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ORIGINAL ARTICLE

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Mitochondrial DNA mutation "m.3243A>G"—Heterogeneous clinical picture for cardiologists ("m.3243A>G": A phenotypic chameleon)

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Abstract

Objective: In general, a mitochondrial disorder is diagnosed on the basis of symptom combinations and confirmed by genetic findings. However, patients carrying the *m.3243A>G* mutation in the mitochondrial tRNA leucine 1 (MT-TL1) do not always meet all the proposed criteria for the most frequently encountered mitochondrial syndrome "MELAS," an acronym for **M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and at least one **S**troke-like episode. We here present various phenotypic characteristics of the mitochondrial mutation *m.3243A>G* with particular focus on cardiac manifestations.

Methods and Results: We followed nine patients (1 month to 68 years old; median 42 years; four female and five male) from nine different families with this *m.3243A>G* mutation in the MT-TL1. The classical "MELAS" criteria are met by only three of these patients. Electrocardiography (ECG) shows preexcitation pattern with short PR intervals and delta waves (Wolff-Parkinson-White) in three patients and sick sinus syndrome plus atrioventricular block I in one patient. Hypertrophic cardiomyopathy was found in eight patients with moderate to severe regurgitation of various valves.

Conclusion: Cardiac manifestation can encompass hypertrophic or dilated cardiomyopathy, as well as preexcitation syndromes or conduction delay. In general, the clinical presentation to meet the "MELAS" criteria varies due to heteroplasmy. Thus, cardiologists should screen patients with unexplained cardiac features in the context of deafness, short stature and learning disabilities for mtDNA mutations, especially the *m.3243A>G* mutation. A clear diagnosis is essential as a basis for prognostic advice concerning the disease course and clinical impact on family testing.

KEYWORDS

adults, cardiomyopathy, children, m.3243A>G, MELAS, mitochondrial disease

1 | INTRODUCTION

"MELAS" is frequent among mitochondrial syndromes. It is an acronym for **M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and at least one **S**troke-like episode. In about 80% of patients, it is caused by a maternally transmitted mutation *m.3243A>G* in the mitochondrial tRNA leucine 1 (MT-TL1).[1,2] The highest prevalence of the "MELAS" mutation (*m.3243A>G*) is estimated to be 7.59 per 100 000 persons in northeast England, 16.3 per 100 000 in northern Finland, and 236 per 100 000 in Australia. So far, no correlation to ethnic origin has been described.[2]

Apart from the classical "MELAS" syndrome, other phenotypic variants of the mitochondrial DNA mutation *m.3243A>G* have been reported. These include "MELAS"-similar encephalomyopathy, but without stroke-like episodes, or maternally inherited diabetes and deafness, and others—without central nervous system (CNS) involvement.[3–5] Thus, patients carrying the *m.3243A>G* mutation in the MT-TL1 do not always meet all the criteria for MELAS.

The proportion of normal and mutated DNA copies in the mitochondrion may vary among cells (heteroplasmy) and organs.[1] A large amount of mutant mitochondrial DNA is found in the skeletal muscle and other organs like heart, kidney or liver.

This article focuses especially on cardiac involvement and different progression of cardiac disease in children, adolescents, and adults affected by the *m.3243A>G* mutation.

2 | PATIENTS

We followed nine patients with the *m.3243A>G* mitochondrial mutation and particularly focused on myocardial involvement. We also describe additional symptoms and biochemical findings as well as patient outcomes (Table 1):

Patient 1 was born at 38 weeks gestational age by primary Caesarean section. His 33-year-old mother had a history of three miscarriages and two cesarean deliveries. This pregnancy was uncomplicated. Birth weight was 2.395 kg (<3rd percentile), vertex-breech length 46 cm (<3rd percentile) and head circumference 32 cm (<3rd percentile). His mother is small-sized (as well as his sister) and suffers from a hearing impairment.

A few hours after birth, tachypnea and spasmodic strictures were recognized. He had subcutaneous edema and perioral cyanosis was visible. A systolic-diastolic murmur in the second left intercostal space was auscultated. On echocardiography, a patent ductus arteriosus

TABLE 1 Comparison of symptoms of nine patients with *m.3243A>G* mutation

(Gender; current age)	Patient 1 (♂; 1 mo)	Patient 2 (♀; 14 y)	Patient 3 (♀; 23 y)	Patient 4 (♂; 24 y)	Patient 5 (♀; 42 y)	Patient 6 (♂; 43 y)	Patient 7 (♂; 45 y)	Patient 8 (♀; 61 y)	Patient 9 (♂; 68 y)
Onset of symptoms	Postpartum	8 y	10 y	5 y	36 y	21 y	37 y	41 y	52 y
Height [cm]	~ 46	130	137.3	~ 160	160	161	174	156	165
Current weight [kg]	2.9	15.7	34.5	51.7	50.5	68	70	48	68
Diabetes mellitus	–	–	–	–	+	+	+	+	+
Sensorineural hearing loss	–	+	+	–	+	+	+	+	+
Eyes	Ptosis	Blindness	Strabismus	-	Venous thrombosis	Oculomotor apraxia	Cataracta senilis	-	Fundus hypertonicus I°
Activity	↓↓	↓↓↓	↓↓↓	↔	↔ (bt)	↔	↔	↓	↓↓
Power	↓↓	↓↓↓	↓↓	↓↓↓	↔ (bt)	↔	↔	↓	↓↓
CMP	+	+	+	–	+ (bt)	+	+	+	+
Valve regurgitation	TR I°, MR I°	TR III°, MR III°	TR II-III°, MR I°	MR I°	TR I°, MR II°, AR I° (bt)	MR I°	PR I°	TR I°, PR I°	TR I°, MR I°
Effusions	-	Pericardial, pleural	-	-	- (bt)	-	-	Pericardial	Pericardial
ECG pathology	WPW syndrome	Short PQ/PR	WPW syndrome	-	- (bt)	-	Sick-sinus-syndrome, AV I	-	-
Stroke-like episodes	-	3	-	3	-	1 (?)	-	-	-

Notations: –, not present; +, present (intensity: +, ++, +++); ↓, decreased; ↔, constant, equal; bt, before heart transplantation; a.t., after heart transplantation; Abbreviations: CMP, cardiomyopathy; ECG, electrocardiogram.

(PDA) was evident. In addition, the myocardium was hypertrophic and the ejection fraction was decreased to 50%. Electrocardiogram (ECG) findings were consistent with Wolff-Parkinson-White (WPW) syndrome. Laboratory investigations showed high serum concentrations of L lactate (8.66 mmol/L), pyruvate (106.4 µmol/L) and elevated kidney and liver parameters (Table 3). A sonogram of the abdomen showed multiple subcortical cysts. Several subependymal cysts near the caudate nucleus were found in the sonogram of the cerebrum. Neurological examination revealed muscular hypotonia and bilateral ptosis. Due to muscular weakness nutrition was administered mostly by gavage. Over the next days, the PDA was closed with ibuprofen. Nevertheless, the infant developed progressive heart failure and died within three months. *m.3243A>G* was found in muscle (92%) and fibroblasts (90%).

Family testing was performed postmortem and revealed that not only the mother (age 34.8 years; leukocytes 31%), but also the siblings (10-year-old sister and 4-year-old brother; both asymptomatic; leukocytes 31% and 46%) of Patient 1 also carry the *m.3243A>G* mutation.

Patient 2 is a 14-year-old female, who developed normally until 8 years of age.

She first presented with sensorineural hearing loss at the age of 8 years and has worn hearing aid devices since that time. She presented with focal seizures focused on the right occipital lobe when she was 10 years old. The electroencephalogram (EEG) showed right-sided irregular spike-wave activity with secondary generalization. In total, she has suffered three strokes. Stroke and seizures at the age of 14 resulted in permanent blindness. At the age of 13, she was diagnosed with hypertrophic cardiomyopathy (left ventricle (LV) wall thickness diameter 11 mm, LV dimensions 31 mm in systole, 37 mm in diastole, fractional shortening (FS) 16%) and severe mitral (cerebrovascular [CV] Doppler 105 mm Hg) and tricuspid (CV Doppler 30 mm Hg) regurgitation. Moreover, pericardial and pleural effusions were found by echocardiography (Figure 1). Over the next months, the girl progressively suffered from heart failure including muscular weakness and exercise intolerance. When she was 14 years of age, listing for heart transplantation was considered but abandoned because of malnutrition (poor general condition). Stabilization was achieved to a large extent with oral furosemide, spironolactone, and phosphodiesterase inhibitors.

Motor and intellectual development were normal during infancy. There was no family history of neurological disease. At the age of 14 she is 130 cm tall and has a body weight of 15.7 kg, both below the 3rd percentile, whereas head circumference at 54 cm is normal (50th percentile).

Laboratory investigations showed elevated concentrations of L lactate (up to 3.69 mmol/L); pyruvate was within the reference values. Kidney, liver, and heart parameters were elevated (Table 3).

Patient 3 is a 23-year-old woman, who was first seen at the tertiary hospital when she underwent magnetic resonance imaging (MRI) because of delayed milestones at age 10 years. She began to sit without help at age 9 months. She started walking and spoke her first words at the age of 2 years, but presented with moderate ataxia and muscular hypotonia. Divergent strabismus was diagnosed when she was 1 year old. The MRI showed hypoplasia of the cerebellar vermis.

At the age of 13 years she was diagnosed with hypertrophic cardiomyopathy and severe mitral and tricuspid regurgitation. Short PR intervals (0.09°seconds) and delta waves on ECG were consistent with WPW syndrome. Over the last years, the patient progressively suffered from muscular weakness and exercise intolerance. She presented with sensorineural hearing loss since the age of 20 and has worn hearing aid devices since age 21. The *m.3243A>G* mutation was detected in her mother and her maternal uncle. Both also suffer from sensorineural hearing loss, are small-sized and have cardiomyopathy.

Now at the age of 23 she is 137 cm tall, weighs 41 kg and has a head circumference of 51 cm.

Laboratory investigations show large concentrations of L lactate; pyruvate was not elevated. Kidney, liver, and heart parameters are normal (Table 3). She has suffered no strokes or stroke-like episodes.

Patient 4 is a 24-year-old male. Onset of symptoms was at age 5 years. At that time, he was hospitalized with general muscle weakness and gait disturbance. Seizures and stroke-like episodes started in adolescence. To date, he has suffered four strokes. A current neurologic examination showed diminished muscle tone and atrophic muscle mass, especially in the lower extremities. High-frequency, polyphase voltage was seen in the electromyogram (EMG) performed at age 8 years. A muscle biopsy was performed and showed ragged red fibers as well as paracrystalline inclusions in mitochondria. A specific diagnostic approach with respirometry of saponin-skinned muscle fibers showed low levels of pyruvate, glutamate, octanoylcarnitine, palmitoylcarnitine, and succinate respiration (Table 2), pointing to a Complex I deficiency in the muscle, which was later confirmed in individual enzyme measurements.

Transthoracic echocardiography showed no cardiac involvement, only minimal mitral regurgitation, and no cardiomyopathy.

Motor and intellectual development were normal during infancy. There is no family history of neurological disease. Now at the age of 24 he is around 160 cm tall and weighs 51.7 kg.

High concentrations of L lactate and pyruvate were a constant finding. Kidney, liver, and heart parameters were intermittently elevated (Table 3).

Patient 5 is a 42-year-old woman. She experienced her first symptoms at the age of 36. The patient presented with sensorineural hearing loss at age 33 years and was recently fitted with hearing aid devices. Dysarthria for some minutes, but no seizures or stroke-like episodes, have been reported, although some parenchymal cortical defects were found. At age 37, she suffered from psychoorganic syndrome, but is now stable. At age 38, MELAS-related diabetes mellitus was diagnosed and treated with insulin. The echocardiography performed at that time showed hypertrophic cardiomyopathy (for M-mode results, see Figure 2) as well as regurgitation of the mitral (E/A 0.8, E/E′ 9.6), tricuspid (CV Doppler 21 mm Hg) and aortic valves. She experienced exercise intolerance with weakness over the last years. Thus, regular intake of candesartan, nebivolol, furosemide, and spironolactone was necessary; serious enough to

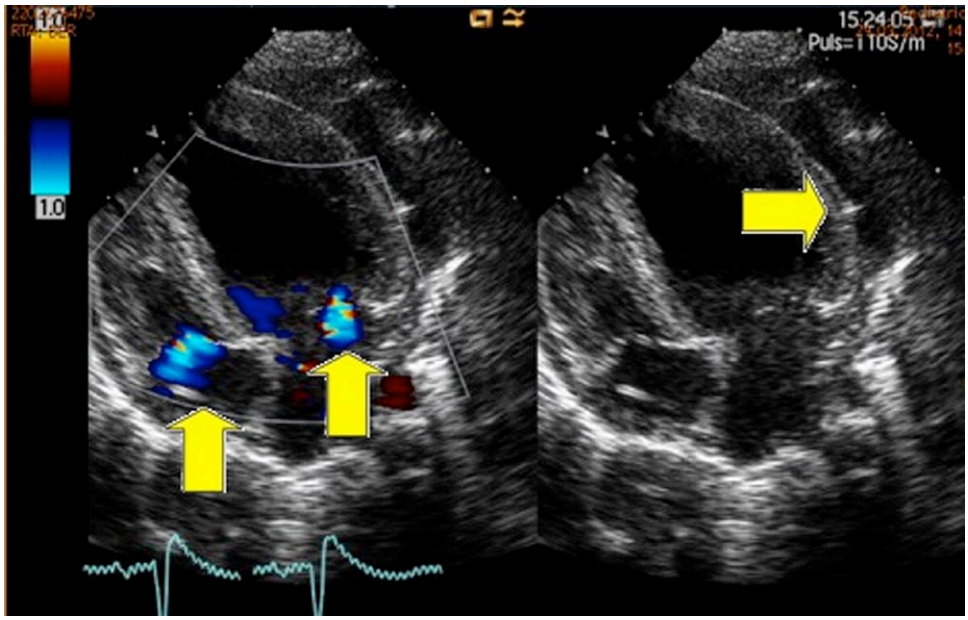

FIGURE 1 Echocardiography of Patient 2 (♀; 14 years) at age 13 showing hypertrophic cardiomyopathy and regurgitation of tricuspid and mitral valves as well as pericardial effusions

be discussed for heart transplantation. At the age of 40, she received a combined heart and renal transplantation without technical difficulties. Cyclosporine A and mycophenolate mofetil were chosen beside prednisolone as immunosuppressive therapy. Now at the age of 42 she is well, full of strength and shows no evidence of graft-versus-host disease (ISHLT 2004-grading 0R). Her renal function was most recently restricted, namely creatinine levels of 152.05 µmol/L, urea levels of 29.20 mmol/L, and cystatin C of 1.85 mg/L. Last year during a routine checkup, a retinal hemorrhage was noticed due to a venous thrombosis. Consequently, therapy with acetylsalicylic acid was started and dexamethasone was administered intravitreal.

She developed normally in childhood and adolescence until age 36. She is 160 cm tall and weighs 50.5 kg. Her head circumference is normal (55 cm). While her family history is uneventful, her mother was also small-sized, but showed no other symptoms.

L lactate was elevated. Kidney, liver, and heart parameters were also intermittently elevated before and after transplant (Table 3). *m.3243A>G* was found in blood (29%), urine (73%), kidney (89%), and oral mucosa (52%).

Patient 6 is a 43-year-old man,[5] who developed normally until age 21 years. He has worn hearing aid devices due to sensorineural hearing loss since age 25 years. He has recurrent headaches and problems with eye movement (oculomotor apraxia). He reports dysarthria for around 10 minutes once at age 36, but no seizures or stroke-like episodes. He suffers from insulin-dependent diabetes mellitus and has taken insulin since age 21.

In the last three years, he has reported exercise intolerance without muscle pain. Echocardiography showed hypertrophic cardiomyopathy (LVIDd 51 mm, LVIDs 39.30 mm, LVPWd 14.40 mm, LVPWs 20.80 mm, IVSd 20.40 mm, IVSs 15.50 mm, FS 22.9%) with a restricted systolic left ventricular function and an abnormal diastolic relaxation as well as severe mitral valve regurgitation (E/A 0.6, E/E′ 16). Treatment of chronic heart failure includes lisinopril, hydrochlorothiazide, and furosemide.

His parents died at age 41 (mother) and age 75 (father) due to cerebral insults. The patient is 161 cm tall and weighs 68 kg. His head circumference is normal (57 cm).

Laboratory investigations show large concentrations of L lactate. Kidney, liver, and heart parameters have been mildly elevated intermittently (Table 3).

Patient 7 is a 45-year-old man, who developed normally until age 21 years. He presented with sensorineural hearing loss since the age of 37 and has worn hearing aid devices since age 40. A current neurologic exam shows moderate ataxia, but no seizures or stroke-like

TABLE 2 Results of single muscle fiber respirometry performed in patient 4 at age 8 years in a biopsy of musculus quadirceps

Pyruvate	0.39 ± 0.03	Reference: 1.25 ± 0.39
Glutamate	0.37 ± 0.07	Reference: 1.15 ± 0.33
Octanoylcarnitine	0.39	Reference: 0.89 ± 0.21
Palmitoylcarnitine	0.32	Reference: 0.67 ± 0.02
Succinate	0.97 ± 0.22	Reference: 1.19 ± 0.39

Results for Patient 4 (♂; 24 y) in the single muscle fiber respirometry at age 8 years. All substrates that are oxidized through complex I of the mitochondrial respiratory chain (pyruvate, glutameta, octanoyl- and palmitoylcarnitine) show impaired oxidative respiration, whereas succinate which is oxidized through complex II shows normal respiration. Values given as nmol O_2/min/mg muscle wet weight.

TABLE 3 Laboratory parameters, kidney, heart and liver parameters in Patients 1-9 with *m.3243G>A* mutation. Increased alanine concentrations point to long-term lactate elevation; alanine-lysine ratio is a marker for impaired mitochondrial versus cytoplasmatic metabolism (normal < 3)

(Gender; current age)	Patient 1 (♂; 1 mo)	Patient 2 (♀; 14 y)	Patient 3 (♀; 23 y)	Patient 4 (♂; 24 y)	Patient 5 (♀; 42 y)	Patient 6 (♂; 43 y)	Patient 7 (♂; 45 y)	Patient 8 (♀; 61 y)	Patient 9 (♂; 68 y)	Normal values
L-lactate [mmol/L]	8.66 ↑	3.69 ↑	4.20 ↑	10.32 ↑	2.31 ↑	3.30 ↑	nd	nd	nd	(0.5–2.2)
Pyruvate [μmol/L]	106.4 ↑	nd	28 ↓	166.5 ↑	nd	nd	nd	nd	nd	(34–102)
Lactate-pyruvate ratio	49 ↑	nd	15	62 ↑	nd	nd	nd	nd	nd	(<15)
Triglyceride [mmol/L]	1.39	1.67 ↑	nd	nd	2.35 ↑	3.08 ↑	1.91 ↑	nd	2.73 ↑	(0.61–1.2)
Urea [mmol/L]	17.86 ↑	19.14 ↑	6.50	5.71	29.20 ↑	31.42 ↑	18.07 ↑	16.96 ↑	21.53 ↑	(3.0–7.0)
Creatinine [μmol/L]	35.36 ↓	30.06 ↓	55.93	37.13 ↓	152.05 ↑	132.60 ↑	88.40	76.91	90.17	(50–118)
NT-proBNP [ng/L]	nd	2346 ↑	nd	nd	3006 ↑ (bt);	813 ↑	944 ↑	429 ↑	1989 ↑	(0–242)
Troponin T [ng/L]		35.4 ↑			753 ↑ (at)	77.9 ↑	35.5 ↑	241.7 ↑	41.7 ↑	(0–14)
					51.1 ↑ (bt);					
					12.2 (at)					
GOT [U/L]	61 ↑	48 ↑	30	45 ↑	21	50 ↑	51 ↑	19	25	(10–35)
GPT [U/L]	10	111 ↑	24	19	10	59 ↑	84 ↑	13	28	(10–35)
γ-GT [U/L]	60 ↑	224 ↑	20	43 ↑	13	278 ↑	298 ↑	16	23	(6–42)
Alanine [μmol/L]	1024.2 ↑	374.4 ↑	nd	700 ↑	466.5 ↑	491.9 ↑	nd	nd	nd	(99–410; age
Alanine-lysine ratio	5.9 ↑	3.6 ↑			3.4 ↑	3.1 ↑				related) (<3)

episodes have been recognized to date. Furthermore, during a routine examination bilateral cataracta senilis were found. He suffers from diabetes mellitus and has taken metformin since age 21. The patient is 174 cm tall and weighs 70 kg.

In the last years, he has reported exercise intolerance without muscle pain and was admitted to hospital for the first time at age 44 years. ECG showed a sick sinus syndrome with inappropriate sinus bradycardia (50/min) with chronotropic incompetence and atrioventricular block I° (PQ 0.21 seconds). Echocardiography revealed dilated cardiomyopathy (LVIDd 52.10 mm, LVIDs 39.60 mm, LVPWd 14.40 mm, LVPWs 9.17 mm, IVSd 15.40 mm, IVSs 19.10 mm, FS 24.0%) with restricted systolic left ventricular function and diastolic dysfunction II° (E/A 1.40) as well as mild pulmonary valve regurgitation. Cardiac catheterisation shows a reduced cardiac index with 1.9 l/min/m^2. Treatment of chronic heart failure includes lisinopril, nicorandil, and furosemide.

Kidney, liver, and heart parameters have been mildly elevated intermittently (Table 3). A percentage of *m.3243A>G* was found in blood (20%), urine (88%), and myocardium (86%).

Patient 8 is a 61-year-old woman. At the age of 41 years, she was diagnosed with diabetes mellitus and therapy consisting of insulin and metformin was started. Now at the age of 61, she is 156 cm tall and weighs 48 kg. Hypoacusis has been known for several years, but no further investigations have been performed.

At the age of 60 years, she was diagnosed with dilated cardiomyopathy (LVIDd 54.10 mm, LVIDs 43.10 mm, LVPWd 13.20 mm, LVPWs 17.0 mm, IVSd 8.32 mm, IVSs 15.10 mm, FS 20.3%), mild pulmonary and tricuspid regurgitation as well as pericardial effusion. Over the last year, the patient progressively suffered from muscular weakness and exercise intolerance.

Laboratory investigations were done; beside elevated heart parameters, no other specific findings (especially concerning kidney or liver) were detected (Table 3). She has suffered no strokes or stroke-like episodes.

Patient 9 is a 68-year-old man, who developed normally until age 52 years. An audiogram showed a sensorineural hearing loss on both sides, whereas the patient complains only about left-sided hypoacusis. He has suffered from diabetes mellitus since age 52 and has taken insulin for the last 10 years. The patient is 165 cm tall and weighs 68 kg. His head circumference is normal (56 cm).

In the last four years, he has reported exercise intolerance without muscle pain. He was first seen at the tertiary hospital when he underwent exercise testing. Blood pressure and heart frequency during exercise showed normal elevations, whereas maximal work capacity was reduced to 56% (75 Watt; normal 133 Watt). Intermittent premature supra- and ventricular contractions were found, but no other signs of arrhythmia. ECG and echocardiography showed left ventricular hypertrophy, but no restricted function (LVIDd 48.40 mm, LVIDs 31.40 mm, LVPWd 13.20 mm, LVPWs 17.00 mm, IVSd 18.10 mm, IVSs 21.90 mm, FS 35.1%). Furthermore, mild regurgitation of the tricuspid (CV Doppler 45 mm Hg) and the mitral valve (E/A 0.6, E/E′ 13.1) and pericardial effusion were found discretely.

His mother died at age 62 due to sudden cardiac death, but showed no other symptoms.

Kidney and heart parameters have been mildly elevated intermittently (Table 3).

3 | DISCUSSION

To widen the range of clinical presentation of phenotypes associated with the *m.3243A>G* mutation, we present nine patients with a mitochondrial disease, proven *m.3243A>G* mutation and focus on cardiac involvement. Mitochondrial disorders are multi-systemic and show various clinical symptoms. Therefore, larger contemporary studies focusing on long-term prognosis regarding brain and heart manifestation are important.[6,7] All patients report exercise intolerance increasing over the course of disease. In addition to the echocardiographic findings our nine patients mostly have sensorineural hearing loss (five patients wear hearing aid devices) and present with short stature (three out of nine patients). Both younger patients (Patients 2 and 4) suffered stroke-like episodes in childhood and thereby meet the criteria for classical "MELAS," whereas the adults (Patients 3, 5, 6, 7, 8, and 9) do not. The observation period for Patient 1 was only 3 months, so it is not known whether he would have met the criteria. As not all phenotypes associated with *m.3234A>G* meet all criteria for MELAS, we propose that the underlying disease be called "*mitochondrial disease with underlying m.3243A>G mutation*."

Heteroplasmy—the presence of normal and mutant mtDNA within the same cell population—causes the different cardiac phenotypes in patients.[7] Roach et al[8] listed the clinical symptoms in 110 patients carrying the *m.3243A>G* mutation and found WPW syndrome in 14% and congestive heart failure in 18%. In our small cohort, three of the nine patients (at the focus of this publication) showed WPW syndrome with short PR intervals and delta waves and one even with sick sinus syndrome and AV block I. Furthermore, eight of the nine patients presented with hypertrophic/dilated cardiomyopathy and moderate to severe regurgitation of various valves. As a result, we would like to point out that our case series emphasizes the strong impact of cardiac involvement in phenotypes associated with the *m.3243A>G* mutation, as previously presented by Wahbi et al[6] and Malfatti et al.[9]

Thus, in the presence of cardiomyopathy, especially in addition to other symptoms, that is sensorineural hearing loss, diabetes mellitus, short stature, and even in the absence of stroke-like episodes or neurological symptoms, a mitochondrial disorder should be suspected (organ screening, lactate in different compartments, possibly specialized investigations, that is mtDNA mutations, activity of mitochondrial respiratory chain in viable tissue and frozen samples [muscle, heart, fibroblasts]). Furthermore, family testing should be discussed, because sudden death syndrome is an important cause of death in patients with the *m.3243A>G* mutation.[6]

To date there is no cure for these mitochondrial diseases, but in addition to receiving symptomatic treatment for their sensorineural hearing loss, heart insufficiency and diabetes mellitus, all eight patients are being treated with 2-8 mg/kg to a maximum of 600 mg coenzyme Q10, 50-400 mg riboflavin and 10-100 mg/kg to a maximum of 1000 mg L carnitine per day.[10] Depending on organic involvement, other drugs (including L arginine 0.5 mg/kg after initial bolus) have been used to prevent or ameliorate

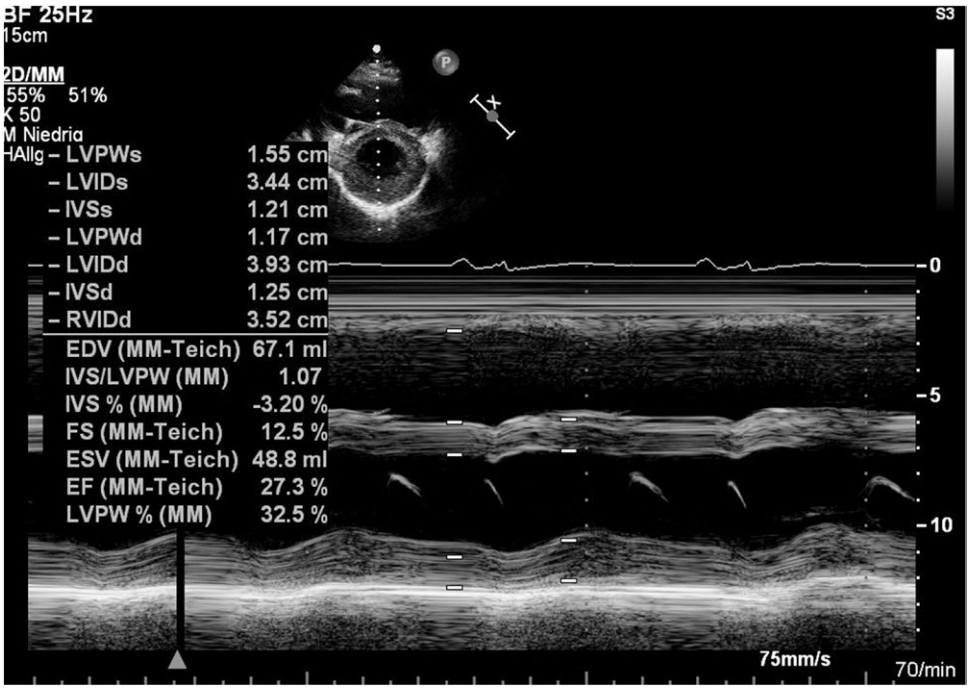

FIGURE 2 Echocardiography of Patient 5 (♀; 42 years) at age 39 showing hypertrophic cardiomyopathy with restricted systolic left ventricular function and abnormal diastolic relaxation (M-mode through left ventricle)

neurological symptoms, especially in the acute phase.[10–14] In patients with progressive cardiomyopathy heart transplantation is only rarely an option,[15] but should be discussed in detail and can lead to a successful outcome.

4 | CONCLUSION

"**M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and at least one **S**troke-like episode," is the typical "MELAS" syndrome with underlying *m.3243A>G* mutation.[1,2] However, phenotypic presentation can vary, even in patients carrying the same mutation. Thus, not all patients with a mitochondrial disorder due to *m.3243A>G* fulfill the criteria for "MELAS," but present with cardiac involvement.

Hypertrophic or dilated cardiomyopathy, as well as preexcitation syndromes or conduction blocks are common in patients with the *m.3243A>G* mutation. Thus, cardiologists should screen patients with unexplained cardiac features in the context of deafness, short stature, and learning disabilities for mtDNA mutations. Exclusion or verification of the *m.3243A>G* mutation might be helpful, for example when giving prognostic advice concerning the disease course. Furthermore, for this mutation family testing is recommended because cardiomyopathy due to mitochondrial disorders is maternally transmitted, whereas "the" classical cardiomyopathy follows an autosomal dominant pattern (all first-degree relatives at 50% risk).

To date there is no cure for these mitochondrial diseases, but some patients may benefit from coenzyme Q10 and riboflavin. In particular, the use of L arginine in patients with stroke-like episodes might be advantageous.[10–14]

CONFLICT OF INTEREST

The authors have no financial conflicts of interest.

AUTHOR CONTRIBUTIONS

Katharina Niedermayr and Daniela Karall: Concept, data collection, drafting the article. Gerhard Pölzl, Sabine Scholl-Bürgi, Christine Fauth, Ulrich Schweigmann, Edda Haberlandt, Ursula Albrecht, Manuela Zlamy, Wolfgang Sperl and Johannes A. Mayr: Patient care, critical revision and approval of the article.

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