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Endocrine Dysfunction in Patients with Fabry Disease

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Background: Fabry disease (FD) is a genetic disorder caused by lysosomal α-galactosidase-A deficiency and is characterized by the systemic accumulation of globotriaosylceramide. All endocrine glands are susceptible to globotriaosylceramide accumulation because of their high vascularization and low cellular proliferation rate. Nevertheless, this endocrine system has never been investigated in detail.

Objective: We aimed to investigate the function and morphology of the endocrine glands in FD.

Patients: The thyroid, gonadal, adrenal, and GH/IGF-I axes were evaluated in 18 FD patients (nine females and nine males, aged 21–64 yr) and 18 sex- and age-matched healthy subjects.

Study design: We conducted an observational, analytical, open, prospective study.

Interventions: Ten of the 18 patients received enzyme replacement therapy (ERT) with recombinant human α-galactosidase-A (agalsidase β) at a dose of 1 mg/kg body weight every 2 wk.

Results: FD patients had higher baseline TSH levels than controls ($P < 0.01$). Three subjects were diagnosed with an early stage of subclinical primary hypothyroidism associated with negative antithyroid antibodies. A history of menses abnormalities, miscarriage, or assisted delivery was found in 89% of FD women. Asthenozoospermia, oligozoospermia, or both were found in all FD men through seminal fluid analysis. FD patients had significantly higher circulating ACTH and lower cortisol levels than controls ($P < 0.05$). In patients under ERT, a suboptimal cortisol response to the 250-μg ACTH test was found in 10%, and the ACTH-stimulated cortisol peak was significantly correlated to the health status profile ($P < 0.05$).

Conclusion: A variety of latent endocrine dysfunctions, including life-threatening conditions, occur in patients with FD. Endocrine dysfunctions are also present in patients already receiving ERT and are in part related to their persistent poor quality of life. An endocrine work-up should be recommended in all FD patients. Adequate monitoring and hormonal therapy, when required, have to be performed in cases of subclinical endocrine dysfunction to avoid life-threatening events. **(*J Clin Endocrinol Metab* 91: 4319–4325, 2006)**

FABRY DISEASE (FD) was first described in 1898 by two dermatologists who published two cases of diffuse angiokeratoma (1). During the last century, involvement of the heart, kidney, brain, and gastrointestinal system has enriched the clinical picture of FD, which has been recognized as a multiorgan disease caused by α-galactosidase-A (α-gal) deficiency and consequent systemic accumulation of globotriaosylceramide (Gb3) (2–9).

The multiorgan manifestations of FD resemble medical endocrinological diseases (10). Furthermore, the incompleteness of well-being recovery after recombinant human α-gal enzyme replacement therapy (ERT) might be related to subtle endocrine dysfunctions. Because physicians have been mainly attracted by life-threatening cardiac and renal complications of this disease, the involvement of endocrine glands in FD has never been investigated in detail. Nevertheless, endocrine glands are likely to be susceptible to Gb3 storage because of their high vascularization and low proliferation rate. Glycolipid deposits have indeed been reported to accumulate within the testes and thyroid of FD males (11, 12).

To provide a detailed analysis of endocrine dysfunction in patients with FD, we designed this observational, analytical, open, prospective study.

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Abbreviations: Δ4, Δ4-Androstenedione; CV, coefficients of variation; DHEA-S, dehydroepiandrosterone sulfate; E2, 17β-estradiol; ERT, enzyme replacement therapy; F, cortisol; FD, Fabry disease; fT_3, free T_3; α-gal, α-galactosidase-A; Gb3, globotriaosylceramide; IGFBP-3, IGF-binding protein 3; IRMA, immunoradiometric assay; 17-OHP, 17-hydroxyprogesterone; PRL, prolactin; SF, Short Form; T, testosterone; Tg, thyroglobulin; TPO, thyroid peroxidase; UFC, urinary free cortisol; US, ultrasonography.

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Patients and Methods

Patients

Eighteen FD patients (nine females and nine males), with a mean age of 40.2 ± 3.5 yr (range, 21–64 yr), were enrolled in the study after their informed consent had been obtained. Male patients had a diagnosis of classic FD, with a plasma level of α-gal activity of less than 1.5 nmol/h·mg (normal subjects, 8–19 nmol/h·mg) (13). In female FD patients, the plasma α-gal activity ranged from 0.2–5.9 nmol/h·mg (Table 1). An α-gal gene mutation was analyzed by direct sequencing in five of seven families and 13 of 18 patients. A causal mutation/deletion was identified in all of the five families who had undergone genetic screening (T483C and 512delA/exon-3, G749A/exon-5, G274S/exon-6, and C1133G/exon-7). In the remaining two families and five patients, the diagnosis was made from the finding of specific accumulation of Gb3 at renal biopsy because of persistent urinary sediment anomalies.

The age at the time of FD diagnosis was 31.3 ± 4.4 yr (range, 8–60 yr). Accurate neurological, ophthalmological, dermatological, renal, and cardiac clinical follow-up visits have been periodically carried out in all patients since the time of diagnosis. Table 1 shows the FD-related clinical manifestations in individual patients. Five patients had chronic kidney disease stage III–V according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines (14).

TABLE 1. FD-related clinical manifestations

Gender/age (yr)	α-Gal activity (nmol/h·mg)	FD-related clinical manifestations
1. Male/26	0.2	LVH, acroparesthesias, angiokeratoma, hypohidrosis, proteinuria,
2. Male/32	0.3	LVH, acroparesthesias, angiokeratoma, hypohidrosis
3. Female/54	2.1	LVH, angina pectoris, proteinuria
4. Male/33	0.2	LVH, acroparesthesias, angiokeratoma, hypohidrosis, GFR = 28 ml/min·1.73 m^2 (stage IV)
5. Female/62	2.9	LVH, ictus (cerebrovascular ischemic attack), microalbuminuria
6. Female/22	2.4	LVH
7. Male/48	0.2	LVH, acroparesthesias, angiokeratoma, hypohidrosis, hemodialysis (stage V)
8. Female/21	5.6	
9. Male/33	0.1	LVH, acroparesthesias, angiokeratoma, hypohidrosis, GFR = 26 ml/min·1.73 m^2 (stage IV)
10. Female/61	2.9	LVH, aortic insufficiency
11. Male/35	0.1	LVH, acroparesthesias, angiokeratoma, hypohidrosis, GFR = 32 ml/min·1.73 m^2 (stage III)
12. Female/64	0.2	LVH, hemodialysis (stage V)
13. Female/41	5.4	LVH, proteinuria
14. Male/23	0.2	Acroparesthesias, angiokeratoma, proteinuria
15. Female/56	3.9	
16. Male/24	0.1	Angiokeratoma
17. Female/46	5.9	
18. Male/42	0.2	LVH, angiokeratoma, proteinuria

GFR, Glomerular filtration rate; LVH, left ventricular hypertrophy.

At the time of the study, six patients received treatment with antihypertensive drugs (ACE inhibitors and calcium antagonists), three patients with acetylsalicylate, two patients with lipid-lowering agents, and two patients with erythropoietin. Among the nine females, four were in their reproductive age and five in their menopausal age. ERT, consisting of iv infusion of recombinant α-gal (agalsidase β; Fabrazyme; Genzyme, Cambridge, MA), was given to 10 of 18 patients at a dose of 1 mg/kg body weight every 2 wks, 14–60 months before the study. The remaining eight patients had never received ERT before the study.

Controls

Eighteen healthy subjects, age and gender matched with the patients, served as controls. All controls agreed to participate in the study and were recruited among the medical and paramedical personnel of the Department of Molecular and Clinical Endocrinology and Oncology of the University "Federico II" of Naples. None of these subjects suffered from or had been previously affected by endocrine diseases, and none of them were treated with hormones or drugs known to influence endocrine function.

Study protocol

Basal serum TSH, fT_3, fT_4, FSH, LH, prolactin (PRL), GH, IGF-I, IGF-binding protein 3 (IGFBP-3), testosterone (T), 17β-estradiol (E2), cortisol (F), dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), and Δ4-androstenedione (Δ4), plasma ACTH, and urinary free cortisol (UFC) were assayed in FD patients and controls. Antithyroglobulin (anti-Tg) and anti-thyroid-peroxidase (anti-TPO) antibodies were also evaluated in all patients and controls. A dynamic hormonal investigation included TRH plus LHRH, GHRH plus arginine, and ACTH tests. In detail, TSH, PRL, LH, and FSH levels were measured before and 30, 45, 60, and 90 min after iv injection of 200 μg TRH plus 100 μg LHRH; GH levels were measured before and 30, 45, 60, and 90 min after iv injection of 100 μg GHRH plus 30 g arginine chloride; and F levels were measured before and 60 min after iv injection of 250 μg ACTH. The GHRH plus arginine and the ACTH stimulation tests were performed only in the 10 patients who were under ERT at the time of the study. In all patients, serum IGF-I and IGFBP-3 concentrations were assayed in duplicate in a single sample. Physical and biochemical examinations for clinical and metabolic signs and symptoms of endocrine disorders were performed in all subjects. Health-related quality of life was measured in all FD patients at the time of the study using the Short Form (SF)-36 health survey and compared with the SF-36 scores obtained from the age- and gender-matched normal subjects. For the 10 patients under ERT at the time of the study, SF-36 scores observed at the time of the study were also compared with baseline scores as well as with scores observed in subjects matched for age, gender, and renal status. The morphology of the thyroid and gonads was investigated in all subjects by ultrasonography (US). In FD males, a seminal fluid analysis was also performed.

Hormonal assessment

An 0800-h blood sample was obtained for all hormones under examination but ACTH and F, which were measured twice a day (at 0800 and 2400 h) to evaluate their physiological circadian rhythm. Circulating concentrations of TSH, fT_4, fT_3, anti-Tg and anti-TPO antibodies, FSH, LH, T, E2, ACTH, F, 17-OHP, and Δ4 as well as 24-h UFC were assayed using commercially available kits. Anti-Tg or anti-TPO titer 3 SD above the mean was considered as positive. Serum GH levels were measured by immunoradiometric assay (IRMA), using commercially available kits (hGH-CTK-IRMA; Sorin, Saluggia, Italy). The sensitivity of the assay was 0.02 μg/liter. The intra- and interassay coefficients of variation (CV) were 4.5 and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction using DSL kits (Diagnostic Systems Laboratories, Inc., Webster, TX). The sensitivity of the assay was 0.8 μg/liter. The intraassay CV were 3.4, 3.0, and 1.5% for the low, medium, and high points on the standard curve, respectively. The interassay CV were 8.2, 1.5, and 3.7% for the low, medium, and high points on the standard curve. In our laboratory, the normal IGF-I ranges were 100–502 μg/liter for patients aged 20–40 yr, 100–303 μg/liter for patients aged 41–60 yr, and 78–258 μg/liter for 60-yr-old or older patients. Plasma IGFBP-3 was measured by RIA after ethanol extraction, using kits from Diagnostic Systems Laboratories. The sensitivity of the assay was 0.5 μg/liter. The intraassay CV were 3.9, 3.2, and 1.8% for the low, medium, and high points on the standard curve, respectively. The interassay CV were 0.6, 0.5, and 1.6% for the low, medium, and high points on the standard curve. The normal IGFBP-3 ranges were 2700–7200 μg/liter for patients aged 20–40 yr, 2000–4300 μg/liter for patients aged 41–60 yr, and 2000–4000 μg/liter for 60-yr-old or older patients. The GH response to the GHRH plus arginine test was considered normal when more than 16.5 μg/liter (15).

Physical and metabolic work-up

A physical and metabolic work-up was performed in all patients and controls as described in a previous study (16). Body mass index and measurements of heart rate and systolic and diastolic blood pressure were evaluated by standard methods. In patients treated with antihypertensive drugs, pretreatment blood pressure values were considered for the diagnosis and evaluation of the severity of hypertension. Moreover, fasting glucose, triglycerides, and cholesterol were measured by standard procedures.

SF-36 health survey

The SF-36 is a scientifically validated survey instrument for people 14 yr of age or older designed to measure overall physical and mental health status outcomes. The survey instrument, consisting of 36 items, is self-administered and usually requires less than 10 min to complete. The eight scales measured by the SF-36 are mental health, role emotional, social functioning, vitality, general health, bodily pain, role physical, and physical functioning. Scale scores range from 0–100 with higher scores representing better-perceived health (17).

Morphological study

US of the thyroid, testis, and ovaries was carried out by a commercially available real-time instrument, using a 5- to 7.5-MHz transducer, as appropriate. Goiter was diagnosed when the anteroposterior diameter in both lobes was at least 20 mm, whereas a nonhomogeneous thyroid pattern was characterized by the presence of diffuse hypoechogenicity, without well-defined nodular areas. US studies were performed by a single operator (G.V.) blind in respect to patient or control study.

Seminal fluid analysis

A seminal fluid analysis was performed after 3–5 d of abstinence in line with the guidelines described in the *World Health Organization Laboratory Manual* (18). The evaluation of number and motility of the sperm was carried out in a Makler counting chamber (×40); the morphology was analyzed after dilution (1:1) with saline phosphate buffer and Giemsa. The normal ranges of sperm patterns following the World Health Organization manuals are volume more than 2 ml, pH 7.2–8.0, sperm concentration more than 20×10^6 spermatozoa/ml, total sperm count more than 40×10^6 spermatozoa per ejaculate, total motility 50% or more or 25% or more forward progression within 60 min of ejaculation, morphology 30% or more with normal forms, and vitality 75% or more live.

Statistical analysis

Data are expressed as mean ± SE. The statistical analysis was performed by SPSS for Windows version 10 (SPSS, Inc., Chicago, IL). The comparisons between the numerical data were performed by the Student's *t* test. The comparisons between the categorical data were performed by the χ^2 test with the Yates correction, Fisher exact test, or McNemar test, as appropriate. The correlation study was performed by the linear regression analysis calculating the Pearson's coefficient. The multiple regression analysis was performed among the variables correlated at the linear correlation. *P* values are given for these analyses. The significance was set at 5%.

Results

Clinical and metabolic profile

None of the FD patients and controls showed overt symptoms related to thyroid or adrenal insufficiency such as edema, arterial hypotension, hyponatremia, and hypoglycemia. A mild to moderate weakness, however, was referred by 67% of patients. As expected, the SF-36 scores were significantly lower in FD patients than in controls for all domains ($P < 0.01$). In the subgroup of the 10 patients who were under ERT at the time of the study, the SF-36 scores were improved compared with baseline for every domain, but they were still lower when compared with control group I for every domain and with control group II for role emotional, vitality, bodily pain, and role physical.

Metabolic parameters were similar in patients and controls. Impaired fasting glucose was found in one patient, dyslipidemia in four, mild arterial hypertension in two, and overweight and obesity in six patients and one patient, respectively.

Hormonal profile

Thyroid axis. Serum fT_3 and fT_4 and TRH-stimulated TSH peak were similar in patients and controls, whereas patients showed significantly higher basal TSH levels than controls (1.6 ± 0.2 *vs.* 1.1 ± 0.1 mU/liter; $P < 0.01$) (Table 2). The average TRH-stimulated TSH increase from baseline (TSH-Δ) was lower in the group of patients than in controls (395 ± 59 *vs.* 624 ± 73%; $P < 0.05$). However, three patients had a TSH peak higher than 15 mU/liter compared with basal TSH levels more than 3 mU/liter but had negative serum antithyroid antibodies and a hypoechoic US pattern. As a whole, serum antithyroid antibody levels were similar in patients and controls, with positive anti-Tg and/or anti-

TABLE 2. Hormonal parameters in patients with FD and in controls (mean ± SE)

	Basal value		Peak value under stimulation test	
	Patients	Controls	Patients	Controls
TSH (mU/liter)	1.62 ± 0.16[a]	1.07 ± 0.08	7.69 ± 1.05	7.14 ± 0.46
fT_3 (pmol/liter)	4.48 ± 0.15	4.79 ± 0.18		
fT_4 (pmol/liter)	13.8 ± 0.26	14.6 ± 2.58		
PRL (mU/liter)	338 ± 74.1	225 ± 20.7	1115 ± 256	750 ± 80.6
FSH (U/liter)	8.05 ± 3.49	4.52 ± 0.59	13.2 ± 6.33[c]	9.38 ± 1.18[c]
LH (U/liter)	9.96 ± 3.20	5.24 ± 0.72	26.1 ± 4.55[c]	26.3 ± 3.03[c]
T (nmol/liter)	19.8 ± 1.79[d]	22.2 ± 1.92[d]		
E2 (pmol/liter)	65.8 ± 10.7[e]	81.2 ± 12.9[e]		
ACTH (pmol/liter)	6.70 ± 0.52[b]	5.01 ± 0.56		
F (nmol/liter)	339 ± 24.2[b]	412 ± 21.9	771 ± 56.5[f]	818 ± 43.1[f]
DHEA-S (mmol/liter)	4.13 ± 0.77	4.98 ± 0.41		
17-OHP (nmol/liter)	6.08 ± 1.54	5.27 ± 0.56		
Δ 4 (nmol/liter)	6.76 ± 1.25	9.05 ± 0.79		
GH (mU/liter)	0.69 ± 0.33	1.27 ± 0.20	89.9 ± 16.8[f]	96.4 ± 10.8[f]
IGF-I (μg/liter)	294 ± 35.6	268 ± 30.8		
IGFBP-3 (μg/liter)	4213 ± 300	4045 ± 282		

[a] $P < 0.01$.
[b] $P < 0.05$.
[c] Excluded the five patients in postmenopausal age.
[d] Assessed in the nine male patients and the nine sex- and age-matched controls.
[e] Assessed in the nine female patients and the nine sex- and age-matched controls.
[f] Assessed in the 10 patients treated with ERT and 10 sex- and age-matched controls.

TPO titer in three patients (16.7%) and two controls (11.1%). By considering patients with and without ERT separately, basal TSH levels, but not TSH-Δ, persisted significantly higher in patients than in matched controls ($P < 0.05$).

At US, a nodular goiter was found in two patients and controls each (11.1%), whereas a mild hypoechoic US pattern was found in 12 patients (66.7%) and three controls (16.7%; $P < 0.05$). In FD patients, the abnormal thyroid US pattern was independent by age, gender, genotype, plasma α-gal activity, and FD-related comorbidities such as renal and heart failure. TSH levels were not correlated with age, duration of disease activity, plasma α-gal activity, or creatinine clearance, whereas TSH-Δ was significantly correlated to plasma α-gal activity ($r = 0.51$; $P < 0.05$) and creatinine clearance ($r = 0.73$; $P = 0.001$) but only to the latter at the multiple regression analysis ($t = 2.9$; $P < 0.05$).

Gonadal axis

A history of menses abnormalities, miscarriage, or assisted delivery was found in eight of the nine FD women (89%). In particular, menses abnormalities were consistent with oligomenorrhea in four women and polymenorrhea in two women, whereas three women had suffered from spontaneous miscarriage and two from assisted delivery. Eight of 18 patients (three of nine men and five of nine women) had children (44%). Among the five FD males who underwent seminal fluid analysis, 100% showed abnormalities, including asthenozoospermia in two, oligozoospermia in one, and oligo-asthenozoospermia in two other patients. This result occurred independently of age, gender, genotype, plasma α-gal activity, ERT, and FD-related comorbidities such as renal and heart failure. No morphological alteration was pointed out by US examination of the gonads.

In the nine males and four females in their fertile age, neither basal and stimulated FSH and LH levels nor sexual hormone levels significantly differed from controls (Table 2 and Fig. 1). No correlation was found with age, duration of disease activity, or plasma α-gal activity. No difference existed between the patients receiving ERT and those untreated. A condition of hypergonadotropic hypogonadism was found in one male who suffered from renal insufficiency. Basal LH and PRL levels were significantly and inversely correlated to creatinine clearance ($r = -0.61$, $P < 0.05$; and $r = -0.74$, $P < 0.01$, respectively).

Adrenal axis

Basal 0800-h serum F and plasma ACTH concentrations were lower and higher, respectively, in FD patients than in controls ($P < 0.05$, Table 2), without any difference between patients under ERT or not. No correlation was found between basal ACTH and F levels and age, duration of disease activity, plasma α-gal activity, or creatinine clearance. Neither UFC variation nor impairment of the physiological circadian rhythm was observed. Similarly, DHEA-S, 17-OHP, and Δ4 did not differ between patients and controls. An ACTH stimulation test was performed in the 10 patients under ERT, revealing a suboptimal F response in one (10%) who had normal adrenal morphology at the CT scan, negative adrenal cortex autoantibodies, and normal glomerular filtration rate. In these 10 patients, a significant correlation was found between the ACTH-stimulated F peak and the physical component summary SF-36 score ($r = 0.72$; $P < 0.05$).

The GH/IGF-I axis

The GH/IGF-I axis was normal in all FD patients (Table 2). In all patients under ERT, the GH response to the GHRH plus arginine test was more than 16.5 μg/ml. Basal IGF-I and IGFBP-3 levels were in the normal range in all the patients except in two males with chronic renal insufficiency, who were above the upper limit of the normal range (Fig. 2). Circulating levels of IGF-I ($r = -0.53$; $P < 0.05$) and IGFBP-3 ($r = -0.65$; $P < 0.05$) were inversely correlated to creatinine clearance. IGF-I and IGFBP-3 levels were not correlated with duration of disease activity or plasma α-gal activity. The

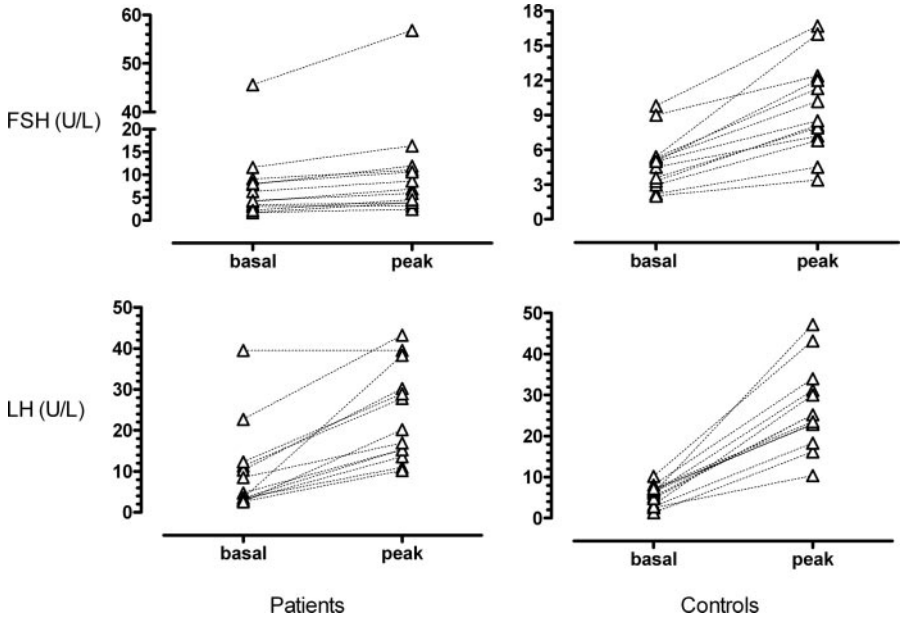

FIG. 1. Basal and stimulated FSH and LH in patients with FD and in age- and gender-matched controls.

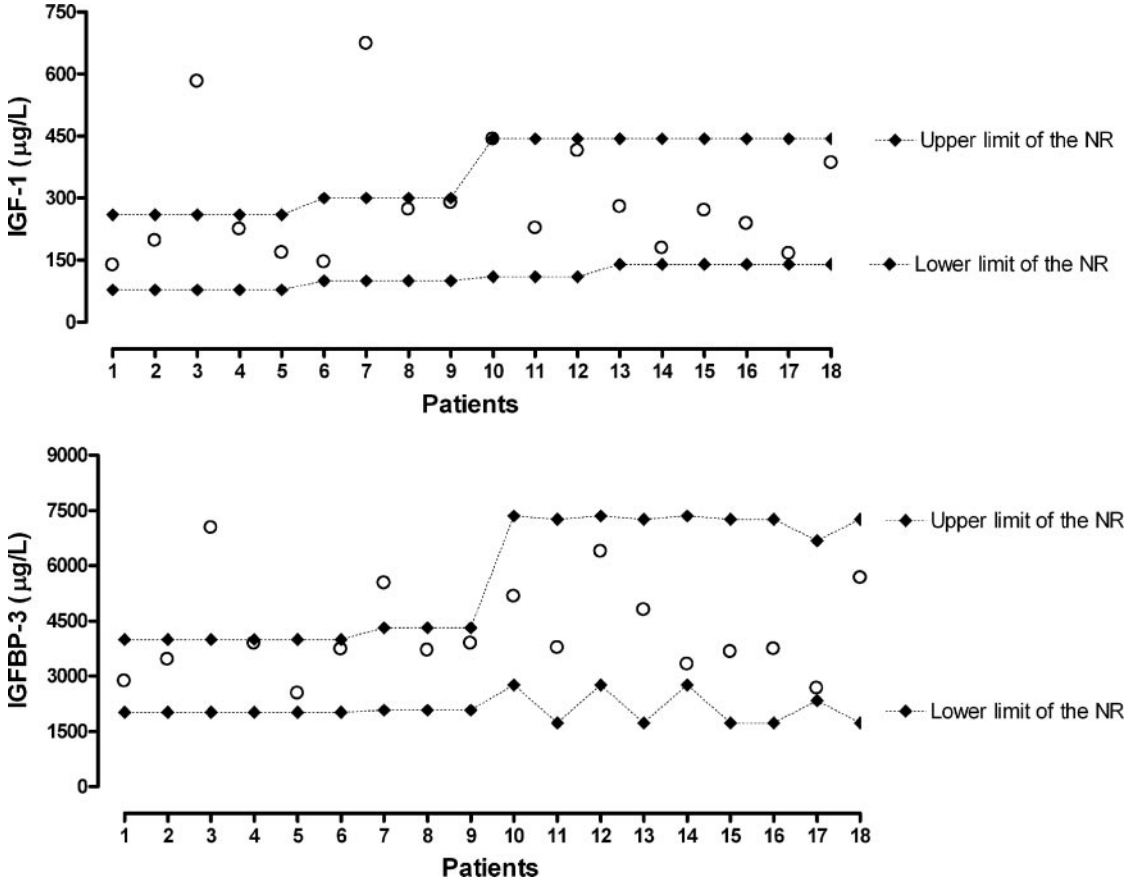

FIG. 2. IGF-I and IGFBP-3 plasma concentrations in patients with FD compared with reference values.

GH/IGF-I axis was similar in patients receiving ERT and in those untreated.

When the five patients with renal failure stages 2–5 were excluded from the analysis, basal TSH and ACTH concentrations were still significantly higher, whereas basal F levels but not TSH-Δ levels were still significantly lower in patients than in control subjects ($P < 0.05$).

Discussion

This study points out that a wide spectrum of latent endocrine dysfunctions occur in patients with FD; they include life-threatening conditions such as adrenal insufficiency and conditions related to severe inability and decreased quality of life such as an early-stage primary hypothyroidism and impaired spermatic count in men as well as a high rate of menses abnormalities, miscarriage, or assisted delivery in women.

The potential involvement of the endocrine system in FD arises from different observations. First, deficiency of lysosomal α-gal and consequent accumulation of the substrate Gb3 represents the pathogenic event leading to the development of heart, kidney, and central nervous system impairment, which depicts the classical clinical picture of the FD (2–5, 7–9). More recently, gastrointestinal disorders have also been described in these patients (6, 7), suggesting that the damage from Gb3 storage is systemic. Thus, in analogy with other organs, endocrine glands may store up Gb3 deposits, thus causing potential impairment in hormonal secretion. The demonstration of α-gal accumulation into endocrine glands, such as thyroid and gonads, strengthens this hypothesis (11, 12).

Second, the physiology of endocrine glands is consistent with a high susceptibility to concentrate unmetabolized substances. This depends on the low cellular proliferation rate of endocrine cells such as thyrocytes, which have been estimated to undergo a total of six to seven mitoses during a life span (19). On the other hand, all endocrine glands are highly vascularized organs; therefore, based on these foregoing endocrine glands, they are all sensible targets of lipid storage in patients with FD.

Third, the recent availability of the recombinant human α-gal enzyme has improved the quality of life of these patients (20, 21). However, complete well-being is seldom achieved despite the removal of organ deposits containing Gb3 (22). This fact might be at least partly related to FD-induced endocrine dysfunctions that could also persist after ERT.

Fourth, FD patients may present symptoms such as asthenia, hypohidrosis, dry skin, and gastrointestinal complaints, which are also common in conditions of endocrine hypofunction such as hypothyroidism and adrenal insufficiency (9, 23, 24).

These observations provided the rationale to investigate the endocrine function in patients with FD. Thus far, extensive studies have not been available to address this objective. Only sporadic case reports have been published where single FD patients were described to harbor gonad, thyroid, or adrenal involvement (11, 12, 25). In one case, functional impairment was

related to lipid storage within the endocrine parenchyma of the thyroid (12), and recently, an occurrence of subclinical primary hypothyroidism in 36.4% of 11 patients with FD has been reported (26). This is in line with the results of the current study where in 20% of the FD population, an early stage of subclinical primary hypothyroidism could be diagnosed in accordance with recent guidelines for the diagnosis of thyroid disease (27, 28). Antithyroid autoimmunity does not seem to represent the pathogenic mechanism for FD-related hypothyroidism because of the negativity of antithyroid autoantibodies both in the current and previous study (26). However, our study highlights that the thyroid US pattern was not completely normal but appeared mildly hypoechoic in most of the patients without an ERT-related difference. In light of the previously demonstrated glycolipid deposits within the Fabry thyroid (12), we can rationally assume that the thyroid is a target for Gb3 storage, which may persist even in patients under ERT because of its low cellular proliferation rate. However, a FD-related stimulation of antithyroid autoimmunity cannot be ruled out in view of the recent finding that a hypoechoic US pattern precedes anti-TPO positivity in the development of autoimmune thyroid disorder (29). The hypothalamus-pituitary regulation of the thyroid axis as well as of the gonad, adrenal, and GH/IGF-I axis turned out to be normal in FD; however, there was a decrease in the pituitary response to the hypothalamus releasing factors that correlates to a decreased renal function.

In one other case report, glycolipid deposits have been detected in the Leydig cells as well as in the epithelial lining of both the ductuli efferentes and the ductus of the epididymis without relevant functional impairment, as indicated by the normal fertility rate of this young Fabry male who died because of disease-related renal insufficiency (11). Here, we report the lack of morphological alterations in the testis and ovaries, by US, together with normal basal and stimulated sexual hormones and gonadotropins, in line with a previous study evaluating basal gonadotropins and sexual steroids in 13 untreated FD patients (30). The only impairment in the gonad hormone regulation was related to the renal insufficiency, which is known to induce a decrease in T levels associated with an increase in LH and PRL levels (31, 32). On the contrary, the most relevant finding resulting from the investigation of gonad function was oligo-asthenozoospermia in men as well as a high rate of menses abnormalities, miscarriage, and assisted delivery in women. This finding occurred in 100% of Fabry males and 89% of females. Thus, a disturbance in fertility seems to be a generalized phenomenon involving the majority of Fabry patients, regardless of gender, age, disease severity and duration, comorbidity with renal and heart failure, and ERT. In a previous study, the reproductive history of FD patients was found to be normal (30). The small number of patients included in the study and the lack of a sensitive procedure such as the seminal fluid analysis, here reported for the first time in FD, may explain this discrepancy. Because Fabry patients are known to suffer from microvessel alterations (33, 34), one may hypothesize that oligo-asthenozoospermia in males and a high prevalence of menses abnormalities, miscarriage, and assisted delivery in females are the consequence of vascular disturbances. In fact, hypoxia-related ischemic damage to testes such as the effect of hydrostatic pressure increases in the venous drainage system, which exceeds the pressures in the testicular arterial microcirculation, is the pathogenic mechanism for the impaired spermatogenesis observed in patients with varicocele (35). Similarly, because angiogenesis occurs in the female reproductive organs as a normal process and because periodic changes in the rates of blood flow are the basis for the normal functioning of specific structures involved in female fertility such as corpus luteum (36), it is possible to hypothesize that FD-induced vascular alterations may result in an impairment of the physiology of corpus luteum or other structures involved in fertility.

On the other hand, because glycolipids have been reported to form deposits in the Fabry gonads (11), it cannot be ruled out that Gb3 storage disrupts the normal physiology of testis and ovary hormone secretion, resulting in a decrease of the paracrine activity of inhibins or other hormones and biological molecules produced by Sertoli and granulosa cells (37). Both glycolipid storage and vascular abnormalities might alter the physiology of pregnancy and delivery and be responsible for adverse fetal outcome among Fabry women. Therefore, pregnancy in Fabry carriers needs to be carefully monitored.

An important point for clinical practice is that patients with FD may be affected by adrenal insufficiency. This is a life-threatening condition characterized by severe and progressive asthenia, hypotension, hypoglycemia, and hyperkalemia. If this condition goes unrecognized for a long time, it can occur suddenly during a stressful condition such as surgery, delivery, or a traumatic event, which could result in acute hypoadrenalism, thus putting the patient's life in severe danger (38). In this study, basal cortisol levels were lower in Fabry patients than in the general population, and one of 10 patients under ERT had a suboptimal cortisol response at the ACTH stimulation test. A previous study, which assessed only basal cortisol levels in 13 FD patients, found the mean cortisol levels to be at the low levels of the normality range (30). These patients had normal adrenal morphology and negative antiadrenal autoantibodies and were not affected by tuberculosis. This finding, together with the decreased levels of cortisol in the Fabry population and the relationship between low cortisol response to stimulating test and low performance score in patients under ERT, might express a latent adrenal dysfunction caused by lipid storage within the gland. A histological study needs to be performed on adrenal samples from FD patients to clarify whether the occurrence of adrenal dysfunction may be related to Gb3 storage within the gland. The possible occurrence of a potentially lethal endocrinological condition in Fabry patients, together with the possibility to recognize this condition easily and safely before it becomes clinically evident, has to be emphasized. In particular, adrenal function needs to be carefully investigated in pregnant women because of the high risk of developing acute adrenal insufficiency during the obstetric outcome (39). The risk is even higher if a condition of subclinical hypothyroidism, which is associated with fetal malformation and reduced fetal survival (40), coexists in the same patient.

Finally, the GH/IGF-I axis does not seem to be altered in FD because none of the Fabry patients showed low levels of IGF-I and inadequate GH response to a stimulation test. Interestingly, the GH response to GHRH plus arginine stimulation was even more exaggerated in patients than controls. This finding has already been reported in one patient with FD (12). Because an IGF-I decrease was not observed and, therefore, not imputable for this impairment, a possible explanation may be a deficiency

in the negative feedback exerted by somatostatin on the GH release that counteracts the GHRH activity. Additional studies will be necessary to address this point.

This study shows that patients with FD present a wide spectrum of latent endocrine dysfunctions, including subclinical adrenal insufficiency, early-stage subclinical primary hypothyroidism, and gonadic abnormalities such as impaired spermatogenesis in males and a high rate of menses abnormalities, miscarriage, or assisted delivery in females. The prevalence of endocrine disturbances is not different whether or not an ERT is started.

An endocrine work-up should be included in the clinical evaluation of a Fabry patient through the use of highly sensitive hormonal and instrumental investigation to reveal subclinical conditions undetectable by standard hormonal assessments. In patients with subclinical endocrine dysfunction, accurate monitoring is necessary, whereas an adequate hormonal therapy has to be started in case of progression toward an overt endocrine syndrome as well as in case of obstetric outcome, surgery, or other psycho-physical stress-related conditions to avoid life-threatening events.

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