Endocrine
DOI 10.1007/s12020-015-0604-z

ORIGINAL ARTICLE

Pituitary function and morphology in Fabry disease

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Received: 5 March 2015 / Accepted: 12 April 2015

Abstract Endocrine abnormalities are known to affect patients with Fabry disease (FD). Pituitary gland theoretically represents an ideal target for FD because of high vascularization and low proliferation rate. We explored pituitary morphology and function in a cohort of FD patients through a prospectic, monocentric study at an Academic Tertiary Center. The study population included 28 FD patients and 42 sex and age-matched normal subjects. The protocol included a contrast enhancement pituitary MRI, the assessment of pituitary hormones, anti-pituitary, and anti-hypothalamus antibodies. At pituitary MRI, an empty sella was found in 11 (39 %) FD patients, and in 2 (5 %) controls ($p < 0.001$). Pituitary volume was significantly smaller in FD than in controls ($p < 0.001$). Determinants of pituitary volume were age and alpha-galactosidase enzyme activity. Both parameters resulted independently correlated at multivariate analysis. Pituitary function was substantially preserved in FD patients. Empty sella is a common finding in patients with FD. The major prevalence in the elderly supports the hypothesis of a progressive pituitary shrinkage overtime. Pituitary function seems not to be impaired in FD. An endocrine workup with pituitary hormone assessment should be periodically performed in FD patients, who are already at risk of cardiovascular complications.

Keywords Fabry disease · Pituitary · Diencephalic MRI · Empty sella

Background

Fabry–Anderson disease (FD, MIM #301500) is a multisystemic disorder mainly affecting heart, kidney, central nervous system, gastrointestinal, and endocrine systems [1–3]. Pathogenesis is related to alpha-galactosidase deficiency that leads to intralysosomial glycolipid accumulation within target organs. These deposits often determine morphological changes because of architectural disarrangement with subsequent functional impairment. Endocrine system involvement seems to be specifically dependent on the basis of relatively high vascularization coupled to low proliferation rate [4] Glycolipid accumulation has been demonstrated within the thyroid and gonadal tissues [5, 6]. Pituitary gland represents an ideal target for FD, because of the complex vascular architecture and the abundant blood flow rate. Our aim was to evaluate pituitary morphology and function in FD patients.

Electronic supplementary material The online version of this article (doi:10.1007/s12020-015-0604-z) contains supplementary material, which is available to authorized users.

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Published online: 21 April 2015

Materials and methods

Patients

Twenty-eight FD patients and 42 healthy controls were prospectively enrolled in this study. All the participants were adult, gave a written informed consent, in keeping with Italian Bioethics Law and the Declaration of Helsinki, and after approval of Federico II Hospital Ethics Committee. Main population characteristics are summarized in Table 1.

Diagnosis of FD was confirmed by low levels of leukocyte-derived alpha-galactosidase activity (normal subjects, 8–19 nmol $h^{-1} \times$ mg). Alpha-galactosidase (*GLA*) gene mutations were analyzed by Sangers' sequencing in all patients.

None of the control subjects suffered from or had been previously affected by endocrine or reproductive diseases, and none of them were treated with hormones or drugs known to affect endocrine function. By contrast, six FD patients received thyroxine for underlying thyroidal disorder, and two patients were treated with glucocorticoids at the time of visit (see Table 1).

At the time of the study, 21 patients with FD received enzyme replacement therapy in addition to supportive management: seven were administered agalsidase alfa (Replagal; Shire Human Genetic Therapies AB, Danderyd, Sweden), and 14 agalsidase beta (Fabrazyme; Genzyme Corporation, Cambridge, MA), according to current management protocols [7].

MRI

All patients and controls underwent diencephalic MRI. MRI examination was performed with a 1.5-Tesla system (excite HD; General Electric System). Sections were acquired on FSE T1-weighted on the sagittal and coronal plane (TR 550 ms; TE 15 ms; NEX: 5.00; FOV: 17; slice thickness: 2.5 mm), and FSE T2 on coronal plane (TR 4400 ms; TE 120 ms; NEX: 5.00; FOV: 17; slice thickness: 2.5 mm).

After administration of the contrast media (gadoteric acid 27,932 g endovenous solution) a dynamic acquisition 2D on coronal plane (TR 425 ms; TE 20 ms; NEX: 1.00; FOV: 20; slice thickness: 2.5 mm) was performed. A high-resolution volumetric T1-weighted SPGR was taken on coronal and sagittal plane (TR 8.7 ms; TE min1.9–max2.11 ms; NEX:3.00; FOV:17; flip angle:15, slice thickness: 1 mm). Pituitary gland surface was measured on T1-sagittal and coronal planes. Pituitary volume resulted from reconstitution of pituitary surfaces in all planes, and was calculated by segmentation by means of a dedicated computed software (Osirix method). The normalization for cranial size was performed by measuring the bi-orbital distance from the coronal plane and the fronto-clinoidal distance from the sagittal plane, as previously described [8]. Pituitary volumes were calculated by two independent readers blinded to the patient group assignment.

Hormone and biochemical analyses

Hormone levels were determined as previously reported [4]. Blood samples were taken between 08.00 and 09.00. Circulating concentrations of TSH, FT4, FT3, FSH, LH, testosterone, 17-beta-estradiol, ACTH, cortisol, and 24 h UFC were assayed using commercially available kits. Serum GH levels were measured by immunoradiometric assay (IRMA), using a commercially available kit (hGH-CTK-IRMA; Sorin, Saluggia, Italy), and plasma IGF-I was measured by IRMA after ethanol extraction using DSL kits (Diagnostic Systems Laboratories, Inc., Webster, TX). IGF-I levels were expressed as absolute values in ng ml^{-1}, as deviations from standard reference for age and gender (z score method) and as percentage above the upper age-adjusted normal limit (ULN). ACTH stimulation test [ACTH (1 mcg Synacthen; Novartis Pharma B.V., Arnhem, The Netherlands)] was administered i.v. and the response of cortisol was assessed in a single blood sample obtained 30 min after ACTH injection. A cutoff value of cortisol greater than 0.55 μmol l^{-1} was used to define normal adrenal function.

Diabetes insipidus was excluded by clinical inquiry and normal urinalysis. No water deprivation test was performed in patients with normal basic weight of urines and with less than 3 l daily liquid intake at clinical investigation.

Anti-pituitary and anti-hypothalamus antibodies were detected by a simple indirect immunofluorescence method on cryostat sections of young baboon hypothalamus as previously described [9].

Biochemical analyses consisted in glucidic and lipidic metabolism on blood samples, urinalysis and renal function by serum creatinine and calculation of creatinine clearance (Cockroft and MDRD methods).

Statistical analyses

Data are reported as mean ± SD if not otherwise indicated. The non-parametric Mann–Whitney U test was used to compare quantitative data between FD patients and controls. The χ^2 test and Fisher's exact test were used to compare categorical data. Differences were considered statistically significant at $p < 0.05$. Univariate and multivariate analyses were conducted by means of SPSS 16.0 package (SPSS, Inc., Chicago, IL).

Table 1 Demographic, clinical, biochemical, and genetic characteristics of patients with Fabry disease (FD) and controls

	FD ($n = 28$)	Controls ($n = 42$)	p
Clinical features			
Age (years)	42 ± 15	41 ± 14	ns
Males (%)	13 (46.4)	21 (50)	ns
Height (cm)	163 ± 8.7	167 ± 9.3	ns
BMI (kg m^{-2})	26.9 ± 7.9	28.1 ± 5.6	ns
Craniometry			
Bi-orbital distance (coronal plane, mm)	88.1 ± 6	88.7 ± 6	ns
Fronto-clinoidal distance (sagittal plane, mm)	55.3 ± 3.9	54.5 ± 3.1	ns
Endocrine functions			
F (nmol l^{-1})[a]	332 ± 111	436 ± 262	ns
F peak under 250 mcg ACTH (nmol l^{-1})[a]	797 ± 178	832 ± 96	ns
ACTH (pg ml^{-1})	15.7 ± 19	11.4 ± 8.3	ns
GH (ng ml^{-1})	0.45 ± 0.3	0.3 ± 0.3	ns
IGF-I (ng ml^{-1})	156 ± 97	193 ± 84	0.02
z-Standard deviation for IGF-I	−1.08 ± 1.5	−0.59 ± 1.3	ns
IGF-I (upper limit of normal, %)	44 ± 26	52.4 ± 24	ns
Prolactin (mIU l^{-1})	210 ± 93	232 ± 194	ns
FSH, premenopausal (mIU ml^{-1})	5.8 ± 3.8	5.7 ± 4	ns
LH, premenopausal (mIU ml^{-1})	8.4 ± 10.3	4.5 ± 3.3	ns
FSH, postmenopausal (mIU ml^{-1})[b]	57 ± 25	57 ± 19	ns
LH, postmenopausal (mIU ml^{-1})[b]	21 ± 8	27 ± 11	ns
Total testosterone (nmol l^{-1})[c]	20.2 ± 5.3	18.6 ± 6.2	ns
Total estradiol (pg ml^{-1})[d]	106 ± 53	91.5 ± 37	ns
TSH (mIU ml^{-1})[e]	1.6 ± 0.7	1.7 ± 1	ns
FT4 (pmol l^{-1})	14.8 ± 3	12 ± 3	ns
FT3 (pmol l^{-1})	4.8 ± 0.7	4.6 ± 1.5	ns
Anti-pituitary autoantibodies, no. of positive (%)	1 (3.6)	1 (2.4)	ns
Anti-hypothalamus autoantibodies, no. of positive (%)	2 (7.1)	1 (2.4)	ns
GLA mutations, *N* (%)			
W162R	3 (10.7)		
G171D	3 (10.7)		
G250D	3 (10.7)		
A288D	1 (3.8)		
R356W	13 (46.4)		
IVS4 + 5G > 7	1 (3.8)		

Data are expressed as mean ± SD or number (percentage)

ns non-significant, *FD* Fabry disease, *F* cortisol

[a] Basal and stimulated cortisol is referred to patients not receiving glucocorticoids ($n = 26$)

[b] FSH and LH postmenopausal levels refer to six FD women and nine controls

[c] Total testosterone was measured in 13 FD men, and in 21 male controls

[d] Total estradiol was assessed in nine FD and in 12 control women

[e] TSH was determined in patients not receiving hormone substituting therapy ($n = 22$ FD patients, all controls)

Results

MR study

Total or partial empty sella was found in 11 (39 %) FD patients, and in 2 (5 %) controls ($p < 0.001$). Pituitary volume was lower in FD patients than in controls ($p < 0.001$, Fig. 1). It was inversely correlated to age (r −0.43, $p = 0.029$, see Supplemental Fig. S1), in FD population but not in healthy controls. When the populations were subdivided in two subclasses according to the median age, pituitary size was significantly lower in FD

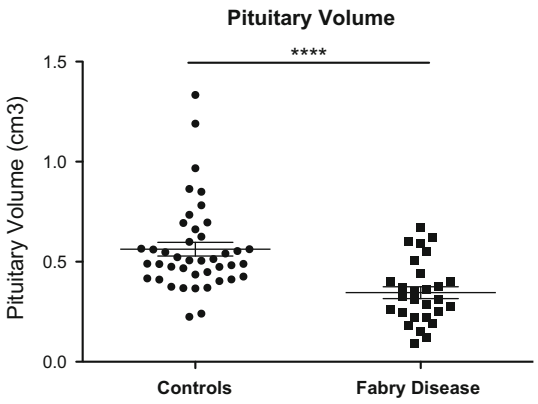

Fig. 1 Pituitary volume in healthy controls and in patients with Fabry disease. Data are reported as individual values and mean ± SEM. ****$p < 0.001$

than in controls in the elder group, with no difference in the younger. In line with these findings, the difference in pituitary volume between FD and controls was significant in only elder people and was abolished when considering subjects under 30.

In the overall population, pituitary size was not different according to gender. However, in the male population, FD had lower pituitary volumes than controls ($p < 0.001$), while no difference was found between FD and control women (Supplemental Fig. S2).

A positive correlation was also found between pituitary volume and GLA enzymatic activity (r 0.42, $p = 0.035$, Supplemental Fig. S3). Pituitary volumes did not differ between patients with and those without enzyme replacement therapy. Accordingly, dosage, duration, and isoform of treatment did not affect pituitary size. Bi-orbital and fronto-clinoidal distance did not differ between FD patients and controls. None of the FD patients or the two healthy controls with empty sella suffered from rhinorrhea, intracranial hypertension, or visual defects. FD neurological picture was largely dominated by peripheral neuropathy and paresthesia.

In three FD patients pituitary morphology was analyzed by comparing historical diencephalic MRI (mean 62 ± 33 months). Despite the different image acquisition protocol, we found in all subjects a slight reduction in pituitary size.

Hormone study

Basal hormone concentrations were not different between FD and controls, except IGF-I that was lower in FD than in controls ($p = 0.023$). z-Standard normalization of IGF-I for age and sex, however, attenuated this difference at non-significant levels ($p = 0.074$), Table 1. Although non-significant, pituitary size tended to be higher in patients with higher levels of TSH ($r = 0.55$, $p = 0.061$), prolactin ($r = 0.45$, $p = 0.074$), basal ($r = 0.23$, $p = 0.335$) and stimulated ($r = 0.25$, $p = 0.441$) cortisol, DHEA-S ($r = 0.35$, $p = 0.269$), and IGF-I ($r = 0.35$, $p = 0.165$). No correlations were found between each of the biochemical parameters and the creatinine clearance and pituitary volume.

No difference in pituitary volume as well as in serum hormone concentrations was found between subjects with and those without anti-pituitary and anti-hypothalamus-targeted autoantibodies. Pituitary volumes did not differ on the basis of individual *GLA* mutations.

Multivariate analysis

Univariate analysis confirmed the correlation between pituitary volume, age, and enzymatic activity. At multivariate analyses, enzymatic activity and age were independently associated with pituitary volume ($t = 2.89$, $p = 0.008$, *and* $t = -2.62$, $p = 0.016$, *respectively).*

Discussion

Endocrine system represents a target for FD in the frame of the multiorgan lipid storage disease. In particular, it seems that systems and organs with a low proliferation rate and a high vascularization are more likely to constitute targets for intra-lysosomal substrate accumulation. Accordingly, we already showed subtle impairment in thyroid and adrenal function in FD [4], but no studies to date focused on the pituitary.

The complex and delicate hypophyseal vessel architecture makes the pituitary gland an ideal target for the FD-related pathogenic events. Blood flow supply to the pituitary ranges from 100 to 170 ml 100 $g^{-1}min^{-1}$ depending on different species and is consistently high especially considering the small tissular mass [10, 11]. In addition, cell proliferation seems globally fainted in adult pituitary. Studies using both PCNA and Ki-67 labeling show that the normal pituitary gland has a very low proliferation rate, with nearly all pituicytes arrested in G0.G1 cell cycle phase [12, 13].

FD lesions within target organs are essentially related to glycosphingolipid accumulation within endothelial cells, pericytes and fibroblasts, smooth muscles of capillaries, venules and arterioles, and more rarely within parenchymas. Disarrangement of vasculature might lead to distortion of anatomic structures, reduction in blood supply or nutrient delivery with ultimate repercussions on organ morphology and function.

In line with this hypothesis, we explored pituitary gland morphology and function in FD population. We clearly

show high prevalence of empty sella and a marked reduction in pituitary gland size in FD compared to a matched normal population. After considering the relatively high variability of sellar morphology, interclinoid and intercarotid distance and the floor asymmetry that are often seen in normal individuals, we have preferred to more precisely measure gland volume through high-resolution MRI and to quantify gland parenchyma. Magnetic resonance allows an accurate evaluation of pituitary volume and structure. This technique results feasible, reliable, and substantially devoid of adverse events, the major limit being solely represented by specific contraindications. In most patients, the reduction in pituitary size reflects the simultaneous intrasellar liquor excess. In the absence of histological samples, it is debatable if the pituitary small size might be related to organ reduction in favor of extra diaphragmatic liquor leakage, or to a congenitally impaired pituitary development.

The former hypothesis seems more consistent, since in FD population pituitary size is inversely related with age and consistently lower in older FD patients than in younger when subdivided according to age. In only three patients, we were able to analyze pituitary morphology over time by analyzing historical diencephalic MRI. Despite the different image acquisition protocol, the slight reduction in pituitary size in all subjects reinforces the hypothesis that a progressive pituitary reduction is observed overtime in FD.

We surprisingly found that, in spite of what is known for myocardial, neuropathic, or renal complications, age is a stronger determinant than gender for pituitary size [1, 14, 15]. This is not explained by gender imbalance in older FD. Despite the X-linked inheritance makes men theoretically more prone to develop severe disease with fatal complications, the impact on disease gravity is essentially related to the detriment of enzymatic activity more than gender itself.

Indeed, a consistent correlation is observed between pituitary volume and GLA activity. Enzyme activity reflects residual capacity to dispose of globotriaosyl-ceramide from lysosomal accumulation and reflects also the inconstant and variable manifestations of disease in FD females. Multivariate analysis revealed that enzyme activity is the strongest predictor of pituitary volume independently from age.

Despite marked morphological changes, pituitary function seems not or only very slightly impaired in adult FD patients. In a previous report, we showed no major pituitary dysfunction in FD [4]. When excluding patients under hormone replacement treatments, levels of TSH, basal and stimulated cortisol did not differ between FD and controls. In this larger sample population, we have not found other clinical or biochemical signs of hypopituitarism. No significant correlation was found between pituitary volume and hormone levels, although a trend was observed for almost all pituitary hormones. IGF-I was lower in FD than in controls only when expressed in absolute values. By contrast, no difference was found after gender and age normalization by either *z*-standard or percentage above the upper limit of normality, two reliable methods for a more correct interpretation of the somatotrope function, as ascertained in GH-deficient as well as in acromegalic patients [16, 17]. Similarly, pituitary size was similar in patients under and those not receiving enzyme recombinant therapy, and was not related to treatment type, regimen, or duration.

It is intriguing to speculate about the nature of pituitary lesions. A progressive involvement of microvasculature and pericytic smooth muscles might lead to blood supply restriction and concomitant reduction of target organ size. Pituitary gland is siege for different granulomatous, infiltrative and storage diseases often affecting either parenchyma or stalk. In granulomatous diseases and in autoimmune hypophysitis, enlargement of pituitary stalk or a suprasellar 'tongue-like' extension is generally reported [18, 19]. In a later phase, however, when inflammatory infiltrates lean toward auto limitation, an empty sella might represent the ultimate vestige of intrasellar rearrangement [20]. In our series, we never found pituitary enlargement, stalk compression, or mass-effect symptoms, independently on age or on stage disease. Additionally, diabetes insipidus has never been observed in our patients with FD.

Although we never found pituitary enlargement, we cannot formally exclude the possibility that a small pituitary might represent a late sign of gland involvement with ultimate shrinkage, similarly to what reported in dynamic intrasellar changes like adenomatous rearrangements, intratumoral necrosis, pharmacological treatments (like somatostatin or cabergoline), or late stage fibrosis as in autoimmune hypophysitis. In this setting, we have not found higher prevalence of anti-pituitary or anti-hypothalamus antibodies, suggesting that autoimmune pathogenesis does not participate in determining FD-related pituitary lesions. This may be considered a parallel to the previously described FD-related hypothyroidism, since the rate of anti-thyroid autoimmunity results not different between patients and controls [21].

As pituitary volumes are smaller in the elderly, a complete pituitary hormonal assessment during senescence is envisaged repeatedly. Until the availability of recombinant replacement therapy, mortality in FD was essentially related to renal failure [1]. With the advent of enzyme replacement therapy, cardiac events are emerging as main causes of FD morbidity and mortality [22]. Despite no pituitary dysfunctions were found in FD patients, a longitudinal evaluation might be needed. In addition, as in other cases of primary empty sella, an endocrine workup should

be periodically suggested. In case of subclinical or overt hormone deficiency occurring later in life, medical intervention with appropriate hormonal therapies might represent an optimal tool to treat conditions which could have repercussions on morbidity and mortality, and ultimately lead to a deterioration of quality of life.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures were in accordance with the ethical standards of the institutional and National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. In particular, an additional informed consent for the conservation and analysis of biological samples and genetic data has been obtained from each participant, in agreement with current Italian and EU Regulations.

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