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What the Cardiologist Should Know About Mitochondrial Cardiomyopathy?

Guillaume St-Pierre, MD, FRCPC,[a] Christian Steinberg, MD, FRCPC,[a] Michelle Dubois, RN, BSc,[b] and Mario Sénéchal, MD, FRCPC[a]

[a] *Department of Cardiology, Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, Quebec City, Quebec, Canada*

[b] *Research center, Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, Quebec City, Quebec, Canada*

ABSTRACT

Mitochondrial diseases are a heterogeneous group of rare hereditary disorders that may manifest with single organ involvement or as multisystemic disease. The pathophysiology of mitochondrial disease is complex and related to mutations of genes encoding mitochondrial proteins that are crucial to the cellular respiratory chain. Given its almost exclusive aerobic metabolism, the heart is particularly susceptible to mitochondrial dysfunction and commonly involved in mitochondrial disorders. Various clinical presentations are described, making clinical recognition challenging. Some patients may evolve towards the early need for heart transplantation, which emphasizes the importance of appropriate diagnosis and referral to a specialized centre.

RÉSUMÉ

Les maladies mitochondriales sont un groupe hétérogène d'anomalies héréditaires rares qui peuvent se manifester par l'atteinte d'un seul organe ou une atteinte multisystémique. La physiopathologie des maladies mitochondriales est complexe et liée à des mutations de gènes codant pour des protéines mitochondriales qui sont essentielles à la chaîne respiratoire cellulaire. Étant donné son métabolisme aérobie presque exclusif, le cœur est particulièrement susceptible de dysfonction mitochondriale et est fréquemment touché lors d'anomalies des mitochondries. Les divers tableaux cliniques décrits rendent difficile la reconnaissance de ces maladies sur le plan clinique. Puisque certains patients peuvent évoluer vers une transplantation cardiaque précoce, cela montre bien l'importance de poser un diagnostic approprié et de les orienter à un centre spécialisé.

Case Report

We report the case of a 27-year-old man transferred to our centre in 1997 for possible angina pectoris. His past medical history was significant for insulin-treated diabetes mellitus, stage 3-4 chronic renal failure (baseline creatinine of 217 µmol/L, estimated glomerular filtration rate 32 mL/min/1.73 m^2), symmetric peripheral neuropathy, and bilateral sensorineural deafness. Family history revealed diabetes in the patient's mother and his maternal grandmother presumably died from a cardiomyopathy of unknown origin. The patient's symptoms were dominated by an NYHA class II dyspnea associated with atypical chest pain and nonspecific palpitations. On physical examination, vital signs were normal. Cardiac auscultation revealed a holosystolic murmur grade 2/6 at the apex with an S3. There were no signs of congestive heart failure. Basic laboratory results were normal, including repeat cardiac troponin measurements. His electrocardiogram (ECG) revealed sinus rhythm and the presence of a Wolff-Parkinson-White pattern. There were no ECG signs of acute ischemia (Fig. 1). Echocardiogram showed a reduced left ventricular (LV) ejection fraction at 25%, diffuse concentric LV hypertrophy with suspicion of LV noncompaction (end-diastolic diameter 58 mm, end-systolic diameter 50 mm, LV mass 208 g/m^2) associated with moderate functional mitral regurgitation and severe atrial dilatation (Videos 1 and 2, view videos online; and Fig. 1). There was no coronary stenosis on angiography. An endomyocardial biopsy with standard and electronic microscopy was performed but pathology results were inconclusive. Unfortunately, no immunohistochemical staining targeting markers of mitochondrial disease was performed. The patient was discharged with carvedilol 6.25 mg BID, hydralazine 50 mg TID, and isosorbide mononitrate 60 mg OD because of hyperkalemia with angiotensin-converting enzyme inhibitor. One year later, he required an ablation of his Wolff-Parkinson-White because of symptomatic supraventricular tachycardia. Over the next few years, he developed worsening heart failure

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Corresponding author: Dr Mario Sénéchal, Institut universitaire de cardiologie et de pneumologie de Québec, Laval University, 2725 Chemin Ste-Foy, Quebec City, Quebec G1V 4G5, Canada. Tel.: +1-418-656-8711.

E-mail: mario.senechal@criucpq.ulaval.ca

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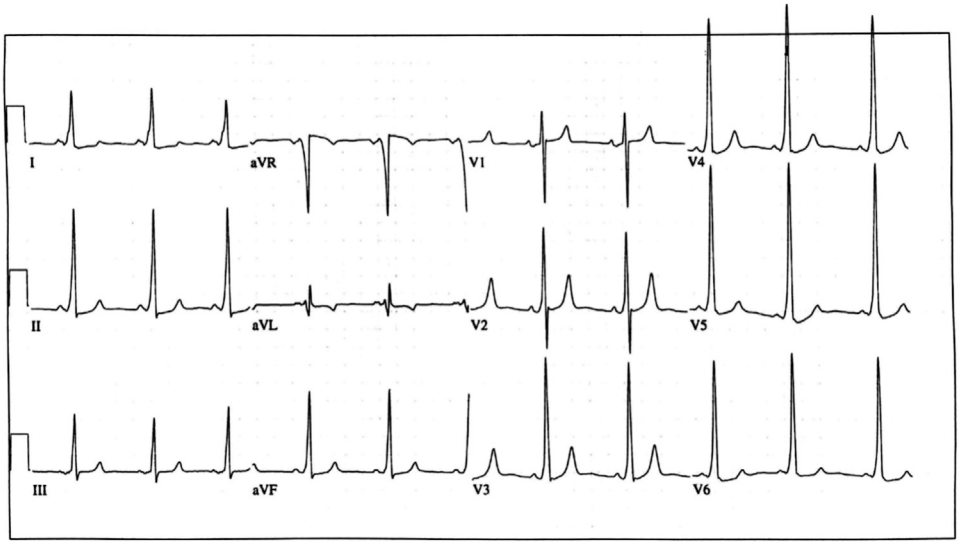

Figure 1. Electrocardiogram showing the pre-excitation pattern.

(NHYA III) and required mitral valve replacement (mechanical prosthesis). Surgery did not improve his functional capacity and the patient remained highly symptomatic. The patient declined an initial evaluation for heart transplantation and underwent eventually implantation of a cardioverter defibrillator for primary prevention. In 2009, 12 years after the initial presentation, the patient had evolved towards end-stage heart failure. His LV ejection fraction had declined down to 15% in conjunction with severe LV dilatation (end-diastolic diameter 65 mm, end-systolic diameter 60 mm) and he required milrinone infusion twice a week. At that time, the patient was wheelchair bound because of muscle weakness. Cardiac magnetic resonance imaging (CMR) could not be performed because of his implantable cardioverter defibrillator. Biopsy of the quadriceps muscle was performed, and the diagnosis of mitochondrial disease with cardiac involvement was evoked based on abnormal immunohistochemical staining of cytochrome-c oxydase (SDH^+ and COX^- fibres). In addition, abnormal serum concentrations of various amino acids and acylcarnitine further strengthened the working diagnosis of mitochondrial cardiomyopathy. Unfortunately, no genetic testing was performed because of the lack of a specialized cardiogenetic clinic in our institution at that time. High doses of coenzyme Q10 were prescribed with transient amelioration of weakness but dyspnea persisted. The patient eventually evolved towards intractable congestive heart failure requiring continuous milrinone infusion. In 2014, he decided to withdraw active treatments and expired a few days later.

Discussion

Mitochondrial disease is a challenging diagnosis and occurs with an estimated incidence of 1:4000-1:5000.[1]. Twenty-five percent (and up to 40%) of those patients will present with some form of cardiac involvement[1] that is often a major determinant of morbidity and mortality.[1-3]

The genetics of mitochondrial disorders are complex, as mitochondrial proteins are encoded by nuclear DNA (gDNA) and partially by mitochondrial DNA (mtDNA).[4,5] In contrast to gDNA, mtDNA is exclusively maternally inherited. Approximately 15% of mitochondrial disorders are caused by mutations of mtDNA genes. Quantification of mtDNA by real-time polymerase chain reaction and documentation of increased or reduced mtDNA contents may be a first hint of a mitochondrial disease.[4,5] Thus, genetic testing for mitochondrial disease should always include analysis of gDNA and mtDNA. Cellular effects of mitochondrial disease may be homoplasmic (all cellular mitochondria are mutants) or heteroplasmic (cellular mosaic of normal and mutant mitochondria).[4,5] Those phenomena add further complexity to the pathophysiology and degree of disease manifestation highlighting the importance of highly specialized genetic and pathology laboratories. A close collaboration between the treating cardiologist and a specialized cardiogenetic clinic is recommended to ensure accurate diagnostic workup and family screening.

Mitochondrial disease can present as a systemic disease or with single organ involvement.[1] When cardiac involvement is the presenting feature, physicians must have a high level of suspicion to search for other features that can lead to the diagnosis of a mitochondrial disorder. Systemic findings pointing towards mitochondrial disease may include insulin-dependent diabetes mellitus, early bilateral sensorineural deafness, growth retardation, muscle weakness, and chronic kidney disease that may not correlate with diabetes duration and severity.[1] Although neurologic symptoms are frequent, as many as 40% of all patients will not have cognitive degeneration.[1-5] Moreover, in syndromic disorders, physicians must search for cardiac involvement because morbidity and mortality are high among those patients.[2] Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome is the prototype of systemic mitochondrial disorders and accounts for 25% of all mitochondrial disorders. Cardiomyopathy affects one-third of patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome.[1-5] Onset and degree of cardiac involvement are highly variable among mitochondrial diseases. Mitochondrial cardiomyopathies are predominantly characterized by a restrictive pathophysiology that is related to

Table 1. Multisystemic manifestations of mitochondrial disorders

System	Clinical manifestations	Testing
Cardiac	Cardiomyopathy: Diffuse hypertrophic cardiomyopathy Dilated cardiomyopathy Left ventricular noncompaction Electrophysiological abnormalities: Premature ventricular contractions Wolff-Parkinson-White Arrhythmias Sudden death	Echocardiography, electrocardiogram, Holter
Neurologic	Stroke-like episodes Mental retardation or premature cognitive impairment Premature sensorineural deafness	Head computed tomography, audiologic studies
Skeletal muscle	Muscle weakness Short stature Diaphragmatic weakness with dyspnea/orthopnea	Quadriceps muscle biopsy, creatine kinase, lactate, LDH
Endocrine	Most common: Insulin-dependent diabetes Hypothyroidism Any endocrine deficiency can occur	Fasting blood glucose, HbA1c, TSH, T4, T3, others if clinical suspicion
Renal	Chronic renal failure that may not correlate with diabetes severity and duration	Creatinine, urinary protein measurement
Gastrointestinal	Various degrees of liver dysfunction Abdominal pain, nausea and vomiting Malabsorption, villous atrophy, diarrhea	Liver enzymes, vitamins' measurement

diffuse ventricular hypertrophy. Progressive diastolic dysfunction and heart failure with preserved ejection fraction are typical for the early stages of mitochondrial cardiomyopathies. The absence of specific findings on echocardiography or CMR makes the diagnosis challenging and opens a broad differential diagnosis. The most common finding on echocardiography includes symmetric concentric LV hypertrophy and can be found in up to 40% patients and may be difficult to distinguish from sarcomeric hypertrophic cardiomyopathy.[1] Dilated cardiomyopathy can be the initial pattern but represents more likely a consequence of long-standing LV dysfunction in a patient with pre-existing hypertrophy.[1] Another manifestation may include LV noncompaction, as seen in our patient.

Electrophysiological abnormalities are common but nonspecific in patients with mitochondrial cardiomyopathy. In a cohort of 32 patients, Limongelli et al.[2] found that up to 68% have an abnormal ECG. The LV pre-excitation pattern was present in 22%, intraventricular conduction abnormalities in 22%, LV hypertrophy in 31%, and T-wave abnormalities in 47%. Atrial fibrillation can be associated. Kearns-Sayre syndrome, a multisystemic mitochondrial disorder, can present with any form of atrioventricular block, with an 84% prevalence of conduction defects in those patients.[1]

Accurate diagnosis of mitochondrial cardiomyopathies requires a multidisciplinary approach: a high degree of clinical suspicion is warranted, given the absence of pathognomonic findings on cardiac imaging. Baseline testing should include a transthoracic echocardiogram, CMR, and testing to eliminate coronary artery disease. Biochemical screening should include dosing of LDH, lactate, and creatine kinase that can be elevated in certain forms and in mitochondrial crisis, requiring prompt recognition and treatment (Supplemental Table S1).[1-5] Moreover, other laboratory abnormalities suspicious of mitochondrial disorders are high blood glucose, haemoglobin A1c and creatinine, abnormal thyroid function tests, and various degree of liver dysfunction[3] (Table 1). Analysis of plasma amino acid profiles may be considered as part of additional testing, although there is no pathognomonic profile related to a specific mitochondrial disease. CMR is still an ongoing study field regarding tissue characterization in patients with mitochondrial cardiomyopathy and further studies are required. In the meanwhile, CMR can be used to accurately measure cardiac chamber volumes and exclude other diagnosis.[1] Histopathologic analysis with immunostaining of fresh skeletal muscle biopsy, typically the quadriceps, remains the gold standard to diagnose mitochondrial disorders. Typical histologic findings include a disarray of muscle fibres with abnormal mitochondria.[4] Immunohistochemical staining of proteins of the respiratory chain (cytochrome c-oxydase and succinate dehydrogenase) is nowadays routinely performed and complementary testing may include analysis of enzymatic activity of key proteins of the respiratory chain. Histopathologic analysis should be performed by a specialized pathologist with experience in cardiogenetic or neuromuscular diseases. Genetic testing should include analysis of gDNA (peripheral blood sample) and mtDNA (necessity of cryoconservation of fresh muscle tissue for DNA extraction).

Cardiac biopsy is more invasive but can be the only way to make a diagnosis in patients with negative initial testing or with cardiac involvement as the only manifestation.[1] However, the typical muscle fibres disarray is seen predominately in late-stage disease and can therefore be missed.[3] Genetic counselling and testing is part of the diagnostic workup and should be performed by a specialized clinic. A 3-generation pedigree of the patient's family should be obtained and all first-degree relatives should be referred to a dedicated cardiogenetic clinic. In the absence of genetic substrate, clinical

screening of family members should include thorough history and physical examination, ECG, and basic biochemistry as well as an echocardiogram.

The management of mitochondrial cardiomyopathy is challenging. Usual care with guidelines-directed medical therapy regarding heart failure and arrhythmias should be offered to every patient. Transplantation for end-stage heart failure remains controversial in patients with systemic mitochondrial disease but may be considered in selected patients with cardiac involvement as the sole manifestation. Cardiologists should also be aware of mitochondrial crisis, an abrupt multisystemic decompensation in context of fever, illness, medications, or heat. Lactates are usually elevated. Mitochondrial crisis can respond dramatically to standard support intervention and various dietary supplements, including coenzyme Q10.[3] However, there are few reports on the role of the long-term use of dietary supplements for mitochondrial cardiomyopathy.

In conclusion, mitochondrial cardiomyopathy is a challenging diagnosis. Cardiologists should have a high degree of suspicion in patients with hearing loss, diabetes mellitus, renal dysfunction, peripheral myopathy, and familial history of cardiomyopathy. A purely maternal inheritance of familial cardiomyopathy is highly suspicious of mitochondrial disease. Echocardiography findings are variable: a pattern of hypertrophic cardiomyopathy is the most common phenotype. The diagnosis is usually based on muscle biopsy, functional assays, and genetic testing. Patients should be early referred to a cardiogenetics clinic for evaluation and genetic counselling because mitochondrial diseases with cardiac involvement are associated with high morbidity and mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.11.018.