OLGU SUNUMU / CASE REPORT

Erişkin kalp hastalarında atlanan bir tanı: Fabry hastalığı

Fabry disease: An overlooked diagnosis in adult cardiac patients

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Özet- Fabry hastalığı X'kromozomuna bağlı geçiş gösteren nadir bir glikosfingolipid birikim hastalığıdır. a-galak- tosidaz enzim eksikliği sonucu sinir, böbrek, kalp ve cilt gibi birçok farklı dokuda globotriozilzseramitin birikimi ile sonuçlanan çoklu sistem hastalığıdır. Erkekler daha sık ve daha ciddi etkilense de heterozigot kadınlar da etkilenebil- mekte, ancak bulgular daha geç yaşlarda ortaya çıkmaktadır. Kalp tutulumu, sol ventrikül hipertrofisi, ileti sistemi bozuklukları, aritmiler, kapak bozuklukları ve kalp yetersizliği ile seyredebilmektedir. Hastalığın bir türü ise sadece kalp dokusunu tutmakta ve genellikle açıklanamayan sol ventrikül hipertrofisi ile ortaya çıkmaktadır. Fabry hastalığı olan iki olgu üzerinden hastalığın kalp tutulumu bulguları, semptomları ve geri dönüşümsüz doku hasarı gelişmeden enzim replasman tedavisine başlamak için erken tanının önemi tartışılacaktır.

Summary- Fabry disease is a rare, X-linked, lysosomal glycosphingolipid storage disorder. A deficiency of the enzyme alpha-galactosidase results in intracellular accumulation of globotriaosylceramide in multiple cell types, such as those of the nerves, kidneys, cardiac, and cutaneous tissues, leading to a multisystem disease. Male patients are more severely affected; however, heterozygous female patients may also be afflicted, though often the symptoms develop later. Cardiac involvement can include left ventricular hypertrophy, conduction abnormalities, arrhythmias, valvular abnormalities, and heart failure. A variant of the disease affects only cardiac tissue and mostly manifests as unexplained ventricular hypertrophy. Presently 2 cases of Fabry disease and the signs and symptoms of cardiac involvement , and the importance of early diagnosis to start enzyme replacement therapy before the development of irreversible tissue damage will be discussed .

Fabry-Anderson disease which was firstly described in the year 1898 is a lysosomal depot disease characterized with progressive damage caused by accumulation of glycosphingomyelins (globotriosylceramide etc) in all tissues, and especially vascular endothelium due to deficiency of α-galactosidase A (α-GLA) .[1] Organ involvements, and their clinical findings are summarized in Table 1. Since Fabry disease is an important determinant of mortality with predominant cardiovascular findings, it should be recognized by cardiologists. In our country data related to Fabry disease are limited to reports of scarce number of cases diagnosed based on its nephrologic, ophthalmologic, and dermatological involvements, and small-scale screening studies performed in hemodialysis patients [2,3] Up to now in our country any article on direct cardiac involvement in Fabry disease has not been published yet. In this paper we aimed to attract attention on cardiac involvement present in two adult patients with Fabry disease

Abbreviations

a-GLA	*a-galactosidase*
EKG	*Electrocasrdiography*
ERT	*Enzyme replacement treatment*
IKD	*Implantable cardioverter defibrilatör*
IVS	*Interventricular septum*
KAG	*Koroner anjiyografi*
MRG	*Manyetik rezonans görüntüleme*
OM1	*1. obtus marjinal*
SağV	*Sağ ventrikül*
SolVH	*Sol ventrikül hipertrofisi*
VT	*Ventriküler taşikardi*

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CASE PRESENTATION

Case 1- A 69-year –old male patient applied to our clinic with gradually worsening exertional angina for the last two months. From his history we learnt that he had applied frequently to various health institutes, and at a few year intervals he had three times undergone coronary angiography (CAG), and medical treatment had been recommended.

Lastly two years ago he had applied to a center with complaint of abdominal pain, and undergone CAG with the diagnosis of acute coronary syndrome. His 1. obtuse marginal artery (OMI) had been found to be 100% occluded, and his medical treatment was arranged. When the patient consulted our clinic, he was receiving acetylsalicylic acid, nitrate, and statins. His family history revealed that his brother was a hemodialysis patient. Besides during blood screening for hemodialysis, both his brother, and his grandson received the diagnosis of a genetic disease (Fabry disease). However the whole family rejected treatment.

Because of his progressive anginal complaints the patient was hospitalized in coronary intensive care unit with initial diagnosis of unstable angina pectoris. Clinical, and laboratory findings of the patient are summarized in Table 2. His electrocardiographic (EKG) examination findings were as follows: sinus rhythm, prolonged PR interval (300 ms), left anterior hemiblock, and left ventricular hypertrophy (LVH), (sum of V2S, and V2S waves was 45 mm according to Skolow- Lyon index), and loss of progression in R wave at V2-V4 leads. On CAG, 30% narrowing of the proximal segment of the circumflex artery, 100% stenotic OMI, presence of plaques on left common coronary, left anterior descending, and right coronary arteries were detected. On echocardiograms biventricular hypertrophy, left ventricular diastolic dysfunction (LVDD), and second degree mitral insufficiency were noted. (Figure 1a). Tissue Doppler examination of the case with normal ejection fraction, and systolic pulmonary artery pressure revealed decreases in systolic, and diastolic velocities of inferior septum and basal parts of the lateral wall (Figure 1b-c). Deformation analyses of septum, and lateral wall disclosed lower strain values of middle regions, more markedly basal regions (Figure 1d). On parasternal long-axis sections of septum, a hypoechoic thin borderline between hyperechoic endocardium, and myocardium, and endocardium which was termed as a specific “binary sign” of Fabry disease was visualized.(Figure 1a).

Typical LVH sign on electrocardiogram, and family history was evaluated in combination, and initial diagnosis of Fabry disease was made, and measurements of enzyme levels were recommended. However it was learnt that he had been previously diagnosed as Fabry disease Then cardiac magnetic resonance imaging (MRI) performed and measurements of the thickness of interventricular septum (İVS) (1.6 cm), inferior wall (1.3 cm), lateral, and anterior walls (0.9 cm) were made.

Table 1. Systemic findings of Fabry disease

Cardiovascular involvement
Left ventricular hypertrophy
Left ventricular systolic, and diastolic dysfunction
Atrioventricular conduction disorders
Atrial and ventricular arrhytmias, sudden cardiac death
Valvular insufficiency
Aortic dilatation
Hypertension
Skin involvement
Angiokeratoma
Telengiectasias
Hypohydrosis
Raynaud phenomenon
Neurologic involvement
Painful crises
Acroparesthesia
Transient ischemic attack-stroke
Depression
Autonomic dysfunction (hot-cold intolerance, fever)
Renal involvement
Microalbuminuria, proteinuria
Hematuria
Chronic renal failure
Audiovestibular
Sensorineural hearing loss
Tinnitus
Vertigo
Ophthalmologic involvement
Corneal opacities-cornea verticillata
Ischemic optic neuropathy
Pulmonary involvement
Coughing
Airway obstruction
Decrease in diffusion capacity
Gastrointestinal system
Abdominal pain
Dyspepsia
Nausea-vomiting
Diarrhea
Other
Growth –developmental delay
Short stature
Osteopenia-osteoporosis
Avascular necrosis of the bone
Hypothyroidism

Focal perfusion defects were detected on interventricular septum. On delayed contrast-enhanced images, gadolinium-contrast uptake in consistent with coronary ischemia which could not be explained with occlusion of an OMI branch was observed. This gadolinum hyperenhancement involved all of LV walls, and tapered towards apex, and appeared as rather focal contrast retention on IVS, and as streaks on lateral wall generally sparing subendocardium (Figure 2).

In addition to increase in the thickness of the free wall of the RV (0.9 cm), delayed gadolinium-contrast enhancement was detected on the basal part .

Table 2. Clinical characteristics of cases with Fabry

	Case 1	**Case 2**
Gender / age	Male / 69	Male / 45
Admission complaint	Unstable angina pectoris	Acute anteroseptal MI
History	Coronary angiography was performed because of attacks of angina pectoris experienced thrice,.100% occluded OM1', and atherosclerotic plaques on other coronary arteries were detected, and medical follow-up was conducted Hypertension	Absence of any known cardiovascular system pathology Hemodialysis patient for 3 years
Family history	Brother and his grandson had Fabry disease	Uncle, and nephew had Fabry disease
Diagnosis	Based on screening of the relatives of the diseased brother	Based on screening of the relatives of the diseased uncle
Extra-cardiovascular system findings	Proteinuria	Chronic renal failure
	Short stature	Short stature
	Sensorineural hearing loss	Sensorineural hearing loss
		Angiokeratoma, hypohydrosis
	Periventricular chronic ischemic gliosis, and areas of lacunar infarct on cranial MRI	Periventricular chronic ischemic gliosis, and areas of lacunar infarct in basal ganglia on cranial MRI
Cardiovascular system findings		
• EKG	Signs of left ventricular hypertrophy Prolonged PR interval	Signs of left ventricular hypertrophy
• Echocardiography	IVS: 1.6 cm	IVS: 1.6 cm
	Posterior wall: 1.2 cm	Posterior wall: 1.3 cm
	RV: 0.9 cm	RV: 0.7 cm
	LV diastolic dysfunction ,	LV diastolic dysfunction ,
	LV ejection fraction : 60% MF: 2°	LV ejection fraction : 50% MF: 3°
	Septal Sm: 7 cm/sn Lateral Sm: 6 cm/sn	Septal Sm: 7 cm/s Lateral Sm: 6 cm/s
• Cardiac MRI	Delayed contrast enhancement at basal, and mid-ventricular levels bilaterally	Delayed contrast enhancement on IVS extending and becoming more prominent from mid-ventricular level up to apex
Enzyme level	0.21 nmol/ml/hr	0.03 nmol/ml/hr
(Reference range : 21.8±10.29 nmol/ml/hr)		
Genetic analysis	Hemizygous p.R112L	Hemizygous c.963_964delinsCA

İVS: İnterventricular septum; MI: Myocardial infarction ; MRI: Magnetic resonance imaging RV: Right ventricle; LV:Left ventricle; OM: Obtus marginalis.

In addition to these findings, 24-hour urinalysis revealed the presence of proteinuria, and on cranial MR images chronic lacunary infarct sequelae in right basal ganglions, and hyperdensities in periventricular white matter consistent with chronic ischemia were detected. All of the results of these examinations were in concordance with Fabry disease which affected heart, kidneys, and central nervous system Besides the patient had short stature, and hearing deficit. Genetic analyses performed in the light of all these findings disclosed hemizygous p.R112L mutation on GLA gene. Enzyme replacement treatment (ERT)was recommended for the second time.

Case 2- A 45-year-old male patient was hospitalized in our clinic with the diagnosis of hyperacute anteroseptal myocardial infarction On coronary angiograms 10% stenotic proximal segment of the right coronary artery, and 90% stenotic middle segment of the left anterior descending artery were seen. Drug-eluting stent was inserted into anterior descending artery. It was learnt that uncle, and nephew of the patient who had been under hemodialysis therapy for three years, had received treatment abroad for Fabry disease. Family history revealed that screening tests performed among family members had demonstrated low levels of α-GA, and genetic tests established the diagnosis of Fabry disease. Clinical, and laboratory findings of the case are summarized in Table 2. EKG obtained following revascularization the signs of LVH (according to Skolow-Lyon index sum of V2 S , and VSR waves was 36 mm) incomplete right bundle branch block, symmetric deep T wave negativity in V2-V6, DI, aVL leads were observed . On echocardiograms marked LVH was detected, and ejection fraction was 50%. Lower velocities and strain values were estimated for interventricular septum, and LV lateral wall using tissue Doppler US (Table 1). On cardiac MRI global LV concentric hypertrophy (thickness of the septum, 1.7 cm), and on postcontrast evaluation delayed gadolinium enhancement starting from midsegment of the interventricular septum and extending towards apical segment as scattered areas, and on other regions, and midmyocardial region as linear images were observed. In addition to chronic renal failure sensorineural hearing loss, hypohydrosis, and angiokeratomas were detected. On cranial MRI, chronic ischemic changes on periventricular area, and areas of lacunar infarcts were seen similar to those observed in the first case. Immunohistochemical analysis of the dry blood sample obtained for definitive diagnosis revealed very low enzymatic activity (0.03 mmoL/mL/hr). GLA mutation analysis disclosed the presence of hemizygous c.963_964dlinsCA mutation. Upon establishment of final diagnosis, ERT was initiated. The patient's disease is leading a stable course at the third year of his treatment

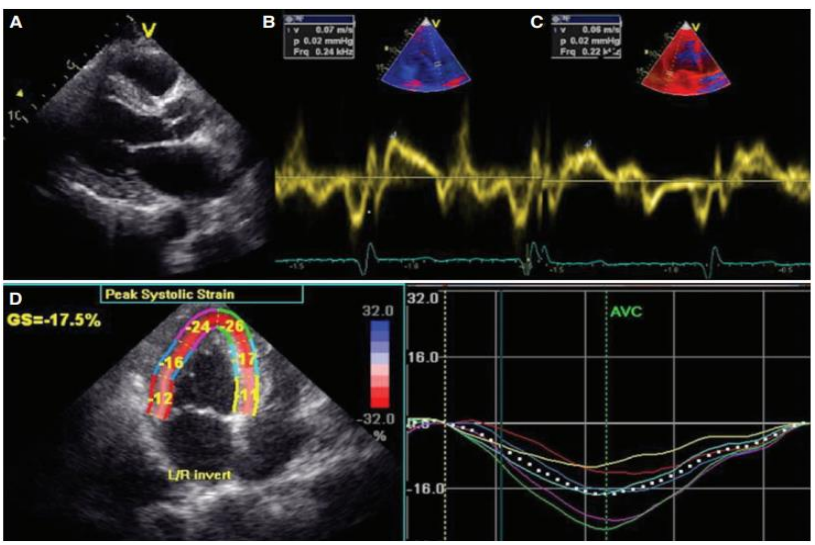

Figure 1. Echocardiographic findings of Case 1 **(A)** Increase in the thickness of the septum, and posterior wall, "binary sign" appearance defined as hyperechoic endocardium, underlying hypoechoic region, and finally hyperechoic myocardium **(B)** Decreased systolic tissue Doppler velocities in the basal part of the septum **(C)** Decreased systolic tissue Doppler velocities in the basal part of the lateral wall **(D)** In apical 4-chamber sections "strain" images on the septum, and lateral wall, and lower mid-basilar "strain" images mostly conspicuous on basal parts

DISCUSSION

Although actual incidence of Fabry disease is not known for sure, during our daily cardiology practice we encounter patients with Fabry disease above the overall prevalence cited for this disease. In 0.5-4 % of the patients with unexplained LVH, and in 3-4% of the patients with cryptogenic stroke and referred to cardiology polyclinics for suspect cardioembolism, Fabry disease has been detected.[45]

Fabry disease involves multiple systems, and therefore requires team work of different fields of specialization In this team cardiologists have two basic tasks. Namely they are to consider Fabry disease in the differential diagnosis of the patient group diagnosed as hypertrophic cardiomyopathy because of inability to establish definitive diagnosis. They should also follow up the progression of cardiovascular involvement in the patients diagnosed as Fabry disease

Clinical signs become manifest in parallel with tissue, and organ dysfunction developed secondary to the accumulation of glycosphingolipids in many different tissues due to lack of or deficiency of a-GLA enzyme. Generally accumulation is a slowly progressing process. The first symptoms are numbness developing on hands, and feet (acroparesthesia), episodes of nausea, vomiting, and abdominal pain. Other characteristic symptoms include decreased sweeting, vascular papules on periumbilical, inguinal regions, and hip which are all termed as angiokeratoma corporis. Later on growth retardation, and developmental delay, corneal opacities, and hearing disorders may be observed. (Table 1, Figure 3).[6] With ageing, symptoms related to renal, cerebral, and cardiovascular system emerge. Generally proteinuria becomes manifest at 2. decade, while chronic renal failure, cerebral, and cardiac symptoms at 3. decade. This disease demonstrates recessive transmission linked to X chromosome. Although this disease has an early onset, and leads a more aggressive course among men, it also affects women. A very rarely seen “cardiac variant” of the disease courses with cardiac involvement without any systemic effect .[7] The Case 1 with mainly cardiovascular system findings and less disturbing symptoms of systemic involvement more closely resembled cardiac variant, while Case 2 may be evaluated as a classical type Fabry disease with widespread, amd marked systemic symptoms as chronic renal failure, cerebrovascular, cardiovascular , and, cutaneous symptoms, hearing deficicts, and growth retardation.

In patients with Fabry disease cardiovascular involvement is one of the causes of mortality.

In adult patients at the time of diagnosis cardiac symptoms are observed in nearly 60% of the cases. Glycosphingolipids can accumulate on conduction system, valvular tissue, coronary arteries, and aorta apart from myocardium. However LVH is the most frequently seen symptom. LVH is not only due to the accumulation of glycosphingolipids, but also myocyte hypertrophy accompanies the LVH. Therefore different from cardiac amyloidosis, as seen in our both cases signs of LVH were detected on EKG. Firstly concentric remodelling, then concentric hypertrophy, and in advanced cases eccentric hypertrophy develop. Generally symmetric hypertrophy develops, in some patients, thinning of the basal posterior wall secondary to fibrosis, and asymmetric septal hypertrophy are seen. Dynamic LV outflow obstruction is rarely seen.[7] In advanced stages of the disease, irreversible LV fibrosis develops . In Fabry disease, in association with the presence and severity of LV involvement, RV may develop as seen in both of our cases.[8]

In some patients at the time of diagnosis, the first symptom is only angina pectoris. On coronary angiogram generally epicardial coronary arteries are intact. The disease leads to accumulation of sphingomyelins on vascular smooth muscle cells, luminal narrowing due to proliferation of vascular smooth muscle cells finally resulting in small vessel disease. These patients, as was seen in our Case 1, generally undergo more than one CAGs before establishment of diagnosis because of their anginal complaints. Fabry disease *per se* does not accelerate atherosclerotic process.

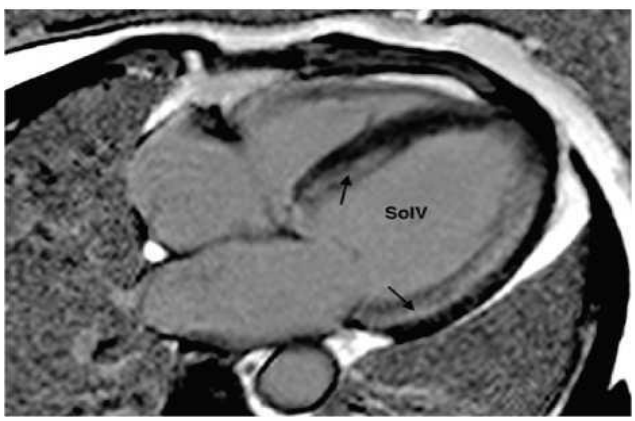

Figure 2. Gadolinium enhancement seen on late-phase contrasted MR image of Case 1.On late-phase contrasted 4-chamber image demonstrating gadolinium enhancement on septum, mid-, and basal parts of the lateral wall (black arrow) typically with intact subendocardium

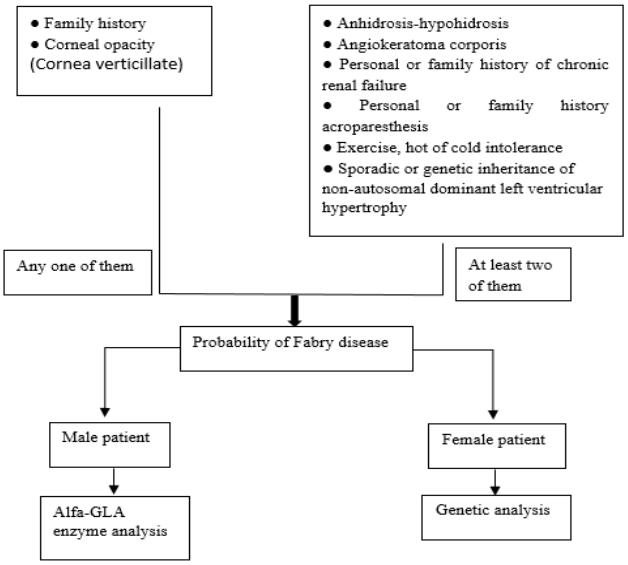

Figure 3 The symptoms which raise the suspicion of Fabry disease

However one should not forget that in these patients incidentally concurrent atherosclerotic narrowings or aneurysms due to increased atherosclerotic risk secondary to renal failure may be seen.[9] Similarly, aneurysmal aortic dilations may occur due to accumulation of glycosphingomyelins or renal failure Even though mild-moderate degrees of valvular insufficiency due to accumulation of glycosphingomyelins on heart valves is detected, as was seen in our patients, surgical intervention is not required.

During early phases of the disease atrioventricular conduction accelerates, while with time atrioventricular block, and sinus bradycardia may develop. Atrial fibrillation is also seen frequently. Ventricular arrhytmiaa developing as a result of ventricular fibrosis is one of the causes of mortality among patients with Fabry disease. Even risk measurement scales for sudden cardiac death from hypertrophic cardiomyopathy are not available, persistent or intermittent episodes of ventricular tachycardia (VT) as detected onn Holter EKG in patients with a history of syncope, and signs of severe myocardial fibrosis detected on cardiac MRI are evaluated as cases with high risk. Although a definitive consensus does not exist, implantation of cardioverter defibrillator (ICD) has been recommended.[10] In both of our cases, delayed gadolinium enhancements were detected on cardiac MRI, however during follow-up or these case ICD was not implanted because lack of signs suggesting VT on Holter EKG.

For the diagnosis of Fabry disease measurement of blood enzyme levels in male patients generally suffices, however for women genetic mutation analysis is recommended. Guiding tools for the detection of cardiovascular enhancement include echocardiography, cardiac MRI, and EKG. Unexplained left ventricular hypertrophy based on echocardiographic findings should absolutely suggest Fabry disease in the differential diagnosis. Families of the individuals diagnosed as Fabry disease should be also screened for the presence of this disease. Diagnosis of both cases was established based on family screening.

Echocardiographic findings of papillary muscle hypertrophy, and "binary sign" aid in the differentiation between Fabry disease, and other causes of LVHs. It has been reported that echocardiographic findings of papillary muscle hypertrophy not observed in hypertension, and amiloidosis could identify Fabry disease in 75 % sensitivty, and 86% specificity.[11] Observation of "binary sign" which describes hyperechoeic endocardium of septum, and underlying hypoechoeic line has been reported to have 15-35% sensitivity, and 75-80 % specificity fofr the diagnosis of Fabry disease .[12] Binary sign was detected in our Case 1, while papillary muscle hypertrophy was not detected in any one of our case.

Tissue Doppler US, and deformation aanalyses have demonstrated the presence of systolic, and diastolic dysfunction before development of LVH. In Fabry disease patients without LVH septal, and lateral Sm values below 10 cm/s have 100 % sensitivity, and specificity as for cardiac involvement. In deformation analyses only drop in "radial strain" values in patients who did not develop LVH, and if SVH develops then decreases in both "longitudinal and radial strain values" are seen. In both of our cases lower strain values for septum, and lateral walls, most prominently for basal parts were measured.

Delayed gadolinium enhancement has been observed on cardiac MRI involving inferolateral, and posterior, and especially basal parts, and partailly midventricular regions. In the differentiation from ischemia –related fibrosis as was seen in both of our cases presence of intact subendocardium is an important sign. Although fibrosis develops generally on the background of LVH, especially in women fibrosis may develop without preexisting LVH.[13] Fibrosis represents an irreversible step for the disease which is associated with malignant arrhytmias, and sudden cardiac death.[10]

Nowadays, ERT which is administered in Fabry disease as biweekly intravenous infusions of alpha, and beta galactosidase. Basic target in ERT is prevention of *de novo* accumulation of glycosphingolipids, and cessation of progressive organ damage. It has been demonstrated that.

ERT may have protective effects on renal functions. However inadequate data are available concerning the effects of ERT on cardiovascular involvement.[13] Although some small-scale studies have demonstrated that ERT may preclude the development of LVH, and improve deteriorated deformation parametres, while some other studies displayed its failure in changing the natural course of the disease . [14] Current opinion favours administration of ERT if symptoms, and signs of cardiac involvement are detected in a patient with established diagnosis of Fabry disease devoid of end-stage cardiac disease progressing with irreversible and diffuse myocardial fibrosis .[15]

The method, and frequency of patient follow-ups vary dependent on the age, and progression rate of the disease. The disease may take different courses even among family members having the same genetic mutations. In children where cardiovascular involvement is rarely seen, follow-ups at 2-3 year-intervals are recommended. Yearly follow-ups are recommended for men after 20, and women after 30 years of age. At these follow-ups EKG, tissue Doppler US, "strain", and "strain rate" echocardiographies, Holter EKG examinations should be performed. For the monitorization of myocardial fibrosis some centers recommend yearly, some others 5-yearly cardiac MRI examinations. In our center we perform MRIs every 2 or 3 years.

In conclusion, especially in every adult patient with unexplained LVH, Fabry disease should be kept in mind. Early diagnosis is important for the prevention of cardiovascular complications. Because of complex nature of the disease, and its variable course, the patients should be followed up in centers with experienced team of specialists.

Written, and undersigned informed consent was obtained from both patients

Conflict of interest: None declared

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Anahtar sözcükler: Ekookardiyografi; Fabry hastalığı; lizozomal depo hastalıkları; sol ventrikül hipertrofisi.

Keywords: Echocardiography; Fabry disease; lysosomal storage disorder; left ventricular hypertrophy.

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