

Clinical manifestations and treatment of Anderson-Fabry disease in a middle age man (RCD code: III-2B.2a)

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Abstract

Fabry disease is a genetic lysosomal storage disease (X-linked inheritance), also known as Anderson Fabry disease. It is a lifelong progressive disease, and it develops in patients with the lack of lysosomal enzyme alpha-galactosidase (a-Gal A) and for that reason the globotriaosylceramide (GL-3) accumulates in the endothelium of blood vessels and internal organs, then injury of various organ systems occurs, as renal insufficiency, gastrointestinal disorders, specific changes of the eye fundus, injury of the coronary arteries, hypertrophy of the left ventricle, cardiomyopathy, disorders of the nervous system, specific skin rashes (known as angiokeratoma), etc. Therefore, patients with Fabry disease may occur in the practice of each speciality physician. A minor disease course, that occurs in older patients, mainly affects the cardiovascular system and may be undiagnosed. JRC D 2014; 2 (1): 15–17

Key words: Fabry disease, left ventricular hypertrophy, alpha-galactosidase

Case presentation

A 41-year-old man was hospitalized in the department of cardiology in the clinics of Lithuanian University of Health Sciences (LUHS) for coronary angiography in planning to enroll the patient in the waiting list for a kidney transplant.

Complaints

General weakness, physical exercise intolerance, dyspnea, squeezing type chest pain, persistent headache, hand and feet ache (since childhood), spasmodic abdominal pains, (the cause had never been found out).

History

Two years ago the patient had sudden swollen legs, shortness of breath and the end stage renal failure was diagnosed. Hemodialysis had been applied, but the cause of the renal failure was not determined. Since July 2012 permanent hemodialysis has been applied in the Kaunas Clinics of LUHS. Blood pressure has been high for several years and it was not constantly treated. The pa-

tient has been suffering from rash at the waist area since 15 years old, therefore he was consulted by dermatologists but the cause of the rash was not determined.

He was consulted by rheumatologists also, but the systemic autoimmune disease has not been detected.

Physical examination

Body mass index (BMI) was 26 kg/m². Fine converging spot rashes in the area of waist, navel and upper arm were observed (angiokeratoma in figure 1, 2). Heart rate was 64 bpm, blood pressure (BP) – 150/90 mm Hg. Systolic murmur of the second degree was heard at the apex of the heart. Weaker vesicular breathing in the left side of lungs and sporadic moist crackles in the lower parts of lungs were heard. No edema in the legs was observed.

General blood test: erythrocytes – 4,55 × 10¹²/l, hemoglobin – 115 g/l, leucocytes 7,51 × 10⁹/l, platelets – 348 × 10⁹/l, creatinine – 936 μmol/l, potassium – 4,6 mmol/l, glucose – 4,6 mmol/l, total cholesterol 3,84 mmol/l.

The electrocardiogram showed sinus rhythm with significant left ventricular (LV) hypertrophy (Electrocardiogram in figure 3).

Conflict of interest: none declared.

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Figure 1. Widespread angiokeratomas, most dense over the umbilical region



Figure 2. Angiokeratoma, spread in the upper arm

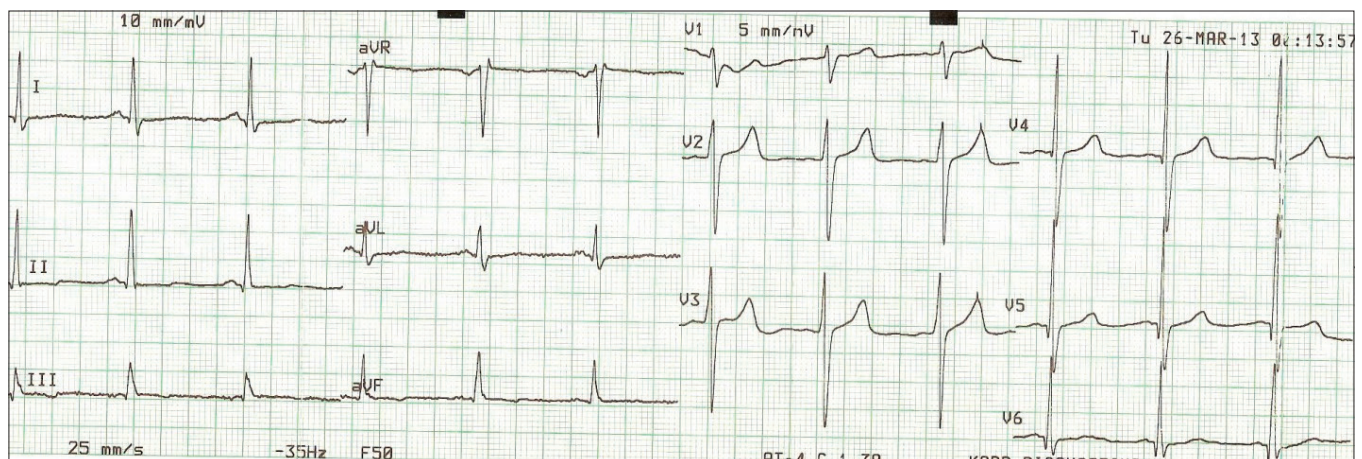


Figure 3. Electrocardiography. Signs of left ventricular hypertrophy signs in ECG

Transthoracic echocardiography disclosed severe left ventricular (LV) concentric hypertrophy (Figure 4) – data typical of myocardial accumulation disease with reduced ejection fraction.

While carrying out the coronary angiography, stenosis of 75 percent had been found in the 7th segment (S7) of left anterior interventricular artery and percutaneous transluminal coronary angioplasty and stenting with bare metal stent 3×24 mm of S7 was successfully performed.

Oculist's consultation: uneven blood vessels of both conjunctivae, with telangiectasias, microaneurysms, also lymphatic vessels of conjunctiva were thickened and enlarged. Uneven and full-blooded veins. There were tangled blood vessels and microaneurysms in the area of macula and twig-like opacities similar to amiodarone keratopathy in the cornea. Correct shape pupils with silhouetted structure of lenses.

The testing of dried blood spot showed that the quantity of alpha-galactosidase of that patient significantly decreased (0,5 μmol/l/per hour.). This indicated that the patient may suffer from Fabry

disease. The genetic testing revealed that the homozygotic mutation of alpha-galactosidase (GLA) gene is in the 6th exon (c.983G>Cp. G328) which confirmed the diagnosis of Fabry disease.

Aspirin 100 mg/day, clopidogrel 75 mg/day, metoprolol succinate 25–50 mg/day, perindopril/amlodipine 10/5 mg/day, torasemide 10 mg/day, atorvastatin 20 mg/day were administered for cardiovascular disease treatment and pantoprazole 40 mg was prescribed additionally. Since 2013 the enzyme replacement therapy by β galactidaze (Fabrazyme) at 1 mg / kg has been prescribed for the patient with Fabry disease. On optimal medication for cardiovascular disease treatment and enzyme replacement therapy, the patient's condition improved. The symptoms of heart failure decreased and the chest pains did not occur. While applying specific treatment, echocardiographic parameters have improved, i.e. LV end diastolic diameter, LV hypertrophy and mitral valve regurgitation have decreased; LV ejection fraction has increased (Table 1). The patient was enrolled into the waiting kidney transplant list.

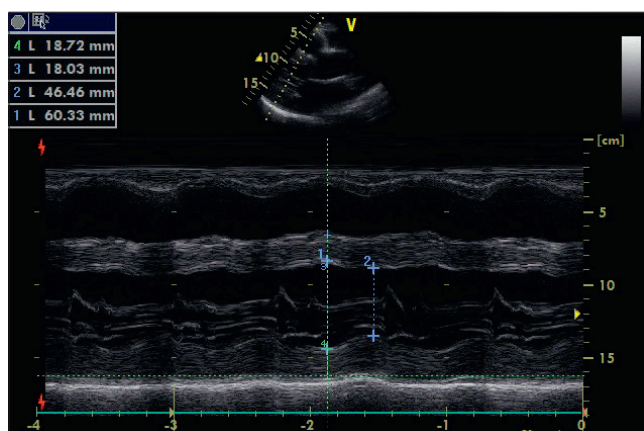


Figure 4. Transthoracic echocardiography. Long axis view. M-mode presentation. Left ventricular hypertrophy. Interventricular septum and posterior wall of 18 mm

Literature review

Anderson-Fabry disease is a metabolic lysosomal storage disorder caused by the functional deficit of the enzyme α -galactosidase A (α -GAL A) [1] that catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3) [1]. The malfunction of α -GAL A leads to a progressive accumulation of Gb3 in all body cells containing lysosomes [2]. The accumulation of Gb3 is particularly prominent in the vascular endothelium, vascular smooth muscle cells, and pericytes. [3-5].

Clinical manifestation of Fabry disease shows characteristic symptoms during childhood and adolescence, such as angiokeratoma, hypohydrosis, acroparesthesia, pain crises and gastrointestinal symptoms like diarrhea [4]. In adulthood, there is progressive cardiac and cerebral involvement, which accounts for the majority of deaths associated with Fabry disease [6]. Cardiac involvement includes concentric left ventricular hypertrophy, heart failure, coronary artery disease, aortic and mitral valve abnormalities, and conduction abnormalities. Cardiac manifestations occur in more than 80 percent of patients with Fabry disease, with a mean age of onset of 42 years. In some patients, these manifestations, particularly left ventricular hypertrophy are the only recognized manifestations of the disease. Echocardiography can be used to detect early stages of the disease mainly characterized by a concentric non-obstructive left ventricular hypertrophy and, in more advanced stages, by an asymmetrical hypertrophy presenting with a grossly thickened septum and less hypertrophy of the posterolateral wall [7].

The following laboratory tests are carried out for the identification of genetic diseases: enzyme activity in leukocytes, plasma, dried blood spot testing and genetic analysis is performed for the confirmation of diagnosis. The gold standard for diagnosis of Fabry disease for males is the measurement of enzyme alpha-galactosidase in leukocytes. Alpha-galactosidase enzyme activity for females may remain within normal limits, therefore in case of suspicion, molecular genetic test should be carried out to confirm the diagnosis. After identification of a new patient, there is a chance to diagnose five Fabry disease cases in the same family [8].

Table 1. Baseline and follow-up cardiac echo findings

	Baseline 2013-04-23	Follow-up 2014-09-26
LV end diastolic diameter (mm)	61	52
Septal thickness (mm)	18	16
Posterior wall thickness (mm)	18,7	16,2
LV mass/BSA (g/m ²)	272,2	165,2
LV ejection fraction (%)	45	50
LA diameter (mm) parasternal long axis	52	42
Mitral regurgitation	II degree	I degree
LV diastolic function	Impaired relaxation	Impaired relaxation

LV – left ventricle, BSA – body surface area

In 2001 special treatment of Fabry disease enzyme replacement therapy (ERT) was found. ERT reduces Gb3 accumulation in the tissues, thus protecting against the disease complications and stabilize the progression of the disease [8]. There are two different kinds of alpha galaktosidase A enzyme products available: agalsidase alfa and agalsidase beta. The preparations are administered intravenously over 40 minutes every two weeks, only their dosage differs: α agalsidase 0.2 mg/kg, β agalsidase – 1 mg/kg, starting from 0.25 mg/min. Studies have shown that long-term treatment with recombinant human α galactosidase A can stop the development of vascular pathology and protect against disease caused by atherosclerotic clinical expressions.

References

1. Brady RO, Gal AE, Bradley RM et al. Enzymatic defect in Fabry's disease: ceramidetrihexosidase deficiency. *The New England Journal of Medicine* 1967; 276: 1163–1167.
2. Desnick RIY, Eng C. Fabry disease: alpha galactosidase A deficiency. *The metabolic and molecular bases of inherited disease*. 1995; 1741–2784.
3. Branton MH, Schiffmann R, Sabnis SG et al. Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. *Medicine (Baltimore)* 2002; 81: 122.
4. Desnick R, Ioannou Y, Eng C. Alpha-galactosidase. A deficiency: Fabry disease. In: *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed, Scriver CR, Beaudet AL, Sly WS, et al. (eds.), McGraw Hill, New York 2001; 3733.
5. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet*. 2001; 38: 750.
6. Waldek S, Patel MR, Banikazemi M et al. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med*. 2009; 11: 790–796.
7. Seydelmann N, Wanner Ch, StörkS et al. Fabry disease and the heart. *Best Pract Res Clin Endocrinol Metab*. 2015; 29: 195–204.
8. Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. *QJM* 2010; 103: 641–659.