

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Letter to the Editor

We read with interest the article by Shinozaki *et al.* regarding a 51-year-old female patient with Turner syndrome who also presented with systemic sclerosis (SS) and phenotypic features of MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and carried the m.3243A>G variant in the *MT-TL1* gene with a heteroplasmy level of 23% [1]. The study is noteworthy, yet several points warrant discussion.

A first point is that the index patient does not meet the diagnostic criteria for MELAS [1]. MELAS is typically diagnosed based on the Japanese criteria or the Hirano criteria (Table 1) [2, 3]. According to the Japanese criteria, MELAS is diagnosed when there are signs of encephalopathy associated with dementia or epilepsy, stroke-like episodes (SLEs) at a younger age, and biochemical evidence of mitochondrial dysfunction, such as acidosis and the presence of "ragged-red fibers" (RRF) in a muscle biopsy [2]. According to the Hirano criteria, a diagnosis of MELAS is made when SLEs occur before the age of 40 and are accompanied by seizures or dementia, lactic acidosis or RRF, normal early development, and recurrent headaches or recurrent vomiting [3]. Based on these considerations, the index patient should not be diagnosed with MELAS syndrome, but rather with a non-syndromic mitochondrial disorder resulting from the m.3243A>G mtDNA variant.

Table 1: Hirano and Japanese criteria for diagnosing MELAS

Diagnostic Criteria	Presence in the index patient
Hirano Criteria	
Absolute Criteria	
Dementia or seizures	yes
SLE before age 40	no
Lactic acidosis or RRFs	yes
Supportive Criteria	
Normal development	no
Recurrent vomiting	no
Recurrent headache	no
Japanese Criteria	
Category A	
Headache with vomiting	no
Seizures	no
Hemiplegia	no
Cortical blindness or hemianopia	no
Stroke-like lesion on imaging	no
Category B	
Increased serum or CSF lactate	yes
Respiratory dysfunction on biochemistry	no
Mitochondrial abnormalities on biopsy	no
Mutation linked to MELAS	yes

Definite MELAS according to Japanese criteria: two items of category A and 2 items of category B, definite MELAS according to Hirano criteria: all absolute criteria and at least two supportive criteria

A second point is that a diagnosis of SSc has not been substantiated ^[1]. SSc is typically diagnosed using the joint ACR/EULAR criteria, with a total score of more than 8 out of a possible 17 points confirming the diagnosis ^[4]. The criteria assessed include: skin thickening on all fingers of both hands extending proximally beyond the metacarpophalangeal (MCP) joints (9 points); skin thickening on the fingers distal to the MCP joints (4 points); fingertip ulcers (2 points); microvascular changes at the nailfold visible via capillary microscopy (2 points); telangiectasias (2 points); Raynaud's phenomenon (3 points); pulmonary involvement (2 points); and SSc-associated autoantibodies (Scl-70, anti-centromere, anti-topoisomerase, anti-RNA polymerase; 3 points) ^[4]. As the index patient scored only 3 points, he did not have SSc. Skin involvement associated with MELAS syndrome was more likely than SSc.

A third point is the absence of a pedigree ^[1]. To assess which family members exhibited phenotypic features of MELAS and who carried the m.3243A>G variant, it is essential to either provide a detailed description or present a pedigree indicating the clinical and genetic findings.

The fourth point is that, although an endomyocardial biopsy was performed on the patient, neither myocardial heteroplasmy was determined nor were biochemical analyses conducted to assess which respiratory chain complexes were functioning inadequately and which were functioning normally.

The fifth point is that it was not explained how hypertrophic cardiomyopathy (HCM) was distinguished from hypertrophy resulting from arterial hypertension. Concentric hypertrophy is typical of arterial hypertension, whereas hypertrophy in HCM is frequently asymmetric. Was the blood pressure well-controlled or poorly controlled? Was systolic anterior motion (SAM) of the mitral valve, a characteristic feature of HCM ^[5], present?

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