Cardiology in the Young

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To prevent sudden death in m.3243A>G carriers, comprehensive neurologic, cardiac, and pulmological examinations are required

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Letter to the Editor

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Abstract

The interesting study has limitations that put the results and their interpretation into perspective. m.3243A>G carriers should undergo prospective testing for multisystem disease to avoid missing subclinical multisystem involvement. m.3243A>G carriers with hypertrophic cardiomyopathy require long-term electrocardiogram recordings to determine whether implantable cardioverter defibrillator implantation is necessary or not. To assess the outcome of m.3243A>G carriers, knowledge of heteroplasmy rates and mtDNA copy numbers is required. It is tempting to assign pathogenicity when any pathogenic variant is seen with genotype-phenotype correlation. However, double hits are possible and if genetic information is to be used to screen or risk-stratify other family members, the standard of care would be to ensure that post-mortem genetic autopsy is performed for a panel of causative genes, and that an autopsy is done to exclude other causes of death, if possible.

We read with interest the article by Byun et al. about a male newborn with hypertrophic cardiomyopathy who was born to a mother with diabetes mellitus-I and died suddenly and unexpectedly at the age of 4 months after severe irritability.[1] Intravitam examination revealed that the patient carried the mtDNA variant m.3243A>G in *MT-TL1*, which was thought to be responsible for hypertrophic cardiomyopathy.[1] The study is compelling but has limitations that are of concern and should be discussed.

We do not agree with the assumption that hypertrophic cardiomyopathy was due to the variant m.3243A>G unless all different causes are sufficiently ruled out. These include diabetes and mutations in hypertrophic cardiomyopathy associated nuclear genes, such as *MYH7, LMNA, TNNT2, MYBPC3*, and *ACAD9*. To date, hypertrophic cardiomyopathy associated with the m.3243A>G variant has only been reported in a few cases. In addition, we should know whether or not the HbA1c level was abnormal at birth or afterwards.

A second point is that heteroplasmy rates have not been determined in any clinically affected or unaffected tissue. Knowledge of heteroplasmy rates is crucial not only for assessing the disease course and therefore the patient's prognosis and outcome but also for genetic counseling of the family. Heteroplasmy rates are also missing in the mother and older brother of the index patient who was also a carrier of the variant m.3243A>G but did not manifest clinically. Heteroplasmy rates should also be determined in the brother and mother to answer the question of whether or not they segregated with the phenotype within the family.

A third point is that the patient was not subjected to an autopsy. An autopsy, particularly of the myocardium, the conduction system, and the brain, could ultimately have clarified the cause of the sudden unexplained death. Histological examination of the myocardium could determine whether the hypertrophy was due to diabetes of the mother or index patient, the underlying m.3243A>G variant, a storage disease such as amyloidosis or glycogenosis, or a valvular abnormality. Brain autopsy could have clarified whether or not there was a cerebral structural lesion, an infection, or an immunological process.

A fourth point is that the cause of death has not been determined. Did the patient die suddenly from cardiac, pulmonary, or neurologic reasons? We should know whether the patient underwent electrocardiogram (ECG) monitoring through Holter recording to determine whether malignant ventricular arrhythmias were present or not. Since m.3243A>G carriers can manifest with epilepsy, it is important to rule out that the patient died of sudden unexpected death in epilepsy. We should know if there were ever any signs of seizures. Has an electroencephalography (EEG) ever been recorded? Did the patient exhibit MELAS features such as hypoacusis, stroke-like episodes, seizures, dysmorphism, vomiting, myopathy, or developmental delay?

In summary, the interesting study has limitations that put the results and their interpretation into perspective. m.3243A>G carriers should undergo prospective testing for multisystem disease to avoid missing subclinical multisystem involvement. m.3243A>G carriers with

hypertrophic cardiomyopathy require long-term ECG recordings to determine whether implantable cardioverter defibrillator implantation is necessary or not. To assess the outcome of m.3243A>G carriers, knowledge of heteroplasmy rates and mtDNA copy numbers is required. It is tempting to assign pathogenicity when any pathogenic variant is seen with genotype–phenotype correlation. However, double hits are possible and if genetic information is to be used to screen or risk stratify other family members, the standard of care would be to ensure that post-mortem genetic autopsy was performed for a panel of causative genes, and that an autopsy was done to exclude other causes of death, if possible.

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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: 1743–1745. DOI: 10.1017/S1047951123000392

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