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# Gonadotroph Pituitary Adenoma Associated with Elevated Circulating Testosterone Levels

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## Abstract

**Background**: Scant data exists regarding gonadotroph pituitary adenoma associated with high plasma testosterone levels.

**Objective**: To describe clinical profile and outcomes of patients of gonadotropin-secreting pituitary adenoma.

**Methods:** Pubmed search from 1970 to February 12, 2021. Search terms include gonadotropins, follicular stimulating hormone (FSH), luteinizing hormone (LH), testosterone, libido, erectile function, erythrocytosis. Case reports, reviews, and guidelines of Endocrine Societies are reviewed.

**Results:** Review of literature revealed 5 men with large pituitary adenomas associated with elevated plasma gonadotropins and testosterone levels. All 5 men presented with pituitary mass effects, mainly visual changes and headache. No symptoms of excess circulating levels of testosterone were reported. However, one patient presented with erythrocytosis that resolved after normalization of plasma testosterone concentrations. Treatment was essentially surgical removal of pituitary tumors. Surgery was followed by hypogonadism and variable degrees of hypopituitarism in 3 cases, and death in one case. Medical therapy was generally ineffective in reducing tumor size but might lower testosterone levels.

**Conclusions:** Gonadotropin-secreting pituitary adenoma causing high circulating testosterone levels are extremely rare. To avoid delay in diagnosis, pituitary imaging should be done in men presenting with repeatedly high plasma testosterone levels of unclear reasons. In addition, testosterone levels should be measured in any man presenting with erythrocytosis of unknown etiology.

**Key Words:** gonadotroph adenoma, pituitary, testosterone, hypophysectomy, testicles, semen

## Introduction:

Gonadotropin (also called gonadotroph) adenomas are the most common type of pituitary adenomas forming approximately 37% of all pituitary adenomas [1]. More than 99% of gonadotroph adenomas are "silent" i.e. do not secrete pituitary hormones at a clinically relevant level [2]. Indeed, gonadotropin adenomas secreting excess FSH and/or LH are rare. Furthermore, among the few cases of gonadotropin pituitary adenomas, it is very rare to encounter cases associated with elevated testosterone plasma testosterone concentrations [3,4]. In a series of 100 gonadotroph pituitary adenomas from Mayo Clinic, not a single case presented with elevated plasma testosterone concentrations [3]. Likewise, Ho et al [4] did not report any case with high testosterone values among 118 patients with gonadotroph adenomas. Scattered case reports reached similar results. Thus, in a 63 year-old man with POEMS syndrome Shichiri et al [5] reported that testosterone plasma levels were within normal limits (8.3 nmol./L, 239.0 ng/dl) despite markedly elevated concomitant LH and FSH levels, 43.4 IU/L and 55.2 IU/L, respectively. [5]. The purpose of this review is to summarize clinical and hormonal profile of patients with gonadotropin pituitary adenoma causing elevated circulating testosterone. The clinical implications of these cases are a also presented.

## Clinical Presentation

| Reference, year | Patient's age (all males) | FSH | LH | Testosterone (total) | Prolactin | Pituitary tumor | Presenting features |
|---|---|---|---|---|---|---|---|
| Ceccato et al 2013 [6] | 43 | 106.6 U/L (1-14) | 19.3 U/L (1,5-9.2) | 52.05 nmol/L (10-29) | 17.3 µg/dl (5-15) | 68x64x60 mm cystic solid invading posterior cranial fossa | Erythrocytosis with hematocrit 61.1% (36-46), facial plethora, mood swings, headache, diplopia |
| Chamoun et al 2012 [7] | 45 | 35.6 IU/L (1.5-12.4) | 10.8 IU/L (1.7-8.6) | > 1500 ng/dl (300-890) | 98.8 ng/ml (2.1-17.7) | "large" sellar and suprasellar macroadenoma | Progressive visual loss bilaterally |
| Dizon & Vesely [8] | 61 | *72.4 mIU/ml | *31.6 mIU/ml | *15.20 ng/ml | Not reported | Soft mass 3.2x2.5 x1.2 cm with upward extension to optic chiasm | Decreased vision in left eye |
| Zarate & Fonesca 1986 [9] | 45 | 3572 ng/ml (70-350) | 1248 ng/ml (20-120) | 16.8 ng/ml (2-8) | 10 ng/ml (<10) | 4x5 cm mass with suprasellar and parasellar extension | Visual loss, headache, **increased sperm count and abnormal forms |
| Snyder &Sterling 1976 [10] | 51 | 30 mIU/ml (4-14) | 23 mIU/ml (4-14) | 1500 ng/dl (400-1200) | 60.3 ng/ml (< 15) | Pituitary adenoma with suprasellar extension (by skull X ray) | Decreased vision in right eye |

Units were depicted as per reference source. Normal values are between parentheses.
*Normal range was not mentioned but described as "all values were above normal".
**numbers of normal and abnormal sperms were not mentioned.

**Table 1:** Cases of gonadotropin-secreting adenomas associated with elevated serum testosterone levels

All reported cases had symptoms due to mass effects of pituitary adenoma, namely decreased vision, headache, diplopia, orthostatic dizziness [6-10]. These symptoms were expected given the substantial tumor size, with the largest dimension ranges from 32 to 68 mm (table 1). In fact, these symptoms were the reasons that led to brain imaging and discovery of the pituitary mass. Apart from the elevated gonadotrophins and mild elevation of prolactin due to deviation of pituitary stalk, other pituitary hormones on presentation were normal except of mild central hypothyroidism in one case [7]. As far as symptoms of testosterone excess were concerned, all patients reported normal libido and erectile function. No increase in aggressiveness or increase muscle mass was reported. Testicular volume and consistency were normal by scrotal ultrasound [6] and by physical exam [7,8]. Interestingly, the patient described by Ceccato et al [6] had erythrocytosis and facial plethora for 5 years before the diagnosis of pituitary tumor and subsequent demonstration of high testosterone levels. In the latter case, erythrocytosis was most likely a sign of excess circulating testosterone levels. In fact, it is well-known that the commonest adverse effect of testosterone therapy is erythrocytosis [11]. Conversely, testosterone deficiency may lead to anemia [12]. Indeed, when testosterone levels normalized with octreotide and cabergoline therapy in the case reported by Ceccato et al [6], erythrocytosis resolved and therapeutic phlebotomies were discontinued.

Surprisingly, Zarato and Fonesca et al [9] reported that "patient's spermogram showed a marked increase in the total sperm count and a number of abnormal forms". However, these authors did not mention the actual sperm count, number of abnormal forms, and did not repeat semen analysis as per guidelines [13]. This increase in sperm count is unexpected and seems paradoxical because testosterone administration is a well-established contraceptive method in men by means of suppression of spermatogenesis [14].

## Treatment

### Medical Treatment

In general, medical treatment of gonadotropin pituitary adenoma was minimally effective with respect to reduction of tumor size, but its effect on lowering testosterone levels was variable. Thus, in one patient, clomiphene citrate 100 mg/day was used for 10 days before hypophysectomy had no effect on gonadotropins or testosterone levels [9]. Meanwhile, pre-operative treatment that consisted of high-dose somatostatin analogue, octreotide 0.5 mg 3 times a day combined with the dopamine agonist cabergoline 4 mg/week for 4 months, was associated with normalization of testosterone levels, a slight shrinkage of the pituitary tumor, but worsening of diplopia and headache [6]. Subcutaneous administration of luteinizing releasing hormone (LRH) analogue was used post-hypophysectomy in a dose of 100 µg bi-weekly in the patient of Zarate and Fonesca and resulted in mild reduction in residual tumor size [9].

## Surgical Treatment and Outcomes

The mainstay of treatment of gonadotroph adenoma is surgical removal by hypophysectomy for rapid relief of compression symptoms. In fact, hypophysectomy was performed in all cases [6-10] and was followed by radiotherapy in 2 patients [9,10]. Effects of hypophysectomy on visual acuity was variable. Thus, vision either improved [7,8], did not change [9], or worsened [10] after hypophysectomy.

Hormonal abnormalities also varied following hypophysectomy. In the patient of Zarate and Fonseca [9], testosterone levels remained elevated after surgery and cranial radiation. Post-

operative complete anterior hypopituitarism occurred in one patient [7], whereas another patient had only hypogonadotropic hypogonadism [8], Permanent diabetes insipidus developed after the second operation in the patient reported by Snyder and Sterling implying damage of posterior lobe of pituitary gland [10]. Finally, death occurred in one patient 3 days after transcranial hypophysectomy as result of severe intracranial hypertension and intraventricular bleeding [6].

## Immunohistochemistry Results

Immunohistochemistry (IHC) was positive for both FSH and LH confirming the diagnosis of gonadotropin-secreting adenoma in most cases [6,8,9]. However, in the case reported by Chamoun et al [7], IHC was positive only for FSH, and not LH. The explanation of the latter finding is unclear, knowing that LH is the main stimulus of testosterone secretion by Leydig cells of testis [15].

## Histopathology results

All pathological sections of post-operative pituitary specimens were consistent with a benign adenoma despite invasion of the posterior cranial fossa [6] and sphenoid sinus [8].

## Conclusions and Clinical Implications

Gonadotropin-secreting pituitary adenomas associated with high circulating testosterone levels are extremely rare, but possibly underreported. Main presenting symptoms are mass effects from the pituitary tumor, which is already large (more than 30 mm) on presentation. Although excess testosterone levels were generally asymptomatic, one patient presented with erythrocytosis, which was attributed to other causes until testosterone levels were checked 5 years later [6]. Therefore, to avoid delay in diagnosis of gonadotroph pituitary adenoma, testosterone measurement should be included in the work-up of erythrocytosis in men. In addition, pituitary imaging should be done in any man with repeatedly elevated testosterone levels after ruling out abuse of testosterone and related androgens.

**Conflict of Interest:** The author has no conflict of interest to declare.

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