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Work-Up for Cardiac Involvement in M.3243A>G Carriers Requires Comprehensive and Long-Term Work-Up

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Letter to the Editor:

In a recent article, Niedermayr et al. reported about the clinical and genetic findings in 9 patients carrying the mtDNA variant m.3243A>G and manifesting with heterogeneous phenotypes¹. We have the following comments and concerns.

Cardiac involvement in m.3243A>G carriers not only include hypertrophic and dilated cardiomyopathy, pre-excitation, AV-block-I, sick-sinus syndrome, and wave regurgitation¹ but also noncompaction, also known as left ventricular hypertrabeculation, myocardial fibrosis, systolic dysfunction, heart failure, and arterial hypertension². Arrhythmias reported in m.3243A>G-carriers include paroxysmal supraventricular or ventricular arrhythmias, including sinus-tachycardia, atrial fibrillation and non-sustained ventricular tachycardia, and sudden cardiac death (SCD)². Concerning conduction defects, not only WPW-syndrome but also left and right bundle branch block has been reported².

Myocardial fibrosis can be a rare phenotypic feature in m.3243A>G carriers³. Myocardial fibrosis can be best visualised by cardiac MRI or at endomyocardial biopsy or autopsy. On cardiac MRI it manifests as late gadolinium enhancement (LGE), 10-15 minutes after application of the contrast medium⁴. How many of the 9 included patients underwent cardiac MRI and in how many of them was LGE detected? In addition to cardiac MRI, tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) may be applied in MID patients and reveal regional myocardial dysfunction. Which abnormalities were found in the 9 included patients when applying these newer techniques for assessing CI in adult m.3243A>G mutation carriers?

Arrhythmias and conduction defects may often not be detected on routine ECG recording but only on long-term ECG recordings by means of a Holter or reveal recorder. Which were the results of long-term ECG recordings in the included patients? How many had a reveal recorder implanted? Detection of particularly ventricular arrhythmias is of paramount importance as m.3243A>G carriers may experience SCD, which can be prevented by implantation of an implantable cardioverter defibrillator (ICD)⁵. Did any of the 9 included patients require implantation of an ICD?

Rare cardiac manifestations in patients with a mitochondrial disorder (MID) may be aortic stenosis, pulmonary

hypertension, or aortic root ectasia^{6,7}. Were the included patients prospectively investigated for these abnormalities?

Little is known about heteroplasmy rates in the myocardium. How many of the patients underwent endomyocardial biopsy? In how many of those undergoing biopsy was the heteroplasmy rate of the myocardium determined and was it increased compared to other organs? Of particular interest is patient 5 who underwent heart transplantation¹. Were heteroplasmy rate in the explanted heart similar to those of lymphocytes or the muscle?

Since arterial hypertension may be a primary cardiac manifestation of MIDs⁸, it is essential to be informed how many of the included patients had arterial hypertension, and in how many of these it was attributable to the underlying genetic defect.

In patient 1 multiple subcortical cysts were described on ultrasonography of the abdomen, but the organ carrying these cysts was not mentioned. Was it the kidneys, the pancreas, or the liver? This is of relevance since renal cysts can be a phenotypic manifestation of a MID in general⁹.

Overall, this interesting study could be more meaningful if the points mentioned above would be appropriately addressed, if findings of long-term ECG recording would have been presented, and if cardiac MRI, TDI, or STE would have been carried out.

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