Mitochondriopathy: a rare aetiology of restrictive cardiomyopathy

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When diagnosing a restrictive hypertrophied cardiomyopathy, most echocardiographists consider cardiac amyloidosis as a possible cause, especially after the appearance of ‘granular’ sparkling echoes on a transthoracic echocardiography (TTE). However, other infiltrative diseases (i.e. metabolic myopathies, Gaucher, Hunter’s, and Hurler’s diseases) or storage cardiomyopathies (haemochromatosis, Fabry’s disease, glycogen storage, and Niemann–Pick disease) should be considered. In this paper, we report on another unusual cause of restrictive cardiomyopathy of which all cardiologists should be aware.

KEYWORDS
Mitochondriopathy; Restrictive cardiomyopathy; Heart failure

Introduction

When diagnosing a restrictive hypertrophied cardiomyopathy, most echocardiographists consider cardiac amyloidosis as a possible cause, especially after the appearance of ‘granular’ sparkling echoes on a transthoracic echocardiography (TTE). However, other infiltrative diseases (i.e. metabolic myopathies, Gaucher, Hunter’s, and Hurler’s diseases) or storage cardiomyopathies (haemochromatosis, Fabry’s disease, glycogen storage, and Niemann–Pick disease) should be considered. In this paper, we report on another unusual cause of restrictive cardiomyopathy of which all cardiologists should be aware.

Case report

A 54-year-old woman was referred for a TTE because of dyspnoea. Her personal history consisted of bilateral sensory hearing loss, a short stature (weight: 40 kg, BMI = 17.7 kg/m²), and diabetes mellitus diagnosed during an anaesthesiologist visit for cochlear implant surgery. Her mother also suffered from diabetes mellitus and deafness.

On admission, a physical exam showed marked signs of heart failure and a chest X-ray showed pleural effusion and cardiomegaly. An electrocardiogram revealed (Figure 1) sinus tachycardia, left ventricular (LV) hypertrophy with strain pattern, and intraventricular conduction disturbance. A TTE (Figures 2 and 3, see Supplementary data online, Video S1) (General Electrics Health Care, VIVID 7, Horton, Norway) showed a diffuse hypokinetic motion of the LV [LV ejection fraction (LVEF): 25% according to Simpson’s method] with mild hypertrophy [interventricular septum diameter (IVSd): 13 mm] and a severe restrictive pattern without any caricatural atrial enlargement usually associated with amyloidosis. Her NT-pro-brain natriuretic peptide (NT-proBNP) level was 438 pg/ml (>222 pg/ml) with a normal renal function.

No monoclonal gammopathy was found in her serum nor urine, and no amyloid deposit was found on biopsy of the salivary glands.

A coronary angiography did not reveal any significant stenosis. After clinical stabilization, endomyocardial biopsies were performed to exclude localized cardiac amyloidosis and other restrictive cardiomyopathies. Myocytes’ microvacuolization was noted with an absence of amyloid deposit. A high mitochondria density with abnormal size, shape, and glycogen overfill was noted on a light and electron microscopy (Figures 4 and 5).

The patient’s deafness, short stature, and late diabetes mellitus with hypertrophic cardiopathy were suggestive of mitochondrial disease. A point mutation of the mitochondrial tRNA 3243 gene was identified using polymerase chain reaction, confirming the mitochondrial diabetes.

A cardiac MRI (clinical 3-T ACHIEVA™; Philips Medical Systems, Eindhoven, The Netherlands) was performed during the initial hospitalization: cine MRI (gradient echo)
Figure 1  ECG showing sinus tachycardia, left ventricular hypertrophy with strain pattern.

Figure 2  Transthoracic echocardiography showing diffused LV hypertrophy with enlarged atrias, restrictive filling pattern with S' velocity and $E' < 5 \text{ cm/s}$. The pulmonary vein flow shows a blunted S-wave and a large A-reversal wave (longer than mitral A-wave).
showed a global hypokinetic LV (LVEF: 34%). Measurement of the LV showed a moderate hypertrophy (LV mass: 107 g/m², IVSd: 14 mm). Morphological sequences (T2-weighted spin echo sequences, + fat saturation) did not show any significant hypersignal (Figures 6 and 7), contrary to the cardiac amyloidosis. The patient was treated with an angiotensin-converting enzyme inhibitor, a beta-blocker, and a low dose of diuretics. An oral co-enzyme Q10 (150 mg per day) was administered in light of case reports showing favourable benefits for endogenous insulin secretion, preventing hearing loss, reduced lactate production during test exercise, and improvement in the exercise tolerance and LV function.

A follow-up at 2 months showed an improvement on the TTE (LVEF 50%) (Figure 8, see Supplementary data online, Video S2) with remaining sparkling echoes. Her NT pro-BNP level had decreased (316 pg/ml) confirming the clinical
status evaluation. Family screening has been launched: one of her two daughters was found positive for the mutation, but no evidence of clinical expression was present at the time of molecular diagnosis.

Discussion

Maternally inherited diabetes and deafness is found in 0.5–2.8% of all diabetic patients.\textsuperscript{8} The relationship between the gene mutation, myocardial hypertrophy, and dysfunction remains obscure. However, light and electron microscopy of endomyocardial specimens of MELAS-patients (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) with diabetes has shown abnormal mitochondria, with a marked increase in their number and size as we observed. These abnormalities of the cardiac mitochondria are considered to be a compensatory reaction to its metabolic alterations.\textsuperscript{9,10}

Figure 5  Electronic microscopy showing enlarged mitochondria with glycogen overfill.

Figure 6  No late gadolinium enhancement on T1-weighted inversion recovery sequences in short axis and two chambers view. This excludes fibrosis or an ischaemic area.
Figure 7  T2-weighted sequences: absence of hypersignal indicating absence of myocardial inflammation or oedema. It also excludes amyloidosis.

Figure 8  Two-dimensional-strain analysis showing an impaired left ventricular longitudinal function initially and an improvement after 2 months of dedicated treatment. The radial strain improved slightly and the circumferential strain stayed ‘identical’ after 2 months.
Infiltrative pathologies are the most common aetiologies of restrictive cardiomyopathy, often characterized by echocardiographic restrictive pattern. A cardiac MRI could prove effective in distinguishing amyloid deposit from other infiltrative causes. Considering the specific imaging features on TTE and MRI for each aetiology, one has useful tools for quick screening when facing secondary infiltrative cardiomyopathy:2,11

(i) amyloidosis: concentric hypertrophy with sparkling echoes, enlarged atrias on TTE and diffused late gadolinium enhancement (LGE) on delay contrast enhancement MRI (DE-MRI)
(ii) sarcoidosis: localized septal hypertrophy on TTE and LGE on mid-myocardial wall or epicardium on DE-MRI
(iii) haemochromatosis: LV enlargement with no or mild hypertrophy on TTE and measure of cardiac iron load on relaxation time T2*
(iv) Fabry’s disease: concentric hypertrophy with post-hypertensive remodelling shape on TTE and LGE localized on basal inferolateral wall on DE-MRI

The restrictive pattern seen on the patient’s TTE at admission disappeared and the systolic function improved after 2 months of treatment. This observation is exceptional as it shows the MRI characteristics of cardiac mitochondriopathy as well as significant change in LV systolic function and diastolic filling pattern, noted after 2 months of conventional and Q-10 co-enzyme treatment.

Supplementary data

Supplementary data are available at European Journal of Echocardiography online.

References