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CASE REPORT
Heart failure

Bilateral deafness, diabetes, and different types of cardiomyopathy in family members with m.3243A > g mutation: a case report

Florian Seiler [1]*, Philipp Ruile [1], Martin Moser [1], and Thomas Helbing [1,2,3]

[1]Department of Cardiology and Angiology, University Heart Center Freiburg-Bad Krozingen, University of Freiburg, Hugstetter Straße 55, 79106 Freiburg, Germany; [2]Department of Cardiology, Heart Center Oldenburg, University of Oldenburg, Rahel-Straus-Straße 10 26133 Oldenburg, Germany; and [3]Department of Cardiology, Angiology, Haemostaseology and Medical Intensive Care, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

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Background The point mutation at position 3243 in the mitochondrial *MT-TL1* gene (m.3243A > G) is a rare cause of hypertrophic cardiomyopathy (HCM). Information about HCM progression over time and occurrence of different cardiomyopathies in m.3243A > G carriers of the same family is still lacking.

Case summary A 48-year-old male patient was admitted to a tertiary care hospital with chest pain and dyspnoea. Bilateral hearing loss required hearing aids at the age of 40. A short PQ interval, narrow QRS complex, and inverted T-waves in lateral leads were present on the electrocardiogram. HbA1c of 7.3 mmol/L indicated prediabetes. Echocardiography excluded valvular heart disease and detected non-obstructive HCM with slightly reduced left ventricular ejection fraction (48%). Coronary artery disease was ruled out by coronary angiography. Myocardial fibrosis determined by repeated cardiac MRI progressed over time. Endomyocardial biopsy excluded storage disease, Fabry disease, and infiltrative and inflammatory cardiac disease. Genetic testing revealed m.3243A > G mutation in the *MT-TL1* gene associated with mitochondrial disease. Clinical evaluation and genetic testing of the patients' family revealed five genotype-positive relatives with heterogeneous clinical phenotypes including deafness, diabetes mellitus, kidney disease, and both hypertrophic and dilated cardiomyopathy.

Discussion In patients with unexplained symmetric HCM with heterogenic clinical phenotypes at the organ levels, mitochondrial disease should be taken into consideration, particularly in the context of matrilinear transmission. m.3243A > G mutation is associated with mitochondrial disease in the index patient and five family members and leads to the diagnosis of maternally inherited diabetes and deafness with intra-familial variability of different cardiomyopathy forms.

Keywords Hypertrophic cardiomyopathy • m.3243A > G mutation • Mitochondrial disease • MIDD • Case report

ESC Curriculum 2.3 Cardiac magnetic resonance • 6.1 Symptoms and signs of heart failure • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy • 9.7 Adult congenital heart disease

* Corresponding author. Tel: +49 761 270 34010, Email: florian.seiler@uniklinik-freiburg.de
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Learning points

- The wide spectrum of clinical phenotypes leads to delayed diagnosis of mitochondrial disorders.
- Mitochondrial disease should be considered as a cause for unexplained cardiomyopathies, especially in combination with matrilinear transmission patterns.
- m.3243A > G mutation can cause deafness, diabetes, kidney disease, short PQ syndrome, and different forms of cardiomyopathy in the same family.

Introduction

The prevalence of unexplained asymptomatic ventricular hypertrophy has been reported to range from 1:200 to 1:500. Symptomatic hypertrophy has been estimated at <1:3000 in adults.[1] Diagnosis of hypertrophic cardiomyopathy (HCM) is defined by a wall thickness ≥ 15 mm in one or more LV myocardial segments measured by echocardiography or MRI that cannot be explained solely by loading conditions. Besides increased LV wall thickness, HCM can comprise myocardial fibrosis, morphologic abnormalities of the mitral valve apparatus, abnormal coronary microcirculation, and electrocardiographic abnormalities.[2] Detection of increased LV thickness that is unexplained by physical training, arterial hypertension, or valve disease (e.g. aortic stenosis) should prompt a systematic search for its underlying cause. The diagnosis of HCM requires evaluation of family history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities, multi-modality cardiac imaging, specialized laboratory testing, and in some circumstances genetic analyses. Management of HCM patients includes medical therapies, septal reduction therapies, lifestyle considerations, and sudden cardiac arrest assessment and prevention.[1,3]

Timeline

Timeline (age)	
2000 (30 years old)	Hearing loss: audiometry
2010 (40 years old)	Bilateral hearing aids. No further diagnostics due to lack of other symptoms
10/2012 (42 years old)	Chest pain and dyspnoea, diagnosis of non-obstructive HCM: TTE
12/2015 (45 years old)	Chest pain and dyspnoea: cardiac MRI, genetic testing for mutations in cardiac sarcomeric genes
12/2018 (48 years old)	Chest pain and dyspnoea: cardiac MRI, coronary angiography, myocardial biopsy
06/2019 (48 years old)	Advanced genetic testing: m.3243A > G mutation associated with mitochondrial disorder
10/2019 (49 years old)	Clinical and genetic screening of family members

Case summary

In December 2018, a 48-year-old Caucasian male (179 cm, BMI 26.5 kg/m^2) presented with chest pain (CCS III) and dyspnoea (NYHA III). He had a history of bilateral sensorineural hypacusis and hearing aids since the age of 40. This unusual finding was not investigated further at that time due to lack of other symptoms. Cardiac examination revealed that heart rhythm was regular without extra heart sounds. Blood pressure was similar in both arms (~115/80 mmHg) and excluded uncontrolled arterial hypertension.

Electrocardiogram (ECG) showed a short PR interval without delta-waves (PQ 94 ms); narrow QRS complex; inversion of T-waves in V4–V6, I, and aVL; and non-significant depression of ST segments (−0.12 mV) in I, II, and aVL (*Figure 1*). Laboratory results revealed elevated values of high sensitive troponin t without relevant kinetics (0.046 ng/L; normal <0.014 ng/L) and N-terminal proBNP (252 pg/mL; normal < 125 pg/mL). Creatinine kinase level was normal (121 ng/L; normal <174 ng/L). The HbA1c of 7.3 mmol/L revealed a prediabetic metabolic state. Slightly elevated ferritin (674 ng/mL; normal 30–400 ng/mL) excluded relevant iron overload.

Coronary angiography excluded coronary artery disease. Echocardiography detected symmetric non-obstructive HCM with diffuse reduced left ventricular ejection fraction (LVEF) (48%) and symmetric increase in myocardial wall thickness [intraventricular septum (IVS) 15 mm, posterior left ventricular wall (LVPW) 14 mm]. LV wall thickness could not be explained by physical training or valve disease. Arterial hypertension was excluded by non-invasive ambulatory blood pressure monitoring. LV intracavitary gradient was below 30 mmHg at rest and during the Valsalva manoeuver eliminating relevant LV outflow obstruction. Elevation of LV filling pressure was diagnosed by an increase of E/e` (17.5; normal < 15). The left ventricular mass index was increased at 178 g/m^2 (normal <115 g/m^2). Based on an inconspicuous strain analysis without a typical 'apical sparing' pattern, cardiac amyloidosis was unlikely (global longitudinal strain was −18.3%; normal −15.9 to −22.1%; *Figure 2*). The diameter and function of the right ventricle were normal (TAPSE 27 mm). Cardiac MRI confirmed mildly reduced LV function [LVEF 48%; LV end-diastolic volume 170 mL (reference range: 77–195 mL), LV end-systolic volume 88 mL (reference range: 19–72 mL); cardiac index: 2.94 L/min/m^2 (reference range: 2.5–4.2 L/min/m^2)]. MRI parameters of RV size and function were regular [RV wall thickness: 3 mm (reference range: 2–5 mm); RV end-diastolic volume 130 mL (reference range: 88–227 mL); RV end-systolic volume 51 mL (reference range: 23–103 mL); cardiac index 2.85 L/min/m^2]. Myocardial fibrosis detected by late gadolinium enhancement (LGE) on MRI was observed in LV predominantly mid-myocardial and epicardial (*Figure 3* A&B). LGE mass increased from cardiac MRI in 2015 (*Figure 3C and D*) to cardiac MRI in 2018 (*Figure 3A and B*) indicating that myocardial fibrosis was progressive in the index patient.

Given negative genetic testing for mutations of sarcomeric genes (MYBPC3, MYH7, TNNT2, TNNI3) in 2015, an endomyocardial biopsy (EMB) was performed to diagnose storage diseases or identify acquired causes of HCM. EMB confirmed hypertrophy of cardiomyocytes and diffuse fibrosis. Signs of infiltrative or active inflammatory disease or storage diseases (e.g. amyloidosis and Fabry, Pompe, or Danon disease) were not observed. Normal plasma activity of α-D-galactosidase-A excluded Fabry disease (0.150 mU/mL, standard range 0.070–0.300 mU/mL). In a first round of genetic testing, the patient was subjected to next-generation sequencing (NGS) of all coding regions, as well as neighbouring introns of basic genes relevant for HCM, i.e. ACTC1, ACTN2, MYBPC3, MYH7, MYL2, MYL3, PLN, TCAP, TNNC1, TNNI3, TNNT2, and TPM1. Advanced genetic analyses using NGS were

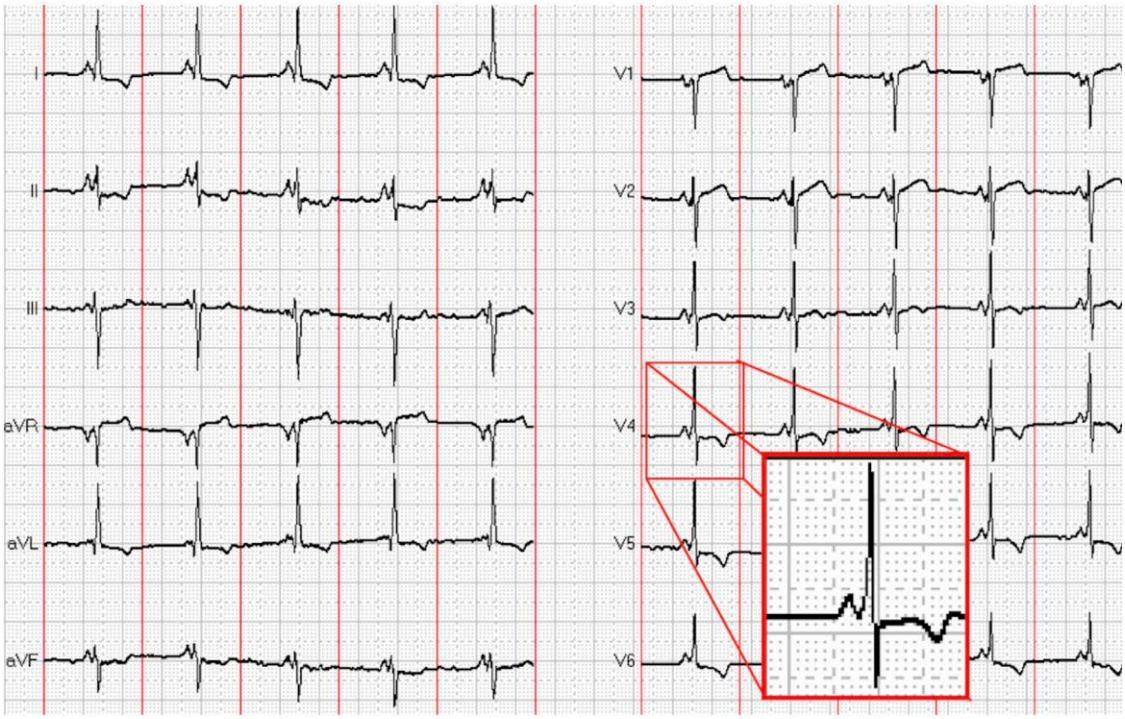

Figure 1 Electrocardiogram of index patient at admission showed a short PR interval without delta-wave (PQ 94 ms), a narrow QRS complex, and an inversion of T-wave in V4–V6, I, II, and aVL reflecting conduction abnormalities and disturbances of repolarization due to hypertrophic cardiomyopathy and mitochrondrial disease.

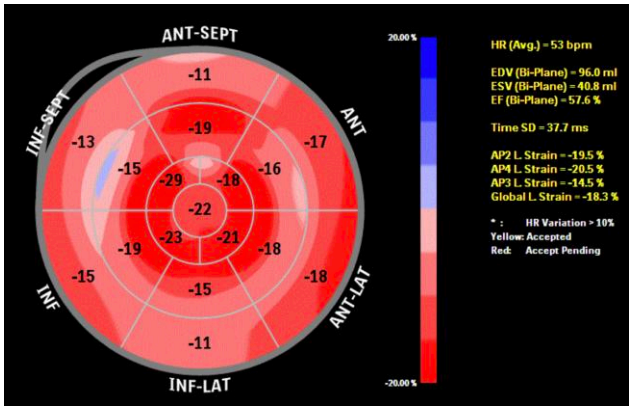

Figure 2 Strain analysis ruled out cardiac amyloidosis.

performed to identify pathogenic mutations in mitochondrial deoxyribonucleic acid (DNA). NGS revealed the presence of an A-to-G transition at nucleotide 3243 (m.3243A > G mutation) in 25% of the extracted mitochondrial DNA from patient's peripheral blood leukocytes. This pathogenic variant of mitochondrial DNA is known to cause mitochondrial disorders and explains the patient's phenotype. Holter monitoring did not detect ventricular tachycardia, an independent predictor of sudden cardiac death (SCD). According to the estimated risk for SCD at 5 years using the ESC HCM risk SCD calculator, an implantable cardioverter defibrillator (ICD) therapy was not recommended in the index patient (2018 risk of SCD at 5 years: 2.43%; age 48 years, max. wall thickness 15 mm, left atrium (LA) size 45 mm, max. left ventricular outflow tract (LVOT) gradient 4 mmHg).[2]

Family report

Clinical and genetic analyses of the patient's family identified the presence of m.3243A > G mutation in one half-brother (KF), one sister

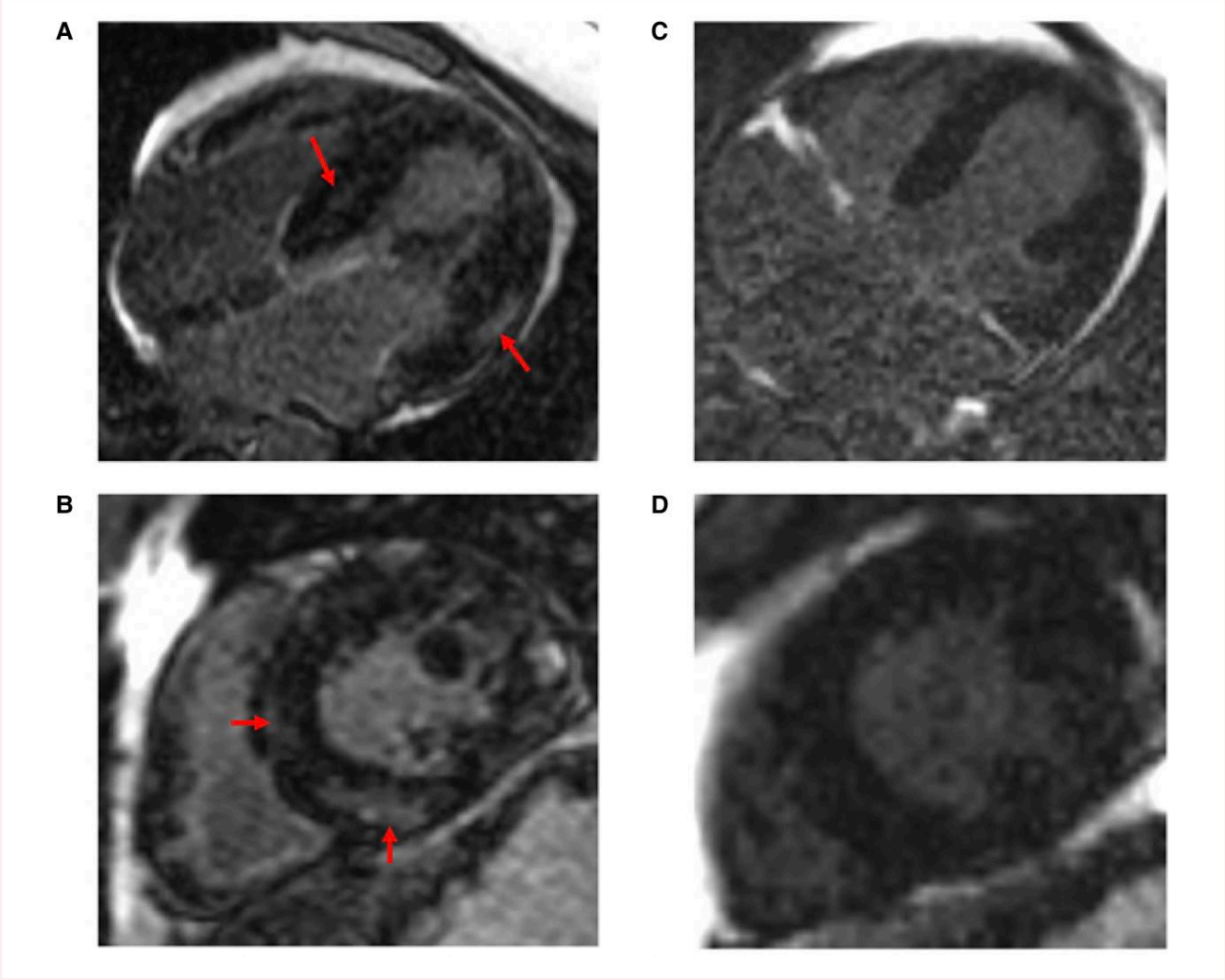

Figure 3 Comparison of late gadolinium enhancement/fibrosis extent between cardiac magnetic resonance imaging 2018 (*A&B*) and 2015 (*C&D*). Arrows indicate new regions of late gadolinium enhancement/fibrosis in 2018 (*A&B*) and demonstrate late gadolinium enhancement/fibrosis progression compared to 2015 (*C&D*).

(MS), and two half-nephews (Je, Mo) (*Figure 4*, *Table 1*). Clinically affected family members with cardiomyopathy were the patient's father (KS, ischemic CMP), his mother (EM, DCM), and his half-brothers JF (DCM) and KF (HCM). Heart failure with reduced ejection fraction was diagnosed in his mother (EM) in 1988 at the age of 52. A coronary angiography was recommended but refused by EM. Six months later, EM was hospitalized with symptoms of heart failure (breathlessness, ankle swelling, and fatigue) and TTE revealed severe LV dysfunction and LV dilatation. A thrombus was detected in the LV. During this hospital stay, EM developed a cardioembolic stroke and died subsequently from sepsis-induced multiple organ dysfunction syndrome at the age of 52. JF died suddenly at the age of 53 indicating reduced life expectancy (*Figure 4*). For KF, the HCM was first diagnosed in 2013. Initially, ECG showed shortened PQ time (PQ 97 ms, QRS 102 ms) without delta-wave. KF's LVEF was 28% and remained below 35% in 2019. His CMR showed no pathologic LGE. IVS and LVPW thickness were 13 mm. During coronary angiography in 2016, his ICD terminated a ventricular tachycardia. Further arrhythmias have not been reported. QRS broadened over time into a complete left branch bundle block (QRS 161 ms) so that the ICD was upgraded to resynchronization therapy defibrillator (CRT-D).

Follow-up (06/2019)

Symptoms of the index patient (NYHA III, CCS III) remained unchanged at 6-month follow-up. LV wall thickness and LVEF remained unchanged obtained by echocardiography. Holter monitoring excluded ventricular tachycardia. At follow-up, ICD was not recommended (2019 risk of SCD at 5 years: 2.27%; age 48 years., max. wall thickness 14 mm, LA size 45 mm, max. LVOT gradient 6 mmHg).[2] Heart failure medications were intended to improve symptoms. The next follow-up was scheduled in the outpatient clinic at 3 months thereafter.

Discussion

The diagnosis of HCM is predominantly clinical and relies on non-invasive testing, pedigree analysis, laboratory testing, and molecular genetic analysis.[3] Endomyocardial biopsy (EMB) is not part of the routine diagnostic workup and may only be considered in special clinical scenarios, if imaging or genetic testing does not provide a definitive diagnosis.[3] In the present case, EMB was performed after negative genetic testing for mutations in sarcomeric genes and careful evaluation of risks and benefits.

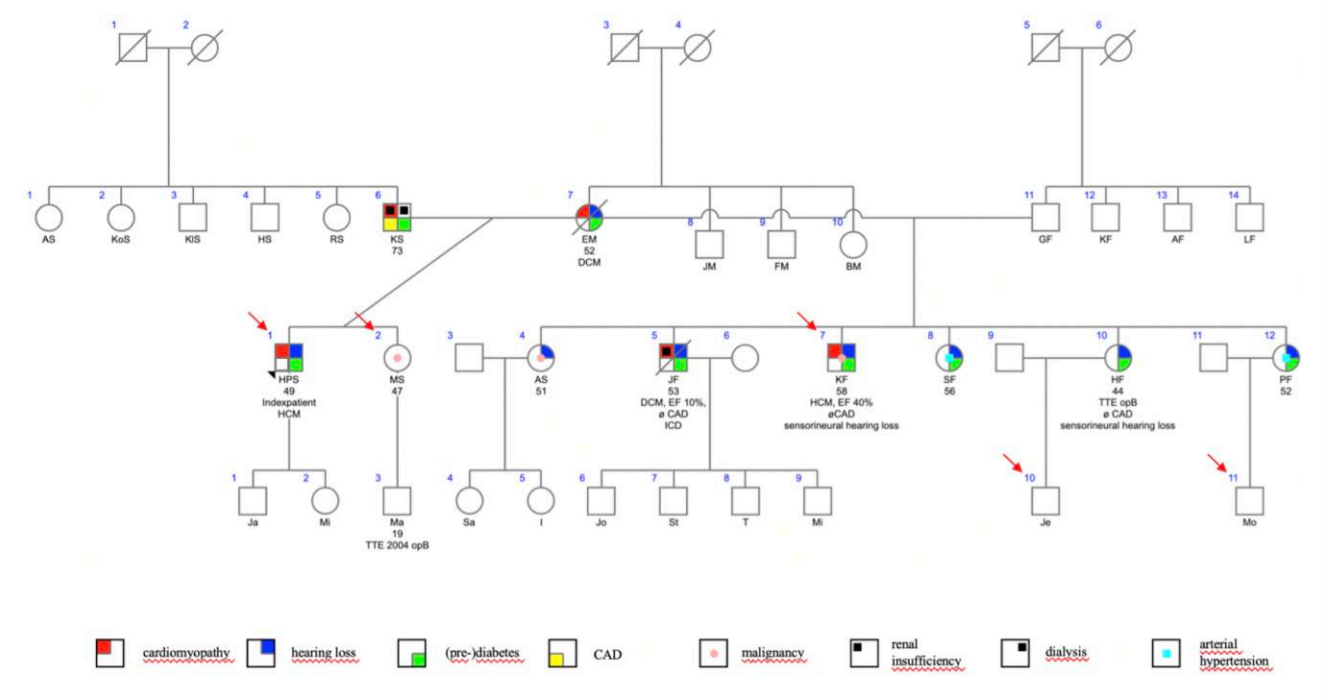

Figure 4 Pedigree chart depicting family tree including clinical data (□ males, ○females, crossed-out squares or circles reflect deceased individuals). The red arrows indicate proof of m.3243A > G mutation.

Table 1 Clinical phenotype of family members with and without proof of m.3243A > G mutation. ∅ = test denied or deceased but affected or affected direct descendant; iCM, ischemic cardiomyopathy; DCM, dilative cardiomyopathy; HCM, hypertrophic cardiomyopathy

	KS	EM	HPS	AS	MS	JF	KF	SF	HF	PF	Je	Mo
m.3243A > G mutation	–	∅	+	∅	+	∅	+	∅	∅	∅	+	+
Cardiomyopathy	iCM	DCM	HCM	–	–	DCM	HCM	–	–	–	–	–
Hearing loss	–	+	+	+	–	+	+	+	+	+	–	–
Prediabetes	+	+	+	–	–	+	+	+	+	+	–	–
Renal insufficiency	+	–	–	–	–	+	–	–	–	–	–	–

A point mutation at position 3243 with an A to G transition (3243A > G) in the mitochondrial leucine tRNA (*MT-TL1*) gene can affect the oxidative phosphorylation system and subsequently cellular energy production in multiple organs. The m.3243A > G mutation can cause heterogeneous phenotypes based on mutation load, tissue distribution of the mutant, and possibly environmental factors.[4] Cardiomyopathy can be an isolated finding in m.3243A > G mutation carriers or be associated with a wide spectrum of syndromes including MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), MIDD (maternally inherited diabetes with deafness), MERRF (myoclonic epilepsy and ragged red fibre disease), Leigh syndrome, or Kearns–Sayre syndrome.[4] MELAS and MERRF were excluded in this family as none of the family members presented epilepsy, and the mother's stroke was of clear cardioembolic origin. Neither the index patient nor other mutation carriers fulfilled the criteria for diagnosis of Leigh syndrome or Kearns–Sayre syndrome. The clinical phenotype of the index patient included hearing loss and short PQ syndrome in addition to HCM. While prediabetes in the index patient required no medical therapy, six family members showed maternally inherited diabetes and deafness. In addition to m.3243A > G mutation, this led to the diagnosis of MIDD that is predominantly inherited from the mother due to the maternal inheritance pattern of mitochondrial DNA.[5] The first clinical manifestations may appear at any age, but the disease is generally diagnosed in young adults with deafness appearing before diabetes.[5] In our case, there were no further investigations conducted as the unusual finding of loss of hearing in a young patient occurred. It is speculative if further diagnostics could already have revealed HCM or prediabetic state, but it would have significantly shortened the time from the first symptom to the final diagnosis. Family members at risk should be screened for the mutation. For those members carrying the m.3243A > G mutation without clinical manifestation, screening for diabetes and monitoring of kidney function, hearing, and cardiac function is recommended.[5]

Cardiomyopathy and its time course in m.3243A > G carriers is poorly defined.[6] In the present case, cardiac MRI detected symmetric myocardial thickening and fibrosis of the LV with mid-myocardial LGE 2015. In 2018, the extent of LGE increased and proved progression of myocardial fibrosis and scarring (*Figure 3*). LGE in mid-wall pattern in hypertrophied segments is consistent with HCM and a predictor of adverse cardiovascular outcomes associated with increased mortality, heart failure hospitalization, and sudden cardiac death.[3,7] Repeated cardiac MRIs are recommended every 3–5 years in patients with HCM.[1] Progression of LGE in HCM helps to guide risk stratification, and ongoing risk stratification is needed in this family given the premature death of KS and JF in their early fifties (*Figure 4*). According to ESC recommendations, ICD placement for primary prevention was not indicated for the index patient at time of diagnosis and follow-up in 2019. Recommendation for ICD therapy should be reassessed at 1-year intervals or whenever there are relevant changes in clinical status or Holter monitoring.[2]

Conclusions

Information about the intra-familial phenotypic cardiomyopathy variability of m.3243A > G carriers is still lacking. A review reported that cardiac hypertrophy is more prevalent than dilation in different m.3243A > G carriers.[8] This case report illustrates the heterogeneous spectrum of cardiomyopathies in members of the same family with m.3243A > G mutation: the index patient (HPM) and a stepbrother (KF) developed HCM while the mother (EM) and another stepbrother (JF) presented with dilated cardiomyopathy (*Figure 4*). Further studies are needed to analyse the intra-familial phenotype variability of cardiac disease in m.3243A > G mutation carriers.

Lead author biography

Dr. Florian Seiler earned his medical degrees at the Albert Ludwig University in Freiburg, Germany, in 2017. He is a fourth year intern at the Department of Cardiology and Angiology of the Heart Center Freiburg University in Germany and is currently working in the intensive care unit.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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Data availability

Data sharing is not applicable to this case report as no datasets were generated or analysed.

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