

Research Article

Gonadal Abnormalities in Men with Prolactinomas

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- Sperm account

Abstract

Gonadal abnormalities (GA) in women with prolactinomas (P) are well documented. But, large series concerning males are lacking. Our aim was to analyze GA in 60 men with P.

Material/methods: median age=34+/-13years, median prolactin (PRL)=2569ng/ml. 55 were macroadenomas (height>1cm) with pituitary insufficiency (≥ 2 axes) in 27. We took into account patients' complaints and clinical examination. Hormonal data were based on PRL, total testosterone (TT), follicle stimulating hormone (FSH), and luteinizing hormone (LH) with respective normal values: 5-20ng/ml, 3-9ng/ml, 1-9mIU/ml, and 1-12mIU/ml. 16 had LHRH test (100mcg). The sperm count was analyzed in 9 cases. Student's t-test was used to compare gonadotropins of 2 Groups: G1=normal TT and G2=low TT, with $p < 0.05$.

Results: delayed puberty=6 (10%). In the remaining group ($n=54$), decreased libido=75%, and erectile dysfunction=79.6%. Facial and body hair growth, and testicular volume were reduced in respectively 44.5% and 35%. Galactorrhea was observed in 22% and gynecomastia in 14%.

Low TT (< 3 ng/ml) =74%. FSH was normal-low except in one patient (FSH=15). LH was low in 23%. LHRH test showed normal response for FSH, LH response was insufficient in 38%. Comparison between groups showed FSH and LH of G1 were significantly higher than the ones of G2 (respectively: 3.23 ± 1.64 mu/ml vs 2.21 ± 1.58 mu/ml, $p < 0.001$, and 3.46 ± 1.43 mu/ml vs 2.07 ± 1.48 $p < 0.001$).

For the sperm count, it was normal in 5 cases (4 with low TT), 4 had oligospermia and/or astheno-teratospermia (one with high FSH).

Conclusion: 79% complained of gonadal dysfunction. Except in one case low TT=75% is due to hypothalamic-pituitary damage.

ABBREVIATIONS

GA: Gonadal Abnormalities; P: Prolactinomas; Prolactin: PRL; TT: Total Testosterone; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; LHRH: Luteinizing Hormone-Releasing Hormone; G1: Group1; G2: Group2; ng/ml: nanogram/milliliter; mIU/ml: milli International Units/milliliter; mcg=micrograms; vs: versus

INTRODUCTION

In medical endocrine departments, prolactinomas are the most frequent pituitary tumors, but their frequency varies according to the age, sex, and mode of recruitment. In general, it is well known that prolactinomas are more frequent in women than in men with female-to-male ratio approximately equal to

10/1 [1]. But, prolactinomas are greater, more invasive and more aggressive in males [2,3]. Prolactin secretion is also higher than in females probably because of late diagnosis and higher index of tumor proliferation and secretion. In women gonadal dysfunction may be functional due to high prolactin concentration which inhibits ovarian function and/or reduces gonadotropins' pulsatility [4]. It can also be organic and irreversible due to a large pituitary process.

Large tumors observed in men explain high frequency in ophthalmological disorders, neurological and psychiatric problems, and pituitary insufficiency. Among pituitary disorders, gonadal function is the first to be affected and can be irreversible because of large, invasive, and destructive tumors.

If gonadal abnormalities in females harboring prolactinomas

are well documented by many authors [4-8], large series concerning gonadal function in men with hyper prolactinemia are lacking because of the rarity of male prolactinomas [9-11]. Our aim was to analyze gonadal function in a consistent series composed of 60 men harboring prolactinomas.

MATERIALS AND METHODS

In this study, 60 men with hyper prolactinemia were analyzed. Files with clinical and biological missing information were excluded. Our population's median age was 34 +/- 13years (15-68). Median prolactin was 2569ng/ml (68-28000). 5 cases were micro adenomas (height <10mm) and 55 were macro adenomas (height>1cm). Among macro adenomas 28 were giant (≥4cm) and/or invasive (invasion of one or both cavernous sinuses). Total or partial (at least two deficits) pituitary insufficiency was observed in 50% among macro adenomas. Apart from diabetes mellitus, without any complication, observed in 3 cases, there was not any disease interfering on gonadal function. No one was taken medicine which can act on gonadal function.

It was a retro-and prospective study which took into account: the consultation motive, patients' complaints, and clinical examination to seek gynecomastia and galactorrhea. Testicular volume, facial and body hair growth, and hormonal assessment were analyzed too.

Hormonal data were based on prolactin (PRL) with dilution, total testosterone (TT), follicle stimulating hormone (FSH), and luteinizing hormone (LH). These hormones were analyzed by radioimmunoassays. Normal ranges were: 3-9ng/ml for TT, 5-20ng/ml for PRL, 1-9mUI/ml for FSH, and 1-12mUI/ml for LH. LHRH test (100mcg) was done in 16 patients. The sperm count was analyzed in only 9 cases because of erectile dysfunction.

For statistical analysis, the results have been expressed as medians and ranges. Then, we used the Student's t-test to compare FSH and LH of two groups: G1 with normal testosterone and G2 with low testosterone. The difference was considered as significant if p was <0.05.

RESULTS

Lack or arrested puberty was observed in 6 patients (10%). In the remaining group (n=54) 41=75% complained of reduction in their libido. 43 (79.6%) suffered from erectile dysfunction. On clinical examination, facial and body hair growth were reduced in 44.5% (n=24), and testicular volume was decreased in 35% (n=19). Galactorrhea and gynecomastia were observed in respectively 22% (n=12) and 14% (n=8).

Hormonal results showed low testosterone (<3ng/ml) in 74% (n=40). FSH was normal-low in 96.2% (n=52), and in one case FSH was increased (15mIU). LH was normal in 77% (n=42) and low in 23%. LHRH test showed normal response for FSH. But, for LH the response was normal in 62% (n=32) and insufficient or null in 38%.

The comparison between G1 and G2 showed FSH of patients with normal testosterone was significantly higher than the one of subjects with low T (respectively: $3.23 \pm 1.64\text{mu/ml}$ vs $2.21 \pm 1.58\text{mu/ml}$, $p<0.001$), LH of patients with normal testosterone

was significantly higher than the one of subjects with low Testosterone: $3.46 \pm 1.43\text{mu/ml}$ vs 2.07 ± 1.48 $p<0.001$.

For the sperm count, it was normal in 5 cases (although testosterone was low in 4), but FSH and LH were normal. 4 cases had oligospermia and/ or astheno-teratospermia. In this last group testosterone was low in all cases and FSH and LH were normal-low except in one case where FSH was high because of primary hypogonadism.

DISCUSSION

Prolactinomas are a common cause of gonadal dysfunction and infertility in men [12]. Apart from hypothalamic pituitary axis abnormalities observed in large tumors, plasma and probably intra gonadal prolactin (PRL) concentrations play also a role in testosterone secretion and in the spermatogenesis process as normal PRL levels are required for normal testicular function [13].

In this study which included males harboring large and/or invasive prolactinomas, with 50% of partial or total pituitary insufficiency, 6 (10%) had a lack of pubertal development comparatively to 2.5-10% in literature [14, 15]. A decreased libido was found in 75% compared to 47-85% for other authors [16,17]. 79.2% complained of a profound erectile dysfunction compared to 51-80% [15,18]. A reduction in facial and body hair growth was observed in 45% versus 21-41% [16,18] and a reduction in testicular size was noted in 34% comparatively to 3.7-10% [16,14]. The high rate of small testes observed in our group could be explained by a late diagnosis and large tumors with pituitary insufficiencies, but also by echosonography (done in some cases) which is more objective than clinical examination. Galactorrhea was observed in 21% compared to 5.4-24 [19, 15] and even 38% [8] and gynecomastia was found in 14% compared to 16-39% [19,15]. Our percentage concerning gynecomastia is certainly underestimated as echosonography and mammography were not done systematically. Hormonal results showed a deficit in total testosterone secretion in 74% compared to 59-90% in literature [19,18]. Sperm count abnormalities were seen in 44.4% of our patients. It is difficult to compare our results to literature review because of conflicting results concerning sperm analyzes.

According to our results gonadal abnormalities are apparently due to a deficit in gonadotropins secretion/liberation as FSH and LH of people with low testosterone are significantly lower than those of people with normal testosterone. Our results are broadly similar to those published by other researchers [18-22]. Reduction in gonadotropins can be easily explained by compression and or destruction in FSH/LH cells by large tumors or by a reduction in LHRH pulsatility. The decrease in the amplitude or in the number of hypothalamic LHRH pulses could be also responsible for pituitary LHRH receptors reduction and lack of FSH and LH pulses and/or secretion.

On another hand, it seems that normal serum PRL levels and normal intra gonadal prolactin concentration are required for normal testicular function [13]. As PRL receptors are observed in the testis, high plasma prolactin concentration may probably be responsible for testis insensitivity to FSH and LH with a consequent reduction in testosterone biosynthesis and

spermatogenesis. Reduction in testosterone can also exaggerate sperm abnormalities.

Apart the impact of high plasma prolactin, intra testicular prolactin concentration could also participate in the inhibition of testosterone biosynthesis and spermatogenesis.

On another hand, some authors incriminated the impact of hyper prolactinemia on peripheral or target tissues. It is thought that hyper prolactinemia causes a reduction in 5 α -reductase (which transforms testosterone to dihydro testosterone or DHT). An increase in aromatization of androgen to estradiol in peripheral adipose tissue is also discussed to explain gynecomastia which is observed in males with hyper prolactinemia.

Increase in serum prolactin seems also to play a great role on different steps of sperm production which explains sperm qualitative (mobility and vitality) and quantitative (oligo or poly-zoospermia) abnormalities observed in men with hyper prolactinemia.

For sperm count literature review showed very few studies with conflicting results. Some authors observed normal counts; others demonstrated oligo-spermia and the third group found an exaggeration in sperm account, but that one may be due to a long period of sexual inactivity. De Roza [22] who analyzed 26 men with hyper prolactinemia observed oligoasthenospermia in 100 %. But, after 6 months of cabergoline intake there was a significant increase in the number, the mobility and sperm vitality. This modification argues for a direct role of high prolactin on the testis, as pituitary tumors did not disappear totally after six month cabergoline.

The deficit in glucocorticoids, somatotrop and thyroid hormones in people with pituitary deficits could also be a supplementary cause for testosterone deficiency and sperm abnormalities [23]. So, some researchers think that gonadal insufficiency in men with hyper prolactinemia may be a consequence of several inhibiting mechanisms, among which hypothalamic and pituitary alterations are the most prevailing especially in men with large pituitary tumors as in our group.

CONCLUSION

In this large series composed especially of giant and or invasive macroprolactinomas, 79% of our population complained of erectile dysfunction with reduced or lack of libido. For the mechanism, except for one case with hyper gonadotropic hypogonadism (probable fortuitous association), low total testosterone, observed in 74%, with or without abnormal sperm count, is apparently due to the hypothalamic-pituitary damage responsible for normal-low gonadotropins \pm other pituitary deficits. Our results agree with previous studies, but for future works, prospective analyses with free testosterone assessment and other tests are recommended for a better understanding of this hypogonadism.

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