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PRL Secreting Adenomas in Male Patients

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Abstract. **Prolactinomas are the most frequent pituitary tumors and their frequency varies with age and sex, occurring most frequently in females between 20–50 yr-old. In men, hyperprolactinaemia is often present for many years without symptoms, as generally the most important symptoms are the decrease in libido and/or sexual potency both underestimated by the majority of the patients. Prolactin (PRL) plays a role in the process of spermatogenesis, and normal serum PRL levels are required for normal testicular function. On the other hand, hyperprolactinaemia has multiple negative effects on the gonadal axis. As a consequences hyperprolactinemic males show alteration of sexual potency and seminal fluid quality. Cabergoline treatments is able to induce normalization of PRL levels and a reduction of tumor mass in the majority of patients and consequently restoring the normal semen quality and ameliorating the quality of life of men with pituitary PRL-secreting adenoma.**

Key Words. **prolactin, prolactinomas, cabergoline, dopamine, seminal fluid, spermatozoa, male fertility**

Introduction

Prolactinomas represent the most common type of clinically recognized pituitary tumor, accounting for approximately 40–45% of all [1]. Their frequency varies with age and sex. In fact, they are relatively rare in males and occur most frequently in females between 20–50 yr-old, when the ratio between the sexes is estimated to be 10:1. After the fifth decade of life the frequency of Prolactinomas is similar between women and men. Women usually present with microadenomas revealed by the classical amenorrhea-galactorrhea syndrome. The clinical presentation of hyperprolactinaemic men is much more polymorphic and can be misleading [2]. Impotence and decreased libido are the most frequent symptoms, but the diagnosis is often made when signs of compression due to the tumor develop [2].

In men, hyperprolactinaemia is often present for many years because the symptoms, decrease in libido and/or sexual potency, are underestimated by the majority of the patients. Consequently, the mean age at diagnosis is 10 years greater in men than in women [3,4]. This delay in the diagnosis in men probably accounts for the greater incidence of macroadenomas with visual field defects and hypopituitarism at first presentation, as compared to women [3]. It is unclear whether this finding is correlated to a delay in diagnosis or gender specific differences in tumor pathogenesis. Moreover, others data shown that a subset of men may have rapidly growing prolactinomas with elevated markers of cellular proliferation [5,6]. Thus, it is necessary to consider also differences in the biological behavior of tumors in men compared to women [3,5,6]. However, data on hyperprolactinaemia in men are still limited compared with women and have usually been analyzed in small retrospective studies [4,6].

PRL-secreting adenoma and gender differences

It is clear that the clinical setting of PRL-secreting pituitary adenoma varies greatly with sex. The reason for the preponderance of large tumors in men remains to be elucidated. For most researchers, represent the early and late stages of the same pathological process, and a delay in seeking medical attention explains why tumors are larger in men. However, studies comparing the clinical and pathological correlates of growth of these tumors in both sexes are lacking and a more aggressive course of the disease in men has not been ruled out. Delgrange *et al.* showed that the difference between sexes in tumor diameter is present even in young patients, that the growth potential of macroprolactinomas seems greater in men than in women, given a male preponderance of aggressive forms of the disease (i.e. giant, invasive and malignant prolactinomas) despite the overall incresed prevalence of prolactinoma in women and, finally, that prolactinomas in males had higher proliferative indexes (Ki-67 and PCNA) than similar tumors in females [5]. These data must be interpretated with caution for two reason: (1) the onset of clinical manifestation of hyperprolactinaemia is often insidious and syptoms of sexual dysfunction may be ignored by the patient; (2) the length of the asymptomatic phase may

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be important as the male reproductive axis seems more resistant to hyperprolactinaemia than the female one [7]. Indeed normal testosterone levels may be observed in many patients with mild hyperprolactinaemia [8] and in up to 30% of patients with prolactinomas [8]. Thus, men lack an objective clinical marker to identify the onset of disease. In females, the duration of symptoms more accurately reflects the duration of disease, as the onset of menstrual dysfunction or galactorrhea is clear-cut and commonly seen with minimal PRL elevations [7]. However, often, in women tumor size is not correlated to duration of disease and the usual small size of prolactinomas in women is not due to precocity of diagnosis.

On the other hand Colao *et al.* showed a normalization of PRL levels after cabergoline treatment higher in micro- than in macroprolactinoma patients, as expected, but, without any difference related to gender and, similarly, without difference in cabergoline dosage [2]. Moreover the prevalence and entity of tumor shrinkage was also similar between sexes [2]. Additionally they not found any difference between the prevalence and severity of neurological signs, as an expression of tumor invasiveness but only larger tumors in men correlated with higher prolactin levels [2]. In another study on male patients with PRL pituitary adenoma, Colao *et al.* showed a same percentage of PRL normalization in those with micro (80%) or macroprolactinoma (75.6%) with a remarkable tumor shrinkage (>30% decrease of the maximal tumor diameter) [9]. These data ruled out the hypothesis that men bear more aggressive tumors less likely to be responsive to pharmacotherapy than women, because the outcome of cabergoline treatment did not differ from that reported in other studies with similar treatment duration [6,10].

Hyperprolactinaemia, sexual potency and seminal fluid quality

Prolactin is a functional modulator of the hypothalamus-pituitary-gonadal axis. It affects the testis directly in most mammals. PRL receptors are present in all stages of the cycle of the seminiferous epithelium, the surface of Sertoli and Leydig cells, and all phases of spermatogonia and spermatocytes in male rats [11]. In Leydig cells, PRL is involved in the manteinance of cellular morphology, increase LH receptor number, and along with LH, decreases aromatase activity and increases steroidogenesis and androgen production [11]. In Sertoli cells, PRL has been shown to increase FSH receptor numbers. Several effects on spermatozoa have been reported, including an increase of calcium binding and/or transport of ejaculated and epidymal spermatozoa as well as an increase in energy metabolism, a maintenance of mobility and attachment to the oocyte and a reduction in the time required to achieve capacitation [11]. These findings imply that PRL plays a role in the process of spermatogenesis, and normal serum PRL levels are required for normal testicular function. On the other hand, hyperprolactinaemia has multiple negative effects on the gonadal axis. High levels of PRL suppress GnRH secretion and, consequently, decrease gonadotropin and testosterone production [12]. In some cases, hyperprolactinaemia induces clinical hypogonadism notwithstanding normal serum FSH, LH, and testosterone levels. There is an exaggerated diurnal variation in testosterone in men with prolactinomas, so that normal morning values do not guarantee normal values throughout the day [13]. Others have suggested a reduced conversion of testosterone to dihydrotestosterone [14]. If so, the hypogonadism associated with hyperprolactinaemia may not solely result from the decrease in serum testosterone. In fact, testosterone replacement therapy may not reverse the loss of libido that is typical of men with prolactinoma until the PRL level is normalized by the administration of a dopamine agonist [9]. Another mechanism to explain the suppression of gonadal function in men with prolactinoma is a direct tumor mass effects on gonadotroph cells. Large adenomas often causes deficiency of anterior pituitary hormones, including gonadotropins. However, a tumor mass effect is less important than hyperprolactinaemia in the development of hypogonadism in prolactinomas. In fact there is no significance difference in the prevalence of testosterone deficiency between micro- and macroprolactinomas, either before or after medical treatment [9]. Thus hyperprolactinaemia modifies seminal fluid quality trough many different mechanism. In particular, it causes spermiogenic arrest and impaired sperm motility and/or quality with cytological findings, similar to that observed in the prepubertal testis [15].

Data on hyperprolactinaemia in men and its control with dopamine agonists are still limited compared with women and have usually been analyzed in small retrospective studies. In a 5 yr prospecive study on 219 patients with hyperprolactinaemia, Colao *et al.* showed the role of cabergoline to normalize, after only six month, the PRL levels without difference between men and women [2]. Moreover, until now, scant data are available on the recovery of sperm function in men with prolactinoma. In the recent years we have hard investigated the alterations of semen quality, and its recovery after cabergoline treatment, in hyperprolactinemic males. We found a significant increase of number, motility at first hour, forward progression, and normal morphology of sperm after either bromocriptine, quinagolide or cabergoline treatments but improvement of sperm and sexual function was more consistent and rapid in pateints treated with cabergoline [16–17]. Recently we have further investigated the outcome of 24-months cabergoline treatment in hyperprolactinemic male [9]. At 24-month follow-up, PRL levels were normalized in the 75.6% of patients with macroprolactinoma and in the 80% of patients with microprolactinoma with a median dose of 1 mg/wk for micro and 1.5 mg/wk for macroprolactinomas [9]. In patients achieved PRL normalization a significant improvement of semen parameters was

observed during the follow-up [9]. After 6 and 12 months of cabergoline therapy, despite the normalization of testosterone levels, without testosterone replacement therapy, seminal parameters remained impaired compared with controls, whereas after 24 months of therapy all seminal parameters (seminal volume, sperm count, total sperm count, sperm total motility and forward progression) were similar to controls [9] (Fig. 1). In particular sperm volume and number were normalized in all patients, achieving normal testosterone levels during the first 12 months, whereas motility and forward progression normalized in more than 80% of cases after 24 months of therapy [9].

Finally, in another open longitudinal study we investigated the sexual potency in hyperprolactinemic males monitoring nocturnal penile tumescence (NPT) [18]. Abnormal NPT values were found in all macroprolactinomas and in the 80% of microprolactinomas with a relevant difference between the subjective perception of sexual failure, present in only 50% of patients, and its objective demostration. In the patients the number of qualified erectile events per night during NPT was correlated with PRL levels but not with testosterone levels or age, whereas in controls it was correlated with age, testosterone and PRL levels [18]. After six months of cabergoline treatment there was a clear improvement of NPT results in patients who achieved a PRL normalization even when testosterone levels were not normalized [18]. Conversely in patients who did not have PRL normalization only a modest improvement was observed [18].

Hyperprolactinaemia and Prostate Hypertrophy

Prolactin regulates prostate development, growth and differentiation [11]. In fact it has an androgen indipendent effect on growth and differentiated functions of prostate [19]. The *in vitro* and *in vivo* studies corfimed that PRL is able to stimulate the proliferation and secretion and to increase the survival of prostate epithelium [11]. On the other hand, little is known about the specific and direct effects of PRL on the human prostate, and the mechanisms underlying the responses of prostate cells to PRL remain unclear [19].

Recently Colao *et al.* have evaluated the effects of hyperprolactinaemia and its control by dopamine agonist cabergoline on prostate structure in young men with prolactinoma [20]. We found, as expected, lower serum testosterone and dihydrotestosterone (DHT), and higher PRL levels in the patients than in the controls, but, surprisingly, the prostate volume was lower in hyperprolactinemic men than in normal subjects [20]. It is very likely that in the human model of prolactinoma, testosterone and DHT levels lower than normal or in the low normal range have the major effect on prostate size. In fact, normalization of PRL, testosterone and DHT levels after 24 months of cabergoline treatment normalized prostate size without any change in prostate structure [20].

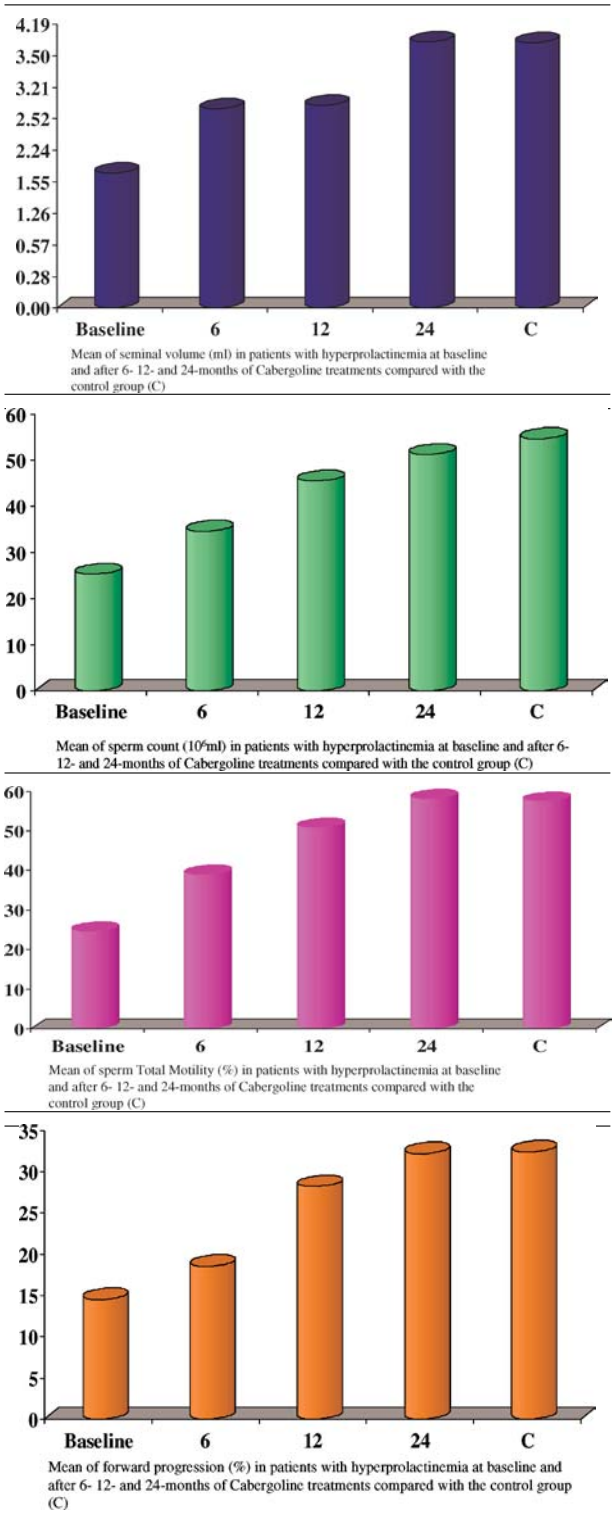

Fig. 1. *Mean of seminal volume (ml), sperm count (10^6ml), sperm total motility (%) and forward progression (%) in patients with hyperprolactinemia at baseline and after 6- 12- and 24-months of Cabergoline treatments compared with the control group (C). Data derived from Calao A. et al. J Clin Endocrinol Metab 2004;89:1704–1711.*

Conclusions

In conclusion the clinical presentation of hyperprolactinaemic men is polymorphic and can be misleading. The treatment with dopamine agonists induced normalization of PRL levels in the majority of patients with a remarkable tumor shrinkage even in those not achieving normal PRL values. Moreover PRL normalization is followed by restoration, after long-term cabergoline treatment, of an adeguate sexual potency and a normal semen fluid quality.

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