

Myocardial infarction in Fabry disease – misfortune or companion? Case report and review of the literature (RCD code: III-3B.2)

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Abstract

We discuss a 56-year-old man with Fabry disease (FD), a genetic X-linked glycolipid storage disorder. The patient presented at the Emergency Room in a local hospital due to tachycardia-associated chest pain, which had occurred occasionally in the past, but on that occasion was long-lasting (>12h) and distressing. The patient had been diagnosed with FD at the age of 42. He presented a range of symptoms characteristic for the condition, including hypertrophic cardiac myopathy with impaired left ventricular relaxation, angiokeratomas, cornea verticillata, hypohidrosis and acroparesthesia. Residual alpha-galactosidase A activity at diagnosis was ≈3%. The Enzyme Replacement Therapy (ERT) with the agalsidase alpha was induced. A year later pacemaker implantation was performed due to sick sinus syndrome with symptomatic, severe episodes of bradycardia. The initial diagnosis was tachycardia-associated chest pain with troponin release in the context of FD left ventricular hypertrophy. However, a decision was made to perform an urgent angiographic evaluation to exclude coronary pathology as a potential factor in the clinical picture. Coronary angiography showed a critical, flow-limiting, stenosis of the left anterior descending artery (LAD) which changed the initial type 2 myocardial infarction (MI) diagnosis to the type 1 MI. Percutaneous stent-assisted treatment was performed with an optimal angiographic and clinical outcome. However, 5 days later the patient developed a minor left hemispheric ischaemic stroke. In conclusion, the clinical course of a rare pathology such as FD may be importantly complicated by other (more common) pathologies. Physicians, in their diagnostic and therapeutic decision-making, need to be open to thinking beyond the patient label. JRC D 2018; 3 (7): 246–252

Key words: rare disease, echocardiography, enzyme replacement therapy, percutaneous transluminal coronary angioplasty, echocardiography, ischemic stroke

A 56-year-old male presented in the Admission Room in local hospital due to tachycardia-accompanied severe chest pain. The patient had exercise-induced chest pain for the previous three weeks (Canadian Cardiovascular Society [CCS] II/III), although pain at rest occurred since the day before the admission.

Past medical history

In 2003, at the age of 41, the patient was evaluated for exercise-induced angina (CCS III) and dyspnoea (New York Heart Association [NYHA] II). Transthoracic echocardiography (TTE) revealed the hypertrophic cardiomyopathy with impaired relaxation of the left ventricle. In addition, angiokeratomas, cornea verticillata and hypohidrosis were detected, all characteristic for Fabry disease (FD). Kidney function was normal. FD diagno-

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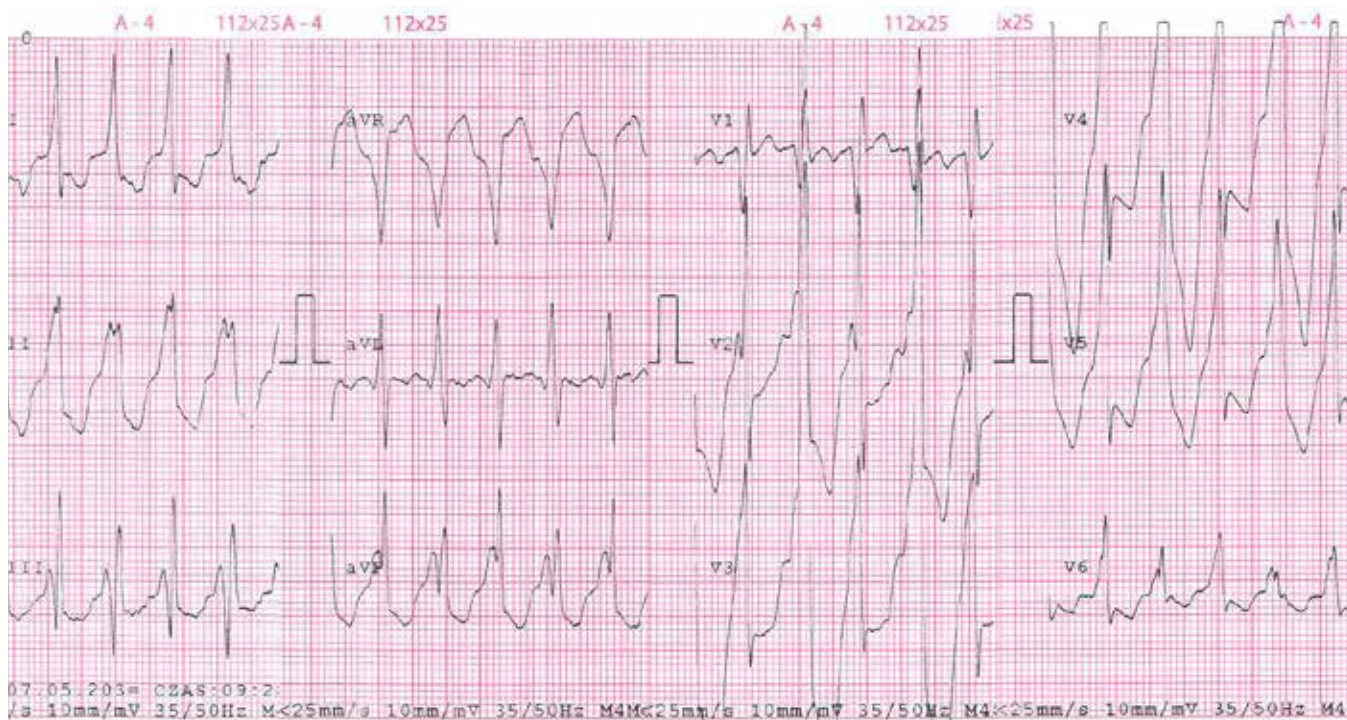


Figure 1. Electrographic examination at the point of hospital admission (local hospital) demonstrating narrow QRS tachycardia 180/min

sis was made based on the assessment of the alfa-galactosidase (α -Gal A) activity (residual level 0.9 μ kat/kg protein; reference range: 22–36, Sahlgrén's University Hospital, Molndal, Sweden), as well as genetic testing that revealed mutation in exon 3 of the alpha-galactosidase A (GLA) gene (c.386T>C [L129P], Rostock University, Germany). The patient was referred for Enzyme Replacement Therapy (ERT) with the agalsidase alpha (Replagal), which started in 2004. ERT involved Replagal 3 amp a 3.5 mg and paracetamol 0.5 g every two weeks. Following FD diagnosis in the patient, his mother and sister were identified with the GLA gene mutation and diagnosed with FD as well. The patient's sister complained of similar, yet less severe, symptoms. In addition, family history included myocardial infarction in the patient's mother at age of 45 and stroke leading to death at 77. In 2005 dual-chamber, rate-modulated (DDDR) pacemaker was implanted due to sick sinus syndrome (SSS) with episodes of severe, symptomatic (pre-syncope) bradycardia. Exercise-induced chest pain had occurred episodically since 2003. In 2014 during routine check-up spirometry, chronic obstructive pulmonary disease (COPD) was diagnosed in absence of a history of tobacco use. COPD is a common co-morbidity in FD patients, related to the accumulation of pathologic sphingolipids in the lung tissue. Treatment with long-acting β_2 agonist significantly improved exercise tolerance. Since childhood a pain in distal extremities slowly developed (acroparesthesia). The patient described it as burning and stabbing, radiating from proximal to distal extremities. Although the pain was rather constant, patient correlated changes in its intensity with weather and temperature. There was no need for regular

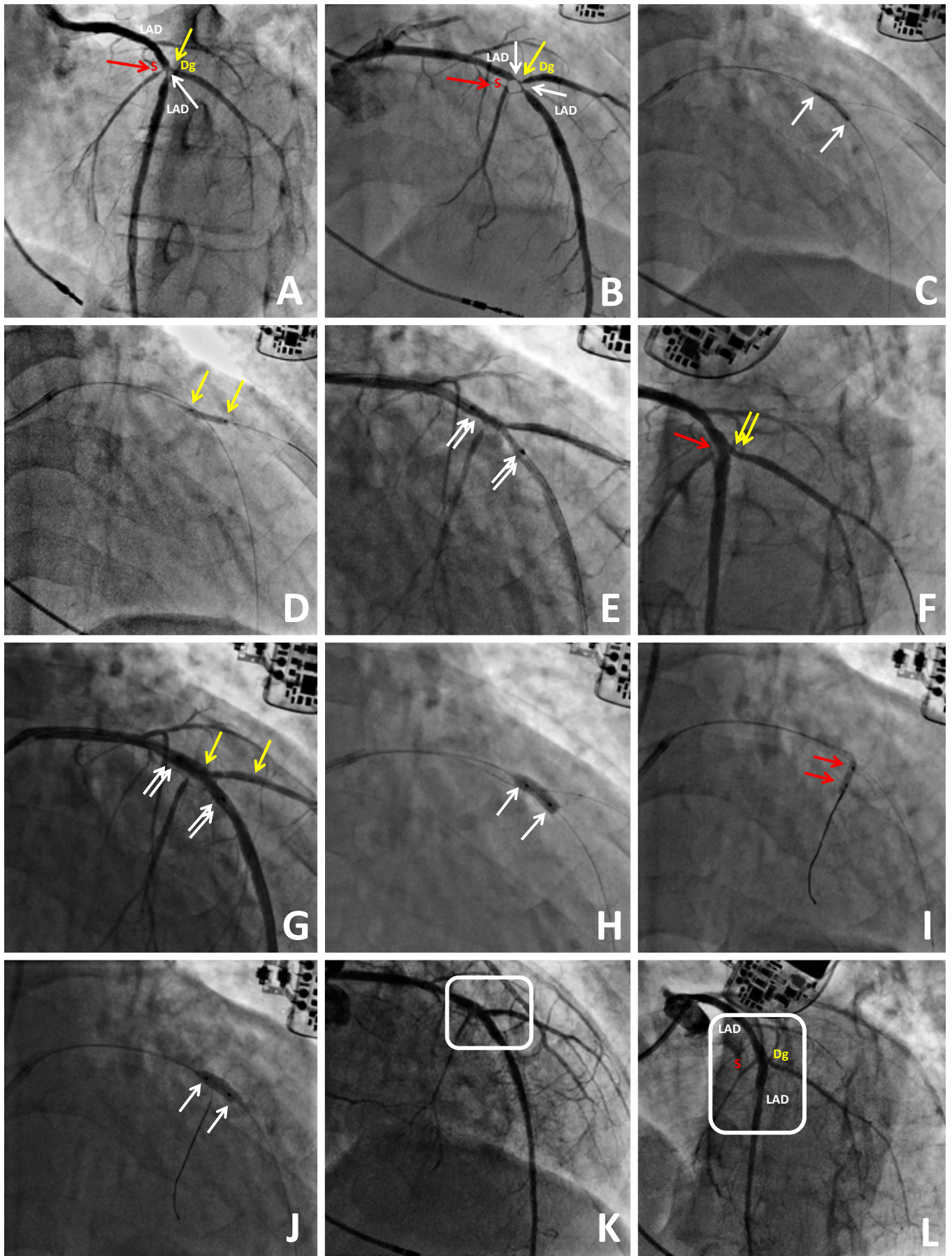
analgesics administration. Moreover, regular episodes of severe headache were reported.

On admission to a local hospital, the patient had tachycardia 180/min, with the arterial blood pressure of 90/65 mm Hg. Physical examination revealed 3/6 in Levin scale systolic murmur. Laboratory tests showed mildly elevated cardiac Troponin T level with normal kidney parameters.

On electrocardiography (ECG), narrow QRS tachycardia 180/min, QRS morphology of left bundle branch block type with normal axis, the feature of 'QRS alternans', equiphasic rSR in V_1 , left ventricular hypertrophy, pseudo-delta wave (Figure 1). Electrophysiological features of 'T alternans', could not exclude atrioventricular reentrant tachycardia or bi-directional ventricular tachycardia. The exact mechanism of supraventricular electrical activity could not be determined due to significantly decreased intervals between QRS complexes.

The patient was referred by telephone to John Paul II Hospital for consultation regarding potential consideration of interventional evaluation (versus conservative treatment of supraventricular tachycardia-associated type 2 myocardial infarction [MI]). Decision was made to complete the diagnostic process by determining the status of coronary arteries as this would have a potentially significant impact on management and prognosis. Forty minutes later, on arrival to our center biochemical analysis revealed increased levels of troponin hST 8.260 ng/mL (normal range: <0.014), creatine kinase 1346 U/L (normal range: 0–190) and creatine kinase-MB 146 U/L (normal range: 0–24). Non ST-elevation Acute Coronary Syndrome (NSTEMI-ACS) diagnosis was made.

Coronary angiography (CAG) was performed on an urgent basis due to on-going chest pain, and showed an anatomical variant



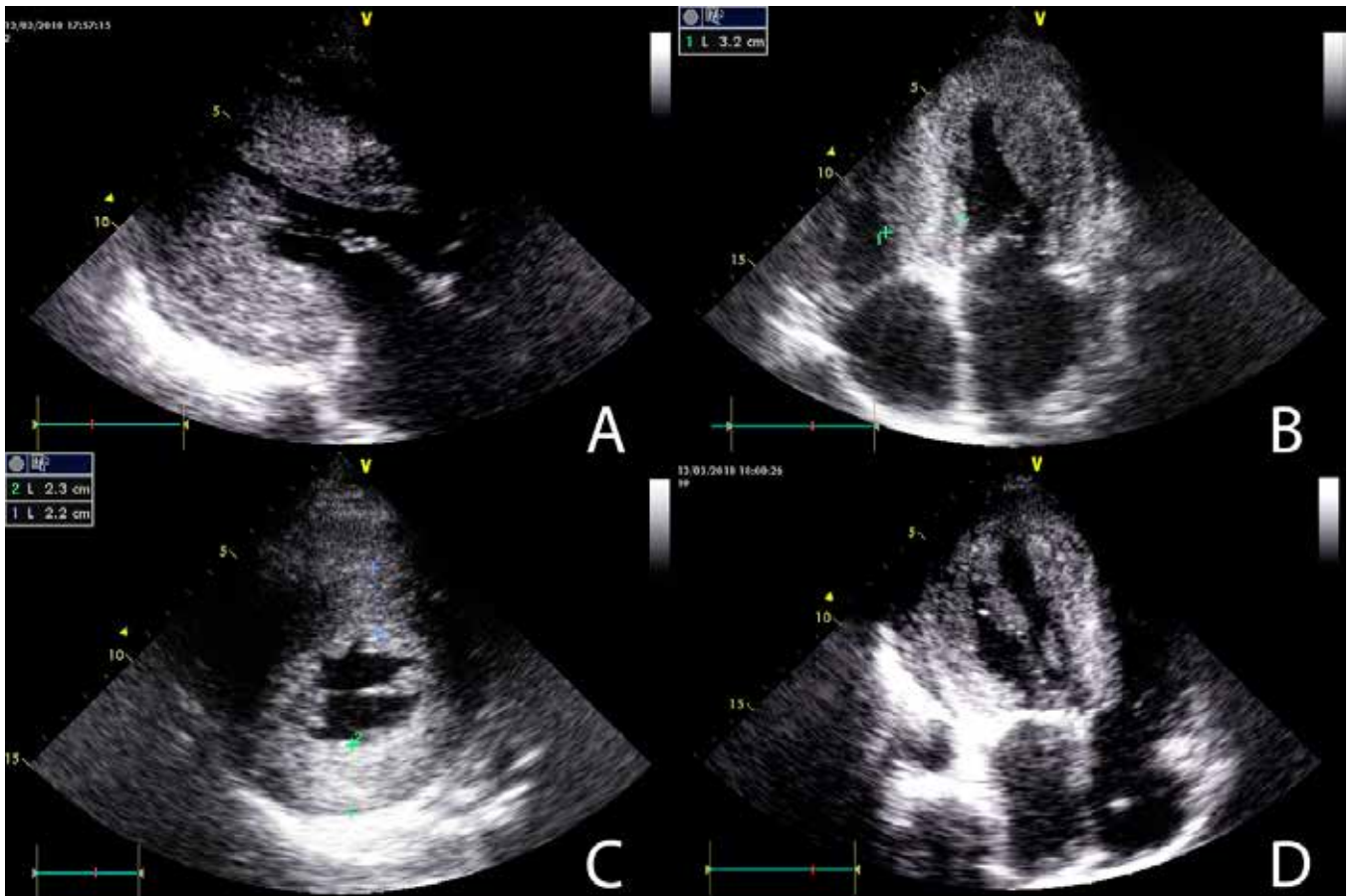


Figure 3. Echocardiographic examination at the point of admission for follow-up. A – Modified parasternal long axis view showing thickened interventricular septum and posterior wall. B – Typical four-chamber view showing thickening of the interventricular septum and lateral wall. C – Parasternal short axis at the level of papillary muscles showing hypertrophic left ventricle. D – Modified apical view showing prominent papillary muscle as well as thickening of the ventricular myocardium

Figure 2. Angiographic images of the left anterior descending coronary artery critical trifurcation lesion and its effective percutaneous management using a single-stent technique. Coronary angiography (A and B) showed a very tight lesion in proximal/mid portion of the left anterior descending coronary artery (LAD, white arrows) involving a large septal branch with its (S, red arrow, critical stenosis) and a large diagonal branch (Dg, yellow arrow, critical stenosis). At first, LAD and Dg were wired (C) and LAD was pre-dilated with a 2.5x12 mm balloon at 14 atm (C, white arrows). Balloon angioplasty of the LAD/Dg lesion followed, using a 2.5x12 mm balloon (D, yellow arrows) at 14-18 atm. A drug-eluting stent (3.0x15 mm) was implanted in the LAD (E, stent markers depicted with double-arrows), covering the S and Dg ostia. Then the Dg branch was re-wired (G) and a kissing balloon inflation was performed at the LAD (3.0x15 mm balloon, white double-arrows) and Dg (2.5x12 mm balloon, yellow double-arrows) bifurcation at 12-14 atm. Mid portion of the stent was optimized using 3.5x12 mm non-compliant balloon at 16 atm (H, white arrows). The Dg wire was then placed in the septal branch (I) where balloon angioplasty was performed using a 2.0x12 mm balloon at 10-14 atm (2 x 60 sec). Final optimization of the LAD stent was performed (3.5x12 mm non-compliant balloon at up to 20 atm (J, white arrows). K and L show an optimal angiographic result with no residual stenoses or dissections at the LAD, Dg or S; the angiographic effect was associated with full symptom resolution

(separate origination of the left Circumflex (Cx) and Left Anterior Descending (LAD) arteries) and a significant (80%) focal LAD stenosis involving LAD trifurcation (LAD, septal branch, diagonal branch) (Figure 2)

Patient management and follow-up

A single stent (Xience 3.5x15 mm drug-eluting stent [DES] in LAD) percutaneous treatment was performed, with optimal balloon angioplasty of the septal and diagonal branch (Figure 2).

TTE revealed diffuse/symmetrical hypertrophy of non-dilated left ventricle (LV internal diameter diastole/systole: 37/19 mm, Interventricular septum: 23/28 mm, Posterior wall: 22/29 mm) and mild enlargement of right ventricle (Basal RV diameter (RVD 1): 32 mm, Mid-cavity diameter (RVD2): 34.5 mm, Longitudinal dimension (RVD3): 73 mm, decreased LV global contractility with ejection fraction of 45%, without segmental disorders, enlarged left atrium (128 ml), restrictive LV filling pattern. No left ventricular outflow tract obstruction (LVOTO) could be detected. Moderate mitral insufficiency, tricuspid annulus dilatation with otherwise normal valve function and morphology were recognized. Heteroechoic, granular pattern of the myocardium was consistent

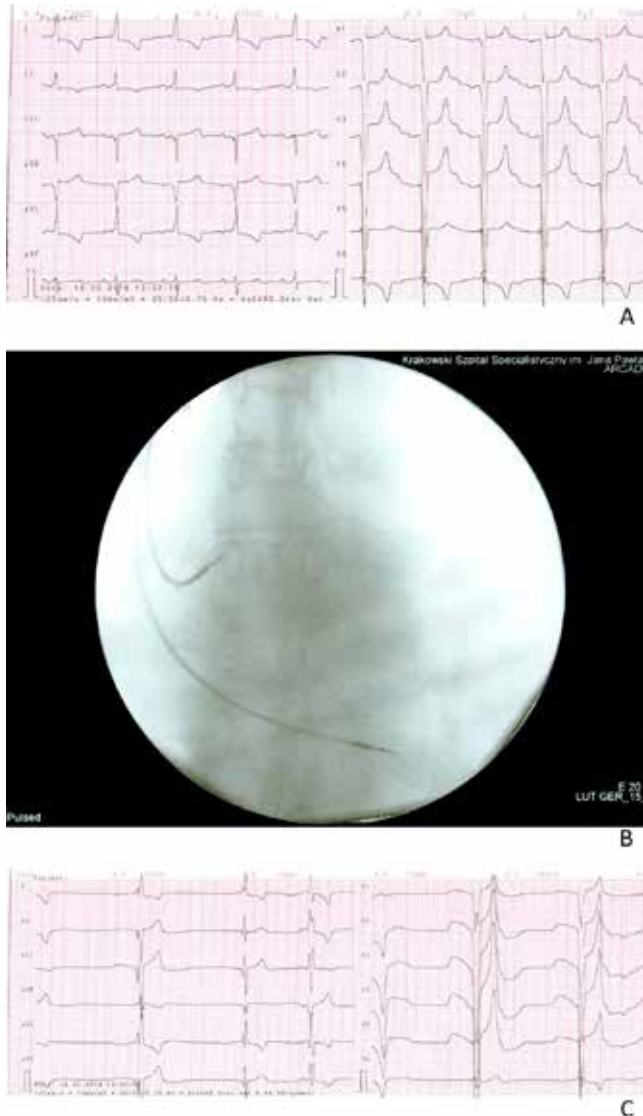


Figure 4. Electrographic examination three months after the hospitalization. A – Dual chamber pacing (DDD pacemaker) at 70/min; X-ray (B) shows two endocardial leads: one in right atrial appendage and the other one in left ventricular apex. C – Rhythm after switching the pacemaker parameters to VVI 30/min

with myocardial replacement fibrosis. Pacing electrode was present in the right heart chambers. (Figure 3)

On the 5th day of hospitalization a mild speech disorder occurred (on urgent neurological consultation – moderate Wernicke-Brocka's aphasia). No paresis was detected. Immediate computer tomography (CT) revealed ischemic areas of a temporal and partly frontal lobe. Left hemisphere ischemic stroke was diagnosed, with National Institutes of Health Stroke Scale (NIHSS) score 2 (minor stroke).

The patient was transferred to Stroke Unit for management and the post-stroke rehabilitation. The patient did not fulfil criteria for fibrinolytic therapy as the exact time of onset was unknown, the neurological deficit was mild (minor sensory-motor aphasia) and the ischemic areas were clearly depicted on CT. No significant carotid artery disease was present on duplex sonogram. Dual antiplatelet therapy was maintained. Following a major speech im-

provement, the patient was discharged home on day 14th of the hospitalization.

Three months later, the patient underwent cardiologic and neurologic follow-up on an outpatient basis. The overall clinical condition was good, with a marked improved neurological status and absence of aphasia.

ECG showed dual chamber pacing at 70/min. QRS width 100 ms. Left axis deviation negative QRS polarity in V_1 - V_6 . QS-complexes in V_1 - V_4 , ST-elevation in II, aVR, V_1 - V_5 . ST-depression in I, II, aVL, V_6 . Negative T in I, II, aVL, V_6 . (Figure 4A; note absence of atrial and ventricular spikes are not visible due to bipolar pacing mode).

To obtain the intrinsic rate pacemaker upper pacing rate was switched temporarily to ventricular demand pacing 30/min. QRS 160 ms with left axis deviation intermittent p-wave emerging conducted physiologically to ventricles with RBBB and left axis morphology. In between junctional beats with the fusion morphology. (Figure 4B) X-ray shows two endocardial leads: in the right atrial appendage and in the left ventricular apex. Active fixation. (Figure 4C) The patient was scheduled for the electrophysiological follow-up to evaluate the mechanism of arrhythmia.

Review of literature

FD is an X-linked systemic disorder in which globotriaosylceramide (Gb3) progressively accumulates in lysosomes of various tissues and organs, including heart, kidney and nerve system [1]. The incidence of FD is estimated at 1:50.000 to 1:117.000 males [2]. The disease is caused by a mutation in GLA gene that results in the absence or extreme reduction in α -Gal A enzyme, which normally catalyses Gb3 [2].

FD affects mostly man and has more severe progress in this group [2]. Heterozygous females may be asymptomatic except for corneal opacities, acroparesthesia and angiokeratomas. However, depending on lyonization or random X-inactivation, they may be as severely affected as homozygous males [2]. Recent studies suggest that milder forms of the disease that present later in life and primarily affect the cardiovascular, cerebrovascular or renal system may be more common and may be underdiagnosed [2].

Due to residual alpha-galactosidase activity, FD is divided into two types. The classic form, occurring in males and females with significantly low α -Gal A enzyme activity, usually has its onset in childhood or early adolescence. Most common symptoms of classic form of FD are concentric left ventricular hypertrophy (LVH), periodic crises of severe pain in the extremities (acroparesthesia), vascular cutaneous lesions (angiokeratomas), sweating abnormalities (anhidrosis, hypohidrosis, and rarely hyperhidrosis), characteristic corneal and lenticular opacities, unexplained stroke and renal insufficiency of unknown etiology including unexplained proteinuria or microalbuminuria. Patients with higher enzyme activity vary in clinical manifestation and have either cardiac or renal variant phenotype, or cerebrovascular disease presenting as stroke or transient ischemic attack (TIA) [2]. Most of atypical variants have later onset and less clinical symptoms compared to the classical Fabry patients [1], [2]. Cardiac involvement is present in more than a half of Fabry patients [1]. Progressive concentric LVH, often associated with hy-

perthrophy of the interventricular septum [2], is the most common symptom [1]. Hence, electrocardiographic hallmarks are a positive Sokolow-Lyon index and a negative T-wave in the precordial leads [2, 3].

Histologically, the Fabry cardiomyopathy is characterized by myocyte hypertrophy and vacuolation [4]. Typically wall thickening is not caused by LVOTO and ejection fraction is preserved, although early stages of diastolic dysfunction are present [1]. These features may be used for a screening for FD among patients with unexplained hypertrophic cardiomyopathy [5]. The most common tool to screen for Fabry cardiomyopathy is echocardiography [1]. Mitral insufficiency may be present in childhood or adolescence [2]. The end-stage Fabry cardiomyopathy is characterized by intramural replacement fibrosis, which leads to motion abnormalities and cardiac arrhythmias, including sinus bradycardia, bradyarrhythmias and malignant ventricular arrhythmias. Fibrosis replacement is a poor prognostic factor [1]. Magnetic resonance imaging (MRI) is a non-invasive 'gold-standard' in imagining myocardial replacement fibrosis [6].

Introduced in 2001, ERT is the only available treatment. The drug replaces missing enzyme and catabolizes the lipid deposits [1, 2]. There are two recombinant forms of alpha-galactosidase – agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme), both effective in clinical trials [7, 8]. First one is produced from a stable transfected line of cultured human skin fibroblasts, second by the expression of human alpha-galactosidase DNA in Chinese hamster ovary cells. They differ in the glycosylation pattern of the protein, which depends on the originating cell line [2]. Many studies proved ERT's positive impact on clearance of Gb3 from the endothelial cells [9], neuropathic pain [10], left ventricular hypertrophy [11], renal function [11] and in overall may improve life expectancy [12]. Both drugs show similar efficacy [7, 8]. The ERT infusion has to be given intravenously every two weeks throughout life [1]. Both drugs are approved by the European Agency for Evaluation of Medical Products, while only Fabrazyme was approved by the Food and Drug Administration for use in the United States [2].

Additional therapy may include usage of angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blockers, b-adrenergic blocking or implantation of a cardio-defibrillator (ICD) if necessary. Amiodarone therapy should be avoided as it interacts with ERT drugs [1].

Life expectancy of patients with FD is 58 years for males and 75 years for females. Prompt initiation of ERT is expected to extend the lifespan, but this has not yet been convincingly demonstrated. Importantly, the most common cause of death among both genders is cardiovascular disease [13].

Discussion

Patients with a cardiac variant of FD are usually diagnosed at or after the age of 40 [2]. The patient we describe presented symptoms typical for the cardiac variant of FD, however angiokeratoma, acroparesthesia, hypohidrosis and corneal opacity are uncommon findings for the non-classical type being characteristic for the classical one [2]. Prominent fact was no involvement of

the kidneys with no signs of nephropathy many years after the diagnosis.

Cardiac involvement occurs in more than half of patients with FD and manifests usually as a LVH [1]. On TTE (a first-line screening tool in FD [1]), the patient presented characteristic symptoms of Fabry cardiomyopathy. Although valvular abnormalities are frequently reported in Fabry patients, valve function and morphology rarely have a clinical impact on the survival. Only trifling population of Fabry patients exhibit mild or moderate aortic, mitral and tricuspid insufficiency, especially in end-stage cardiomyopathy [14]. In the reported case, the patient had a moderate mitral insufficiency. The patient suffered from SSS with episodes of severe, symptomatic (pre-syncope) bradycardia. Fibrosis is believed to be the leading cause of cardiac arrhythmias [3]. The end-stage Fabry cardiomyopathy is characterized by intramural replacement fibrosis [14], which unlike Gb3 accumulation, is irreversible [15]. Although MRI is the worldwide golden-standard for cardiac fibrosis detection [6], it could not be used in the presented case as patient's pacemaker was not suitable with MRI. Symptoms presented in the Admission Room were typical for FD. Angina pectoris and tachycardia are a common manifestation of the disease and are frequently reported in the literature. Electrocardiographic examination of Fabry patient may contain disturbed patterns, including ST segment depressions and T-wave inversions [1, 3], hence might be the cause of misdiagnosis of acute myocardial infarction [16]. Moreover, in FD coronary reserve is significantly reduced and cardiac necrosis markers may be elevated even in asymptomatic subjects [17]. In 5 years perspective observation of Fabry Outcome Survey, revascularisation due to the presence of stenotic lesions was reported only in 5 out of 752 patients (<1%) [17]. Notwithstanding, decision to perform coronary angiography was made to exclude coronary pathology. Lesions in coronary arteries were identified. The myocardial infarction turned out to have probably mixed origin, coronary artery stenosis (type 1 MI) and increased oxygen demand in tachycardia (type 2). Focal character of lesion suggested atherosclerotic etiology of the obstruction as deposits of Gb3 in endothelial cells tend to be diffuse [18]. An endothelial inflammation is an important pathogenic factor in FD. It has been shown that the storage of Gb3 increases oxidative stress and up-regulates the expression of adherence molecules in vascular endothelium [19]. Other data suggest that Gb3 may cause the release of pro-inflammatory cytokines [20]. Nevertheless, FD is rather considered as a risk factor for atherosclerosis in the context of other risk factors, such as renal insufficiency, diabetes and hypertension [21]. Although atherosclerotic lesions are not a consistent finding in most of the patients, the impact of Fabry disease on atherosclerosis is widely debated [21,22].

The most prominent central nervous system manifestations in FD are cerebrovascular events such as ischemic strokes (IS) and TIAs [23]. Retrospective studies in small cohorts of Fabry patients have reported a wide range of IS incidence (24%–48%) [24]. An analysis of a large cohort of patients in the Fabry Registry reported that IS occurs in 6.9% of men and 4.3% of women. Of these, 87% of first IS were found to be ischemic. The incidence of IS increases with age of patients with FD [23]. In the Fabry Registry cohort, a majority of Fabry patients experienced a first IS between the age of 20 and

50 years as in the current case. For more than 70% of patients IS was the first serious FD complication [25]. Although the pathophysiological mechanism of IS in FD is complex and not yet well understood, induce oxidative stress, increased platelet reactivity and endothelial dysfunction are believed to play the main roles [23]. What is more, patients with unstable angina have often present morphological characteristics of the instability of carotid artery plaques, what may result in cerebrovascular ischemic events [26]. However, no significant plaque was found in the described patient. IS is not only a frequent indication of FD, but also one of complications after percutaneous intervention angioplasty. A large study on European population reported that their incidence for acute coronary syndrome is as high as 0.6% during the hospitalization [27].

Initial biopsy studies proved ERT ability to clear deposits of Gb3 in endothelial cells, which may induce cardiac benefits as a decrease of left ventricle mass and enhance of regional myocardial function. The therapeutic success of ERT on cardiomyopathy depends highly on baseline myocardial fibrosis. Patients with myocardial fibrosis have only limited or no benefit from ERT [1]. In the current case, the patient had ERT started by age of 43 years, when fibrotic replacement and LVH have had probably already developed. Thus, the most current literature emphasizes that ERT should be instituted upon confirming the diagnosis of FD as it can stop disease progression and provide a better quality of life [28].

Conclusion

Fabry disease, with its periods of exacerbation and relapse, may be associated with exercise-induced and/or tachycardia-induced chest pain due to a delivery/requirement mismatch in LVH—a hallmark of FD. However, it is important to bear in mind that pathologies other than FD may contribute to the clinical picture. Although FD is a rare genetic disorder, cardiologists must stay alert as hypertrophic cardiomyopathy with accompanying angina may be the first manifestation of the disease. ERT should be initiated promptly after diagnosis as it can modify the course of disease including severity of symptoms (thus the quality of life) and, potentially, prognosis.

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