

Fabry disease – a long way to diagnosis in a 43-year-old patient. “Dr Google” is not always so bad...

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Abstract

Fabry disease (FD) is a rare genetic disease that leads to the accumulation of sphingolipids in cells due to the lack or deficiency of the alpha-galactosidase (alpha-GAL), lysosomal enzyme. It presents a lot of difficulties, despite typical pattern of symptoms. The drug program for patients with Fabry disease, which is available in Poland is an enzyme replacement therapy with proven effectiveness. Starting treatment at an early stage delay or eliminate the symptoms, while at severe disease leads to regression of myocardial hypertrophy. We report a case study of a patient who was diagnosed unsuccessfully for over three decades by doctors of many specialities. Diagnosis, thanks to the skin and cardiological manifestation, owes his persistence and Internet search engine.

Key words: Fabry disease, cardiomyopathy, keratomas, paresthesia

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Introduction

Fabry disease (FD) inheritance is gender-linked, but it is not typically recessive, as less severe symptoms are seen in women. The enzyme gene is located on the X chromosome (Xq22.1). Mutation in the alpha-GAL encoding gene (GLA) causes a deficiency or lack of an enzyme, resulting in the accumulation of glycosphingolipids (globotriazinylyceramide [GL-3]) in cells, which impairs organs function [1, 2]. FD incidence is estimated at 1/40,000 male births [3]. The clinical manifestation may vary depending on the function of the residual enzyme activity. Classic symptoms (when the enzyme activity > 1%) occur in men. In contrast, women’s symptoms are less severe and appear later in

life, which results from the degree of penetration of the mutated allele [3]. Typical symptoms of FD appearing early in childhood are painful paresthesias of the hands and feet, exercise intolerance, paroxysmal fevers, and keratoses of the skin. Renal failure, cerebrovascular incidents, visual disturbances and left ventricular (LV) hypertrophy as a phenocopy of hypertrophic cardiomyopathy (HCM) occur after the age of 30 and are a consequence of disease progression. This is a typical, classic form of this disease. The so-called cardiological variant is manifested only by LV hypertrophy (usually concentric). Diagnosis in men is established on the basis of alpha-GAL activity in peripheral blood leukocytes and plasma, while in women is based on genetic testing [4, 5].

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Figure 1. Skin hemangiomas

Despite the typical symptoms, it may take many years to diagnose, as in the case at hand. The diagnosis is important because a drug program with enzyme replacement therapy (agalsidase alfa and beta) is available for patients.

Case report

A 42-year-old man with paroxysmal hand and foot pain and feverish conditions from the age of 6 came to the rheumatological clinic. Physical examination revealed the presence of multiple angiomas of the abdominal skin and massive, pitting oedema of the lower limbs (Figure 1).

At school age, despite normal uric acid levels and a low-purine diet, the patient was diagnosed with gout and treated with allopurinol. In later years, the diagnosis was verified as rheumatic fever, and conventional antibiotic therapy was used. During puberty, small red-purple lesions (later referred to as keratomas) and intolerance to heat and exercise appeared.

At the age of 20, the patient was seen in a gastrological outpatient clinic due to abdominal pain and diarrhoea. The cause of the discomfort has not been established. At 30, he was diagnosed with venous thrombosis. At the age of 40, this patient attended an emergency department due to resting shortness of breath and palpitations after fracture of the metatarsal bone. Pulmonary

embolism (PE) was diagnosed on the basis of chest angiography and high concentration of D-dimers. Massive double-sided PE was found. The patient was admitted to the intensive care unit, where he was treated with low molecular weight heparin, followed by rivaroxaban 20 mg. The results of conducted later diagnostic tests for thrombophilia and antiphospholipid syndrome were negative. The transthoracic echocardiographic examination of the heart showed asymmetric LV muscle hypertrophy with good global contractility. The heart cavities were not enlarged. HCM was suspected, and additional diagnostic tests were recommended.

Two years later, the patient was admitted to the clinic for internal diseases due to liver damage (alanine aminotransferase activity of 209 U/L, aspartate aminotransferase activity of 101 U/L. Other liver function parameters (bilirubin, alkaline phosphatase, protein and albumin, coagulation system) were normal. No antibodies to the hepatitis C virus (HCV) or hepatitis B surface antigen (HBs) were found. Microalbuminuria has been demonstrated in the urine. Due to the increasing activity of the patient's transaminases, secondary to the suspected drug-induced liver damage (by rivaroxaban), the patient was transferred to the clinic of infectious diseases. Dabigatran was used for anticoagulation. The patient continued HCM diagnostics in an outpatient cardiology clinic, where amyloidosis was suspected. Magnetic resonance imaging of the heart was performed, with results as follow: left ventricular end-diastolic volume (LVEDv) of 197 mL (norm 102–235 mL), and 111 mL/m² (norm 53–112 mL/m²), and end-systolic (LVESv) of 61 mL (norm 29–93 mL), and 34 mL/m² (norm 15–45 mL/m²); left ventricular ejection fraction (LVEF) of 69%, left ventricular cardiac output (LVCO) of 7.3 L/min, its indicator left ventricular cardiac output index (LVCI) of 4.1 L/min/m², left ventricular end-diastolic diameter (LVEDd) of 57 mm, left ventricular end-systolic diameter (LVESd) of 41 mm, left atrial diameter (LAd) of 35 mm, left atrial surface (LAs) of 24.9 cm², right ventricular end-diastolic volume (RVED) of 197 mL (norm 47–111 mL), and 46 mL/m² (norm 25–53 mL/m²); right ventricular ejection fraction (RVEF) of 59%; right ventricular minute capacity (RVCO) of 6.3 L/min, right ventricular cardiac output index (RVCI) of 3.6 L/min/m²; right ventricular end-diastolic dimension (RVEDd) of 51 mm, right ventricular systolic diameter (RVESd) of 35 mm, right atrial surface (RAs) of 27.2 cm², left ventricular end-diastolic mass (LVEDm) of 182 g (norm 85–181 g), and 103 g/m² (norm 46–83 g/m²); LV wall thickness in the middle segments: anterior 7/16 mm, anteroseptal 7/17 mm, inferoseptal 10/18 mm, inferior 7/16 mm, inferolateral 6/16 mm, anterolateral 6/15 mm; LV wall thickness irregular, segmental thickening of some segments did not meet the HCM criterion, the thickest segment 5 of 14 mm and segments 4, 9, 16 of 10 mm (ED);

free wall thickness of the right ventricle (ED/ES) 4/8 mm; myocardium lacked typical features of amyloidosis or features of the fibrous remodeling; low aortic regurgitation; dilatation of pelvicalyceal system in both kidneys partially covered by the study; asymmetry of the skeletal muscle thickness of the chest and upper limbs partially covered by the study, thicker on the left; conclusions: hyperkinetic myocardium, segmental thickening of the LV wall with borderline values for HCM diagnosis – the picture may correspond to HCM with incomplete phenotypic expression.

A biopsy of the abdominal subcutaneous fat was also performed. The histopathological examination did not reveal amyloid.

After exclusion of systemic connective tissue disease and gout by consulting rheumatologist, the patient was referred to a rare disease clinic. The opinion that there are no grounds for suspecting a rare disease was issued. A determined patient searched the information available on the Internet, set himself a preliminary diagnosis (FD) and asked for help from the association of patients (“Association of Families with Fabry Disease”). He obtained relevant data about the places where one should report for biochemical tests and consultation. On the basis of determined enzyme activity, followed by subsequent genetic testing (genetic mutation – c.679C>T (p.Arg227Ter) was found, FD was diagnosed, and indications for enzymatic replacement therapy were confirmed. The patient is awaiting qualification for the drug program. Advanced changes in the central nervous system could be disqualifying.

Discussion

The case is presented, which in the opinion of the authors deserved to be discussed due to the very long period of time that elapsed to form a diagnosis. Paresthesia of the hands and feet, which already appeared in childhood, was mistaken for arthritis and erroneously assessed as gout. Moiseev et al. [6] report that 28/107 patients with FD were diagnosed with the rheumatological condition for many years before the correct diagnosis [6]. Skin lesions typical of FD have been ignored by dermatologists. No one thought about childhood intolerance of heat and physical activity. Cardiovascular symptoms initiated cardiological diagnostics. Changes in the echocardiographic image are typical for FD: LV hypertrophy (usually concentric, and its limitation is an indicator of proper therapy), parallel (ventricular right ventricle) hypertrophy (RV), papillary muscle hypertrophy or dilatation of the ascending aorta (rarely aneurysms). The atria can be enlarged, and benign valve defects occur, and LVEF is usually preserved. Sometimes the visible double outline of the endocardium is associated with the layering of glycosphingolipid accumulation [7–10]. As the disease progresses, LV fibrosis appears, but not RV.

The patient’s echocardiographic picture suggested the possibility of HCM phenocopy, but with increasing pitting edema of the lower extremities and recurring joint pain, the diagnostics process was focused on amyloidosis. A visit to the expert centre was not helpful. The long-term diagnostic process lacked not only knowledge (this can be explained by the rarity of the disease), but also discussions between doctors of various specialities. It seems that an attempt to combine the symptoms of many organs and numerous, very unambiguous imaging tests could result in an accurate diagnosis. This story illustrates the need for a broader and multidisciplinary view of the patient – beyond the scope of one speciality.

The Internet search engine, which has been a source of false information many times, has been great for the patient this time.

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