Letter to the Editor

Carriers of the m.3243A>G variant require comprehensive work-up for subclinical or mild clinical phenotypic manifestations

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Introduction

We read with interest the article by Lee *et al*. on a 51-years-old female with mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome due to the variant m.3243A>G in *MT-TL1* [1]. The variant manifested phenotypically with high degree atrio-ventricular block requiring implantation of a pacemaker at age 27 years, thyroidectomy for papillary thyroid cancer at age 28 years, diabetes since age 28 years, and hypoacusis requiring hearing aids since age 39 years [1]. Endo-myocardial biopsy revealed disarrangement of mitochondrial cristae, suggestive of mitochondrial cardiomyopathy [1]. The study is excellent but raises concerns that should be discussed.

A limitation of the study is that no heteroplasmy rates were provided. Knowing heteroplasmy rates in the index patient is crucial for assessing the severity of the phenotype, for assessing the disease course and for genetic counselling. Of particular interest is the heteroplasmy rate in one of the most affected tissues, the myocardium. Because the patient had undergone endo-myocardial biopsy, heteroplasmy rates should be determined, for example by digital PCR [2].

A second limitation is that no biochemical investigations of the endo-myocardial biopsy were carried out to assess whether the function of a single respiratory chain complex or of multiple respiratory chain complexes was impaired. Knowing the respiratory chain defect is crucial for applying supplementary and supportive treatment.

A third limitation is that the cause of paresthesias of the upper limbs was not identified. We should know whether the patient had diabetic polyneuropathy, and whether paresthesias were a clinical manifestation of diabetic polyneuropathy. What were the HbA1c values at the last follow-up? It is also conceivable that the patient had undergone chemotherapy for thyroid cancer and suffered from toxic polyneuropathy. There is also a need to rule out a spondylogenic cause of paresthesias. Because she had also received antibiotic treatment with azithromycine, it is conceivable that sensory disturbances originated from side effects of the antibiotic treatment.

A fourth limitation is that the patient did not undergo cerebral magnetic resonance imaging (MRI) to rule out that she had suffered a subclinical stroke-like lesion (SLL), the morphological equivalent of a stroke-like episode (SLE). SLLs can end up as fibrosis (white matter lesion), cyst formation, laminar cortical necrosis, toenail sign, or normal brain tissue.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Patients carrying the mtDNA variant m.3243A>G should undergo investigations for subclinical or mild involvement of organs other than the heart, ears, or endocrine glands.

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