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Hypogonadotropic hypogonadism in non-functioning pituitary adenomas: impact of intervention

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Hypogonadotropic hypogonadism in non-functioning pituitary adenomas: impact of intervention

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Hypogonadotropic hypogonadism in non-functioning pituitary adenomas: impact of intervention

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Abstract

Purpose: Determine the prevalence of hypogonadotropic hypogonadism (HH) among patients with non-functioning pituitary adenoma (NFPA) and the impact of surgical intervention on it. Determine the prevalence of erectile dysfunction (ED) on male patients with NFPA, its association with HH and the response to testosterone replacement therapy (TRT).

Methods: Retrospective evaluation of gonadal function in 109 NFPA patients (45 males), with a mean age of 51.8 years, diagnosed on the last 10 years. ED questionnaire applied to 34 male patients.

Results: Male patients with NFPA were significantly older (males 58.1±15.8 vs 47.4±16.94; p=0.001). Most patients had macroadenomas (67%, p=0.001) and only a minority is incidentaloma (19%, p<0.001). Prevalence of HH was 40% (60% on males, 25% on females; p<0.001). Surgery was performed in 54% of all patients (71% of males, 42% of females; p=0.03). After intervention, 14% worsened, 69% maintained previous function and 17% improved. On the questionnaire, 76% reported having ED, 54% of which had HH and 21% were under TRT. Of the patients under TRT, 79% still have ED. Median age of patients with ED was significantly higher [with ED 65 vs without 49 years; p=0.012). There was no BMI difference between patients with or without TRT (28.0 vs 27.4).

Conclusions: Prevalence of NFPA was higher on older patients (71% older than 40 years). Males were older, had more HH and surgery. There was no significant improvement of pituitary function with surgery (17%) and 13% became iatrogenic HH. TRT had a low efficacy to improve ED in these patients.

Key words

Hypogonadotropic hypogonadism – non-functioning – pituitary adenoma – surgery - erectile dysfunction - testosterone replacement therapy

Introduction:

Approximately 14% of all intracranial tumors are pituitary adenomas [1]. These benign tumors are classically divided according to their secreting pattern: functioning and non-functioning adenomas. Functioning adenomas secrete excessive amounts of pituitary hormones, leading to symptoms associated to that hypersecretion. On the other hand, non-functioning adenomas (NFPA) do not secrete biologically active hormones, therefore having a silent evolution [2,3]. The subtlety of the clinical features may delay the diagnosis [3]. If not found incidentally, they most often produce symptoms associated with their growth, compressing adjacent anatomical structures, such as the optic pathways and oculomotor nerves, producing visual deficits, stretching the diaphragma sellae and the sellar dura, resulting in headaches, or compressing the pituitary itself [4,5]. Due to compression of pituitary tissue, pituitary stalk and its vascular supply, partial or total hypopituitarism may occur, resulting in deficit of production of some or all pituitary hormones [6]. The most common pituitary deficit in these patients is hypogonadism [7]. Hypogonadotropic hypogonadism (HH) is due to reduced levels of pituitary gonadotropins (Follicle-Stimulating-Hormone (FSH) and Luteinizing-Hormone (LH)), either from congenital or acquired hypothalamic or pituitary defects, that lead insufficient gonadal function [8]. Female patients with HH may present with menstrual cycle abnormalities, infertility or decreased libido [9]. Male patients with HH manifest impaired testicular function with problems on sperm production and testosterone secretion, resulting in infertility, weight gain, diminished physical strength, behavior changes, decreased libido or erectile dysfunction (ED) (inability to attain and or maintain penile erection sufficient for satisfactory sexual performance [10]) [11,12]. Surgery and radiotherapy are treatment options used to remove or reduce the tumor when the expansion of the mass impairs patients' quality of life. Neurological symptoms, such as visual impairment or headache, and hypopituitarism may improve or disappear with these treatment options. However, some patients will experience worsening of symptoms due to the intervention [3]. In patients that maintain HH after surgical treatment, testosterone replacement therapy (TRT) plays major role in symptomatic treatment [13]. As for weight gain, physical strength, libido and ED, they may improve with TRT [12]. Accurate and systematic detection of these situations on male patients with HH is vital to introduce proper treatment that will improve quality of life.

The aims of this study were: to determine the prevalence of HH among patients with NFPA and the post-surgery outcome on pituitary gonadotropins secretion (PGS); to recognize factors of better or worse outcome, to determine if HH is associated with higher BMI and if there is a decrease in BMI with the improvement of pituitary function; to determine the prevalence of ED on the male patients with NFPA, its association with HH and the impact of TRT.

Patients and Methods:

Patients

All patients with NFPA followed in our Department between 2003 and December 2013 were retrospectively assessed. NFPA was defined by the absence of signs, symptoms or laboratorial findings of hormone hypersecretion of TSH, cortisol, GH or PRL. Although some patients showed small increases of prolactin due to pituitary stalk compression, they were also comprised. Patients with incidentally discovered sellar lesions were also included.

A total of 112 patients (47 males and 65 females) with NFPA were selected, 3 of which (2 males and 1 female) were excluded due to absence of pre-surgical data.

The Body Mass Index (BMI) was determined before and after surgery and compared. Of the 109 patients, only 87 had BMI evaluation before surgery due to lack of either weight or height data. Of the 59 patients subjected to surgery only 52 had BMI evaluation.

Methods

Information of the patients' gender, age, weight, height, intervention (surgery and/or radiotherapy) and hormonal analytical data (FSH, LH, total testosterone, free testosterone, oestradiol and responses to GnRH test) were recorded. Tumors were divided according to size in microadenomas (<10mm) and macroadenomas (>10mm).

Patients were first classified in 2 groups: normal PGS (normal) and hypogonadotropic hypogonadism (HH). Females in menopause with hypergonadotropic hypogonadism were classified as "normal", since this is the physiologic response and translates a functionally normal pituitary. The hormone levels and weight recorded were from the last evaluation before surgery and the first evaluation within 3 to 9 months after surgery for the operated patients. The recorded levels for the patients that did not undergo surgery were from the last known evaluation. The vast majority of patients were tested by our lab. Patients evaluated until 2006 had the determination of FSH, LH, oestradiol and total testosterone made by chemiluminescence on Abbott – Architect. After 2006 they were determined using electrochemiluminescence on Cobas e411. On both periods free testosterone was measured by radioimmunoassay. Used reference ranges were the ones provided by the respective laboratory at the given moment, for the patient's gender and age.

In male patients HH was defined if:

- Testosterone was low and: if both FSH and LH were low; if LH was low; if FSH and LH were within the normal reference range, since the gonadotropins were inappropriately normal (the normal response to low levels of testosterone would be to be elevated) [7,14]
- Testosterone was normal but the patient was under TRT: if both FSH and LH were low; if LH was low [15]

In female patients HH was defined if:

- In pre-menopause: oestradiol was low and both FSH and LH were low; if FSH and LH were inappropriately normal (as explained for males)
- In post-menopause oestradiol is low by definition (hypergonadotropic hypogonadism). To be classified as HH both FSH and LH had to be 20% below the inferior limit of the reference range for that group (higher than pre-menopause females)

If patients were included in the HH group, response to synthetic Gonadotropin-Releasing-Hormone (GnRH) was analyzed. The GnRH test was done by administering 100 μg of synthetic GnRH and drawing blood for FSH and LH values at 0, 15, 30, 60, 90 and 120 minutes. A positive response to the GnRH was established if FSH raised 1.5 times the basal value or if LH raised 2 times the basal value, in females, 3 times the basal value, in males [16,17]. If there was a response to the stimulation with GnRH, the cause of the HH was deficient hypothalamic hormone secretion and the pituitary remained functional. A non-response to GnRH stimulus translated a non-functioning pituitary, with or without hypothalamic damage. Of the 43 patients with HH before intervention (27 males and 16 females), only 30 (21 males and 9 females) had data from GnRH stimulation. Of the 32 patients with HH after surgery (20 males and 12 females) only 17 (9 males and 8 females) had data from GnRH stimulation.

The Androgen Deficiency in Aging Males (ADAM) questionnaire, validated to assess ED was applied to all living male patients. The questionnaire was self-applied, sent by post accompanied with the informed consent. An extra envelope was added for the patients to send the signed informed consent and the questionnaire to the Hospital without cost. The questionnaire is showed on Table 11.

A positive result on the questionnaire was defined as an affirmative answer (''yes'') to questions 1 or 7 or any 3 other questions [18].

An extra 2 questions were added for data gathering purposes: "11 – Do you undertake testosterone replacement therapy at the moment?" and "12 – What is your height?".

From the 45 males, 6 were deceased, so the questionnaire was sent to 39 males. From those 39, 2 didn't have a valid address or contact number and 3 didn't answer from health conditions such as cerebral stroke and mental incapability. A total of 34 valid questionnaires were received.

The study protocol was approved by the Hospital Ethical Committee and all patients provided written informed consent.

Statistical methods

Descriptive characteristics of the study population were tabulated as mean (SD) or median (minimum and maximum) according to the variables distribution, or proportions, as applicable. Student's t-test or Mann-Whitney U test were computed to compare the distributions of continuous variables between two independent samples. Differences of proportions among groups of patients were calculated with chi-square test or Fisher test as appropriate. The significance level was set at 5%.

Results

Of the 109 patients, 62 (33 males and 29 females) underwent one or more surgeries, with or without radiotherapy, but 3 (1 male and 2 females) lacked follow-up data, one of which due to the patient's death. The mean age at diagnosis was 51.8 years ± 17.26 (ranging from 18 to 91).
The population of NFPA was formed by 64 (59%) females and 45 (41%) males. Most tumors were macroadenomas, 73 (67%) vs 36 (33%) microadenomas (p=0.001). Of the males, 40 (88%) had macroadenomas and 5 (12%) had microadenomas (p<0.001). Of the females, 33 (52%) had macroadenomas and 31 (48%) had microadenomas. Of the patients with macroadenomas 40 (55%) were males and 33 (45%) were females, but there is a different proportion of macroadenomas on males and females (88% vs 55%) (p<0.001). The median age of patients with microadenoma was 39 years (18-84), and the median age for macroadenomas was 59 years (24-91) (p<0.001). Only a minority was incidentally diagnosed, a total of 21 (19%) (p<0.001), of the females 12 (20%) and of the males 8 (18%). The median age of patients incidentally discovered was 58 years (34-84), and the median age for patients diagnosed when investigating symptoms related to the pituitary adenoma was 49 years (18-91). Of the incidentalomas, 11 (52%) were macroadenomas and 10 (48%) were microadenomas. Of the patients diagnosed when investigating symptoms (88 patients, 81%), 62 (70%) were macroadenomas and 26 (30%) were microadenomas.

Hormonal analysis:

On the pre-intervention evaluation, of the 109 patients, 66 (60%) were normal and 43 (40%) were HH. Of the 45 males, 18 (40%) were normal and 27 (60%) had HH. Of the 64 females, 48 (75%) were normal and 16 (25%) had HH. From the female normal group 32 (66%) were pre-menopause and 16 (33%) were post-menopause. Males underwent more surgery than females (60 vs 25%) (p<0.001). Of the macroadenomas, 39 (47%) had HH and 34 (53%) didn't, and of the microadenomas, 4 (11%) had HH and 32 (89%) didn't (p<0.001). Of the non-incidentalomas, 39 (44%) were HH and 49 (56%) weren't, and of the incidentalomas, 4 (19%) were HH and 17 (81%) weren't (p=0.03). There was a positive response to the GnRH test in 17 of the 30 patients (57%). Of the males 10 (47%) responded and of the females 7 (78%). There was difference between male and female age at diagnosis (58.1 vs 47.4) (p=0.001). Males were significantly older, more hypogonadal, more surgically or radiotherapy treated.
All patients submitted to radiotherapy had previously undergone surgery. Median of age of patients that were submitted to surgery was 56 years (24-82) and median age for patients that didn't have surgery was 45.5 years (18-91). Of the males, 32 (71%) had surgery, 9 (50%) from the normal group and 23 (85%) from the HH group. Of the females, 27 (42%) had surgery, 16 (33%) from the normal group and 11 (69%) from the HH group. From the normal group 9 (56%) were pre-menopause and 7 (44%) were post-menopause. There was a difference between the number of males that underwent surgery and the females (71% of males, 42% of females) (p=0.03). Which translates that of the 59 patients that had surgery 32 (54%) were males and 27 (46%) were females.

Table 1: Clinical characteristics of the sample

	Males (n=45)	**Females** (n=64)	**Total** (n=109)
Mean age in years mean ± STD (range)	58.1 ±15.86* (20-91)	47.4±16.94* (18-80)	51.8±17.26 (18-91)
Mean BMI mean ± STD	27.5± 3.86	28.2±5.71	27.9 ± 5.00
Hypogonadism n (%)	27 (60) *	16 (25) *	43 (40)
Surgery n (%)	32 (71) *	27 (42) *	59 (54)
Radiotherapy n (%)	7 (16)	0	7 (6)
Macroadenomas n (%)	40 (88) *	33 (52)	73 (67) *
Incidentalomas n (%)	8 (18)	13 (20)	21 (19) *

* marks statistically significant values

Of the patients that had surgery, 57 (97%) were macroadenomas and 2 (3%) were microadenomas ($p<0.001$). Of the macroadenomas 57 (78%) had surgery and of the microadenomas 2 (6%) had surgery ($p=0.001$). Of the patients that had surgery, 4 (7%) were incidentally discovered and 55 (93%) were diagnosed based on symptoms ($p<0.001$). Of the patients that were incidentally discovered only 4 (19%) had surgery ($p<0.001$) and of the non-incidentalomas 55 (63%) had surgery ($p<0.001$). This information is show on table 2.

Table 2: Tumor size and diagnosis relation with surgery

	Surgery (n=59) n (%)	**Median age in years** median (range)
Macroadenomas (n=73)	57 (78)*	59 (24-91)*
Microadenomas (n=36)	2 (6)*	39 (18-84)*
Incidentalomas (n=21)	4 (19)*	58 (34-84)
Non-incidentalomas (n=88)	55 (63)*	49 (18-91)

* marks statistically significant values

Of the males a total of 3 (9%) worsened (patients with previous normal pituitary function that became HH after surgery), 6 (19%) improved (patients with previous HH, gained normal pituitary function after surgery) and 23 (72%) maintained the previous pituitary gonadotropic function (either normal or HH).
Of the normal females who were in pre-menopause, 7 (77%) maintained normal function and 2 (23%) worsened becoming HH. Of the normal females who were post-menopause, 4 (57%) maintained normal function and 3 (43%) worsened. In total, of the normal females intervened, 11 (69%) maintained normal function and 5 (31%) worsened. Of the HH females intervened, 4 (36%) improved for normal function (3 (75%) were pre-menopause and 1 (25%) was post-menopause) and 7 (64%) maintained HH. Of the females a total of 5 (18%) worsened, 4 (15%) improved and 18 (67%) maintained the previous pituitary gonadotropic function.
In total of patients, 8 (14%) worsened, 17 (29%) maintained normal function, 24 (41%) maintained HH and 10 (17%) improved pituitary gonadotropic function (statistically significant) (table 4).

After surgery, of the macroadenomas 34 (60%) had HH and 23 (40%) didn't, and of the microadenomas, both patients didn't have HH. Of the non-incidentalomas, 33 (60%) had HH and 22 (40%) didn't, and of the incidentalomas, 1 (25%) had HH and 3 (75%) didn't. Of the patients that had surgery only 2 had microadenomas and both maintained normal function and of the patients with macroadenomas 8 (14%) worsened, 10 (18%) improved and 39 (68%) maintained previous function.
Prevalence of HH before and after surgery is shown on table 3.
There was a positive response to the GnRH test after surgery in 9 of the 17 patients (53%). Of the males 5 (55%) responded and of the females 4 (50%) (table 5).

Table 3: Hypogonadotropic hypogonadism prevalence

	Males n (%)	**Females** n (%)	**Total** n (%)
	(n=45)	**(n=64)**	**(n=109)**
Before/without surgery	27 (60)*	16 (25)*	43 (40)
	(n=32)	**(n=27)**	**(n=59)**
Before and with surgery	23 (72)	11 (41)	34 (58)
After surgery	20 (62)	12 (44)	32 (54)

*marks statistically significant values

Table 4: Post-surgery outcome

	Improved n (%)	**Maintained Normal** n (%)	**Maintained HH** n (%)	**Worsened** n (%)	**Total** n (%)
Males	6 (60)	6 (35)	17 (71)	3 (38)	32 (54)
Females	4 (40)	11 (65)	7 (29)	5 (62)	27 (46)
Total *	10 (17)	17 (29)	24 (41)	8 (13)	59 (100)

*marks statistically significant values

Table 5: GnRH test on patients with hypogonadotropic hypogonadism

Positive response	**Males** n (%)	**Females** n (%)	**Total** n (%)
Before surgery	**(n=21)**	**(n=9)**	**(n=30)**
	10 (48)	7 (78)	17 (57)
After surgery	**(n=9)**	**(n=8)**	**(n=17)**
	5 (56)	4 (50)	9 (53)

Some of the patients had to be re-intervened after the first surgery. There were statistically significant differences between the groups with different number of surgeries. The outcome of these patients is shown on table 6.

Table 6: Outcome of patients according to number of surgeries (statistically significant)

Number of Surgeries	**Number of patients** n (%)	**Improved or maintained** n (%)	**Worsened** n (%)
1	50 (85)	44 (88)	6 (12)
2	6 (10)	6 (100)	0
3	3 (5)	1 (33)	2 (67)
Total	59	51 (86)	8 (14)

There was no statistically significant difference of outcome with age, gender, menopause or radiotherapy. The variation of the BMI before and after surgery according to their PGS is show on table 7. After surgery, patients with hypogonadism had a higher BMI than normal patients, but these results weren't statistically significant (table 7). Their evolution with outcome is shown on table 8.

Table 7: Median Body Mass Index of all groups

			BMI median (range)
Before surgery	**All patients (**n=87)	**Normal (**n=52)	26.4 (18.4 – 40.6)
		HH (n=35)	27.5 (21.0 – 45.9)
	Patients that had surgery (n=52)	**Normal (**n=19)	25.8 (19.9 – 40.6)
		HH (n=28)	27.9 (21.4 – 35.3)
After surgery (n=52)		**Normal (**n=22)	27.3 (21.3 – 42.7)
		HH (n=30)	29.4 (22.8 – 35.0)

Table 8: BMI of patients after surgery (n=52) and its association with outcome

	Improved	**Maintained**	**Worsened**
Median BMI median (range)	27.1 (23.3-29.1)	27.6 (21.4-42.7)	30.0 (22.8-32.6)

Erectile Dysfunction questionnaire analysis:

Of the 34 valid questionnaires received, 28 (82%) had had surgery and 18 (53%) had HH. After the analysis of the questionnaires, 26 (76%) had symptoms of ED and 14 (21%) reported doing TRT. The median age of the population was 62 years (range 23-88). The median age of the males with ED was 65 and of the males without ED was 49, this difference was statistically significant. BMI of the groups is shown on table 9 and the median age on figure 1.

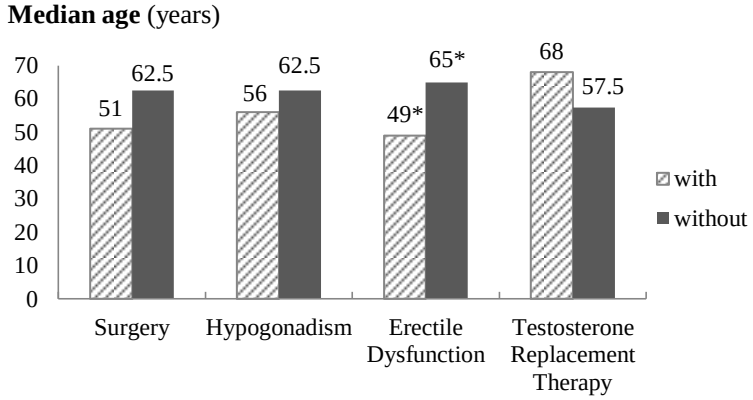
Table 9: Characteristics of the male population that answered the ADAM questionnaire

		Number n (%)	**Median BMI** median (range)
Total		34	27.5 (20.8-36.5)
Surgery	**with**	28 (82)	28.0 (23.2-35.4)
	without	6 (18)	25.9 (20.8-36.5)
Hypogonadism	**with**	18 (53)	27.7 (24.3-35.0)
	without	16 (47)	27.1 (20.8-36.5)
Erectile dysfunction	**with**	26 (76)	27.8 (23.2-36.5)
	without	8 (24)	27.2 (20.8-30.3)
Testosterone Replacement Therapy	**with**	14 (21)	28.0 (23.2-32.5)
	without	20 (79)	27.4 (20.8-36.5)

*marks statistically significant values

Patients with erectile dysfunction had a significantly higher age.

Figure 1: Median age of the male population that answered the ADAM questionnaire



*marks statistically significant values

The results obtained from the questionnaires are shown on table 10. There were no statistically significant associations between the variables.

Table 10: Associations between hypogonadism, erectile dysfunction and testosterone replacement therapy

		Surgery n (%)		**Hypogonadism** n (%)		**Erectile dysfunction** n (%)		**Testosterone Replacement Therapy** n (%)	
		with	**without**	**with**	**without**	**with**	**without**	**with**	**without**
Surgery	**with**(n=28)			17 (61)	11 (39)	22 (79)	6 (21)	13 (46)	15 (54)
	without(n=6)			1 (17)	5 (83)	4 (67)	2 (33)	1 (17)	5 (83)
Hypogonadism	**with**(n=18)	17 (94)	1 (6)			14 (77)	4 (23)	10 (55)	8 (45)
	without(n=16)	11 (69)	5 (31)			12 (75)	4 (25)	4 (25)	12 (75)
Erectile dysfunction	**with**(n=26)	22 (85)	4 (15)	14 (54)	12 (46)			11 (42)	15 (58)
	without(n=8)	6 (75)	2 (25)	4 (50)	4 (50)			3 (38)	5 (62)
Testosterone Replacement Therapy	**with**(n=14)	13 (93)	1 (7)	10 (71)	4 (29)	11 (79)	3 (21)		
	without(n=20)	15 (75)	5 (25)	8 (40)	12 (60)	15 (75)	5 (25)		

Discussion

The population had a slight female predominance, 59% vs 41% males, which is coincident with previous studies [14]. The mean age at diagnosis was 51.8 years, supporting the previous data of the NFPA being frequent on the elderly. In this sample most patients were over 40 years old (71%) [7,19]. Females were younger than males (table 1). Most tumors were macroadenomas (67%, p=0.001) and proportionally males had more macroadenomas than females (88% vs 55%) (p<0.001). In Drange's, 77% of NFPA had macroadenomas and males had more frequently macroadenomas than females (92% vs 68%), and even though all these compared prevalences are higher than in our study, the tendency is similar to ours [14]. Patients with macroadenomas were older than patients with microadenomas (median 39 vs 59) (p<0.001). Patients diagnosed incidentally are much less common (19%, p<0.001) and seem to be older (58 vs 49 years), but this wasn't statistically significant. Of the non-incidentalomas, most of them were macroadenomas (70%), just like in the whole population, and, proportionally, there is a higher number of microadenomas on the incidentally discovered group than the whole population (48% vs 33%), but this isn't statistically significant.

Patients that had surgery seem to be older (median 56 vs 45.5 years), but this tendency is not statistically significant. Our sample has a similar number of patients intervened to other studies: 54% had surgery and 6% had radiotherapy [20]. There is a statistical difference between males and females on this distribution (71% of the males vs 42% of the females had surgery, respectively), which could be attributed to a highest rate of incidentally discovered NFPA on females, that are frequently less severe and less likely to have surgery. Most patients that had surgery were macroadenomas (97%, p<0.001) and most macroadenomas had surgery (78%, p=0.001). Of the patients that didn't have surgery, most of them were microadenomas (68%, p<0.001) and only a minority of microadenomas had surgery (10%, p=0.001). Of the incidentalomas only a minority had surgery (19%, p<0.001) and of the patients that didn't have surgery, 34% were incidentalomas vs 7% on the group that had surgery. But this difference wasn't statistically significant..

The prevalence of HH on our population was 40%, which is within the range found on previous studies (26% – 72.6%) [7,19-21]. The prevalence of HH was higher on males than females, both before and after surgery, 60 vs 25% and 62 vs 44%, respectively, but only the difference before surgery was statistically significant. There was no statistically significant improvement with surgery (only 17%) and some even became HH having previous normal PGS (13%), which is in agreement with other studies [19-21]. Comparing males with females, 19% of the males improved vs 15% of females; 9% of the males worsened vs 18% of the females. Therefore, of the patients that improved, 40% were females vs 60% males and of those who worsened 62% were females vs 38% males. There seems to be a tendency for female patients to be more likely to worsen and less likely to improve than males (results not statistically significant).

HH was less frequent on microadenomas (11% had HH and 89% didn't) (p<0.001). Patients incidentally diagnosed most frequently had normal PGS (81%, p=0.003). After surgery, there was a slight increase in HH on macroadenomas (47% before surgery vs 60% after surgery). Both microadenomas operated remained normal PGS and there was no difference of outcome on macroadenomas comparing with the whole population operated.

When comparing with other pituitary adenomas populations, there are other causes for HH besides those of NFPA, such as direct hormonal interaction. On acromegaly, the mean age at diagnosis is 41-45 years, which is lower than that of NFPA, most patients had macroadenomas (77-86%), which was higher than in our series of NFPA (67%), but we had different proportion of macroadenomas in males vs females (88 vs 52%), unlike acromegaly, in which patients had a similar macroadenoma distribution according to gender [14,22-24]. The prevalence of HH before intervention (surgery, radiotherapy or pharmacological treatment) is 53%, 46-53% on males and 46-60% on females, which is similar to that of NFPA [22,23,25]. The outcome varies significantly with the series and treatment approach, iatrogenic HH as low as 4.9% and as high as 41% [24,26-28]. Prolactinomas are more frequent on females, as seen on NFPA, and the mean age at diagnosis is lower on females than males (32.7 vs 41.6), which is still lower than the mean age at diagnosis made on NFPA [14,29]. The treatment of prolactinomas is in most cases pharmacological, but some patients are subjected to surgery. On Maric's study, 45% of the patients with

prolactinomas had HH and with surgical approach there was a 20% improvement. In this study, most patients had microadenomas, only 36% were macroadenomas, which is the opposite proportion that we observe in NFPA, but on other study the prevalence of macroadenomas on prolactinomas can go up to 50%, which is still not the majority, as seen on NFPA [14,29]. Like in our series of NFPA, on prolactinomas males seem to have more frequently macroadenomas than females (74% vs 40%) [14].
Even though there was a high rate of positive responses to the GnRH test (57% before surgery and 53% after surgery), besides lacking data on a high number of patients (and different missing data numbers on males vs females), no important information could be attained from these results. Even though this information would suggest that the HH on these patients was from hypothalamic and not pituitary causes on approximately half the sample, this test is neither sensitive nor specific for HH and positive response doesn't exclude nor ascertains pituitary or hypothalamic pathology, due to highly variable responses to GnRH stimulation [30,31]. Therefore the clinical importance of this test to HH diagnosis seems to be obsolete, as it was reported previously [32].
Reoperation was done once on 10% of patients and twice on 5%, which is a slightly lower number than other studies (19% had 2 surgeries and 9% had 3 surgeries) [20]. Even though there was a statistically significant difference of outcome between the groups of different number of interventions, there isn't a tendency of increasing number of surgeries associated with worst prognosis, such information would only be supported comparing the group with 1 surgery and 3 surgeries. The increasing number of surgeries should be associated with increasing risk of iatrogenic HH. Nonetheless, the indication for surgery is often insufficient tumor removal on previous surgery or regrowth than presence of HH, which can cause different characteristics on the patients that undergo different number of surgeries, such as bigger tumors or more symptoms, information that is not accounted in this study and that associated with a small sample of patients, results in an impossibility to find that predictable causality of the iatrogenic effect.
Other factors didn't interfere in a statistically significant way on the outcome (such as age, gender or menopause).
There was a tendency of higher BMI for patients with HH than with normal PGS in all groups (before and after surgery). There was a tendency of increasing BMI from best to worst outcome: $27.1<27.6<30.0$ for the improved (regained normal pituitary function), maintained previous pituitary function (either normal or HH) and worsened (became HH after surgery) groups, respectively. Despite these tendencies, these findings weren't statistically significant.

Most of the patients that answered the questionnaire had had surgery (82%) and about half had hypogonadism (53%). Patients that didn't have surgery had less HH (83%), which can arise from the fact that they probably had less severe symptoms or smaller tumors, that interfere less with adjacent structures (which reduces the probably of HH on NFPA patients), and don't have indication for surgery at the moment. This makes it expected that patients that had surgery had more HH (94%), more ED (85%) and were more frequently under TRT (93%) than those who didn't have surgery.
On the questionnaires analysis, we observed a tendency for patients that didn't undergo surgery or patients without HH being younger (51 vs 62.5 years and 56 vs 62.5 years, respectively). The presence of ED also followed this tendency and the difference in the median age was statistically significant between patients with and without ED (65 vs 49 years, respectively). There was a high prevalence of ED on our sample (76%), superior to the prevalence of HH (53%). Even though hypogonadism is a cause of ED, this difference on prevalences is most likely due to the high prevalence of older patients on the males subjected to the questionnaire (median 62 years) which is a known major risk factor for ED [33]. Therefore 46% of the patients with ED didn't have HH, being the ED from other causes.
Only 55% of the patients with HH were under TRT, even if TRT replaces testosterone that should be produced on the end of the gonadal axis, which is damaged on HH. Also, patients under TRT were younger than those without TRT, even though younger patients have less HH and ED. Both these results can be justified by the fact that older patients have more contraindications for TRT (such as prostate pathology, severe cardiovascular diseases) or less potential benefits from improving from ED due to advanced age, which can explain this apparent contradiction of highest prevalence of disease (HH and ED) corresponding to lower use of treatment (TRT).

As we said before, HH can lead to weight gain and therefore obesity, but obesity is also a known factor for HH, so the causality relation between the two variables is unclear and may be a confunding factor [34-36]. There was no statistically significant difference among the groups regarding BMI, even though patients that underwent surgery seem to have higher BMIs comparing with those who didn't (28.0 vs 25.9). Studies mention a consistent decrease in total body fat associated with TRT on HH males, but this fact was not observed on our sample [36]. Since our analysis of BMI and TRT is transversal and the duration of treatment was not recorded, this may be an important fact to cause dispersion of any tendency to lower BMI on patients with HH taking TRT. Simultaneously, the presence of ED on patients under TRT translates inefficient treatment (79% of patients under TRT still have ED). This, associated with the fact that even though TRT could reduce BMI, doesn't improve cholesterol profile or have cardiovascular benefits, it makes us ponder the benefits of this treatment in comparison with its risks, especially since new studies suggest increased cardiovascular risk and all causes mortality on older patients, and on younger patients with pre-existing diagnosed heart disease, that do TRT [37-40].

Study limitations

The small number of patients on our sample damaged our statistical power to show some statistically significant results.

There are many confounding factors on the analysis of these results, since there is direct interference of the variables with one another, leading to blur on the tendencies and no statistical differences between the groups. For instance, patients with HH were treated with TRT, among other effects, to reduce ED, therefore the real prevalence of ED on patients with HH is underestimated.

In conclusion, NFPA were more frequent on older patients. Male patients with NFPA were older, had more HH and surgery. There was no significant improvement of pituitary gonadotropin secretion with surgery (17%) and 13% had iatrogenic HH with surgery. TRT had a low efficacy to improve ED and change BMI in these patients

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Appendix

Table 11. Questions Used as Part of the Saint Louis University ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased ‘‘enjoyment of life’’?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

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Anexos

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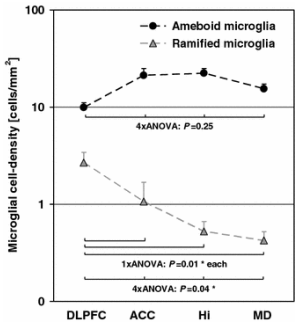
For the best quality final product, it is highly recommended that you submit all of your artwork – photographs, line drawings, etc. – in an electronic format. Your art will then be produced to the highest standards with the greatest accuracy to detail. The published work will directly reflect the quality of the artwork provided.

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



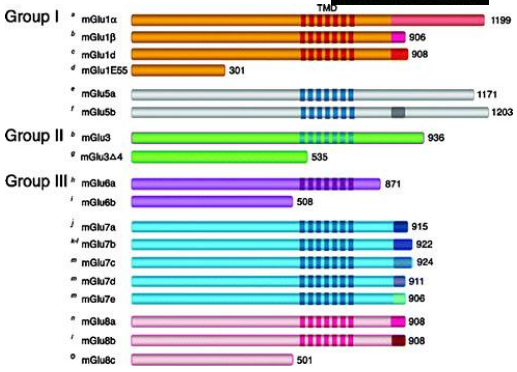
Definition: Black and white graphic with no shading.

- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art

- Definition: Photographs, drawings, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination Art



- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color Art

- Color art is free of charge for online publication.
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- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
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