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Clinical profile and outcome of cardiac involvement in MELAS syndrome

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ABSTRACT

Background: Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like (MELAS) syndrome is a rare condition with heterogeneous clinical presentation. Cardiac involvement commonly develops during adulthood, comprising both structural and conduction/arrhythmic abnormalities; early paediatric onset has rarely been reported. We describe the clinical profile, outcome and clinical implication of MELAS-associated cardiomyopathy at a tertiary referral centre.
Methods: From 2000 to 2016 we enrolled 21 patients affected by genetically-proven MELAS. Patients were followed-up at least annually over a mean of 8.5 years.
Results: All patients carried the MT-TL1 3243A>G mutation. Cardiac involvement was documented in 8 (38%) patients (three <18 years; five ≥18 years), including 6 (75%) with hypertrophic cardiomyopathy, 1 (12.5%) with dilated cardiomyopathy, and 1 (12.5%) with persistent pulmonary hypertension. During follow-up, 3 patients died, all with cardiac onset <18 years. The cause of death, however, was non-cardiac (infections, respiratory failure, stroke). Neither events nor cardiac progression were recorded among patients with onset ≥18 years. Adult cardiologists were responsible for 5/8 of referrals, even in patients with long-standing extra-cardiac involvement.
Conclusions: Cardiac involvement was found in over 1/3 of patients with MELAS syndrome, and exhibited a bimodal age-related distribution with distinct final outcomes. Paediatric-onset cardiomyopathy represented a hallmark of systemic disease severity, without being the main determinant of outcome. Conversely, adult-onset cardiomyopathy appeared to represent a mild and non-progressive mid-term manifestation. Adult cardiologists played an important role in the diagnostic process, triggering suspicion of MELAS in most of patients diagnosis >18 years.

1. Introduction

The mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) syndrome is a genetic, maternally transmitted mitochondrial disease, characterized by multi-organ involvement with heterogeneous clinical spectrum. Altered mitochondrial genome leads to impaired oxidative phosphorylation and inadequate energy production; thus, organs with high-energy demand, such as brain, eye, heart and skeletal muscle, are more severely affected. Cardiac involvement (CI) is reported in up to 55% of patients with the 3243A>G mutation and left ventricular hypertrophy (LVH) is reported as the most common phenotype, possibly evolving in dilated cardiomyopathy at a later stage [1–5]. Conduction defects including atrio-ventricular block and Wolff-Parkinson-White (WPW) syndrome are frequently reported [5,6]. Rhythm disturbances may occur, and include frequent ventricular ectopy, atrial fibrillation, ventricular tachycardia and sinus arrest. Furthermore, pulmonary arterial hypertension associated syndrome has been observed in the context of MELAS [7,8].

An intriguing aspect of MELAS-related cardiomyopathy (MELAS-CMP) is the temporal heterogeneity of its clinical onset, possibly due to varying degrees of heteroplasmy in distinct tissues. Cardiac involvement has been rarely described in infancy [9,10], but most patients only show evidence of MELAS-CMP during adulthood. Whether the timing of onset of heart involvement is relevant for clinical evolution and final outcome, however, is unknown, and the prognostic implications

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of these cardiac abnormalities, often overshadowed by the systemic manifestations of MELAS, remain unclear. In the present study, we assessed the profile and prognostic implications of cardiac involvement associated with MELAS in a consecutive cohort of patients followed at a tertiary referral paediatric centre.

2. Patients and methods

2.1. Clinical and genetic diagnosis

This study was approved by the Ethics Committee of Meyer Children's Hospital (Florence) as a retrospective chart analysis; the study protocol conforms to the ethical guidelines of the Declaration of Helsinki. The Committee waived the need for patient consent.

From January 2000 to December 2016 we enrolled 11 consecutive patients from 10 unrelated families, presenting with a combination of clinical symptoms strongly suggestive for MELAS disease. The initial clinical suspicion was confirmed by genetic diagnosis utilizing polymerase chain reaction with the restriction fragment length polymorphism technique (PCR-RFLP). DNA was obtained from blood samples, urine and/or oral epitelium. Clinical evaluation and molecular analysis extended to living maternal relatives allowed us to identify 10 oligosymptomatic/asymptomatic patients carrying the same mt-DNA mutation. Five additional relatives whose clinical history was evocative of MELAS were excluded as blood and/or tissue samples were not available for genetic testing. Therefore, the final study cohort comprised 21 patients with confirmed diagnosis of MELAS syndrome from 10 families.

2.2. Definition of cardiac involvement

Cardiac involvement was defined by one or more of the followings:

- Hypertrophic cardiomyopathy (HCM) defined as a maximum left ventricular (LV) thickness, in any region of the chamber (generally, the septum) >2 Z-score in infants, children and adolescents and ≥15 mm in adults.
- Dilated cardiomyopathy (DCM), defined by increased ventricular end-diastolic diameter (>2 Z-Score) associated LV systolic dysfunction (left ventricular ejection fraction [LVEF] < 55%).
- Pulmonary hypertension (PH), defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mm Hg at rest as assessed by right heart catheterization.

The presence of electrophysiological abnormalities (WPW, conduction disorders, rhythm anomalies) in absence of structural heart disease was recorded but not considered diagnostic of MELAS-CMP. Age at first objective documentation of cardiac involvement was recorded and patients were divided based on paediatric (<18 years) or adult (≥18 years) onset.

2.3. Follow-up

All patients were evaluated at regular intervals of 6–12 months, or more often depending on clinical status. Assessment of cardiac involvement included complete clinical examination, 12-lead ECG and transthoracic two-dimensional, color Doppler and M-mode echocardiography using commercially available equipment. M-mode measurements were indexed to age and body-surface area and corresponding z-scores were derived. LVEF was measured by the biplane Simpson method (normal value > 55%, mild dysfunction 45–54%, moderate dysfunction 30–44%, severe dysfunction < 30%). 24-hour Holter monitoring, cardiac catheterization and cardiac magnetic resonance imaging (CMR) were performed in selected patients based on compliance and clinical indications. CMR examinations were performed using commercially available scanners (Philips ACS-NT 1.5 T Gyroscan-Intera, Best, Netherlands and General Electric Signa Excite HD 1.5) and work-stations (View Forum, Philips Medical System, Netherlands; Advantage Windows 4.0, General Electric Medical System). The presence of late gadolinium enhancement (LGE) was assessed by visual inspection 15 min after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering; Berlin, Germany) with breath-held segmented inversion-recovery sequence (inversion time 240 to 300 ms) which was acquired in the same views as the cine images. Right heart catheterization was performed in one patient with echocardiographic evidence of pulmonary hypertension, to evaluate pulmonary vascular resistances and pressures. A single adult patient underwent endomyocardial biopsy in a different centre in order to exclude infiltrative cardiac disease.

2.4. Statistical analysis

Variables were expressed as mean ± standard deviation for normally distributed variables, and as median and interquartile range otherwise. Categorical values were expressed as proportions. Continuous variables were compared using Student *t*-test. Categorical variables were compared using Pearson χ^2 test or Fisher's exact test, as appropriate. *P* values are presented with 95% confidence intervals. The STATA statistical software version 14.2 was used for all analyses.

3. Results

3.1. Presenting features and prevalence of cardiac involvement

All 21 patients carried the most common mutation associated with MELAS syndrome, i.e. 3243A>G. Male/female ratio did not demonstrate significant gender imbalance (males/females = 0.9). Mean age at diagnosis was 32 ± 19 years. Classic presenting phenotype with short stature, leanness, muscular hypotrophy and/or myopathy was documented in 9/21 (43%) patients (Table 1). Cardiac involvement was documented in 8 (38%) patients, at a mean age of 22.3 ± 13.5 years, including three children (<18 years of age) and five adults (>18 years). In all but one, cardiac involvement was not the presenting sign; however, it was the reason for referral to our centre since it raised the suspicious of underlying metabolic disorder. Among patients characterized by cardiac involvement, 87% (7/8) had short stature, muscular hypotrophy, diabetes and/or hearing loss as presenting features; these elements had generally been reported since childhood or adolescence, preceding the onset of cardiac disease by up to 30 years (Fig. 1). Average time between the onset of cardiac disease and the diagnosis of MELAS syndrome was 3.9 ± 3.5 years. The remaining patient had cardiac involvement (pulmonary hypertension) in the absence of clear syndromic features.

At initial evaluation, 6 of the 8 patients (75%) reported functional limitation during ordinary physical activity (NYHA Class II), one patient (12.5%) presented with marked limitation (NYHA Class III) and one was asymptomatic (NYHA Class I) (Table 2). ECG anomalies were documented in all patients, and the most common was LV hypertrophy (5/8; 62.5%), although one adult patient had low ECG voltages despite LVH on echocardiography, leading to an initial suspicion of infiltrative disease. Ventricular preexcitation was present in 2 patients (25%), and ventricular ectopy at 24-hour Holter was present in one. At echocardiography, hypertrophic cardiomyopathy was the most common phenotype (6; 75%), whereas dilated cardiomyopathy could be documented only in one patient (12%), who had an LVEF of 25%. In one patient pulmonary hypertension was identified at transthoracic echocardiogram and confirmed at cardiac catheterization. This patient, who presented with failure to thrive, eventually died due to acute respiratory failure after pulmonary infection at the age of 14 years (Supplement 1).

Two patients underwent CMR as part of the diagnostic work-up, with non-specific findings. In the one, asymmetric LV hypertrophy mainly involving the septal wall was observed, with a maximum thickness of 16 mm. The other patient had concentric hypertrophy with marked LV hypertrabeculation involving the apex, distal septal wall and lateral. Neither had late gadolinium enhancement (Supplement 2).

Seven patients (87%) received pharmacologic treatment including beta-blockers, loop diuretics, ace-inhibitors or angiotensine-receptor blockers, calcium-antagonist (amlodipine), and disopyramide. The patient with pulmonary hypertension required treatment with endothelin-receptor antagonist (bosentan). All patients were treated with carnitine and coenzyme Q10.

3.2. Comparison of patients with and without cardiac involvement

The 8 MELAS patients presenting with cardiomyopathy were primarily referred for metabolic investigation by adult cardiologists (5/8; 63%), and paediatricians (2/8; 25%); only one patient was diagnosed by familial screening (12%). Conversely, the 13 patients without cardiac involvement were mainly diagnosed in the context of extended familial investigation (9/13; 69%), while specialist referral (by neurologists or nephrologists) played a lesser role (4/13; 31%). Failure to thrive and skeletal myopathy were significantly more frequent among patients with cardiac involvement (62% and 50%) compared to non-cardiac group (15% and 15% respectively) (Fig. 2). Seven patients (33%) developed neurologic involvement with stroke, epilepsy, recurrent headache or cognitive impairment; distribution of neurological

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Table 1
General features, cause of referral, extra-cardiac involvement and final outcome of enrolled patients.

Clinical features	Overall (n=21)	With Cardiac Involvement (n=8)	Without Cardiac Involvement (n=13)	P value (CI vs non CI)
Male/female	0.9	1.1	0.6	0.5
Age at diagnosis (years, IQ range)	31.5 (11)	28.5 (15.5)	33 (28)	0.2
Positive familiar history (n°;%)	18 (86%)	6 (75%)	12 (92%)	
Referral physicians (n°;%)				
- Cardiologist	5 (24%)	5 (62.5%)	0	
- Neurologist	3 (14%)	0	3 (23%)	
- Paediatrician	2 (9.5%)	2 (25%)	0	
- Nephrologist	1 (4.7%)	0	1 (7.6%)	
- Not referred, familial screening	10 (48%)	1 (12.5%)	9 (77%)	
First presenting symptom (n°;%)				
- Diabetes	5 (24%)	3 (37.5%)	2 (15%)	
- Neurologic	5 (24%)	1 (12.5%)	4 (30%)	
- Cardiovascular	1 (4.7%)	1 (12.5%)	0	
- Hearing loss	2 (9.5%)	1 (12.5%)	1 (7.6%)	
- Muscular weakness	1 (4.7%)	0	1 (7.6%)	
- Renal failure	1 (4.7%)	1 (12.5%)	0	
- Asymptomatic at diagnosis	7 (33%)	1 (12.5%)	6 (46%)	
Mean blood lactate (mM; SDS)	2.7 (±1.9)	3.9 (±1.9)	1.4 (±0.8)	<0.01
Hearing loss (n°; %)	11 (52%)	6 (75%)	5 (38%)	0.10
Diabetes (n°; %)	8 (38%)	5 (62.5%)	3 (23%)	0.07
Myopathy (n°; %)	6 (28%)	4 (50%)	2 (15%)	0.02
Failure to thrive /short stature (n°; %)	7 (33%)	5 (62.5%)	2 (15%)	<0.01
Neurologic involvement. (n°; %)	7 (33%)	2 (25%)	5 (38%)	0.9
- stroke	2	2	0	
- epilepsy	2	1	1	
- neurodevelopmental delay	1	1	0	
- cephalea	4	0	4	
Ocular involvement (n°; %)	5 (24%)	3 (37.5%)	2 (15%)	0.25
Renal failure (n°; %)	3 (14%)	1 (12.5%)	2 (15%)	0.27
Metabolic treatment (n°;%)				
- Coenzyme Q10	21(100%)	8 (10%%)	13 (100%)	
- Carnitine	21(100%)	8 (10%%)	13 (100%)	
Death (n°; %)	3 (14%)	3 (37.5%)	0	0.02

symptoms was similar between the two groups (Table 1). Sensorineural hearing loss was common (11/21; 52%) and was more frequent in the group with cardiac involvement (75%, vs 38% in patients without cardiac abnormalities); however, the difference was not statistically significant ($P = 0.10$). Mean blood lactate levels were significantly more elevated in patients with CI (3.9 ± 1.9 mM) compared with patients without cardiac involvement (1.4 ± 0.8 mM) ($P = 0.006$). Diabetes and renal dysfunction had similar prevalence (38% vs. 14%, respectively; $P = 0.07$; $P = 0.27$). Age at diagnosis of the underlying metabolic disorder also did not differ (median 28.5, IQ range 18.5 years versus 33 years; IQ range 28 years, respectively; $P = 0.2$).

3.3. Paediatric versus adult onset cardiomyopathy and outcome

Mean follow-up was 8.5 ± 4.5 years (range: 3–14 years). At last available follow-up, survival rate was 84%: three deaths occurred in

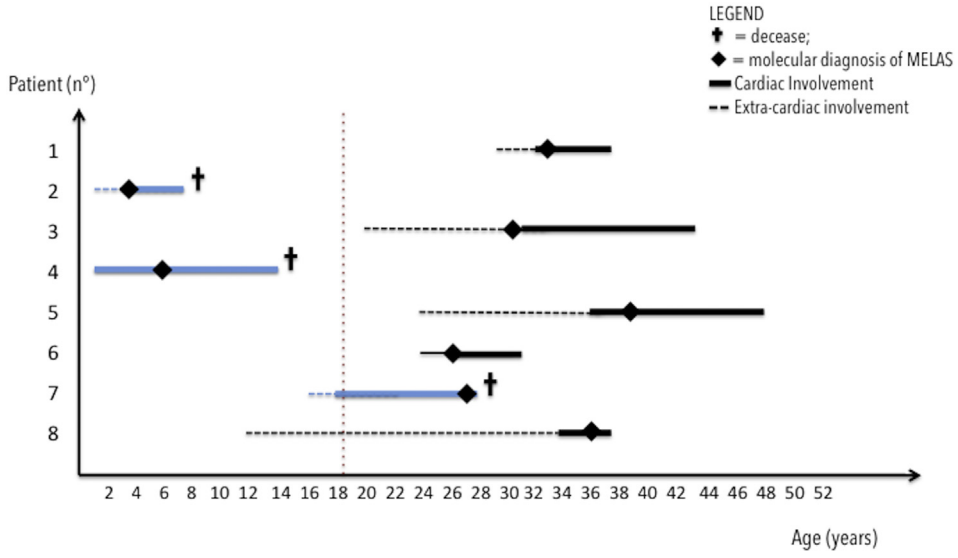

Fig. 1. Onset and evolution of clinical features consistent with MELAS syndrome. Extra-cardiac symptoms are reported in dotted thin lines, whereas thick lines represent cardiac involvement (CI). The dotted vertical line highlights the threshold between early and late CI. Patients presenting with early-onset CI are highlighted in blue. † = decease; ♦ = molecular diagnosis of MELAS syndrome. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Table 2
Clinical features, ECG and echocardiogram of the patients with cardiac involvement at baseline and at last available follow-up.

	Baseline	LFUP
Cardiovascular symptoms (n°;%)	7 (87.5%)	5 (62.5%)
NYHA Functional class (n°;%)		
- I	1 (12.5%)	3(37.5%)
- II	6 (75%)	4 (50%)
- III	1 (12.5%)	1(12.5%)
- IV	0	0
ECG anomalies (n°;%)	8 (100%)	8 (100%)
- Left ventricular hypertrophy	5 (62.5%)	6 (75%)
- Atrial dilatation	1 (12.5%)	2 (25%)
- Ventricular preexcitation	2 (25%)	2 (25%)
- Ventricular ectopy	0 (0%)	1(12.5%)
- Axial deviation	1 (12.5%)	2 (25%)
Echocardiographic anomalies (n°;%)	8 (100%)	8 (100%)
- Ventricular hypertrophy	6 (75%)	6 (75%)
○ LVOT obstruction	1 (17%)	1 (17%)
○ Mean EF (%)	64%	59%
- Dilated cardiomyopathy	1 (12.5%)	1(12.5%)
○ EF (%)	25%	30%
- Left atrial enlargement	2 (25%)	2 (25%)
- Pulmonary hypertension	1 (12.5%)	1(12.5%)

LFUP: last follow-up; LVOT: left ventricular outflow tract; EF: ejection fraction.

patients presenting with cardiac involvement (all with paediatric onset <18 years), while none died in the group with adult-onset cardiomyopathy (>18 years). Of note, however, the cause of death in the three patients was not primarily cardiac. The first patient had been diagnosed with hypertrophic cardiomyopathy at the age of 3 years; during follow-up she developed recurrent pulmonary infections and respiratory failure requiring tracheotomy. At the age of 6 years she was admitted to our hospital for bacterial pneumonia and developed septic shock with multi-organ failure. At last cardiac evaluation she had evidence of biventricular dysfunction (EF 40%, TAPSE 11 mm) and mild concentric left ventricular hypertrophy (septal thickness 8 mm, Z-Score 3.5; LV parietal thickness 8 mm, Z-Score 2.19). The second patient developed persistent pulmonary artery hypertension in his first year of life, requiring treatment with bosentan. An atrial septal defect (ASD) ostium secundum type of small diameter was also detected. At age 14 years, he was hospitalized for pneumonia and hyponatremia and died of refractory respiratory failure. Echocardiographic evaluation documented right ventricular dilatation and moderate tricuspid regurgitation, with a right atrio-ventricular gradient of 70 mm Hg. The last patient presumably died of ischemic stroke following acute development of neurological symptoms; autopsy was not performed. Of the 5 cardiac patients who survived (all with adult-onset cardiomyopathy), 3 were asymptomatic at last evaluation (NHYA Class I), 4 were in NHYA Class II and one patient was in NHYA Class III. None had significant progression of their cardiac findings and none had cardiac events during follow-up.

4. Discussion

In the present study, we observed cardiac involvement in 38% of our patients MELAS; in agreement with previous reports indicating a prevalence ranging from 30 to 56% [1–5]: hypertrophic, non-obstructive cardiomyopathy was the most common phenotype, followed by dilated cardiomyopathy and pulmonary arterial hypertension. Of note, the distribution of cardiac involvement in MELAS syndrome appeared to be bimodal with regard to age of onset, and associated with different outcome. The three young patients experiencing early-onset cardiomyopathy (<18 years) died within the third decade of life, although death occurred due to infections, respiratory failure and cerebral events and could not be attributed primarily to cardiac causes. Thus, in children and adolescents with MELAS, heart disease appeared to be a hallmark of severity, implying risk of early death without necessarily being the main determinant of outcome. Conversely, the 5 patients with adult-onset cardiac involvement remained stable over time, requiring only clinical/instrumental follow-up in the absence of adverse arrhythmic events or heart failure. In agreement with a prior report by Kaufmann et al. [11], quality of life in these patients seemed largely influenced by limited by extra-cardiac manifestations such as neurologic events,

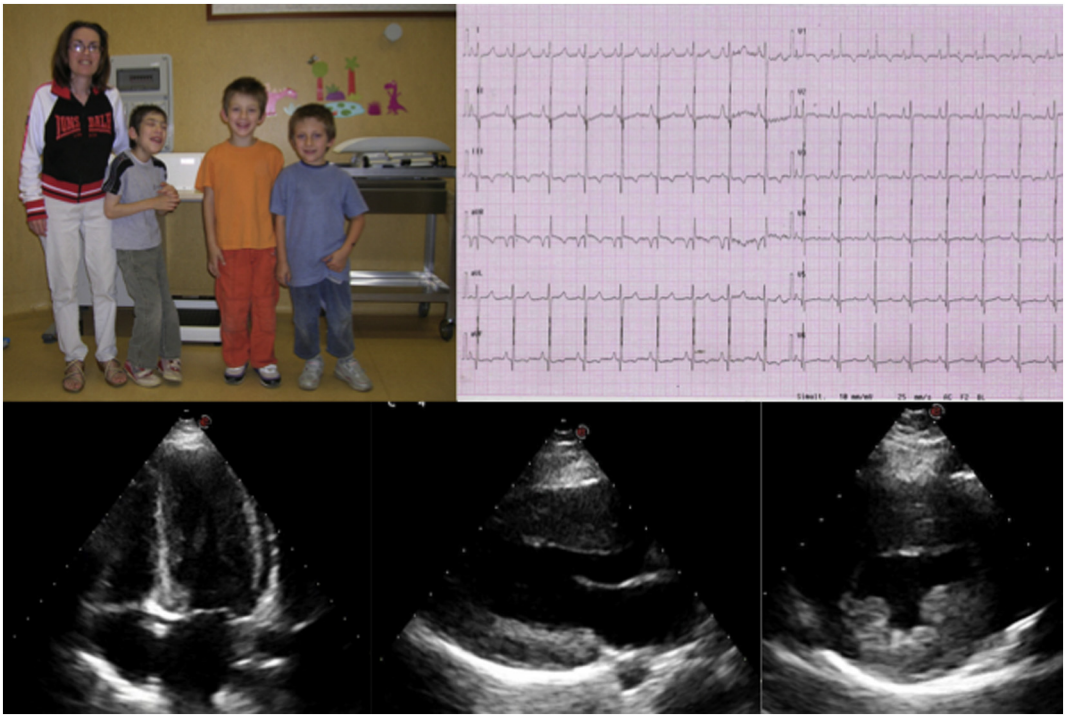

Fig. 2. Clinical, ECG and echocardiographic features of MELAS patients. Panel A depicts a family in which the mother and one of the sons show the classic clinical phenotype (on the left), whereas other two children carrying the same mutation present with normal clinical features. Signs of right atrial enlargement and ventricular repolarization abnormalities were found at the ECG from the first son (Panel B). The echocardiogram of the mother documented concentric left ventricular hypertrophy (Panel C; apical four-chamber, long-axis and short-axis view).

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muscle weakness, fatigue and respiratory failure. In contrast, Malfatti et al. [12], documented a high incidence of cardiac death and life-threatening events in adult MELAS patients; such discrepancy may be partly accounted for by the older age of their cohort. Therefore, it is prudent to suspect that longer observation periods may unmask cardiac morbidity also in our patents with MELAS cardiomyopathy. Recent evidence from patients with sarcomeric hypertrophic cardiomyopathy, for example, shows that two or more decades may be required the disease to reveal its full clinical burden [13]. Multicenter registries and extended follow-up periods are therefore warranted in mitochondrial diseases.

4.1. Mechanisms of cardiac disease in MELAS

The myocardium is a highly oxidative tissue and >90% of its metabolism relies on mitochondrial adenosine triphosphate (ATP) production [14]. In case of mitochondrial dysfunction, energy metabolism is oriented towards anaerobic glucose utilization (i.e. glycolysis), with lactic acid accumulation and energetic deficit in multiple organs (Fig. 3). The severity of respiratory chain deficiency along with the ability to engage alternative metabolic pathways are the major drivers of both cardiac and extra-cardiac involvement. Cardiac hypertrophy is believed to represent an initial compensative effort, often followed by progressive dysfunction in the long-term.

The heterogeneity of clinical phenotypes among MELAS patients has been partially explained by the varying burden of mutant mt-DNA carried by different individuals within different tissues [15]. The degree of heteroplasmy, along with the level of cellular energy requirement, is believed to determine clinical phenotype and rate of progression, although not all authors agree [16]. As consequence of heteroplasmy principle, even organs with high metabolic demands, such as the heart, may be capable of preserving a metabolic balance in MELAS patients, accounting for lack of cardiac manifestations at the end of follow-up in over 60% of our patients. Further understanding of precipitating vs protective mechanisms may be crucial in developing treatments for this condition.

4.2. Role of adult cardiologists in diagnosing MELAS

In our cohort, adult cardiologist played a significant role in the diagnostic process of MELAS patients. In two thirds of the patients presenting with cardiac involvement, and almost a quarter of the whole cohort, suspicion of mitochondrial disease and referral for metabolic evaluation was triggered by cardiologic assessment, even though long-standing extra-cardiac manifestations had been present (Table 1). Detailed clinical history, pedigree and examination generally highlight "red-flags" that may suggest the final diagnosis in patients presenting with hypertrophic cardiomyopathy or unexplained pulmonary hypertension. These include matrilinear transmission, a history of diabetes, recurrent migraine, stroke and/or hearing loss, along with a typical clinical aspect (short stature, leanness, muscular hypotrophy). A final diagnosis requires further evaluation at an expert metabolic unit. Differential diagnoses include a number of other metabolic and neuromuscular disorders, as Anderson-Fabry disease, amyloidosis, muscular dystrophies or fatty-acid beta-oxidation disorders (Supplement 3). Notably, some of our patients had been previously investigated to exclude Anderson-Fabry disease, which represents a known cause of metabolic cardiomyopathy among adults but does not show evidence of cardiac involvement in children or young adults. While Fabry disease and MELAS syndrome may share some features in adult patients, including renal dysfunction and neurologic involvement, the distinct pattern of transmission (matrilineal versus X-linked) and typical associated features (acroparesthesiae, corneal opacities, angiokeratoms, anidrosis,

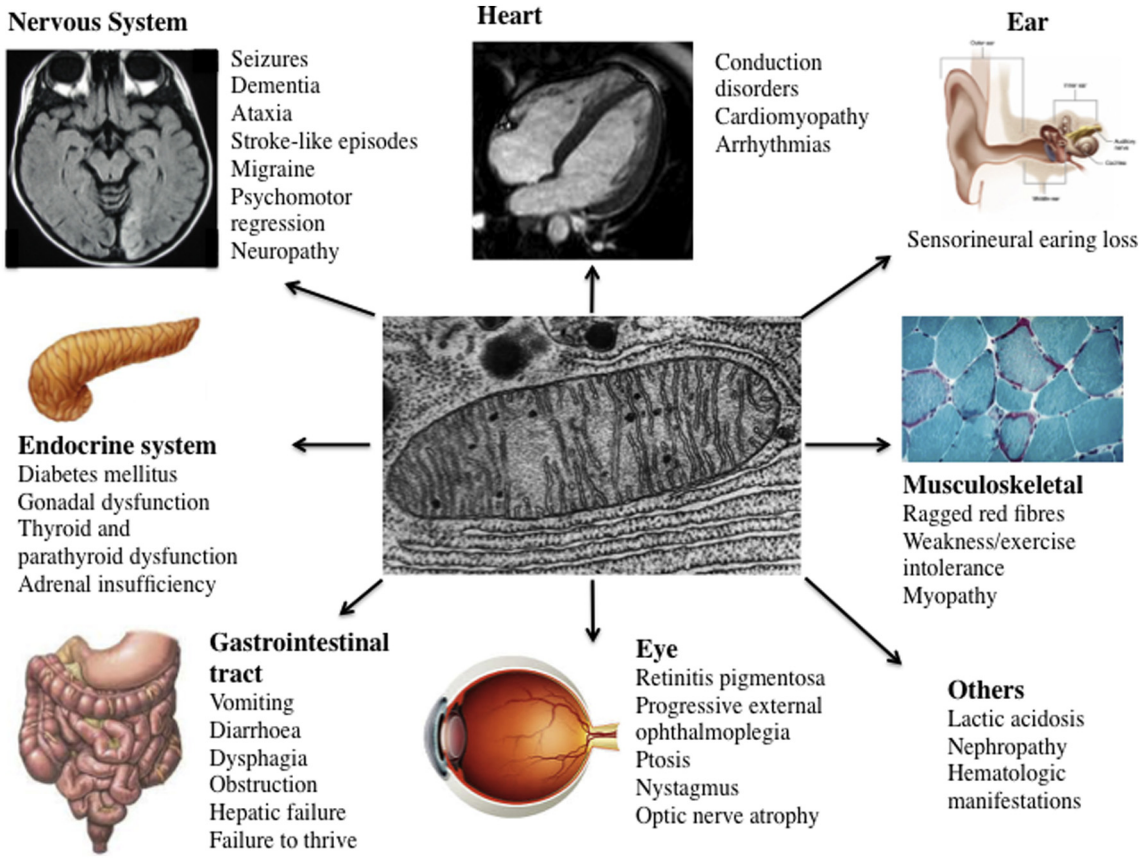

Fig. 3. Pathophysiology. Mitochondrial dysfunction leads to heterogeneous multi-organ involvement. Organs with high-energy demand (nervous system, heart, skeletal muscle, eye, endocrine system) are the more severely compromised.

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gastrointestinal symptoms) generally avoid diagnostic dilemmas [17]. The fact that Fabry disease had been suspected in our patients reflects a marked increase in the awareness of this condition among cardiologists following the introduction of specific treatment. Mitochondrial diseases, however, are orphan conditions and do not share this privilege.

4.3. Study limitations

The main constraint of the study concerns the limited sample of patients, which attenuates the statistical significance of our findings. Given the rarity of the disease, further multi-centric and prospective studies are advocated in order to confirm or to better explain our results.

As retrospective observational study, some information (i.e. cardiac magnetic resonance, NT-Pro BNP plasma level, heteroplasmy rates) was not available for most of patients. Moreover, heteroplasmy rates were tested on heterogeneous samples (blood, muscular tissue, bladder epithelium, oral epithelium), which therefore resulted unsuitable for comparison. As element of interest, we documented considerable differences in heteroplasmy rates between distinct tissues owing to the same patient, probably reflecting the different extent of organ involvement. According to this, the most reliable tool aimed at confirming a correlation between heteroplasmy rates and the severity cardiac involvement presumably consists in myocardial biopsy, which is rarely performed in clinical practice. These data could be a topic of interest for future prospective studies.

5. Conclusions

Cardiac involvement was found in over one third of patients with MELAS syndrome, and exhibited a bimodal age-related distribution with distinct final outcomes. Paediatric-onset cardiomyopathy represented a hallmark of systemic disease severity, without being the main determinant of outcome. In adults, cardiac involvement was stable over time and was not responsible for major events, at least in the mid-term. Adult cardiologists played an important role in the diagnostic process, triggering suspicion of MELAS in most patients >18 years of age.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.051.

Conflict of interest statement and source of funding

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Authors' contribution statement

All authors have equally contributed in the design of the study, data collection, data analysis and interpretation, drafting the article and critical revision. All authors have approved the final version of the manuscript and its submission.

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