Review

Etiological diagnosis of hyperprolactinemia

Diagnostic étiologique d’une hyperprolactinémie

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Available online 23 May 2007

Résumé

Les étiologies de l’hyperprolactinémie, motif fréquent de consultation, sont nombreuses. La démarche diagnostique doit permettre de reconnaître les causes tumorales au premier rang desquelles on trouve les adénomes à prolactine. L’IRM hypothalamo-pituitaire est l’examen morphologique de référence. Elle est en pratique clinique, volontiers réalisée très tôt, dès la mise en évidence d’une augmentation de la concentration plasmatique de PRL. Cette attitude est justifiée si l’élévation de la PRL, en l’absence de traitement hyperprolactinémiants est importante (> 10 fois la norme supérieure du dosage) car le diagnostic d’adénome à PRL est alors très probable. Lorsque l’hyperprolactinémie est modérée, situation la plus fréquente en pratique, toutes les étiologies sont possibles et il est important de garder une démarche diagnostique (interrogatoire recherchant d’éventuels traitements hyperprolactinémiants et précisant les antécédents rénaux ou hépatiques, recherche d’endocrinopathies parfois associées à une hyperprolactinémie telles que l’hypothyroïdie ou le SOPK, confirmation de l’hyperprolactinémie par un deuxième dosage lorsqu’elle est inférieure à cinq fois la norme supérieure du dosage, réalisation d’un test de grossesse chez la femme en période d’activité génitale) dont le but sera d’éliminer les causes non tumorales d’hyperprolactinémie avant de recourir à l’imagerie. L’absence de retentissement de l’hyperprolactinémie sur la fonction gonadique ou l’existence d’une pathologie associée pouvant expliquer les signes cliniques, la mise en évidence de variations importantes des taux de PRL d’un dosage à l’autre chez un même patient auront conduit à rechercher une macroprolactinémie avant de prescrire l’IRM. Cette situation artéfactuelle doit être également évoquée en cas d’IRM normale ou douteuse ou de discordance dans la réponse aux traitements médicaux ou chirurgicaux. Des coupes coronales en acquisition T1 (± injection de gadolinium) et T2 suffisent au diagnostic de microprolactinome. La réalisation de tests dynamiques peut être utile lorsque l’IRM est normale ou douteuse. L’injection de gadolinium et des coupes sagittales voire axiales sont indispensables pour l’étude des lésions volumineuses. Dans ce cas, devant une valeur de PRL peu élevée, il faut évoquer une lésion non lactotrope sans méconnaître la possibilité d’un effet « crochet ». L’analyse soigneuse des clichés permettra de différencier une lésion tumorale d’une hyperplasie hypophysaire (devant faire rechercher une hypothyroïdie périphérique).

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Abstract

There are numerous etiologies of hyperprolactinemia, a common reason for consultation. Diagnostic measures must be capable of identifying the tumors, the most frequent of which are prolactin adenomas. Hypothalamic–pituitary MRI is the reference morphological examination. In clinical practice, it is usually performed very early, following the discovery of increased plasma concentrations of PRL. This approach is warranted for marked increase in PRL in the absence of drugs with hyperprolactinemic effects (> 10 × upper limit of normal) since a diagnosis of PRL adenoma is extremely likely under such circumstances. When hyperprolactinemia is moderate, which is the most common finding in prac-

DOI of original article 10.1016/j.ando.2007.03.014.
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003-4266/$ - see front matter © 2007 Published by Elsevier Masson SAS.
doi:10.1016/j.ando.2007.03.013
tice, all etiologies are possible in theory and it is important to follow a rational diagnostic plan (history-taking to identify use of any drugs with hyperprolactinemic effects paying attention to renal and hepatic history, investigation for endocrine diseases occasionally associated with hyperprolactinemia such as hypothyroidism or polycystic ovary syndrome (PCOS), confirmation of hyperprolactinemia by a second assay when the initial level is less than five times the upper normal limit, pregnancy testing for women of childbearing age) in order to rule out all non-tumoral causes of hyperprolactinemia before proceeding with imaging. Absence of any consequences of hyperprolactinemia on gonadic function or the existence of a concomitant disease that could account for the clinical signs, demonstration of wide variations in PRL from one assay to another in a single patient could prompt screening for macroprolactinemia before MRI is ordered. Macroprolactinemia could also occur in the case of normal or doubtful MRI or discrepancy in response to medical or surgical treatment. T1- and T2-weighted coronal sections (with or without T1 after gadolinium injection) are generally sufficient for diagnosis of microprolactinoma. Dynamic tests may be useful if MRI is normal or unclear. Gadolinium injection with sagittal and axial sections is essential for examination of large lesions. In this case, when the increase of PRL is moderate (< 150 mg/ml), a non-lactotropic lesion may be suspected without misdiagnosing a hook effect. Careful analysis of the images allows differentiation between tumoral lesions and pituitary hyperplasia.

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Mots clés : Hyperprolactinémie ; Étiologie

Keywords: Hyperprolactinemia; Etiology

1. Introduction

An overview of the numerous etiologies of hyperprolactinemia is given in Table 1. The aim of the etiological diagnosis is to avoid misunderstanding of tumor, chief of which is prolactin adenoma. Hypothalamic–pituitary MRI is the reference morphological examination. In clinical practice, it is usually performed very early, following discovery of increased plasma concentrations of PRL. This approach is warranted for marked increase in PRL in the absence of drugs with hyperprolactinemic effects (> 10 × laboratory upper limit of normal – ULN) since a diagnosis of PRL adenoma is extremely likely under such circumstances. When hyperprolactinemia is moderate, which is the most common finding in practice, all etiologies are possible and it is important to follow a rational diagnostic plan in order to rule out all non-tumoral causes of hyperprolactinemia before proceeding with imaging in order to avoid unnecessary MRI, which can yield false positives [13].

2. The first step for moderate hyperprolactinemia is to confirm its existence

In our study (retrospective analysis of 281 patients hospitalized for hyperprolactinemia in 2003 and 2004 in two endocrinology departments in Marseille and Lille), hyperprolactinemia was < 150 ng/ml in 86% of cases. In this context, hyperprolactinemia was not confirmed on the second sample obtained in a hospital setting in 21% of cases. Useless MRI was performed before hospitalization in 53% of these patients. In 18% of cases, history-taking revealed administration of drugs with hyperprolactinemic effects at the first sample time. However, in most cases, there was no clear explanation, particularly when hyperprolactinemia was < 5 × laboratory ULN.

Before continuing the diagnosis, it thus appears useful to confirm hyperprolactinemia when it is < 5 × ULN by means of a second assay (Fig. 1).

3. Should this confirmation assay be carried out under special conditions?

Hyperprolactinemic drugs (Table 2) should be discontinued before a second sample is taken; the duration of withdrawal depends on the half-life of the drug. Details will be given below concerning the special case of patients on neuroleptics. There is no need to suspend contraceptive or estrogen–progestosterone hormone therapy. The doses of ethinyl-estradiol (20 or 30 μg) in current use have little effect on plasma prolactin concentrations.

Certain of the standard sampling conditions (between days 2 and 5 of the menstrual cycle in women of childbearing age, between 10:00 and 12:00 h with subjects fasting, prior insertion of a catheter, withdrawal of two or three samples at 15-min intervals) are excessively restrictive and probably not use-
There is no significant difference in plasma concentrations of PRL between the follicular and luteal phases. Plasma PRL concentrations are slightly higher during the periovulatory period, but values are normal in most cases. A prospective study in 180 patients in Grenoble [9] clearly showed the absence of any difference between PRL values measured by direct needle insertion and those obtained after insertion of a catheter followed by 30 min resting. In a retrospective study, the same team found no significant difference between mean PRL values obtained for three samples taken at 20-min intervals. On the basis of these results, it is possible to advocate measurement of PRL using a single sample obtained by direct venous puncture with subjects at rest. Sampling very early in the morning or less than 1 hour after a copious meal should be avoided for this confirmation assay, particularly when increase in PRL levels at the first assay is very low.

4. What investigations should be carried out before performing MRI?

- **Pregnancy testing** should be performed routinely in women of childbearing age.
reduced metabolic clearance of PRL. However, these causes are generally known by the patients and are readily determined during history-taking.

- While peripheral hypothyroidism is a classical cause of hyperprolactinemia, hyperprolactinemia is rarely the presenting symptom of hypothyroidism (one case/281 patients in our study). Hyperprolactinemia is relatively uncommon in patients with hypothyroidism. In the study by Raber et al. [19], 84 of 1003 patients with peripheral hypothyroidism (8%) presented hyperprolactinemia. 46.5% were taking neuroleptics or antidepressants that could account for the increased plasma concentrations of PRL. In 9.5% of cases, MRI revealed lesions consistent with adenoma, while hyperprolactinemia persisted after treatment with thyroid hormones and correction of TSHs levels, suggesting a combination of hypothryoidism and PRL adenoma. In the absence of any demonstrated favorable cost–benefit ratio for routine assay, measurement of TSHs levels is necessary at this stage only in patients with goiter and/or clinical signs or symptoms evocative of hypothyroidism.

5. When and how should tests be carried out for macroprolactinemia?

Circulating prolactin mainly comprises the monomer form having a molecular-weight of 23 kDa (85–90%). The high molecular-weight forms consist of big prolactin (PRL dimers or trimers of 50–60 kDa) and big big PRL (polymers of 150–170 kDa). In most cases, macroprolactinemia consists of aggregation of monomeric PRL bound to anti-PRL IgG autoantibodies [8]. Less frequently, it consists of covalent or non-covalent PRL polymers. PRL aggregates, whose plasma half-life is increased due to reduced metabolic clearance, are recognized by the majority of automated immunological assay kits currently used but with different degrees of sensitivity [2,7,21,24]. It is important to identify these “false hyperprolactinemias” which, if not recognized, can result in the prescription of needless additional examinations as well as inappropriate therapy.

- It is common in patients with hyperprolactinemia. Two studies in 1225 [15] and 2089 [11] serum samples demonstrated the existence of macroprolactinemia in 26% and 22% of cases, respectively, on routine screening using a precipitation method with polyethylene glycol (PEG). In 85% of cases, it was seen in women of childbearing age, but cases were also reported in men, children and menopausal women.

- Normally, symptoms of hyperprolactinemia are absent or the clinical presentation is atypical. However, on screening for clinical signs evocative of hyperprolactinemia in the group of patients presenting macroprolactinemia, galactorrhea was seen in 22–46% of patients [11,15,26]. Between 30% and 59% of patients had menstrual disorders (mainly oligo- or spaniomenorrhoea). Reduced libido or erectile dys-function prompted PRL assay in 50% of men presenting macroprolactinemia. Reduced fertility was seen in 13–29% of female patients. However, these findings must be tempered by the fact that in one-third of cases, menstrual disorders were possibly associated with an etiology other than macroprolactinemia [26]. Amenorrhea was rare. The typical combination of menstrual disorders (without any other explanation than macroprolactinemia) and galactorrhea were in fact seen in fewer than 6% of cases in the Marseille study [26].

- Hyperprolactinemia is normally moderate. However, in the study by Gibney et al. [11], while the incidence of macroprolactinemia was slightly higher (27%) in patients presenting hyperprolactinemia < 700 mU/l, it remained close to 20% irrespective of plasma PRL concentration. In 8.5–20% of cases, PRL concentration was > 100 ng/ml.

Filtration chromatography on Sephadex G-100 gel is the reference method for detection of macroprolactinemia. This technique separates monomeric PRL from forms of higher molar mass. The different forms are then quantitatively determined in the chromatography eluates. However, because of the complexity and the cost of this method, it is restricted to a small number of specialized centers. The PEG precipitation test, which has been validated with many currently available immunoassay kits, is the most widely used technique [15,21]. This method must be validated in terms of methodology by the laboratory carrying out the test. It is based upon non-specific precipitation of macroprolactinemia by PEG followed by assay of PRL in the supernatant after centrifugation. Precipitation on PEG is nevertheless accompanied by non-specific precipitation of monomeric PRL of around 15%. Diagnosis of macroprolactinemia is usually made if the percentage recovery of PRL in the supernatant is less than 40%. Results are uncertain for percentages between 30% and 60% [21]. This method of expressing the results does not rule out the possibility of a simultaneous increase in the absolute value of monomeric PRL. For certain authors, diagnosis of macroprolactinemia is therefore only made when PRL levels detected in supernatant following precipitation with PEG are below the threshold values established for the assay in a control group [25]. This test may be unsuccessful with rare cases in which only big PRL is present in excess, since precipitation of big PRL in PEG has not been demonstrated.

The incidence of macroprolactinemia, the simplicity and low cost of detection using a PEG precipitation technique, and the apparent absence of a readily identifiable target population have led some authors to propose systematic screening for macroprolactinemia before MRI [11]. However, this approach is probably vercautious, particularly when the clinical presentation is typical. Screening for macroprolactinemia may be proposed:

- in asymptomatic patients;
- when the clinical presentation is not typical, particularly in the absence of any impact of hyperprolactinemia on gonadic function (isolated galactorrhea without ovulation disorders,
infertility without galactorrhea or clear menstrual disorders, absence of biological hypogonadism in men, etc.) [3];
- when menstrual disorders could have another explanation (polycystic ovary syndrome (PCOS), peripheral ovarian deficiency, perimenopausal period, clinical setting suggestive of functional hypothalamic anovulation, etc.);
- when a significant difference exists between plasma PRL concentrations following assays using different kits with varying degrees of sensitivity to macroprolactinemia [2,7, 21,24];
- after failure to achieve normalization of PRL by previous treatment using dopamine agonists.

6. Do dynamic tests serve any purpose at this stage of diagnosis?

The main tests used are TRH and antidopamine (metoclopramide, domperidone) stimulation tests used either alone or in combination on the basis that a normal prolactin response makes the existence of a hypothalamic–pituitary lesion very unlikely and renders MRI unnecessary [6,10]. However, the value of these tests in investigation of hyperprolactinemia is debatable [16,22]. In order to reassess the potential interest of dynamic tests prior to MRI, we performed a retrospective study of patients with hyperprolactinemia confirmed by two samples hospitalized between 2003 and 2004 in Marseille and Lille undergoing dynamic tests and MRI. The TRH test was considered normal when the increase in PRL following IV injection of 200 μg TRH was > 100% ($n = 134$). The metoclopramide test was carried out using two different protocols in Marseille (test considered normal where increase in PRL following IV injection of 10 mg metoclopramide was > 100%, $n = 70$) and in Lille (test considered normal when increase in PRL following IV injection of 2.5 mg metoclopramide was > 100%, $n = 77$) and in Lille (test considered normal when increase in PRL following IV injection of 10 mg metoclopramide was > 200%, $n = 70$). The TRH test was normal in 14 (three microadenomas, seven macroadenomas, one cyst) of 109 patients presenting abnormal MRI (sensitivity: 87.1%). The metoclopramide test was normal in 14 (five microadenomas, one macroadenomas, three cysts, one pituitary metastasis, one craniopharyngioma) of 118 patients presenting abnormal MRI.

The sensitivity of the test was comparable for the two centers (87.8% in Marseille and 88.4% in Lille). The combination of the two tests did not increase the sensitivity (83.6% and 84.6%, respectively, $n = 129$). For the two tests, the overlap in PRL responses seen between the group of patients with normal MRI and the group of patients with pathological MRI results prevented the definition of a threshold value that would allow identification of all subjects having a pathological MRI. The sensitivity of dynamic tests did not appear sufficient to determine whether or not MRI was required.

7. Pituitary MRI (Fig. 2)

At the end of this diagnostic procedure, if the hyperprolactinemia still cannot be accounted for, MRI, the reference examination to investigate for abnormalities of the hypothalamic–pituitary area is carried out. CT scans should only be performed in patients with a contraindication for MRI (pace-maker) or persistent claustrophobia in spite of a suitable preparation.

Sections obtained in the coronal plane using spin echo T1-weighted and spin echo T2-weighted imaging are usually sufficient to allow diagnosis of prolactin microadenoma [4]. Images are generally hypointense on T1 and hyperintense on T2 (80%). They are occasionally hyperintense on T1 in the event of hemorrhage. When microadenomas are isointense, intravenous gadolinium injection boosts the signal of healthy pituitary tissue but not of pituitary adenoma, thus allowing identification of the latter. Delayed sequences (30–40 min) following gadolinium injection can show late increase of the adenoma itself. Some controversy surrounds the value of dynamic imaging after gadolinium injection. It may allow clear distinction between healthy pituitary tissue with a rapid increase after injection and lesions with poor visibility in other sequences, although it can also yield false positives, since uniform opacification of the gland with the contrast medium cannot always be guaranteed [13].

Sagittal and axial sections and sequences following gadolinium injection are essential for the study of large lesions. They provide information concerning the lesion type as well as the relationship with adjacent structures (cavernous sinus, optical chiasm), and they allow identification of healthy pituitary.

There is a good correlation between tumoral-volume and plasma PRL concentration in prolactinomas. Hyperprolactinemia < 150 ng/ml with an MRI showing a large lesion militates in favor of a non-lactotropic lesion. Hyperprolactinemia occurs through reduced inhibitory action of dopamine on normal lactotropic cells by compression, lesion or infiltration of the pituitary stalk. Less frequently, a diagnosis of macroprolactinoma remains possible in the event of extensive necrotic–hemorrhagic modification in the lesion or in the event of a relatively poorly-secretory lactotropic adenoma. It is also important to avoid misdiagnosis of a “hook” effect. PRL assays are currently carried out using a sandwich immunometric method. A first monoclonal antibody bound to a solid surface recognizes an epitope of PRL while a second monoclonal antibody, to which a detection signal is bound, recognizes another epitope of PRL. This is added to the tube at the same time as the serum to be assayed. The PRL molecule acts as a bridge between the two antibodies present in excess. When the liquid phase has been discarded, the signal detected in the solid phase is proportional to the concentration of hormone present in the sample. However, for extremely high concentrations of PRL, the two antibodies are saturated separately, resulting in fairly low or even normal PRL values [20,23] with failure to recognize the diagnosis of macroprolactinoma. Further measurement of PRL following dilution to 1/100 results in recognition of this situation.

Careful examination of the images allows differentiation between pituitary hyperplasia and tumors. In this situation,
TSHu assay has to be performed if not previously carried out [1,18]. When the MRI is normal or the interpretation is unclear, even after repeated reading of the images, screening should be performed for macroprolactinemia and assay of TSHu carried out. Subsequent use of dynamic tests may provide additional diagnostic information. Inadequate stimulation following TRH or metoclopramide suggests the existence of a microprolactinoma in contrast with normal stimulatory responses, which occur very rarely in PRL adenomas (4.9% of microprolactinomas during TRH tests and 1.4% of microadenomas during metoclopramide tests in our experience), but which can be observed in patients with imaging artifacts or intrasellar cysts.

Should precautionary MRI be prescribed for patients with macroprolactinemia in order to detect association with an adenoma [17]? In the Marseille study [26], five of 86 patients with macroprolactinemia undergoing pituitary MRI presented an adenoma. In three cases, associated GH secretion was seen allowing diagnosis without systematic recourse to MRI. Combination of pure PRL adenoma and macroprolactinemia was thus relatively uncommon (2.5%) and systematic MRI is therefore unwarranted in macroprolactinemia. It may be proposed in the event of tumoral syndrome or increased monomeric PRL [17].

### 8. Some special situations

#### 8.1. Hyperprolactinemia in patients on neuroleptics

The efficacy of neuroleptics is due to their antagonistic effect on dopamine D2 receptors in the mesolimbic and mesocortical regions. Blockade of these receptors in lactotropic cells accounts for the hyperprolactinemia observed in patients treated with standard neuroleptics (phenothiazines, butyrophenones, thioxanthenes). The prevalence of hyperprolactinemia is 60–75% in women and 30–45% in men [12]. Plasma PRL concentration increases in the hours post-dosing, and increases in plasma PRL levels is dose-dependent with values sometimes higher than 10 × ULN. The time to normalization of PRL levels following discontinuation of treatment depends on the plasma half-life of the drug as well as its pharmaceutical form, possibly lasting up to several weeks for sustained-release formulations.
“Atypical” neuroleptics have special chemical, pharmacodynamic and pharmacokinetic characteristics able of reducing extra-pyramidal symptoms at therapeutic doses. Some of these drugs have a hyperprolactinemic action as frequent and pronounced as standard neuroleptics (risperidone, amisulpiride). Others such as clozapine and aripiprazole are considered to be without effect on PRL concentrations while increases in PRL levels seen with olanzapine are slight, being observed only with high doses (Table 2).

The management goal for patients on neuroleptics presenting hyperprolactinemia is to ensure that it is purely iatrogenic and to avoid misdiagnosis of a tumoral etiology. The time from the start of treatment to the onset of hyperprolactinemia symptoms may provide useful clues. Ideally, correction of hyperprolactinemia should be verified on withdrawal of neuroleptics. However, it is not always easy to determine the duration of the therapeutic window, which is subject to the characteristics of individual medicines. It is often difficult and may be occasionally dangerous. So a therapeutic window can only be envisaged after consultation with the patient’s psychiatrist. The alternatives comprise neuroleptic dose reduction, and modification of treatment in favor of neuroleptics causing little or no hyperprolactinemia. If none of these solutions are feasible, or if hyperprolactinemia persists despite withdrawal of treatment or change of therapy, a hypothalamic–pituitary MRI should be carried out.

8.2. Hyperprolactinemia and micropolycystic ovary syndrome (MPCOS)

MPCOS is a classic etiology of secondary hyperprolactinemia although the exact incidence of hyperprolactinemia in PCOS is not well known [5]. The existence of such an association has in fact been challenged by certain authors. PRL assay was carried out systematically at the Hospital of Lille in 298 women presenting PCOS diagnosed between 2002 and 2005. Hyperprolactinemia was discovered in 44 of these patients (14.7%). In 88.5% of cases, hyperprolactinemia was <50 ng/ml. PRL levels showed fluctuation in 27% of cases. Tests using TRH and metoclopramide were performed in 75% of cases and normal response to both tests was observed in 85% of cases. The physiopathology of this hyperprolactinemia is poorly understood. The incidence of macroprolactinemia in these patients is not known.

Demonstration of hyperprolactinemia confirmed on two separate occasions in women with PCOS should prompt MRI investigation if, after ruling out macroprolactinemia, PRL is >50 ng/ml and/or if hyperprolactinemia persists after PCOS treatment.

In conclusion, etiological diagnosis of hyperprolactinemia is straightforward in most cases, but is based upon careful semiologic, clinical and laboratory analysis in order to allow judicious use of MRI, the reference morphological examination method. Analysis of images correlated with PRL levels in patients allows etiological diagnosis of hyperprolactinemia in the majority of cases provided due attention is paid to the potential pitfalls.

9. French version

A French version of this article is available at doi:10.1016/j.ando.2007.03.013.

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