LETTER TO THE EDITOR

Ultrastructural Abnormalities of Myocardial Mitochondria in m.3243A>G Carriers May Not Only Be Due to the Mutation

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With interest we read the article by Saku *et al*. about the histological findings of endomyocardial biopsy from the right ventricle in three patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) manifesting with hypertrophic cardiomyopathy (hCMP) (all three patients), hypoacusis (all three patients), diabetes (all three patients), and renal insufficiency (patients one and three).[1] We have the following comments and concerns.

Since mtDNA variants are transmitted through the maternal line in 75% of the cases,[2] it is quite likely that at least the mothers of patients two and three carried the m.3243A>G variant as well. Since one sister of patient-2 had hCMP and diabetes, it is quite likely the she, her sister, and their mother carried the mtDNA variant. Since the mother of patient-3 had diabetes, she presumably is a carrier as well. Even in patient-1 it cannot be excluded that his mother was mildly affected and positive for the mtDNA variant. Thus, it would be interesting to know if the mothers or other first-degree relatives of the three included patients were neurologically investigated and tested for the variant m.3243A>G. Knowing the genetic status of first-degree relatives is crucial for assessing the intra-familial phenotypic heterogeneity, the disease course, and outcome, and for genetic counseling.

Since MELAS is a multisystem disease already at onset or progresses to a multisystem disease during the disease course, not only the ears, heart, pancreas, and kidneys are affected. MELAS typically manifests additionally in the brain with stroke-like episodes (SLEs),[3] seizures, extra-pyramidal abnormalities, migraine, cognitive decline, and psychiatric abnormalities.[4] Thus, we should be informed about the imaging findings in the three included patients, particularly how many of the three had SLE's. Knowing the cerebral status is crucial as cerebral involvement may have an effect on cardiac function and morphology. Most well-known is Takotsubo syndrome (TTS), which is characterized by transient systolic dysfunction. In addition, seizures may impair myocardial function[5] and may cause structural myocardial abnormalities.[6] Thus, we should know how many of the three patients had seizures and in case they had seizures if they were well or poorly controlled.

Missing is the current medication that the three patients were regularly taking. Since some drugs are potentially cardiac-toxic and may contribute to the morphological abnormalities described in the present study, it is essential to report the entire list of remedies.

Since all three patients underwent endomyocardial biopsy, it is conceivable that biochemical investigations of the material were carried out. We should know if activities of respiratory complexes were determined in the myocardial homogenate and which of them were decreased.

Finally, we should know how the authors delineated heart failure and myocardial ischemia from mitochondrial cardiomyopathy as the cause of the ultrastructural mitochondrial abnormalities described in the three patients.

Overall, the interesting study by Saku *et al.* could profit from additional data about the family history and the genetic status of 1st-degree relatives, from providing data about the neurological history and the cerebral findings, and from providing the current medication. There is a need to attribute the morphological findings to heart failure, mitochondrial cardiomyopathy, or to both.

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AUTHOR CONTRIBUTION

JF: Design, literature search, discussion, first draft, and critical comments. The study was approved by the institutional review board

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