Cardiology in the Young

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Letter to the Editor

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Sudden death in non-syndromic mitochondrial disorders due to m.3243A > G may not only be cardiogenic

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With interest we read the article by Byun et al. on a new-born male with neonatal, non-syndromic mitochondrial disorder due to the variant m.3243A > G in *MT-TL1*.[1] The patient presented phenotypically with progressive hypertrophic cardiomyopathy and died suddenly and unexpectedly 4 months after birth.[1] The mother and elder brother also carried the causative variant, but the family history was negative for sudden death.[1] The study is excellent but has limitations that are cause of concerns and should be discussed.

A limitation of the study is that the patient did not undergo long-term electrocardiography (ECG) recordings to assess the propensity to induce malignant ventricular arrhythmias. Neither results from Holter monitoring nor from ECG recordings using loop recording were reported in the article. Because hypertrophic cardiomyopathy carries an increased risk of presenting with malignant ventricular arrhythmias, it is critical that these patients receive long-term ECG recordings in addition to beta-blocker prophylaxis. If ventricular arrhythmias are recorded, implantation of an implantable cardioverter-defibrillator should be considered and could eventually save affected individual's life.

Another limitation of the study is that the index patient was not autopsied. Since sudden death not necessarily was due to cardiac complications but due to other causes, it would have been crucial to clarify whether pulmonary embolism myocardial infarction, stroke, stroke-like episodes, seizures, or autonomic dysreflexia were responsible for sudden death and accordingly excluded. We should also know in this regard whether the family history of any of the first-degree relatives was truly negative for sudden death.

Another limitation of the study is that no heteroplasmy rates of the m.3243A > G variant were reported in either the index patient, his older brother, or his mother, neither of whom manifested clinically. Knewledge of heteroplasmy rates of clinically affected tissues is crucial not only for assessing the rate of progression and expected phenotype severity but also for genetic counselling. A limitation in this regard is that the tissue in which the index patient's mutation was detected was not reported.

A fourth limitation of the study is that no information was provided on whether the index patient was prospectively screened for multi-system involvement. Since syndromic and non-syndromic mitochondrial disorders due to the variant m.3243A > G usually present with multisystem disease either already at the onset of the disease or become a multisystem disease as the disease progresses, it is crucial to have knowledge of the subclinical or clinical involvement of organs other than the heart. Knowing the nature and severity of multiorgan involvement is critical for taking prophylactic measures and preventing unexpected events that can lead to emergencies or sudden death. Organs other than the heart that are commonly involved in carriers of the m.3243A > G variant include the brain (epilepsy, stroke-like episodes, cognitive decline, ataxia), the ears (hypoacusis), the eyes (retinal dystrophy, cataract), the intestines (pancreatitis, vomiting, diarrhoea, and dysmotility), the kidneys (renal insufficiency, stones, and renal tubular acidosis), and the hematopoetic system (anaemia). Accordingly, we should know if any of these manifestations were present in the index patient or his first-degree relatives, particularly in the mother or older brother, both of whom were also carriers of the variant.

Overall, the interesting study has limitations that call the results and their interpretation into question. Addressing these issues would strengthen the conclusions and could improve the status of the study. Carriers of the m.3243A>G variant with hypertrophic cardiomyopathy require long-term ECG recordings to assess the risk of malignant ventricular arrhythmias, which may be preventable by implantation of an implantable cardioverter defibrillator (ICD). In addition, these patients need to be evaluated prospectively for multisystem disease, since disease of other organs can determine the overall outcome of these patients.

Data availability statement. Data that support the findings of the study are available from the corresponding author.

Author contribution. JF: design, literature search, discussion, first draft, critical comments, and final approval.

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Competing interests. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Compliance with Ethics Guidelines: 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.

Ethical approval. The study was approved by the institutional review board (responsible: Finsterer J.) on 4 November, 2022. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Reference

1. Byun JC, Choi HJ. Hypertrophic cardiomyopathy as the initial presentation of mitochondrial disease in an infant born to a diabetic mother. Cardiol Young 2023; 23: 1–3. DOI: 10.1017/S1047951123000392.

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