When chest pain reveals a Fabry disease

Quand une douleur thoracique révèle une maladie de Fabry

The diagnosis of metabolic diseases is often made in adulthood. We report on a 55-year-old female patient who had suffered from chest pain. This symptom and other signs arouse to an inherited metabolic disease.

**Case report**

A 55-year-old female child-care worker was referred with chest pain unrelated to effort. She was very anxious and reported that her father had died suddenly at the age of 40 of unknown cause. She did not report any fever, weight loss or recent upper respiratory tract infection and there was no medical history of thrombophlebitis. Cigarette smoking from the age of 23 to 50 years had resulted in chronic obstructive pulmonary disease. Her blood pressure had always been normal. She had suffered six miscarriages but had a 32-year-old daughter and an 11-year-old son. She complained of unilateral hearing loss and had suffered from vertigo for several years.

On admission, she did not complain of dyspnoea or chest pain. Heart rate was 58 beats per minute and blood pressure was 139/89 mm Hg. Cardiac auscultation was normal and there were no signs of congestive heart failure nor any manifestations of peripheral arterial disease.

During hospitalisation, the patient experienced two further episodes of retrosternal chest pain, the first occurring after a shower and the second at rest. Both episodes lasted for 15 to 20 minutes.

An electrocardiogram (ECG) (figure 1) was recorded after the first episode of chest pain, which demonstrated sinus rhythm with a PR interval of 120 ms and a QRS duration of 80 ms. The most striking abnormalities were diffuse T-wave inversion. The Sokolow index was 28 mm. An ECG performed during the second episode of chest pain as well as all subsequent ECGs showed diffuse T-wave inversion. Serum levels of creatine phosphokinase and troponin I were within the normal range. NT pro-BNP was 494 ng/L (normal < 100 ng/L). Plasma fibrinogen was 2.3 g/l (N: 2–4), CRP was below 0.5 mg/dL, Haemoglobin was 110 g/L, LDL cholesterol was 1.4 g/L and triglycerides were 1.0 g/L.

Coronary angiography revealed normal coronary arteries, with no atherosclerotic lesions. However, echocardiographic examination demonstrated marked homogeneous left ventricular hypertrophy. Interventricular septum and posterior wall thickness taken from time-motion measurements, were 16 and 15 mm, respectively. Echogenicity of the myocardium was normal as were left ventricular end-diastolic dimensions (44 mm). Ejection fraction was estimated at 58% according to the Simpson biplane rule and there was no regional wall motion abnormality. There was no systolic anterior motion of the mitral valve nor any localised acceleration of the left ventricular outflow tract velocity as assessed by continuous-wave Doppler. Systolic pulmonary artery pressure was estimated at 30 mmHg. The left atrium was enlarged (area 26 cm²) and the inter-atrial thickness was normal. There was a restrictive diastolic mitral flow pattern heralding increased left ventricular filling pressure. There were no abnormalities of the right cardiac chambers, no valvular abnormalities and there was no evidence of pericardial effusion. Thus, the diagnosis of hypertrophic cardiomyopathy was made at 55 years of age.

In 2004, the patient experienced a 30 minute episode of aphasia, phonemic paraphasia, and right hemiparesis. A transient ischemic attack was considered and MRI of the brain showed several hyperintense supra-tentorial lesions in the white matter (figure 2) without evidence of ischaemia or embolism. Cerebrospinal fluid analysis was normal.

Multiple sclerosis was considered due to the numerous hyperintense lesions in the white matter, but there were no lesions in the corpus callosum (data not shown) and the white matter lesions were quite far from ventricles and were not perpendicular to them. Because of these atypical features, an alternative diagnosis was suspected (box 1) [1]. White matter lesions associated with small arterial involvement encountered in hypertension could be excluded in this case because of the normal blood pressure. Antiphospholipid syndrome was considered because of the associated miscarriages, but anticardiolipin antibodies and lupus anticoagulant were negative.

Of note, after the TIA, the patient was treated with aspirin 75 mg/day and sotalol 80 mg/day under the tentative diagnosis of Wolff Parkinson White syndrome (short PR interval). Between 2004 and 2008, the patient had presented with telangiectasia in a segmental distribution (figure 3). These cutaneous lesions were limited to the right part of the umbilicus and a complete skin and mucous membrane examination did not reveal other cutaneous lesions except multiple melanocytic...
nevi. A skin biopsy was performed (figure 4), and showed glycosphingolipids deposits (data not shown).

Once it was considered that Fabry disease could explain the cardiac, CNS, and dermatological symptoms, we re-examined the patient and her son and performed additional laboratory tests.

The patient reported suffering from pain in the extremities from the age of 10 to 30 years old with spontaneous regression, and had suffered from effort intolerance since 2004. Moreover, her son, aged 11, had experienced pain in his limbs for several years, triggered by fever or exercise.

In our female patient, other investigations revealed cornea verticillata on slit-lamp examination (figure 5) and an audiogram showed unilateral sensorineural hearing loss of 30 dB. Serum creatinine was normal and urine microalbuminuria was negative. Alpha-galactosidase A was moderately decreased at 46 nmol/hr/mg protein (N: 55–85).

Urinary globotriaosylceramide (Gb3) levels were 43.4 nmol/mmol creatinine (N < 18).

Genetic analysis found two mutations in exon 6 of the GLA gene R301Q or c902G>A, and Q279L or c836A>T. In her son, alpha-galactosidase A was markedly decreased at 3 nmol/hr/mg protein (N: 55–85). The same two mutations in exon 6 were also found.

Agalsidase beta 1 mg/kg EOW was begun in November 2008, along with aspirin 75 mg/day. After one year of enzyme therapy, the patient had not experienced any further chest pain or ischemic attacks.

Commentary

Fabry disease was considered in this woman because of the association of numerous symptoms and signs. These included a past history of pain in the extremities, hypertrophic cardiomyo-
pathy without hypertension, short PR interval on ECG, transient ischemic attack, pseudo multiple sclerosis on brain MRI, sensorineural hearing loss, skin lesions, and because a history of the unexplained early death of her father and pain attacks in the extremities of her 11-year-old son.

Fabry disease is a multisystem syndrome caused by deficiency of the X-linked enzyme, alpha-galactosidase A \[2\]. The frequency of Fabry disease is probably underestimated as illustrated by the delay between the first symptom and final diagnosis which often exceeds 15 years in homozygous males and heterozygous females \[3\]. Females are not only carriers but may also be affected and often exhibit severe organ dysfunction \[4\].

The gold standard for diagnosis of Fabry disease in male patients, is the measurement of leukocyte alpha galactosidase A activity. Genetic analysis is mandatory in women because about 40% of females carrying the mutation have normal alpha galactosidase A activity \[5\].

The R301Q mutation, found in our patient, is known to cause Fabry disease whereas the Q279L mutation, has so far not been described, most likely representing a polymorphism.

Of note, and with exception of the N215S mutation, 93% of female patients with Fabry disease have an elevated level of globotriaosylceramide (Gb3) in urine.

Early-on, systemic disease may include pain in extremities, corneal opacities, anomalies of sweating and skin lesions. Later, the clinical course may be complicated by kidney, heart and cerebrovascular involvement, which may cause early death. In the absence of enzyme replacement therapy, median survival time is 58.2 years for men and 74.7 years for women \[6\]. Pain in the extremities, is a key early symptom and the history in our female patient illustrates that ‘neglected’ pain can delay the diagnosis. Moreover, the pain can sometimes disappear spontaneously during adulthood. Early death of unknown cause...
**Cornea verticillata. Slit-lamp examination is useful for the diagnosis**

In the absence of antimalarial or amiodarone exposure such findings are highly suggestive of Fabry disease.

The unilateral cutaneous involvement as noted in this case is reminiscent of mosaicism but so far remains unexplained. It is unlikely that such a segmental manifestation reflects functional X-chromosome mosaicism because women who are heterozygous for Fabry disease tend to show a non-segmental, symmetrical dissemination of punctiform angiokeratomas [9]. This exception to the general rule has been tentatively explained by the assumption that the alpha-galactosidase mutations of Fabry disease do not interfere with cutaneous embryogenesis [10]. Alternatively, the development of unilateral skin lesions after transient ischemic attack in 2004 could have been favoured by dysautonomia in the hemiparetic side of the body.

Cutaneous biopsy confirmed the presence of telangiectatic vessels in the upper dermis (figure 4).

This case illustrates the difficulties in finding an aetiology for a cardiomyopathy characterized by left ventricular hypertrophy with abnormal diastolic function. Even if Sokolow index was normal, ECG highly suggests hypertrophic cardiomyopathy (figure 1). In our patient, chest pain was probably related to hypertrophic cardiomyopathy by itself. Another explanation could be the diminution of the coronary flow reserve, an index of microvascular function.

Hypertensive cardiomyopathy is common, but could be excluded in this patient because there had been no history of hypertension and blood pressure measurements were consistently less than 140/90 mmHg. Nevertheless, hypertension could be a complication of Fabry disease. Other causes of an increased afterload from obstruction of the left ventricular outflow tract were excluded by the absence of any murmur and the normal echocardiographic findings.

Idiopathic hypertrophic cardiomyopathy, either familial or sporadic, could be a possible diagnosis since in this particular case the left ventricular wall thickness and ECG abnormalities met the major criteria for the diagnosis of hypertrophic cardiomyopathy [11]. The absence of asymmetrical septal hypertrophy and of dynamic obstruction to the left ventricular outflow tract are not sufficient to exclude this diagnosis since obstruction is present in only 25–30% of patients with hypertrophic cardiomyopathy.

Other causes of hypertrophic cardiomyopathy are detailed in (box 2). They form a particularly heterogeneous group in which cardiac involvement is non-specific in most cases, combining anatomic abnormalities (increased left ventricular wall thickness) and functional abnormalities (abnormal diastolic function) to different extents [11]. A diagnosis of endomyocardial restrictive cardiomyopathy could be suspected from the clinical context and from the endocardial abnormalities seen on echocardiography. However, making a diagnosis of secondary myocardial restrictive cardiomyopathy is more difficult to make when the underlying disease has not been diagnosed previously, as in this case, and given the non-specific cardiac presentation. This underlines the need to search for associated non-cardiac symptoms.
Box 2

Main causes of hypertrophic cardiomyopathies in the absence of arterial hypertension or obstruction of left ventricular outflow tract (adapted from [11])

**Familial**
- Familial, unknown gene
- Sarcomeric protein mutations (myosin, troponin, actin…)
- Glycogen storage disease (Pompe*, Forbes*, Danon*)
- Lysosomal storage disease (Fabry*, Hurler’s)
- Disorders of fatty acid metabolism
- Carnitine deficiency
- Phosphorylase B kinase deficiency
- Mitochondrial cytopathies
- Syndromic hypertrophic cardiomyopathies (Noonan’s syndrome, Leopard syndrome, Friedreich’s ataxia…)
- Other (phospholamban syndrome, familial amyloid)

**Non-Familial**
- Obesity
- Athlete’s heart
- Amyloid
- A short PR interval on ECG may be associated

and signs from the patient history and clinical examination which may suggest secondary rather than primary myocardial involvement. From the cardiac features, the short PR interval without delta wave should lead to suspicion of storage diseases such as Fabry’s, Danon’s and Pompe’s disease. Early diagnosis is key to a good prognosis in Fabry disease, as, for example, long-term improvement of myocardial function seems to be better in patients without myocardial fibrosis at the start of specific enzyme therapy [12]. Furthermore, kidney function and daily proteinuria at the beginning of enzyme therapy are highly correlated to efficacy of therapy [13]. Indication for enzyme replacement therapy in female patients should be based on clinical symptoms. Pain despite symptomatic therapy as well as cerebral, cardiac, or renal symptoms are the main indications for enzyme replacement therapy in countries where it is available. In large cohorts of patients it has been noted that Fabry disease is more frequent in populations of patients with hypertrophic cardiomyopathy or stroke at a young age [14].

In conclusion, Fabry disease is an X-linked multisystemic disorder which should nonetheless also be considered in female patients. Family history and genetic analysis are the cornerstones of diagnosis. However, hypertrophic cardiomyopathy without hypertension should alert the clinician to consider other symptoms as clues for an early etiological diagnosis.

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