





LETTER TO THE EDITOR

Pituitary dysfunction of the patient with Fabry disease: an unusual presentation

Hipofizer disfonksiyonu olan Fabry hastası: alışılmadık bir görünüm

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To the Editor;

Fabry disease is a lysosomal storage disorder (LSD) characterized by the deficiency of alpha-galactosidase A (α -GalA) and the consequent accumulation of toxic metabolites such as globotriaosylceramide (Gb3) and globotriaosylsphingosine (lysoGb3)^{1,2}. Fabry disease is X-linked, and hemizygous males typically experience the most severe manifestations; however, heterozygous females can develop complications in major organs³. Renal involvements are the major cause of mortality and morbidity in Fabry Disease. Otherwise, Gb3 accumulation occurs in virtually other major systems (cardiovascular and endocrine, neurological)^{4,5,6}. Therefore, patients were commonly admitted with related symptoms, such as young-aged, cryptogenic stroke, chronic kidney disease and a variant of hypertrophic cardiomyopathy complicated with ventricular tachycardia. Since endocrine manifestations related to Fabry disease could not be recognized easily, long-term consequences of endocrine dysfunction are not known. As is known, endocrine glands, including pituitary, thyroid, adrenal, etc. are likely to be susceptible to Gb3 storage because of their high vascularization and low proliferation rate^{7,8}. Recently, we studied a 66-year old female patient with FD who had hypopituitarism. Pituitary magnetic resonance imaging (MRI) of this patient demonstrated an empty sella, suggesting that panhypopituitarism was closely related to Fabry Disease.

A-66 year- old woman was referred to our hospital for evaluation of an endocrine function abnormality.

In 2017, Fabry Disease was diagnosed in her due to severe complaints including tachycardia, hypertension. At that time, a detailed cardiovascular evaluation was performed and interventricular septal hypertrophy and the left ventricular posterior wall markedly thickened. Genetic analyses for Fabry Disease were hemizygous mutation [*c.427 G>A (p. A143T)*] in GLA gene. Alpha GAL level was below 1 μ mol (L/ hour at that time. And enzyme replacement therapy (recombinant alpha-galactosidase A) was planned, but this patient rejected the enzyme replacement therapy. In 2017, the biochemical parameters of the patient were demonstrated in Table 1. During the follow-up duration, the patient did not apply to any clinic, but two months ago, she applied to our clinic with complaints including weakness, anorexia, and whole body pain. On admission, the blood pressure was 100/60 mm/Hg and the pulse rate was 120/min. The thyroid gland was not palpable. A grade 3/6 systolic murmur was audible at the apex. The lung, abdomen, and neurological examination showed unremarkable findings. The chest roentgenogram showed a cardiothoracic ratio 0.80, due to mainly to gross left ventricular enlargement. An electrocardiogram revealed sinus tachycardia. By M- Mode echocardiography, the left ventricular posterior wall thickness was 16 mm and there was mild tricuspid (2/4) and mitral (2/4) regurgitation.

To better demonstrate cardiovascular involvement, a cardiac MRI was performed. (see detailed results in fig1a).

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Table 1. Biochemical and hormonal data was demonstrated in table 1

	2017 (year)	2021 (1 st visit)	2021 (2 st visit)
Fasting Plasma Glucose (100-126 mg/dL)	95	69	71
Blood Urea Nitrogen (BUN) (8-20 mg/dL)	18	30	31.5
Creatinin (Cr) (0.4-1 mg/dL)	0.7	1.9	1.92
GFR (mg/dL/h)	85	26	27
Sodium (Na ⁺) (136-144 mmol/L)	140	140	-
Potassium (K ⁺) (3.6-5.1 mmol/L)	4.1	4.9	-
Uric aside (2.6-8 mg/dL)	7.5	8.6	-
TSH (0.38-5.3 mIU/L)	3.1	0.2	
Free T4 (0.61-1.12 ng/dL)	-	-	0.4
FSH* (16.74-113 mIU/mL)	-	-	3.07
LH* (10.87-58.6 mIU/mL)	-	-	0.83
Cortisol (6.7-22.6 mcg/dL)	-	-	2.1
ACTH (10-50 pg/mL)	-	-	9
GH (0.24-4.3 ng/mL)	-	-	< 0.05

GFR; Glomerular Filtration Rate, TSH; Thyroid stimulating hormone, FSH; Follicle stimulating hormone, LH; Luteinizing hormone, ACTH, Adrenocorticotroph hormone, GH; Growth hormone, *, Postmenauposal period

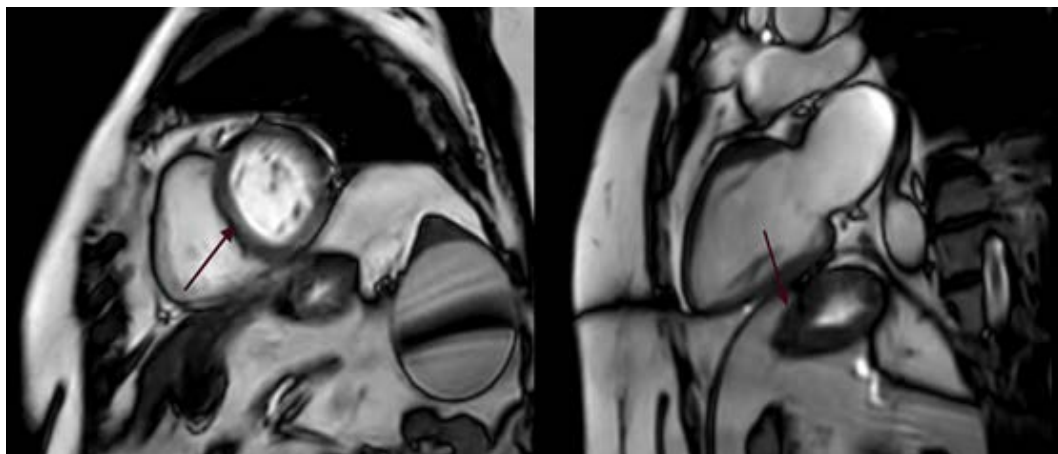


Fig 1a). Magnetic Resonance imaging of the left ventricle from a patient with Fabry Disease. This short axis view is illustrating an area in the posterolateral wall with a mild amount of late enhancement indicated by the red arrows.

Data of biochemical parameters on admission and follow-up were demonstrated in Table 1. Slight anemia was found in the peripheral blood count. Since hypoglycemia and low thyroid stimulating hormone (TSH) levels were found at the first visit, further biochemical and hormonal evaluation was performed. Blood samples were taken between 08.00 and 09.00. Circulating concentrations of TSH, FT4, FT3, FSH, LH, testosterone, 17-beta-estradiol, ACTH, cortisol were assayed using commercially available kits.

All pituitary hormone levels were decreased and indicated panhypopituitarism. As in further examination insulin-induced hypoglycemia (regular insulin 0.1 U/kg) test was performed but there was not a cortisol response. Pituitary MRI marked a reduction of pituitary gland size namely “Empty Sella”. (see fig 1b). Consequently, enzyme replacement therapy (agalsidase beta) for cardiac and renal involvement, hormone replacement therapy for hypopituitarism (L-thyroxine and prednisolone) were started at the same time. Genetic counselling was suggested to all family members.

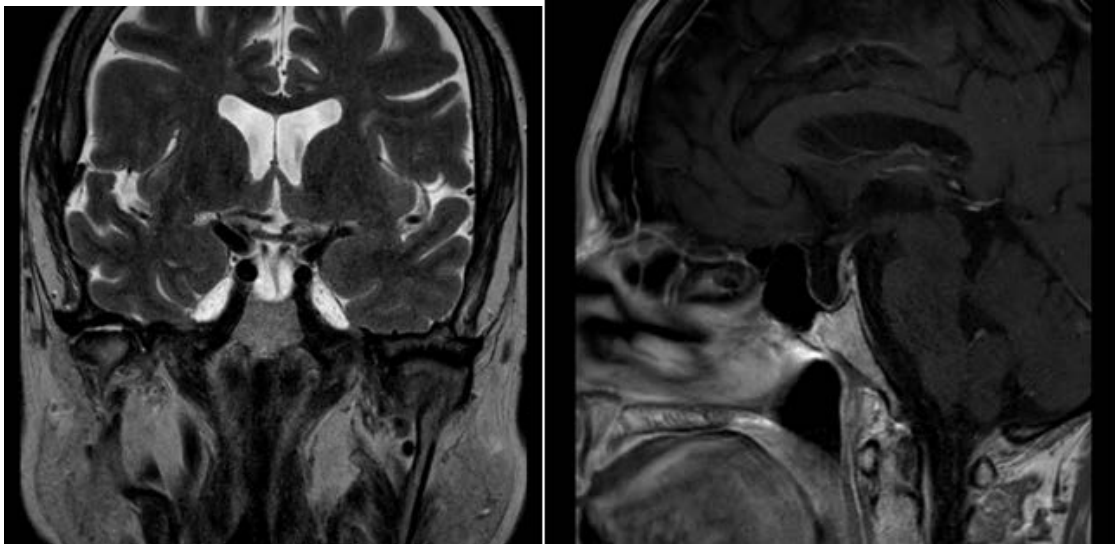


Figure 1b). Coronal and Sagittal post-contrast image shows enlarged sella with marked of the pituitary gland of the stalk.

Clinically, metabolic (cardiac or renal) abnormality becomes more common during adulthood in a hemizygous female patients with Fabry Disease. But endocrin system manifestations especially pituitary, have been rarely indicated. Previously published limited studies^{9,10,11} showed subtle impairment in thyroid and adrenal function in patients with Fabry Disease. In these studies¹¹, baseline thyroid hormone levels of patients with Fabry Disease were higher than controls with negative antithyroid antibodies. Additionally, elevated circulating ACTH and lower cortisol levels were demonstrated in those patients. They argued that thyroid and adrenals could be a target organ for Gb3 storage, which may persist because of low cellular proliferation rate.

Maione et al.¹² detailed investigated pituitary

morphology and function in a cohort of patients with Fabry Disease and aged-matched healthy controls. At pituitary MRI, empty sella was increased in patients with Fabry Disease (39%) than control subjects (5%). Pituitary volume was significantly smaller in patients with Fabry disease than controls ($p < 0.005$). Otherwise, they also showed that pituitary function was substantially preserved in patients.

Our patient was diagnosed with Fabry Disease in 2017, but she did not accept hormone replacement therapy. Although renal and other biochemical parameters of the patient were normal, renal and cardiac involvement have been progressively deteriorated. Since there was low blood glucose, TSH level and unexpectedly FSH, LH values (incompatible postmenopausal period), endocrine

evaluation was performed more comprehensive. All baseline pituitary hormone levels (TSH, Cortisol, ACTH, FSH, LH, GH, 17-beta-estradiol) were decreased. Pituitary MRI showed decreased pituitary size (empty sella) in this patient.

In conclusion, we argued that Gb3 accumulation in the pituitary may cause morphological changes in pituitary and consequently pituitary hormone deficiency. Despite no pituitary dysfunction in previous studies, decreased pituitary volume in patients with Fabry Disease has been shown in MRI. Subclinical or overt hormone deficiency can occur later in life, therefore an endocrine workup, especially pituitary hormone assessment, should be periodically performed in FD patients, who are already at risk of cardiovascular complications.

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