Clinical case

Absence of hypogonadism in a male patient with a giant prolactinoma: A clinical paradox

Absence d’hypogonadisme chez un patient masculin avec prolactinome géant : un paradoxe clinique

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Abstract

Background. – Impotence and decreased libido are the cardinal features of prolactinomas in males. We describe the unusual clinical, pathological and biochemical features in a male patient with a giant prolactinoma and normal gonadal function.

Case Report. – A 57 year-old man presented with visual symptoms related to a 30 × 25 × 60 mm tumor of the sella and skull base. Biopsy revealed a pituitary adenoma and subsequent hormone profiles demonstrated grossly elevated serum prolactin (131,412 ng/ml), LH at the upper limit of normal and normal testosterone. The patient had no symptoms of decreased libido or impotence related to this giant prolactinoma. Immunohistochemistry revealed a tumor that was positive for prolactin, alpha-subunit and LH. Cabergoline greatly reduced prolactin levels but these remained above normal. LH, testosterone and alpha-subunit levels were decreased in parallel. Loss of libido and impotence became apparent when testosterone fell below normal, a situation that resolved with further cabergoline treatment and prolactin inhibition and testosterone therapy.

Conclusions. – Sexual dysfunction is a hallmark of prolactinomas in males. Tumors that co-secrete prolactin and LH are extremely rare and this is the first such case reported in an adult male. In this case, normal testosterone was maintained by intact LH levels even in the face of the highest prolactin level reported to date.

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Résumé

Introduction. – L’impuissance sexuelle et la diminution de libido sont les symptômes principaux du prolactinome chez l’homme. Nous décrivons un cas inhabituel sur les plans clinique, anatomopathologique et biologique chez un homme souffrant d’un prolactinome géant mais gardant une fonction gonadique normale.

Cas clinique. – Un homme de 57 ans s’est présenté à la consultation avec des symptômes visuels en relation avec une tumeur de la selle turcique et de la base du crâne de 30 × 25 × 60 mm. La biopsie a révélé un adénome hypophysaire et les dosages hormonaux qui ont suivi ont révélé un taux de prolactine de 131 412 ng/ml. La LH était à la limite supérieure de la normale et la testostérone était normale. Le patient n’avait pas de diminution de libido, ni d’impuissance sexuelle en relation avec ce prolactinome géant. L’immunohistochimie a révélé une tumeur positive pour la prolactine, la sous-unité alpha et la LH. Un traitement par cabergoline a permis de réduire fortement le taux de prolactine sans toutefois le normaliser. Les taux de LH, testostérone et sous-unité alpha ont été diminués en parallèle. Le patient a alors observé une diminution de libido et une impuissance sexuelle qui sont devenues importantes lorsque la testostérone est tombée sous la barre inférieure de la normale.

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Conclusion. — La dysfonction sexuelle est un signe évident des prolactinomes chez l’homme. Une tumeur qui cosécrite prolactine et LH est extrêmement rare et le cas que nous rapportons est le premier rapporté chez un homme adulte. Dans ce cas, la valeur de testostérone normale était maintenue par la LH intacte qui était sécrétée par la tumeur malgré les valeurs les plus élevées de prolactine rapportées jusqu’à ce jour.

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1. Introduction

Pituitary adenomas occur frequently in the general population, with data from autopsy and radiological studies suggesting 16.7% of unselected individuals have a pituitary adenoma [1]. Many of these adenomas are, however, discovered incidentally and are not associated with clinical effects. The few studies that examined the historical prevalence of clinically active pituitary adenomas reported that they occurred quite rarely at about 20–30 cases/100,000 population [2,3]. In contrast, new epidemiological evidence [from the era of ready access to MRI (Magnetic resonance imaging)] indicates that clinically active pituitary adenomas occur with a prevalence of one in 1064 individuals [4]. Prolactinomas comprise half to two-thirds of cases, which suggests that prolactinomas themselves have a prevalence of up to one in 1600 [2,4]. Giant prolactinomas are defined variously as tumors greater than 4 cm in diameter, with greater than 2 cm of suprasellar extension, with invasive characteristics and marked prolactin hypersecretion greater than 2000–3000 ng/mL [5–7]. Giant prolactinomas comprise only 2% of all pituitary tumors in large series [7–9]. In keeping with the higher incidence of macroprolactinomas in males, giant prolactinomas also demonstrate a male preponderance [10]. It remains unclear, however, whether this gender imbalance is due to later diagnosis in males, molecular pathophysiological characteristics or both.

Giant prolactinomas exhibit a number of diagnostic and therapeutic challenges due to tumor expansion, difficult surgical access and atypical clinical-biochemical correlations. Grossly elevated prolactin secretion from giant prolactinomas may lead to a “hook-effect” in immunoradiometric assays [11]. Marked hyperprolactinemia and minor clinical symptoms should raise the suspicion of macroprolactin secretion [12,13]. In elderly patients a sizeable prolactinoma can remain undiagnosed until the onset of tumor mass-related symptoms [14].

We describe an unusual case that illustrates another discordance that can occur between prolactin hypersecretion and typical symptomatology in the setting of giant prolactinoma. A male patient had no symptoms attributable to hyperprolactinemia despite having the highest prolactin levels reported to date in the literature. This clinical scenario was due to an unusual pattern of hormonal secretion by the large tumor.

2. Clinical case

In mid-2005, a 57-year-old man was referred to the ophthalmology service due to a one-month history of visual disturbance and was found to have a marked right temporal visual field defect. A magnetic resonance imaging scan demonstrated a large lesion (30 × 25 × 60 mm) with suprasellar and infrasellar extension, cavernous sinus invasion and enshrouding of the carotid arteries (Fig. 1a).

The patient was referred to the neurosurgery service and suspecting a malignant skull base tumor, the lesion was biopsied. Histology revealed polygonal, mildly pleomorphic cells of epithelial origin, separated by connective tissue-vascular septa and accompanied by abundant hyaline material with spheroidal dystrophic calcifications. Necrosis was absent and mitotic figures were scarce. The tumor tissue was positive for tumor markers neuron-specific enolase and CD56, while cytokeratin KL1 and CD45 staining were negative. As the biopsy material was consistent with a pituitary adenoma, immunohistochemistry for pituitary hormones was undertaken. This showed uniformly strongly positive staining for prolactin in greater than 95% of cells, mild α-subunit staining in 20–30% of cells and occasional LH-positive cells (4–5% of cells); staining for all other pituitary hormones was negative (Fig. 2). Approximately 5–10% of cells were mildly stained for chromogranin A.

The patient was referred to the Endocrinology service. Specifically, the patient reported no headache, loss of libido or impotence, while galactorrhea and mammary tension were absent. He was otherwise healthy and had fathered two children, now aged in their twenties. Serum hormonal assays were undertaken, which showed a massively elevated serum prolactin of 131,412 ng/ml (normal range: 2.35–23.5 ng/ml); low levels of big (4.5%) and big-big (0.5%) prolactin excluded macroprolactinemia. The alpha-subunit concentration was also greatly elevated at 54.9 ng/ml (normal range: <0.1–0.7 ng/ml).

LH was 9.6 mU/ml (normal range: 2.0–10.0 mU/ml), while FSH (follicle stimulating hormone) was undetectable (<0.3 mU/ml). Total testosterone, although in the normal range, was somewhat higher than expected for the patient’s age (6.25 ng/ml, normal range: 2.5–10 ng/ml). An insulin tolerance test (ITT) showed mild growth hormone deficiency (GH peak: 3.22 ng/ml), although the patient’s IGF-I was within the normal range for age and gender (145 ng/ml). Baseline ACTH was 17 pg/ml (normal range: 10–70 pg/ml) and rose to 83 pg/ml during the ITT, while cortisol achieved an appropriate peak of 227 μg/l (626 nmol/l) during the ITT. Thyroid hormone levels (TSH, T3, T4) were normal.

Treatment with cabergoline was started cautiously (0.25 mg once weekly) and was well tolerated by the patient. One month later, prolactin and alpha-subunit levels had decreased to 83223 ng/ml and 25.4 ng/ml, respectively (Fig. 3). LH and total testosterone levels rose slightly (10.5 mU/ml and 6.39 ng/ml) after a month, but fell to 4.8 mU/ml and 1.70 ng/ml.
respectively after six months of therapy. Cabergoline was increased gradually to 0.5 mg twice weekly and 12 months after starting therapy, continued decreases were seen in prolactin (5694.5 ng/ml), α-subunit (1.80 ng/ml), LH (4.7 mU/ml), and testosterone (2.69 ng/ml) levels. MRI showed progressive reduction of the tumor size from the fourth month of cabergoline treatment and after 12 months, the tumor measured 25 × 12 × 42 mm (Fig. 1b). The ocular signs and symptoms resolved. Despite the significant tumor shrinkage, no major adverse effects (e.g. cerebrospinal fluid leak) were seen. In parallel with the decreased testosterone, the patient noted decreased libido and the onset of impotence, which had not occurred previously. Continued cabergoline therapy for the next year was accompanied by a stabilization of prolactin at approximately 4700 ng/ml, with a modest elevation in α-subunit (1.40 ng/ml). FSH, which had been undetectable before cabergoline therapy rose from <0.3 mU/ml (normal range: 1.0 to 8.0 mU/ml) before treatment to 1.2 mIU/ml after 4 months, and gradually to 1.9 mU/ml at last follow-up in mid-2007. LH was in the normal range and testosterone secretion was stabilized in the low-normal range (2.97 ng/ml in February 2007); supplementation with oral testosterone undecanoate was implemented in March 2007. The patient was asymptomatic and had a normal testosterone level at last follow up in June 2007.

3. Discussion

Hypogonadism and sexual dysfunction are clinical hallmarks of hyperprolactinemia in men with prolactinomas. In 16 studies involving 444 males, Gillam et al. reported that 77.9% of patients had impotence, sizably more frequent than visual field defects (36.6%), hypopituitarism (33.8%), headache (29.1%), and galactorrhea (10.9%) [5]. Sexual dysfunction in men with prolactinoma typically improves with reductions in circul-
Fig. 2. Immunostaining of tumor biopsy sample for prolactin (a), alpha-subunit (b), and LH (c). Images are shown at 400× magnification. Granular cytoplasmic immunopositivity for prolactin (brown) is seen in most tumor cells in (a), alpha-subunit immunoreactivity (brown) in a minority of cells in (b), and faint cytoplasmic staining for LH (black arrowheads) is seen in occasional cells in (c).

Fig. 2. Immunomarquage d’un fragment biopsique tumoral pour la prolactine (a), la sous-unité alpha (b) et la LH (c). L’agrandissement est de 400. L’immunopositivité des granules cytoplasminiques pour la prolactine (en brun) est observée dans la plupart des cellules tumorales de la planche (a), l’immunoréactivité vis-à-vis de la sous-unité alpha est observée dans une minorité de cellules de la planche (b), et un marquage cytoplasmique faible pour la LH est observé (flèches noires) sur quelques cellules de la coupe (c).

The clinical presentation and evolution in the current case was the opposite of what would be usually expected in a male patient with a giant prolactinoma. Even though LH staining was scanty, the size of the tumor in this case permitted sufficient LH secretion to maintain normal testosterone. Thus, even in the face of prolactin levels far in excess of those seen previously in giant prolactinomas, the patient reported neither impotence nor loss of libido. Paradoxically, it was the instigation of cabergoline therapy and the accompanying tumor shrinkage and decrease in LH that allowed typical hypogonadal features to become evident. Interestingly the marked decrease in prolactin was accompanied by a minor rise in LH and testosterone during the first 4 months of cabergoline therapy, suggesting heterogeneous responsiveness to cabergoline among the various component cell sub-types in the tumor. The atypical secretory pattern in this case is the exception that proves the rule that the appearance and disappearance of sexual dysfunction in males with hyperprolactinemia is dependent on circulating testosterone levels. In this case, we elected not to increase cabergoline therapy above 0.5 mg twice a week, in order to avoid potential complications such as cerebrospinal fluid leak [20].

Co-secretion of prolactin and LH (± alpha-subunit) by a pituitary tumor is extremely rare. Only one case of mixed PRL/LH/alpha-subunit-secreting pituitary adenoma has been reported in an adult patient, although this was a macro-adenoma in a female patient [21]. LH secretion in that case was not associated with normal circulating sex hormones, and the patient menstruated but was infertile. Treatment with quinagolide resulted in a small decrease in prolactin and LH, and the patient required lanreotide to normalize prolactin and permit ovulation. No tumor decrease was seen and LH and alpha-subunit remained elevated and the patient eventually underwent successful transphenoidal surgery. Faggiano et al. reported a case of precocious puberty associated with galactorrhea in a four year-old boy due to a pituitary macro-adenoma that secreted prolactin and LH, leading to peripheral elevated testosterone secretion [22]. In that case, surgical resection of a chromophobe adenoma led to resolution of physical symptoms and hormonal normalization;
long-term follow-up was not reported. Finally, Ambrosi et al. reported another case of precocious puberty in a male due to a pituitary macro-adenoma that co-secreted prolactin, LH and FSH, leading to hyperprolactinemia and high circulating testosterone [23]. The patient had short term decreases in prolactin after a trial of bromocriptine, but gonadotroph secretion was unaffected by the dopamine agonist. Therefore, surgery was performed which led to normalization of hormonal and clinical parameters. In contrast to our patient, pathological study of the tumor in that case demonstrated that 70–85% of the tumor cells were immunohistochemically positive for prolactin, LH and FSH within the same granules.

This case combines a number of findings that are unusual even in the setting of giant prolactinomas. The prolactin secretion at diagnosis in this case was extremely elevated and is the highest level reported to date; this supports the view that despite large size and aggressive growth characteristics, giant prolactinomas retain competent secretory function. Despite a prolactin level of more than 130 000 ng/ml, symptoms of hypogonadism were entirely absent, due to the rare co-secretion of LH by the tumor that maintained peripheral testosterone levels within the normal range. Finally, while the treatment with cabergoline would be expected to restore normal testosterone secretion in the setting of a giant prolactinoma, in this case hyperprolactinemia combined with suppression of LH secretion initially produced symptoms of impotence and low libido, previously unseen in this patient. Further suppression of prolactin during long-term treatment led to stability of testosterone in the low-normal range and the return of normal sexual function. Co-secretion of prolactin and LH by a pituitary adenoma can complicate the diagnosis of a giant prolactinoma in a male and, although very rare, it should be borne in mind in the setting of marked hyperprolactinemia in the absence of typical hypogonadal features.

References


