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Pituitary imaging findings in male patients with hypogonadotrophic hypogonadism

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Abstract
Context Data on pituitary imaging in adult male patients presenting with hypogonadotrophic hypogonadism (HH) and no known pituitary disease are scarce.
Objective To assess the usefulness of pituitary imaging in the evaluation of men presenting with HH after excluding known pituitary disorders and hyperprolactinemia.
Design A historical prospective cohort of males with HH.
Patients Men who presented for endocrine evaluation from 2011 to 2014 with testosterone levels <10.4 nmol/L (300 ng/mL), normal LH and FSH levels and no known pituitary disease.
Results Seventy-five men were included in the analysis. Their mean age and BMI were 53.4 ± 14.8 years and 30.7 ± 5.2 kg/m^2, respectively. Mean total testosterone, LH, and FSH were 6.2 ± 1.7 nmol/L, 3.4 ± 2 and 4.7 ± 3.1 mIU/L, respectively. Prolactin level within the normal range was obtained in all men (mean 161 ± 61, range 41–347 mIU/L). Sixty-two men had pituitary MRI and 13 performed CT. In 61 (81.3 %) men pituitary imaging was normal. Microadenoma was found in 8 (10.7 %), empty sella and thickened pituitary stalk in one patient (1.3 %) each. In other four patients (5.3 %) a small or mildly asymmetric pituitary gland was noted. No correlation was found between testosterone level and the presence of pituitary anomalies.
Conclusions This study suggests that the use of routine hypothalamic-pituitary imaging in the evaluation of IHH, in the absence of clinical characteristics of other hormonal loss or sellar compression symptoms, will not increase the diagnostic yield of sellar structural abnormalities over that reported in the general population.

Keywords Hypogonadotrophic hypogonadism · Imaging · Incidentaloma · Male · Testosterone

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Introduction

Hypogondadotrophic hypogonadism (HH) or secondary hypogonadism in men represents a situation of impaired testosterone secretion due to malfunction at the hypothalamic/pituitary level. Congenital HH usually results from isolated GnRH deficiency. Patients with hypogonadotropic hypogonadism and anosmia have been given the diagnosis of Kallmann's syndrome, and those with normal olfaction have been diagnosed as idiopathic hypogonadotropic hypogonadism (IHH) [1]. Adult-onset HH may result from an acquired form of GnRH deficiency and more commonly, due to pituitary insufficiency because of an adenoma (e.g.

prolactinoma or non-functioning pituitary adenoma), trauma, granulomatous or infiltrative diseases.

Sellar imaging is often recommended when there is a suspicion of a pituitary/hypothalamic pathology contributing to hypogonadism. Though some pituitary abnormalities may have significant health implications, the role of hypothalamic-pituitary imaging to evaluate hypogonadism remains unclear. Whereas some authors have argued that the yield for detecting clinically significant lesions is low, others fear missing a treatable pituitary pathology [2–4].

In the present study, we summarized the results of pituitary imaging in male patients with adult-onset HH. Aiming to identify factors that may help the clinician's decision if to order these studies for hypogonadal men, we analyzed the pooled results of the present study and previously published data.

Patients and methods

The study group consisted of a group of consecutive adult men ≥22 years old with HH who underwent pituitary imaging assessment at the Endocrine Institute at Rabin Medical Center, Israel. We retrospectively evaluated 75 HH male patients who were referred to our department between January 2011 and April 2014. Basal serum levels of FSH, LH, testosterone, prolactin TSH and hemoglobin were assessed in all patients, and those with elevated prolactin levels were excluded. Blood samples for serum testosterone were taken in the fasted, early-mid-morning state. Additional blood tests for cortisol, free T4 and IGF-1 were obtained in the majority of the patients. Hormone levels including testosterone were determined by chemiluminescence method using the automated hormone analyzer Immulite 2000 (testosterone assay-specific reference range 8.4–28.7 nmol/L). A repeatedly total testosterone value of <10.4 nmol/L was used to define men with hypogonadism for this study. As there is no consensus regarding "normal" testosterone level, we used a threshold of <8 nmol/L for further analysis. Patients included in the study had normal olfaction and their LH and FSH levels were ≤10 and ≤14 mIU/L, respectively. Men in whom delayed puberty was suspected at the time of recruitment or those taking medications known to decrease testosterone levels or interfere with the hypothalamic-pituitary axis were excluded from the study. Additional exclusion criteria were clinical suspicion of sellar compression and biochemical evidence for other pituitary hormone dysfunction. On imaging studies, special attention was directed to the hypothalamic-pituitary region regarding normal size, configuration, intensity and pattern of enhancement. CT and MRI results were based on written reports in the medical records. Imaging interpretation was done by experts in neuroimaging. The study was approved by our local institutional Ethics Review Board.

Table 1 Clinical and laboratory variables in 75 men with HH

	Mean ± SD	Range
Age (years)	53.4 ± 14.8	22–76
BMI (kg/m^2)	30.7 ± 5.2	19–44
Total testosterone (nmol/L)	6.2 ± 1.7	2–10
LH (mIU/L)	3.4 ± 2	1–10
FSH (mIU/L)	4.7 ± 3.1	1–14
Prolactin (mIU/L)	161 ± 61	41–347
TSH (mIU/L)	2.3 ± 1.5	1–8
FT4 (pmol/L)	13.6 ± 2.8	10.6–20
CORTISOL (nmol/L) n = 45	362 ± 98	232–548
IGF-1 N = 23 (nmol/L)	22.4 ± 8.4	7.2–40
Hemoglobin (g/dL)	13.7 ± 1.3	11–16.8

Table 2 Patients' presenting complaint/finding

Complaint/finding	No. (%)
Erectile dysfunction	52 (69.3)
Infertility	3 (4)
Osteopenia/ osteoporosis	7 (9.3)
Gynecomastia	3 (4)
Weakness	2 (2.7)
Not specified	8 (10.7)

Statistical analysis

Statistical calculations were performed with the SPSS 20.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± SEM. Student's t test and analysis of variance were used to assess the statistical differences between groups, where $p < 0.05$ considered significant.

Results

The study group included 75 men. Study group characteristics and mean hormone values are shown in Table 1. Mean patient age was 53.4 ± 14.8 years (range 22–76 years). Mean total testosterone level was 6.2 nmol/L with a range of 2–10 nmol/L. In eight patients (10.7 %) testosterone level was >8 nmol/L and in four patients (5.8 %) it was measured <4 nmnol/L.

Prolactin level was within the normal range in all men (mean 161 ± 61, range 41–347 mIU/L). Additional blood tests for hormones levels were within the normal range with the exception of three patients having mild subclinical

Table 3 Patients characteristics of 75 men with HH based on testosterone level

Testosterone level quartiles (Testosterone level, nmol/L)					
	1 (1.5–5.4) n = 20	2 (5.4–6.2) n = 17	3 (6.2–7.4) n = 20	4 (7.4–10) n = 18	*p* value
Age (years)	53.2 ± 13.3	50.8 ± 17	58.4 ± 13.5	54 ± 14.1	NS
BMI (kg/m^2)	31.6 ± 6.5	32.9 ± 5.5	29.4 ± 3.5	29.6 ± 3.5	NS
Imaging findings					
No findings	16	13	16	15	NS
Microadenoma	2	3	2	2	
Other	2	1	2	1	

primary hypothyroidism (TSH levels of 5.6–8 mIU/L with normal FT4 level). Both mean and median hemoglobin level (13.7, and 13.9 g/dL, respectively) were within the normal laboratory reference range (13.5–17.5 g/dL). However, in 17 men (22.7 %) hemoglobin level was measured <13 g/dL.

Most patients (52 patients, 69.3 %) underwent gonadal axis evaluation due to erectile dysfunction (ED) and/or decreased libido. A variety of other presenting complaints/findings led to the diagnosis of HH in the remaining 23 patients. Data are shown in Table 2.

Sixty-two men had pituitary MRI and 13 performed CT. Imaging findings are presented in Table 3. In 61 (81.3 %) men pituitary imaging was normal. The most common abnormal finding was pituitary microadenoma detected in 8 (10.7 %) patients. Small or mildly asymmetric pituitary gland was found in 4 (5.3 %) patients whereas empty sella and thickened stalk in one patient (1.3 %), each. None of the patients had evidence of a pituitary macroadenoma or hypothalamic lesion. Analyzing pituitary imaging findings in the 67 patients with testosterone level <8 nmol/L revealed pituitary microadenoma in 8 (11.9 %) and other abnormal findings in five patients (7.5 %). No significant difference in any clinical or biochemical characteristic, including testosterone level, was found between the group of patients with normal pituitary, patients with pituitary adenoma and patients with other sellar abnormalities. Similarly, no difference was found between patients with normal pituitary and patients with any pituitary abnormality.

Dividing patients to quartiles according to testosterone level did not reveal any significant difference between the groups in clinical or biochemical variables including the risk of imaging abnormality. Data are presented it Table 3. We further evaluated the possibility of a threshold in testosterone level below which the risk of hypothalamic or pituitary imaging abnormalities may increase, but could not identify such a threshold. Moreover, excluding the eight patients with testosterone level >8 nmol/L from the analysis did not yield any change in these results.

The clinical and laboratory characteristics and imaging results of patients presenting with ED and those with other complaints are shown in Fig. 1. Patients presenting with ED were significantly older compared to the others, but all other variables including pituitary abnormalities did not differ between the two subgroups of patients.

Four of the eight patients (50 %) in which pituitary microadenoma has been detected, performed a repeated sellar MRI 7–14 months after the one included in the study with no evidence of growth or any other change in the pituitary findings. No one of the six patients with other sellar abnormality has done a repeated imaging study.

Discussion

Most pituitary adenomas are silent and undiagnosed unless they cause clinical symptoms associated with hormonal hypo/hypersecretion or sellar compression [5]. The present study in men presenting with late-onset HH (testosterone level <10.4 nmol/L) revealed pituitary microadenomas in 10.7 % and other minor pituitary abnormalities in additional 7.9 % of the study cohort. Using a lower threshold of testosterone level <8 nmol/L revealed 11.9 and 7.5 % of the above mentioned findings, respectively. These results are not different from the prevalence reported in the general population [6–12]. In combined autopsy data, the average frequency of pituitary adenomas in subjects not suspected to have pituitary disease while alive was 10.6 % with a range of 1.5–27 % [7]. The tumors were distributed equally across genders, and nearly all these incidentalomas were microadenomas [7]. In adults who underwent cranial imaging studies for reasons other than pituitary disease, pituitary microincidentalomas were detected by CT in 4–20 % [8–10] and by MRI in 10–38 % [6] of patients. In contrast to the high prevalence of pituitary microincidentalomas, macroadenomas are rarely found, only in 0.2 and 0.16 % of patients studied by CT scans and MRI, respectively [11, 12]. In our study, none of the patients had a

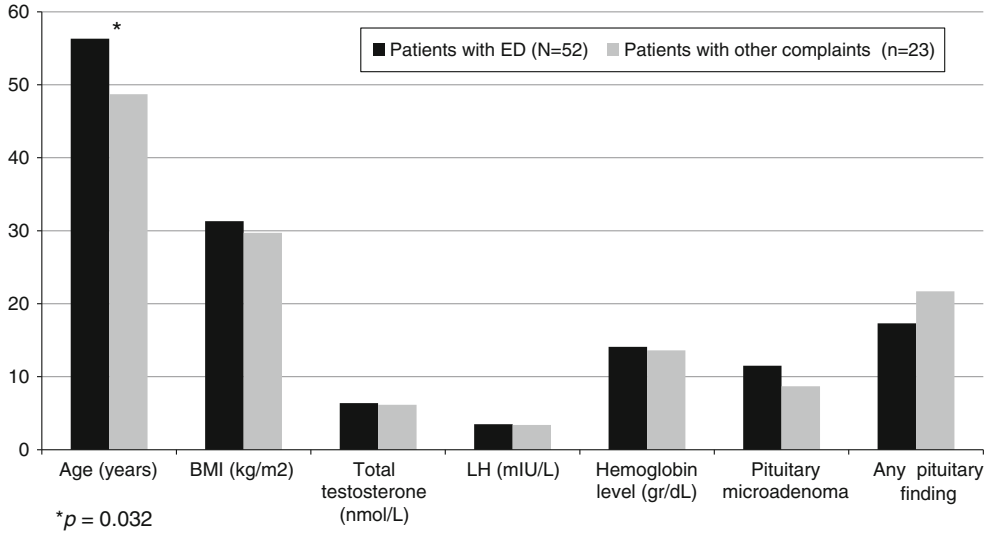

Fig. 1 Clinical and laboratory characteristics (mean) and imaging results (%) in patients presenting with ED compared with patients with other presenting complaints

pituitary macroadenoma. Moreover, neither of the patients had visual disturbances or additional pituitary hormonal abnormalities. Thus, the clinical significance of the pituitary lesions depicted was probably neglectable. The enlargement rate of pituitary microadenomas is low, being reported in 17 of 160 patients (10.6 %) followed from 2.3 to 7 years [13–20]. In a meta-analysis performed, only 1.7 % of microincidentalomas enlarged per year [21]. Importantly, none of the patients with these microincidentalomas developed new visual dysfunction that would have required surgery [21]. Furthermore, routine follow-up endocrine testing is not recommended for microincidentalomas whose clinical picture does not change because the risk of developing new hypopituitarism is extremely low [5]. Most of the patients in the current study underwent testosterone measurement due to erectile dysfunction (ED). Sexual dysfunction is the most specific and common symptom in men with late-onset hypogonadism [22]. The prevalence of ED rises rapidly with age and is a frequent complaint in the clinical practice [23]. Although the etiology of ED is multifactorial, identified endocrinopathies lead to acquired hypogonadism in 10–20 % of men with ED [24]. However, most human studies investigating the association between testosterone level and ED in men are cross sectional and show divergent results. The European Male Ageing Study (EMAS) found that 30 % of European men experienced ED and two-thirds of them were eugonadal [22]. The prevalence of hypogonadism ranges between 23 and 36 % of ED subjects [25] and varies according to the cut-off value adopted for the diagnosis, 7, 23, 33, or 47 % for testosterone levels of <7, 10.4, 12, or 14 nmol/L, respectively [26]. These figures, however, are simple associations that do not imply any causal association between the two conditions [27]. Total and, to a greater extent, free testosterone serum concentration decline at a rate of 1–2 % a year beginning after the age of 30. This decline remains significant in cross-sectional and longitudinal studies that control for potentially confounding variables including overall health, obesity and smoking [28, 29]. It is estimated that approximately 20–30 % of healthy asymptomatic men (50–70 years) have levels of testosterone below the lower limit of normal for younger men (20–40 years) [30]. In the present study, low testosterone level was defined as <10.4 nmol/L, and the mean testosterone level detected was 6.2 nmol/L.

In our cohort, mean hemoglobin levels were within the lower portion of normal range for men (13.7 ± 1.3 g/dL). Older men with hypogonadism frequently have anemia [31]. We have previously shown that in men with macroprolactinomas, anemia is common and is correlated with hypogonadism and tumor size. Importantly, hemoglobin level improved following treatment that normalized PRL and increased testosterone [32]. Thus, hemoglobin level may serve as a biochemical surrogate for low testosterone level. The marginally-low mean hemoglobin level in our patients and the absence of anemia in most of them, probably reflect the relatively mild decrease in patients' testosterone level, a level which may be common in healthy asymptomatic men in this age group as discussed above [30].

Our study population was obese, with a mean body mass index of 30.7 kg/m^2. Obesity by itself contributes to a wide range of endocrine disturbances including reduced testosterone levels. Indeed, among ED patients, obese men present with lower testosterone levels compared to those observed in lean men. One of the most plausible

Table 4 Pooled data on pituitary imaging findings in men with adult-onset HH

References	No. of patients	Age (years) Mean ± SD	Testosterone (nmol/L) Mean ± SD	Pituitary imaging findings; No. (%)			
				None	Micro-adenoma	Macro-adenoma	Other
Cytron et al. [2]	164	61.2 ± 8.9	6.2 ± 1.6	137 (83.5)	10 (6)	4 (2.4)	13 (7.9)
Bunch et al. [3]	29	64.6 ± 10.8	6.4 ± 2.8	25 (86)	1 (3.3)	2 (6.7)	1 (3)
Rhoden et al. [4]*	45	44.9 ± 12.8	9.2 ± 4.5	36 (80)	1 (2.2)	0	8 (17.8)
Current study	75	53.4 ± 14.8	6.2 ± 1.7	61 (81.3)	8 (10.7)	0	6 (7.9)
All	313	57.3	6.6	255 (81.5)	20 (6.4)	6 (1.9)	28 (8.9)

* Data on pituitary imaging after excluding six men with hyperprolactinemia

mechanisms by which obesity contributes to testosterone decline is the adipose tissue dependent aromatization of testosterone to estradiol [33]. Additionally, obesity is an established risk factor for a hypothalamic–pituitary dysfunction and decreased LH pulse amplitude [34].

The cost-effectiveness of pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor is unknown. One survey of men with ED revealed a low prevalence of hypothalamic-pituitary abnormalities [35]. It has been suggested that the diagnostic yield of pituitary imaging to exclude pituitary or hypothalamic tumor can be improved by performing this procedure in men with serum testosterone below 150 ng/dL (5.2 nmol/L), hypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect (headache, visual dysfunction) [2, 36]. Only few previous studies evaluated the yield of pituitary imaging in the context of adult male HH. Citron et al. [2] evaluated 164 men, 27–79 year-old, whose chief complaint was ED and who repeatedly had testosterone level below 230 ng/dL (8 nmol/L). With CT or MRI of the sella they detected pituitary adenomas in 14 patients (8.4 %) and other abnormalities, mostly empty sella, in additional 13 men (7.9 %) (Table 4). Among them, pituitary lesions >5 mm or any hypothalamic lesion were found in 11 men only (6.7 %). The risk for detecting significant pituitary abnormality increased markedly when serum testosterone level was prominently decreased (<104 ng/dL, 3.6 nmol/L) [2]. Bunch et al. [3] evaluated pituitary MRI findings in 29 elderly men with central hypogonadism presenting with ED and testosterone level <300 ng/dL (10.4 nmol/L). Three (10 %) of these patients had pituitary adenoma and one man was diagnosed with empty sella. Similarly, Rhoden et al. [4] evaluated pituitary MRI findings in 51 men with ED or infertility and testosterone level <300 ng/dL (10.4 nmol/L). After excluding six men with hyperprolactinemia, small pituitary gland (the partially empty sella) was noted in 8 (17.8 %) cases and a microadenoma was depicted in another patient [4]. Table 4 summarizes the results of sellar imaging in these studies and in our current report. Normal pituitary was found in the vast majority of patients in all four studies. Pituitary abnormalities were demonstrated in 18.5 % of patients altogether, most were non-clinically significant findings, whereas only six macroadenomas (1.9 %) were detected.

In summary, we presented sellar imaging findings in a relatively large and homogenous series of men with late-onset HH. The results of this study support the existing, albeit limited, literature, showing a small risk of finding a clinically significant lesion in a hypogonadal man without hyperprolactinemia, clinical characteristics of other hormonal deficits or suspected sellar compression. The presence of HH in such a context is not associated with an increased risk of structural hypothalamic–pituitary abnormalities over that in the general population. Nevertheless, the decision of whether to obtain pituitary imaging or not still relies on individual circumstances and the treating physician judgment.

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

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