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Review

Hyperprolactinemia and sexual function in men: a short review

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Erectile dysfunction (ED), generally associated with reduced sexual desire and sometimes with orgasmic or ejaculatory dysfunction, is the major revealing symptom of hyperprolactinemia (HPRL) in men, a condition that should not be neglected since many cases result from pituitary tumors, likely to result in serious complications. It is generally believed that the mechanism of the prolactin (PRL)-induced sexual dysfunctions is a decrease in testosterone secretion. In fact, serum testosterone is normal in many hyperprolactinemic males and there are also testosterone-independent mechanisms, probably mainly set at the level of the brain's neurotransmittor systems. Systematic determinations of serum PRL found very low prevalences of marked HPRL (>35 ng/ml) in ED patients (0.76% in a compilation of over 3200 patients) as well as of pituitary adenomas (0.4%). In addition, the association of HPRL with ED may have been coincidental in some of these cases, since 10% of the HPRLs diagnosed by the usual immunological assays are composed of macroprolactins, which are biologically inactive or little active variants of PRL. Their identification requires a PRL chromatography that is restricted to some specialized laboratories. There is presently no consensus with regards to the screening for HPRL in ED: systematic determination of serum PRL may be justified since HPRL is a serious but reversible disease, while there is presently no reliable clinical, psychometric or hormonal criteria (including serum testosterone level) allowing to restrict its determination to certain categories of the ED patients without risk of neglecting some HPRLs. In case of consistent HPRL, searching for a hypothalamic or pituitary tumor is mandatory. Dopamine-agonist therapy is the first choice treatment for the PRL-induced sexual dysfunctions. Additional sexual counselling may be necessary for certain patients.
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Prolactin (PRL) has no known role in physiological control of human sexual behavior, except a possible contribution of the orgasm-induced PRL secretion to the sexual-satiation mechanisms, since sexual satiation has not been observed in a multiorgasmic male.[1] On the contrary, all types of hyperprolactinemia (HPRL) (idiopathic, tumoral or drug-induced) can inhibit most aspects of male sexual behavior. Therefore, although HPRL is a rather rare condition, it may be a cause of male sexual dysfunction, and should not be neglected since it is reversible, and may result from pituitary tumors likely to result in serious endocrine and visual complications due to the tumor's growth.

Sexual problems of hyperprolactinemic men

A literature review encompassing more than 300 hyperprolactinemic men[2] found sexual dysfunctions in 88%, including erectile dysfunction (ED) almost each time. The most typical pattern associated ED with a reduced sexual desire. Delayed or absent orgasm was associated in some cases, but virtually never isolated. Some cases of retrograde ejaculation were also reported. The non sexual symptoms of HPRL were less frequent: reduced body hair in 40%, gynecomastia in 21%, galactorrhea in 13%. ED is thus the major revealing symptom of HPRL in men.

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Carani *et al*[3] recorded the nocturnal erections of six men with serum PRL over 300 ng/ml with a Rigiscan®: these, as well as the erections induced by audiovisual sexual stimulation, did not differ from those of normal control males.

Mechanisms of the sexual dysfunctions associated with HPRL

HPRL impairs the pulsatile LH release, which results in a decrease of serum testosterone secretion. It is generally believed that this hypogonadism is the main cause of ED. In fact, it may not explain every case. Serum testosterone is in the normal range in nearly half of the ED patients with marked HPRL (for example, seven in a personal series of 16[2]). In addition, serum sex hormone-binding globulin is low in hyperprolactinemic males,[4] which attenuates the biological impact of low total testosterone by increasing its unbound proportion. During treatment of hyperprolactinemic men with the prolactin-lowering agent bromocriptin, sexual improvement correlates better with serum PRL's decrease than with testosterone's increase.[2] Also, erections can return prior to any increase in testosterone. A study by Bancroft *et al*,[5] who compared bromocriptin with a placebo in a single man according to a double-blind design, also tends to support a direct, testosterone-independent effect of HPRL on men's sexual behavior.

The mechanisms nondependent on the circulating testosterone level may include the decrease in testosterone 5 alpha reduction into dihydrotestosterone observed by Lobo and Kletzky[6] in hyperprolactinemic men, since dihydrotestosterone seems the main metabolite accountable for the testosterone effects upon the primate brain centers. However, the main testosterone-independent mechanisms prob-ably depend on PRL interactions with neurotransmitter systems. PRL increases the synthesis, turn-over, and release of central dopamine from hypothalamic neurons, which could explain the biphasic effect of HPRL demonstrated in rats.[7] Dopamine stimulates sexual behavior in most animal species. Its increased release may explain the initial stimulating effect of HPRL on rat's sexual function. The second time, a downregulation of the dopamine receptors due to their excessive stimulation would explain the subsequent inhibitory effect. In addition, HPRL causes marked increases in tyrosine hydroxylase mRNA expression in the hypothalamic arcuate and periventricular nuclei, a region of the brain associated with sexual and erectile function.[8] PRL also interacts with the opioid and serotoninergic systems, both involved in the adjustment of sexual behavior.[9] Recent experiments by Rehman *et al*[10] confirmed the primarily central and testosterone-independent effect of HPRL in rats, since in this species penile reflexes are abolished following PRL injections, although the peripheral mechanisms of erection remain intact, and these reflexes are not restored by testosterone supplementation.

Prevalence of HPRL in ED patients

Systematic determinations of serum PRL found very low prevalences of HPRL in ED patients (1–5%). Compiling the seven largest series leads to a prevalence of marked HPRL (serum PRL $\geq$ 35 ng/ml) at 0.76% (25 of the 3265 patients with specified individual values) and of pituitary adenomas at 0.4% (18 of 4363).[11–17] In addition, some ED patients were found to have mild HPRL (serum PRL from 20–35 ng/ml), at a 1.5% prevalence in a personal series of 1370 consecutive ED patients having undergone systematic PRL determination.[18] It is unlikely that such modest HPRLs were the real cause of ED since none of the 21 cases had a low testosterone level or a pituitary tumor (however, two micro adenomas were found by Johri *et al*[17] in such cases). In addition, only 40% improved as regards their erectile function following administration of bromocriptin. This rate approximates the placebo effect and the 40% success rate reported with bromocriptin in normoprolactinemic ED patients by Ambrosi *et al*.[19] Conversely, bromocriptin restored normal erectile function in two-thirds of a personal series of 12 ED patients with serum PRL over 35 ng/ml,[16] which suggests a causative effect of HPRL in this category. All the more that every four other patients, although still unable to penetrate their partner after restoration of normal PRL levels, reported improved libido and morning erections. Two of them also recovered normal erectile capacity following additional sexual counselling. Schwarz *et al*,[20] from the Masters and Johnson' group, had previously reported that sexual function of markedly hyperprolactinemic men was better improved by bromocriptin than by psycho- or sex-therapy in an, however, uncontrolled study.

When evaluating the association of HPRL with sexual dysfunction, it should also be considered that biologically inactive or little active variants of PRL may be assayed by immunological assays. It is especially the case of the 'big' and 'big–big' PRLs, which have molecular weights of, respectively, 50–60 and 150 kilo Daltons (kDa) compared with the 22 kDa of the biologically active PRL.[21] When detected with these assays, excessive secretion of 'macroprolactins' resembles a classical HPRL, while it has, in fact, generally no pathological consequence. Macroprolactinemias account for 10% of all HPRLs[22] and are typically observed in otherwise normal individuals, mostly women with normal reproductive function despite high PRL levels, but

also some ED patients in whom they seem coincidental.[23,24] In such cases serum testosterone is usually normal, as are CT scans and MRI of the hypothalamic–pituitary area. PRL-lowering agents are ineffective in improving sexual function. It may therefore be suspected that HPRL is not the cause of ED. Such a discrepancy should lead to PRL chromatographic analysis in a laboratory specialized in endocrinology, allowing identification of the macro-PRL. However, a diagnosis of macroprolactinemia in an ED patient should preclude neither MRI testing, since some rare cases are associated with pituitary adenomas, nor a trial of a PRL-lowering agent, since a biological activity of the macroprolactin has been demonstrated in some women, including reversal of amenorrhea and infertility on dopamine-agonist therapy.[22] The early reports of male HPRL cited in this review have certainly included some cases of undiagnosed macroprolactinemia. The fact that we found a trend to a decrease in the HPRL's prevalence with time by systematically determining serum PRL in our ED patients for several decades[16] might result from the improvement with time of the assays' specificity, leading to less confusion with macroprolactinemias. Another explanation could be the relatively large number of HPRLs still undiagnosed at the beginning of our systematic assessment, which started 25 y ago, just at the time methods for PRL assay became available.

Prevalence of HPRL in the other sexual dysfunctions

We systematically determined serum PRL in men consecutively seen for low sexual desire without ED ($n=53$), anorgasmia ($n=74$), and premature ejaculation ($n=124$).[2,18] We found no HPRL in the two former sexual dysfunctions. However, the size of samples was limited and Schwartz *et al*[20] reported on some male HPRLs revealed by isolated low sexual desire or anorgasmia.[20] On the contrary, serum PRL was mildly elevated (20–35 ng/ml) in 13 men with premature ejaculation (10%). This was not the cause of sexual dysfunction since bromocriptin failed in every case to prolong the time to ejaculation. In addition, serum testosterone was normal in all, and no pituitary adenoma was found in any patient.

Diagnosis of HPRL in men with sexual dysfunction

Some precautions are critical to avoid false HPRLs resulting from stress (especially from veinipuncture) and meals. Blood sampling must be performed with fasting, following a 20-min rest in a quiet place. Any elevated serum PRL must be checked again, if possible following the catheter's insertion 20 min before sampling, and after discontinuation of any drug likely to increase PRL (Table 1). In case of discrepancy between high serum PRL and a pattern of nonendocrine sexual dysfunction, the patient should be referred to an endocrinologist who will decide about the usefulness of a PRL's chromatography. As already discussed, the responsibility of mild HPRLs (20–35 ng/ml) in sexual dysfunction is questionable. In this respect, the threshold of significant HPRL is probably in the region of 35 ng/ml or 750 μUI/ml (1 ng/ml = 21 μUI/ml).

Drug-induced HPRL is the first etiology to consider. This easily reversible cause is responsible for a significant proportion of the HPRLs detected in men with sexual dysfunctions. Many types of drugs may increase serum PRL (Table 1). The highest PRL levels are associated with benzamides and metoclopramide. HPRL may also be secondary to hypothyroidism, renal insufficiency, and cirrhosis (mild or moderate in all three conditions) and to any process compressing or interrupting the hypothalamic–pituitary dopaminergic transmission. This includes many types of hypothalamic and pituitary tumors. Primary HPRL results from a primary defect of the dopaminergic inhibitory control of PRL secretion. It may be idiopathic, but in many cases it is associated with prolactin-secreting pituitary adenomas (prolactinomas). These, as the other types of hypothalamic

Table 1 Drugs likely to increase serum PRL (in most cases due to their antidopaminergic activity)

Opiates, Methadone
Psychotropic drugs
  Neuroleptics:
    Benzamides: Amisulpride, Sulpiride, Sultopride, Tiapride
    Phenotiazins: Chlorpromazin, Cyamemazin, Fluphenazin, Levomepromazin, Perphenazin, Pipetiazin, Propericiazin, Thioridazin
    Butyrophenons: Droperidol, Haloperidol, Pipamperon Flupentixol, Loxapin, Olanzapine, Pimozide, Risperidone, Zuclopenthixol
  Tricyclic antidepressants:
    Amitriptyline, Amoxapine, Chlorimipramine, Desipramine, Dosulepine, Doxepine, Imipramine, Maprotiline, Trimipramine
Antiemetics: Metroclopramide, Metopimazide
Antiulcerous: Cimetidine (only at high dose)
Antihypertensives: Reserpinics, α-Methyl-DOPA
Estrogens

or pituitary tumors, are likely to result in tumoral complications (visual disturbances or even blindness due to compression of the optic chiasma, and hypopituitarism, which may become life-threatening if decompensated). Consequently, any man with nondrug-induced HPRL confirmed by a repeat serum PRL determination after blood sampling in appropriate conditions, must benefit from morphological investigations of the hypothalamic–pituitary area (magnetic resonance imaging) for detecting a tumor responsible for the HPRL.

According to many authors, the very low prevalence of significant HPRL can hardly justify routine PRL determination in ED patients, due to their large number and the cost of determinations.[11,12,15,16] Most recommend determination of serum PRL only in case of low testosterone level or of low sexual desire.

However, in a personal series testosterone level was subnormal ($\leq$3 ng/ml) in only 10 of 17 hyperprolactinemic men, including only five of 10 referred for ED.[2] It was in the low normal range (3–4 ng/ml) in four of the seven others and over 4 ng/ml in three. Many other ED patients with normal serum testosterone despite marked HPRL have been reported, including some with pituitary tumors, unlikely to be macroprolactinemias.[2] Determining serum PRL only in case of low testosterone would have led to neglect 50% of the 12 marked HPRL and three of the seven pituitary tumors that we detected in ED patients.[16]

Likewise, sexual desire may be normal, or may seem normal to the patient, in ED patients with HPRL. Johri *et al*[17] found no difference in the mean PRL level according to the fact that sexual desire was quoted normal or low at clinical assessment, or according to the score of the Sexual Desire Domain of the International Index of Erectile Function (IIEF). By determining serum PRL only in case of a score $<$ 3, they would have overlooked 50% of the HPRL they found in their ED patients.

The IIEF might, however, be of interest for screening for HPRL. Indeed, in the Johri *et al*[17] study every nine ED patients with marked or mild HPRL found among the 136 they screened had severe ED according to the IIEF criteria (score $<$10 at the erectile function domain). This has, however, to be confirmed since Carani *et al*[25] found only a slightly disturbed pattern of erections in their hyperprolactinemic men (normal nocturnal erections and normal erectile responses to audio visual sexual stimulation). On the other hand, after having systematically determined serum PRL in 1370 ED patients, we found that by restricting the determination to those men with low sexual desire, gynecomastia, or serum testosterone below 4 ng/ml (therefore low + low normal values), we would have saved more than half of determinations while overlooking only one of 10 marked HPRL, and none of six pituitary tumors.[18]

The cost of conducting a routine serum PRL measurement in ED patients has been calculated by Johri *et al*.[17] They found three marked HPRL in 138 patients, resulting in a cost of US$60.72 for detecting a single case in their institution ($1.32 per determination). Using a private laboratory in their region ($18.5 per determination), the cost would have been $851 per single case of marked HPRL. This led them to consider serum PRL determination as a relatively inexpensive method of detecting a serious, but reversible, disease process.

There is therefore no consensus with regard to serum PRL determination in men with ED: should it be systematic or restricted to men selected according clinical (low sexual desire), psychometric (IIEF) and/or endocrine (low serum testosterone level) criteria? That first depends on the local resources. If PRL determination had to be limited to certain cases, the best screening strategy would have to be determined following a very large-scale study with systematic determination. Anyhow, it should be systematic in case of isolated low sexual desire and retarded or absent orgasm which are more uncommon dysfunctions.

Treatment of men with sexual dysfunction and HPRL

The literature contains some observations of marked improvement following nonspecific treatments like psycho- or sex-therapy[5,20] (in the latter study at a lesser extent than with dopamine-agonist therapy) or, as concerns ED patients, Sildenafil.[17,26] However, PRL-lowering dopamine agonists (bromocriptin, lisuride, quinagolide, and cabergolide, the latter being effective following a single administration per week) most often not only normalize all aspects of sexual function, but also shrink the possible pituitary adenoma, or at least prevent its growth.[2,9,16] In addition, unlike phosphodiesterase type V inhibitors, PRL-lowering agents allow return of sexual desire, and in case of ED of spontaneous erections, avoiding the necessity to plan sexual intercourse according to the time of dosing. Therefore, dopamine agonists should be the first-choice treatment. However, in case of pituitary tumor exceeding 10 mm diameter (macroadenoma), the patient should be referred to an endocrinologist for thorough investigation of its pituitary functions and of the possible indication of its adenoma's removal.

In some cases, hypogonadism persists despite return to a normal PRL level, due to definitive interruption of the hypothalamic-pituitary connections or destruction of the pituitary gonadotrophs by the pituitary tumor or its surgical removal. Such patients require testosterone substitution in addition to dopamine-agonist therapy. However,

testosterone administration may stimulate the growth of a pituitary tumor through its aromatization into estradiol if HPRL is not completely controlled by dopamine-agonist therapy.

Lastly, certain patients may need additional sexual counselling or sexual therapy, especially in case of lifelong sexual dysfunction.[2]

References

1 Haake P *et al*. Absence of orgasm-induced prolactin secretion in a healthy multi-orgasmic male subject. *Int J Impot Res* 2002; **14**: 133–135.
2 Buvat J *et al*. Hyperprolactinemia and sexual function in men. *Hormone Res* 1985; **22**: 196–203.
3 Carani C *et al*. Testosterone and prolactin: behavioural and psychophysiological approaches in men. In: Bancroft J (ed). *The Pharmacology of Sexual Function and Dysfunction*. Esteve Foundation Symposia, Vol. 6, *Excerpta Medica*. Elsevier Science: Amsterdam, 1995; pp 145–150.
4 Vermeulen A, Ando S, Verdonck L. Prolactinomas. Testosterone-binding globulin and androgen metabolism. *J Clin Endocr Metab* 1982; **54**: 409–413.
5 Bancroft J, O'Caroll R, Neilly A, Shaw R W. The effects of bromocriptine on the sexual behavior of hyperprolactinemic man: a controlled case-study. *Clin Endocrinol* 1984; **21**: 131–137.
6 Lobo RA, Kletzky OA. Normalization of androgen and sex-hormone-binding globulin levels after treatment of hyperprolactinemia. *J Clin Endocr Metab* 1982; **56**: 562–566.
7 Drago F, Pellegrini-Quarantotti B, Scapagnini U, Gessa G L. Short-term endogenous hyperprolactinemia and sexual behavior of male rats. *Physiol Behav* 1981; **26**: 277–279.
8 Selmanoff M. Tyrosine hydroxylase and POMC mRNA in the arcuate region are increased by castration and hyperprolactinemia. *Mol Brain Res* 1991; **10**: 277–281.
9 Buvat J. Hormones et comportement sexuel de l'homme: données physiologiques et physiopathologiques. *Contr Fertil Sex* 1996; **24**: 767–778.
10 Rehman J *et al*. Experimental hyperprolactinemia in a rat-model: alteration in centrally mediated neuroerectile mechanisms. *Int J Imp of Res* 2000; **12**: 23–32.
11 Johnson AR, Jarow JP. Is routine endocrine testing of impotent men necessary? *J Urol* 1992; **147**: 1542–1543.
12 Kropman RF *et al*. Routine endocrine screening in impotence: significance and cost-effectiveness. *Int J Impot Res* 1991; **3**: 87–94.
13 Maatman TJ, Montague DK. Routine endocrine screening in impotence. *Urology* 1986; **27**: 499–502.
14 Leonard MP, Nickel CJ, Morales A. Hyperprolactinemia and impotence: why, when, and how to investigate? *J Urol* 1989; **142**: 992–995.
15 Akpunonu BE *et al*. Routine prolactin measurement is not necessary in the initial evaluation of male impotence. *J Gen Intern Med* 1994; **9**: 336–341.
16 Buvat J, Lemaire A. Endocrine screening in 1022 men with erectile dysfunction: clinical significance and cost-effective strategy. *J Urol* 1997; **158**: 1764–1767.
17 Johri AM, Heaton JPW, Morales A. Severe erectile dysfunction is a marker for hyperprolactinemia. *Int J Impot Res* 2001; **13**: 176–182.
18 Buvat J, Lemaire A, Buvat-Herbaut M, Marcolin G. Dosage de la prolactine chez les impuissants. *Presse Med* 1989; **18**: 1167.
19 Ambrosi B *et al*. Studies of the effects of bromocriptine on sexual impotence. *Clin Endocrinol (Oxf.)* 1987; **7**: 417–420.
20 Schwartz MF, Bauman JE, Masters WH. Hyperprolactinemia and sexual disorders in men. *Biol Psychiat* 1982; **17**: 861–876.
21 Sinha YN. Structural variants of prolactin: occurrence and physiological significance. *Endocr Rev* 1995; **16**: 354–369.
22 Vallette-Kasic S *et al*. Macroprolactinemia revisited: a study on 106 patients. *J Clin Endocrinol Metab* 2002; **87**: 581–588.
23 Lemaire C *et al*. Hyperprolactinemia with an excess of high molecular weight prolactin in men. *Int J Impot Res* 1994; **6** (Suppl 1): P79.
24 Guay AT, Sabharwal P, Varma S, Malarkey W B. Delayed diagnosis of psychological erectile dysfunction because of the presence of macroprolactinemia. *J Clin Endocr Metab* 1996; **81**: 2512–2514.
25 Carani C, Granata AR, Fustini MF, Marrama P. Prolactin and testosterone: their role in male sexual function. *Int J Androl* 1996; **19**: 48–54.
26 Garg RK, Khaishgi A, Dandona P. Is management with Sildenafil changing clinical practice? *Lancet* 1999; **353**: 375–376.