**CASE PRESENTATION**

Unexplained left ventricular hypertrophy, arrhythmias and conduction disorders: take into account Anderson-Fabry Disease (AFD). A case report of a diagnosed and under treatment AFD in a heterozygous female, with severe left ventricular hypertrophy and conduction disorders

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**Abstract:** Introduction – Anderson-Fabry disease is a lysosomal disorder where alpha galactosidase deficiency causes accumulation of lipid particles in different cells, including myocardial cells, renal, endothelial cells. Cardiac and renal failure are the main cause of death in Fabry-Anderson disease. Case report – 76 y.o. female, with Anderson-Fabry disease, was diagnosed with intermittent symptomatic second-degree atrioventricular block. Heterozygous patient with measured levels of alpha-galactosidase below normal, is following enzyme replacement therapy. The patient was previously diagnosed with renal impairment and heart disease (left bundle branch block, hypertrophic cardiomyopathy). Concentric left ventricular hypertrophy was confirmed by the transthoracic echocardiography performed at admission (1.5 cm septum and posterior left ventricular wall in parasternal long axis; 1.7 cm mediobasal septum in apical 4 chamber-view; severely abnormal LV mass index – 219 g/m²). Unicameral pacemaker implantation was performed, with favorable evolution. Discussions – It has been stated that Fabry disease remains asymptomatic among heterozygous women; recent information shows the opposite. The patient developed complications of the disease despite enzyme replacement therapy performed correctly since the time of diagnosis. Anderson-Fabry disease should be suspected in young patients with unexplained left ventricular hypertrophy, rhythm and conduction disorders, with coexistent renal or neurological impairment. Keywords: Fabry-Anderson Disease, unexplained left ventricular hypertrophy, arrhythmias, conduction disorders

**INTRODUCTION**

Anderson-Fabry disease (AFD) results from hereditary deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A). This disease is marked by progressive intracellular accumulation of globotriaosylceramide (Gb₃) and digalactosylceramide, the major glycosphingolipid substrates of α-galactosidase A. Many cell types are affected, including renal epithelial cells, myocardial cells, neuronal cells, endothelial cells, pericytes, and vascular smooth muscle cells.

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The α-galactosidase A gene is comprised of seven exons. Molecular analyses have shown that a wide variety of molecular lesions can cause AFD; approximately 57% of disease alleles are missense mutations, 11% nonsense mutations, 18% partial gene deletions, 6% insertion, and 6% RNA processing defects due to aberrant splicing. Mutations are found in all seven exons. The α-galactosidase A gene defect may be associated with no detectable enzyme activity or protein (as a result of an unstable mRNA transcript), no enzymatic activity but detectable levels of enzyme protein (mutations that involve the catalytic site or result in improper folding of the protein), and measurable residual α-galactosidase A activity (mutations that alter protein folding, substrate binding, or the turnover rate). The inheritance pattern of Fabry disease is recessively X-linked. A female carrier of the disease has a 50% chance of transmitting the defective gene to her sons who will develop Fabry disease. In addition, she has a 50% chance of transmitting the gene to her daughters who will be carriers like their mother. If a male with Fabry disease and an unaffected (non-carrier) female have children, all of their daughters will be Fabry carriers and none of their sons will be affected with Fabry disease.

AFD is pan-ethnic, but due to its rarity, determining an accurate disease frequency is difficult. Reported incidences, ranging from 1 in 476,000 to 1 in 117,000 in the general population, may largely underestimate the true prevalence. Newborn screening initiatives have found an unexpectedly high prevalence of the disease, as high as 1 in ~3,100 newborns in Italy and have identified a surprisingly high frequency of newborn males with FD (approximately 1 in 1,500) in Taiwan.

Most patients experience a long diagnostic history before they are finally diagnosed as having Fabry disease. The deficiency of α-galactosidase A is characteristic and pathognomonic for male patients. In contrast, in females, the situation is much more complicated due to mainly normal or subnormal α-galactosidase A activity and a broad phenotypic spectrum, not showing a clear genotype–phenotype correlation. In males, the most efficient and reliable method of diagnosing Fabry disease is the demonstration of deficient α-galactosidase A (α-Gal A) enzyme activity in plasma, isolated leukocytes, and/or cultured cells. In females, measurement of α-Gal A enzyme activity is unreliable; although demonstration of decreased α-Gal A enzyme activity is diagnostic of the carrier state, many carrier females have normal α-Gal A enzyme activity. GLA is the only gene in which mutations are known to cause Fabry disease. Nearly 100% of affected males have an identifiable mutation. Molecular genetic testing is the most reliable method of diagnosing carrier females.

Clinical manifestations of Anderson-Fabry disease include excruciating pain in the extremities (acroparesthesia), skin vessel ectasia (angiokeratoma), corneal and lenticular opacity, cardiovascular disease, stroke and renal failure. One of the earliest and most debilitating symptoms is the onset of acroparesthesia in childhood. During the third and fourth decade of life, the disease is characterized by a progressive course and severe morbidity due to cardiac, renal and cerebrovascular involvement. One of the most severely affected organs in Fabry disease is the kidney. Renal involvement can be detected in early adulthood as mild to heavy proteinuria and microhematuria. The majority of patients show progressive renal failure and eventually develop end-stage renal disease. The leading cardiac manifestation in Fabry disease is concentric left ventricular hypertrophy. Some studies report constructive cardiomyopathy and congestive heart failure as well as disturbances in the conduction system with reduced PR interval. Late cardiac manifestations are hypertrophic cardiomyopathy, myocardial ischemia, heart failure and ventricular arrhythmias associated with sudden cardiac death. The average age of onset for cerebrovascular symptoms in hemizygous individuals is 33 years. It includes hemiparesis, vertigo/dizziness, diplopia, dysarthria, nausea/vomiting, headache and hemiataxia. There is an elevated risk for transient ischemic attacks, premature stroke and dementia.

Enzyme replacement therapy (ERT) is available for the treatment of Fabry disease, but it is a costly treatment. Alternative therapeutic approaches, including small molecule chaperone therapy, are currently being explored. ERT supplies recombinant α-Gal A to cells and reverses several of the metabolic and pathologic abnormalities. ERT has been available for the treatment of Fabry disease since 2001 and is administered intravenously once every two weeks. ERT has been shown to have a positive effect on kidney and heart manifestations at an early phase of the disease, lessening pain and improving quality of life. However, the long-term clinical benefits of ERT for Fabry patients are still unclear, especially regarding its ability to prevent premature strokes. Therapeutic management of Fabry disease requires a multidisciplinary approach by medical specialists experienced in treating this rare condition. Such a team approach necessitates active participation and communication between the geneticist, nephrologist, cardiologist, neurologist, and others.
**CASE REPORT**

We present the case of a 76 y. o. female, who was admitted to our clinic presenting dizziness and pronounced fatigue during ordinary physical activity. The patient was diagnosed in a regional hospital with intermittent second-degree atrioventricular block with 2:1 conduction, and transferred to our clinic for pacemaker implant.

The patient was first diagnosed with AFD in 2006, when she donated a kidney to her son. After a renal biopsy both mother and son were diagnosed with AFD. The son, deceased in 2010 of kidney failure, was hemizygous, and the mother is heterozygous, with a level of plasma alpha galactosidase (measured in 2006) = 6.75 nmol/h/ml (normal values = 7-20 nmol/h/ml). Since 2006 the patient was following enzyme replacement therapy (ERT) with Fabrazyme (agalsidase beta, 1 mg/kg body weight, once every two weeks). During 2006-2014 the patient has developed a number of complications that can be attributed to AFD. The patient was diagnosed with chronic tubulointerstitial nephritis and stage 3 KDOQI chronic renal failure. The patient also developed hypertrophic cardiomyopathy, left bundle branch block and first degree atrioventricular block. The patient is also diagnosed with second degree hypertension, type 2 diabetes balanced through diet, dyslipidemia, cataracts on both eyes (solved by surgery).

Physical examination at admission revealed the presence of pigmented macular lesions bilaterally in the lumbar region – angiokeratoma, skin lesions typical for AFD (Figure 1). The routine admission electrocardiography showed sinus rhythm, heart rate = 70 b/min, first degree atrioventricular block and left bundle branch block (PR interval = 320 ms, QRS complex = 160 ms) (Figure 2). Transthoracic echocardiography (TTE) was performed and revealed important concentric left ventricular hypertrophy (LVH). The septum and the posterior left ventricular wall measured in parasternal long axis were both 1.5 cm (Figure 3). In the apical 4-chamber view the mediobasal septum was 1.7 cm. The TTE also revealed moderate left atrium (LA) dilatation: LA surface = 20 cm², LA volume = 72.9 ml. The patient has a good wall motion, with a calculated ejection fraction = 50% (telediastolic volume = 80 ml, telesistolic volume = 40 ml), MAPSE = 1.3 cm, without significant valvular disease. Diastolic dysfunction was confirmed by the ratio E/Em = 20 (Tissue Doppler: Em = 0.03 m/s, Pulsed Doppler: E = 0.6 m/s, E wave fused with A wave due to the first degree atrioventricular block). We found no evidence of right ventricular hypertrophy.

The patient was first diagnosed with hypertension in 2006, and since then she was under treatment with different classes of antihypertensive drugs. During hospitalization, the patient received treatment with converting enzyme inhibitor and calcium channel blocker, in different doses, with blood pressure values ranging from 160 to 120 mmHg the systolic pressure and 100 – 70 mmHg the diastolic pressure. High blood pressure is an important cause of left ventricular hypertrophy, but in this case it should be noted the increased left ventri-
moment the patient has a normal cholesterol level, in the past she was diagnosed with dyslipidemia, and she received treatment with statins. Taking in account that the patient is also diabetic, we decided to maintain the statin therapy (Rosuvastatin 10 mg/day).

A study published in 2009 from the Fabry Registry advises that all patients with Fabry disease, regardless of age or gender, should be monitored for possible cerebrovascular complications, as stroke can occur in the absence of other key signs of the disease. Considering this information we decided to recommend antiplatelet therapy (Aspirin 100 mg / day).

DISCUSSIONS

Cardiac involvement is common in Fabry disease, both in hemizygous men and heterozygous women, and it is one of the three major causes of morbidity and mortality. Cardiac hypertrophy associated with depressed contractility and diastolic filling impairment often occurs. In addition, coronary insufficiency, atrioventricular conduction disturbances, arrhythmias and valvular involvement may be present. In patients with the atypical ‘cardiac variant’, the disease manifestations may be limited to the heart. Storage of globotriaosylceramide (Gb₃) is found in various cells of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells within all types of vessels, and vascular smooth muscle cells. Gb₃ storage by itself, however, is unable to explain the observed level of cardiac hypertrophy, conduction abnormalities and other cardiac manifestations. Autopsy of an individual with Fabry disease who had an extremely hypertrophied heart revealed a relatively limited contribution of the stored material to the enormous increase in cardiac mass. It appears that storage induces progressive lysosomal and cellular malfunctioning that, in turn, activates common signalling pathways leading to hypertrophy, apoptosis, necrosis and fibrosis. A study published in 2010 concluded that concentric LVH was the predominant cardiac pathology seen in patients with Fabry disease, and was prevalent in both genders by the third decade of life. Left ventricular mass index was inversely correlated with α-Gal A activity, but was prevalent even in younger female. A pattern of progressive involvement was also observed in the conduction system of the heart. Early stages of the disease are associated with accelerated conduction, and late stages are characterized by progressive bradycardia and atrioventricular conduction defects. Permanent cardiac pacing is needed for about 10-20% of patients.

The biological investigations revealed impaired renal function, with a serum creatinine levels between 1.53 – 1.3 mg/dl, corresponding to stage 3 chronic renal failure. Currently the renal pathology is stationary, without notable changes of the biological samples compared to the last three years.

On admission, the patient presented two Holter ECG/12 hours recordings, made in the last month, based on which she was diagnosed with intermittent second-degree atrioventricular block with 2:1 conduction. The AFD is mentioned in the „2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy”, but in the absence of prospective trials the guideline suggest adherence to conventional pacing indications, so the patient has a class I indication, level of evidence C for pacemaker implant. The next day after admission, we performed, under antibiotic protection, single chamber pacemaker implant. We used the left subclavian vein approach, without any intraoperatory or postoperatory complications. The pacemaker was programed VVI 60 beats/minute, and the patient presented intermittent pacing after implantation.

The treatment for this patient requires a multidisciplinary approach, with periodic reassessments. Regarding the cardiologic treatment we have recommended antihypertensive therapy with converting enzyme inhibitor (Zofenoprilum 30 mg/day) and calcium channel blocker (Lercanidipinum 10 mg/day). Although at this moment the patient has a normal cholesterol level, in the past she was diagnosed with dyslipidemia, and she received treatment with statins. Taking in account that the patient is also diabetic, we decided to maintain the statin therapy (Rosuvastatin 10 mg/day).

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Until recently, general medical textbooks have emphasized that females are largely asymptomatic. More recently published textbooks, however, reflect the changing view of the expression of Fabry disease in females. This changing view is reflected in an on-line updated version of Harrison’s Principles of Internal Medicine, where in May 2005 it is written that: “Up to 70% of heterozygous females may exhibit clinical manifestations, including central nervous system and cardiac disease, but usually do not develop renal failure”.

Recent studies have shown that Fabry’s disease may be much more common among patients with left ventricular hypertrophy (LVH) than previously thought. Up to 7% of male patients with left ventricular hypertrophy and up to 12% of female patients with unexplained LVH were found to suffer from Fabry’s disease. Thus, this disease should be considered in patients with unexplained LVH17.

Data from 2848 patients in the Fabry Registry were summarized to analyze the life expectancy at birth in patients with AFD compared with the United States general population. The life expectancy of males with Fabry disease was 75.4 years, compared with 80.0 years in the United States. Most (57%) patients who died of cardiovascular disease had previously received renal replacement therapy18.

Based upon current literature, there is evidence of improvement with ERT in some aspects of AFD: stabilization of nephropathy with stable proteinuria and GFR, stabilization of cardiomyopathy with stable or declining LVMI, LV wall thickness, normalization of PR interval, reduction in neuropathic pain, improvement or resolution of diarrhea, abdominal cramps or pain, nausea, vomiting and heartburn associated with AFD. The Canadian Fabry Disease Treatment Guidelines published in 2012 admits that other clinical features of Fabry disease have not been yet shown to respond to ERT: tachy or brady arrhythmias, stroke, proteinuria, depression, hearing loss. A study published in 2013 about the long term ERT for AFD points out that long term ERT does not prevent disease progression, but the risk of developing a first or second complication decreases with increasing treatment duration. ERT in advanced Fabry disease seems of doubtful benefit. Treatment failure also occurs frequently and seems related to age and severe pre-treatment disease. Early diagnosis appears to be the key to a favorable response to treatment19-21.

Take home messages: Suspected AFD when encountering young patients with a history of stroke, impaired renal function, unexplained left ventricular hypertrophy associated with arrhythmias or conduction disorders. Recommend plasmatic screening for AFD in high risk patients.

Conflict of interest: none declared.

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