CASE REPORT

Asymptomatic 'big' hyperprolactinemia in two men with pituitary adenomas

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Abstract

'Big' and 'big-big' hyperprolactinemia, the presence of increased serum concentrations of high molecular weight (50–60 and 150 kDa respectively) prolactin forms, has mostly been reported in women with idiopathic hyperprolactinemia and normal hypothalamic–pituitary ovarian axis function. It has been suggested that both 'big' and 'big-big' prolactin species are biologically less active than the 22 kDa form predominating in normal individuals.

We report the cases of two men with pituitary adenomas who were secreting significant amounts of 'big' (50–60 kDa) prolactin documented by Sephadex G-100 column chromatography. Both patients reported normal sexual function despite high prolactin levels. Results of nocturnal rigidity and tumescence testing were normal, confirming that significant hyperprolactinemia was not interfering with either patient's sexual function. 'Big' hyperprolactinemia should thus be suspected even in male patients with prolactin-secreting pituitary adenomas who maintain adequate sexual function in the presence of high prolactin levels.

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Introduction

Prolactin-secreting pituitary adenomas are the most common functioning pituitary tumors (1). Individuals with such lesions typically present with various combinations of amenorrhea, infertility, and galactorrhea in females and hypogonadism, impotence, diminished libido, and local compressive symptoms in males (2).

Over the past few years, several prolactin variants have been detected both in normal individuals and in a variety of disease states (3). Among them are the high molecular weight forms named 'big' (50–60 kDa) and 'big-big' (150 kDa) prolactin (4, 5). Macroprolactinemia has been defined as the presence of increased 'big' or 'big-big' serum prolactin levels (6). Both the 'big' and 'big-big' forms of hyperprolactinemia have been reported mostly in women with idiopathic hyperprolactinemia and normal menses and fertility (5, 7).

We have recently reported six men with erectile dysfunction and hyperprolactinemia secondary to high molecular weight prolactin forms ('big' and 'big-big' prolactin) (8). These patients had no radiologic evidence of pituitary or hypothalamic tumor. Both the normal nocturnal rigidity and tumescence studies as well as the resolution of their erectile dysfunction with counseling

supported the diagnosis of psychogenic impotence. We present the cases of two male patients with pituitary tumors and high serum prolactin levels with a predominance of 'big' prolactin on gel filtration. Both men had normal libido and erectile function, suggesting that 'big' hyperprolactinemia was not interfering with their erectile function.

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Case reports

Patient 1

A 35-year-old man was referred to the endocrinology clinic because of the presence of an enlarged sella on sinus films. He reported normal erections and libido. He had no acromegalic features. He had no gynecomastia or galactorrhea. The testes were of normal size and consistency, and pubic hair was normal.

The basal serum prolactin level was 142 080 mU/l (normal, up to 666 mU/l), the serum total testosterone level was 4.1 nmol/l (normal, 13.9–41.6 nmol/l), the

Figure 1 Nocturnal penile tracing in patient 1. Normal tumescence (tum) and rigidity (rig) values were noted both in the base and tip leads.

serum follicle-stimulating hormone level was 2 IU/l (normal, 1–7 IU/l), and the serum luteinizing hormone level was 5 IU/l (normal, 4–13 IU/l). The alpha subunit was 0.3 mg/l (normal, less than 1.0 mg/l). The somatomedin C was 101 mg/l (normal, 90–318 mg/l). The serum thyrotropin level was 1.20 mIU/l (normal, 0.15–3.20 mIU/l), and the free thyroxine level was 7.7 pmol/l (normal, 9.0–21.8 pmol/l). The morning serum cortisol level was less than 27 nmol/l and rose to 298 nmol/l (normal, more than 552 nmol/l) on standard adrenocorticotropin stimulation testing. Serum sodium, potassium, and creatinine levels were normal. Magnetic resonance imaging (MRI) of the hypothalamus and pituitary showed a 3.2 cm sellar mass that was expanding the pituitary fossa. Goldmann perimetry showed a right superior temporal deficit and a full left field.

The patient was treated with bromocriptine, 2.5 mg orally twice a day, and standard glucocorticoid replacement therapy, with improvement in his sense of well-being. Five months later, the serum prolactin level had decreased but was still elevated at 17 760 mU/l, the serum total testosterone level was near normal at 11.6 nmol/l, and the serum free thyroxine level was 11.6 pmol/l. As previously, he claimed that his libido and erectile function were normal. This claim was verified by nocturnal rigidity and tumescence testing,

results of which were normal (Fig. 1). Chromatographic analysis of the serum prolactin level showed that it was 100% 'big' prolactin, eluting with a molecular weight of 60 kDa (Table 1). A repeat MRI showed significant decrease in the size of the tumor (2.0 cm).

Patient 2

A 41-year-old man was first evaluated at our institution 18 months after transsphenoidal resection of a 2.8 cm pituitary tumor that stained positively for prolactin by immunohistochemistry. The preoperative serum prolactin level had been 46 620 mU/l. Because of radiologic evidence of residual pituitary tumor and persistently elevated prolactin levels, he had been treated with bromocriptine, up to 7.5 mg a day, as well as radiotherapy to a total of 5000 cGy. Hypopituitarism had developed in the first year postoperatively, and the patient was given standard glucocorticoid, thyroid hormone, and intramuscular testosterone (300 mg every 3 weeks) replacement. Bromocriptine was discontinued because of nausea. The patient reported normal libido, erectile function, and overall sense of well-being. He had no gynecomastia or galactorrhea. The testes were 3×2 cm each. Pubic hair was normal.

The serum prolactin level ranged between 9324 and 20 868 mU/l when the patient was not taking bromocriptine. The patient reported normal erectile function and libido even after bromocriptine was discontinued, which was verified by normal results on nocturnal tumescence and rigidity testing. At that time, the serum prolactin level was 8880 mU/l (normal, up to 666 mU/l), the serum total testosterone level was 17.2 nmol/l (normal, more than 13.9 nmol/l), the serum free testosterone level was 485.4 pmol/l (normal, more than 173.3 pmol/l), both 1 week after a testosterone injection, and the free thyroxine level was 16.7 pmol/l (normal, 10.3–24.5 pmol/l). Chromatographic analysis of the patient's serum prolactin showed a preponderance of 'big' prolactin (see Table 1). A repeat MRI showed no significant change in the size of the residual tumor.

Materials and methods

Prolactin assay

The serum concentration of prolactin was measured by double antibody RIA, employing ¹²⁵I-human prolactin

Table 1 Chromatographic distribution of serum prolactin (PRL) in two men with prolactin-secreting pituitary tumors and normal erectile function.

Patient	Serum PRL (mU/l)	'Big-big' (150 kDa) PRL (% total)	'Big' (55–60 kDa) PRL (% total)	Monomeric (22 kDa) PRL (% total)
1	17 760	0	100	0
2	8880	0	53	47

Normal concentrations: PRL: 88.8–666 mU/l; 'big-big' PRL: <15%; 'big' PRL: <15%; monomeric PRL: >70%.

(Dupont, Boston, MA, USA), the NIDDK-hPRL-RP-1 human prolactin reference standard, and the NIDDK-hPRL-3 rabbit prolactin antiserum. A second antibody immunoprecipitation antibody step was employed. All samples were assayed in duplicate. The intra-assay and interassay coefficients of variation were 6% and 8% respectively.

Gel filtration chromatography

Gel filtration chromatography was performed using Sephadex (G-100) 90×1.5 cm columns equilibrated and run in a cold room (4°C). Equilibration and running solution contained 25 mM Tris-HCl and 0.1% sodium azide, pH 8.0. Molecular weight markers used for column calibration included dextran blue, ribonuclease, chymotrypsinogen, ovalbumin, ¹²⁵I-prolactin, and aldolase (Sigma, St Louis, MO, USA); 1.5 ml fractions were collected at a flow rate of 9 ml/h. The optical density of all column fractions was measured on a Beckman Du-8 spectrophotometer (Beckman Instruments, Palo Alto, CA, USA), and the prolactin concentration of all fractions was measured by RIA as previously described. 'Big' and 'big-big' prolactin each normally accounts for up to 15% of total prolactin immunoreactivity (6, 8).

Nocturnal penile rigidity and tumescence study

Each patient underwent a formal nocturnal penile rigidity and tumescence study on two consecutive nights using a RigiScan portable home monitor (Dacomed Corp., Minneapolis, MN, USA). Data were analyzed on an IBM 480 microcomputer employing RigiScan Windows software (Dacomed Corp.)

Discussion

Hyperprolactinemia is associated with a variety of sex-specific clinical manifestations, of which erectile dysfunction is consistently present in men. Thus, in a series (9) of 22 male patients with prolactin-secreting pituitary tumors, 91% had erectile dysfunction and decreased libido. In another study (10), as many as 100% of patients with hyperprolactinemia were impotent.

The mechanism by which high serum prolactin levels cause impotence is not universally agreed upon. Interestingly, the serum testosterone level is often normal in patients with hyperprolactinemia who have impotence on presentation. Thus, in one study (1), 7 of 17 patients with impotence and idiopathic hyperprolactinemia had normal serum testosterone levels. Furthermore, bromocriptine therapy decreased serum prolactin levels and restored potency before the serum testosterone level increased into the normal range in five of six patients (11). In a different study (12), two patients with hyperprolactinemia and resistance to

bromocriptine experienced no improvement in erectile function despite testosterone replacement, suggesting that hyperprolactinemia in itself may lead to erectile dysfunction irrespective of testosterone levels.

Over the past few years, there has been growing awareness of the heterogeneity of serum prolactin, with the recognition of 'big' and 'big-big' prolactin (4, 5). In contrast, the prevalence of 'big' or 'big-big' macroprolactinemia in American populations is not known. However, a survey in Japan (4) found that 0.4% of adult women had asymptomatic 'big' macroprolactinemia. The prevalence of hyperprolactinemia in this population was 1.2%. In contrast, in the same study, only 0.02% of adult men had macroprolactinemia. In another study (13), only 1 of 605 healthy individuals (0.15%) and none of 11 patients with prolactinomas were found to have hyperprolactinemia secondary to 'big-big' prolactin. In a different survey from Japan (14), the prevalence of macroprolactinemia secondary to 'big-big' prolactin was 2.9% among pregnant women.

Female patients with macroprolactinemia are mostly asymptomatic (4, 7, 15). In one study (7), only one of five female patients with 'big' macroprolactinemia had radiologic evidence of a pituitary microadenoma. Three additional patients with prolactinomas and increased contribution from high molecular weight prolactin forms have been reported (16). Only one female patient in that report showed a preponderance of 'big-big' prolactin on gel filtration studies.

Reports of men with macroprolactinemia are rare. Wortsman *et al.* (17) reported two adult men with 'big-big' macroprolactinemia and no radiologic evidence of a pituitary tumor, one of whom had normal erectile function. Garnier *et al.* (18) described a series of patients with pituitary tumors and measurable 'big' prolactin levels. Only one man in that series had an excess of 'big' prolactin. However, no comment was made about the patient's erectile function. We (8) recently reported on six adult men with erectile dysfunction and idiopathic 'big' or 'big-big' macroprolactinemia whose symptoms resolved with appropriate counseling. To our knowledge, the two patients presented here are the only reported male subjects with 'big' macroprolactinemia secondary to pituitary adenomas who were documented to have intact erectile function.

Given the fact that the overwhelming majority of men with prolactin-secreting pituitary adenomas have erectile dysfunction, we suggest that documentation of normal erectile function in our patients, despite high 'big' prolactin levels, is evidence for decreased bioactivity of 'big' prolactin. It has been suggested that both 'big' prolactin has decreased receptor affinity (18), whereas 'big-big' prolactin has decreased bioavailability (19). However, it should also be noted that both patients had biochemically documented secondary hypogonadism. Although we cannot exclude the possibility that 'big' prolactin could be playing an etiologic role, we believe that hypogonadism more probably reflected pressure

effects on the gonadotrophs by these large tumors or, in our second patient, the potentially detrimental effects of surgery and radiotherapy on pituitary gonadotrophs.

In summary, we have presented the first two male subjects with pituitary tumors and 'big' macroprolactinemia who were documented to have intact sexual function despite high prolactin levels. Thus 'big' macroprolactinemia should be suspected even in individuals with prolactinomas in the absence of clinical manifestations.

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