Pitfalls in the Diagnostic Evaluation of Hyperprolactinemia

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Keywords

Prolactin · Hyperprolactinemia · Macroprolactinemia · Pitfalls

Abstract

An appropriate diagnostic evaluation is essential for the most appropriate treatment to be performed. Currently, macroprolactinemia is the third most frequent cause of non-physiological hyperprolactinemia after drugs and prolactinomas. Up to 40% of macroprolactinemic patients may present with hypogonadism symptoms, infertility, and/or galactorrhea. Thus, the screening for macroprolactin is indicated not only for asymptomatic subjects but also for those without an obvious cause for their prolactin (PRL) elevation. Before submitting patients to macroprolactin screening and pituitary magnetic resonance imaging, one should rule out pregnancy, drug-induced hyperprolactinemia, primary hypothyroidism, and renal failure. The magnitude of PRL elevation can be useful in determining the etiology of hyperprolactinemia. PRL values >250 ng/mL are highly suggestive of prolactinomas and virtually exclude nonfunctioning pituitary adenomas (NFPAs) and other sellar masses as the etiology of hyperprolactinemia. However, they can also be found in subjects with macroprolactinemia, drug-induced hyperprolactinemia or chronic renal failure. By contrast, most pa-

tients with NFPAs, drug-induced hyperprolactinemia, macroprolactinemia, or systemic diseases present with PRL levels <100 ng/mL. However, exceptions to these rules are not rare. Indeed, up to 25% of patients harboring a microprolactinoma or a cystic macroprolactinoma may also have PRL <100 ng/mL. Falsely low PRL levels may result from the so-called “hook effect,” which should be considered in all cases of large (≥ 3 cm) pituitary adenomas associated with normal or mildly elevated PRL levels (≤ 250 ng/mL). The hook effect may be unmasked by repeating PRL measurement after a 1:100 serum sample dilution.

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Introduction

Hyperprolactinemia, defined by a high level of serum prolactin (PRL) above the standard upper limit of normal range, is a frequent cause of acquired hypogonadotropic hypogonadism [1, 2]. It is thought to be present in 10–25% women with secondary amenorrhea or oligomenorrhea, in approximately 30% of women with galactorrhea or infertility, and in 75% of those with both amenorrhea and galactorrhea [3, 4]. Moreover, the prevalence of hyperprolactinemia was 1.5% in a series of 1,370 consecutive patients with erectile dysfunction [5].

Table 1. Causes of hyperprolactinemia

Physiologic
Pregnancy; lactation; stress; sleep; coitus; exercise, etc.
Pathologic
Systemic diseases – primary hypothyroidism; adrenal insufficiency; polycystic ovary syndrome (?); renal insufficiency; cirrhosis; pseudocyesis; epileptic seizures
Hypothalamic diseases – tumors (craniopharyngiomas, dysgerminomas, meningiomas, etc.); infiltrative disorders (histiocytosis, sarcoidosis, etc.) metastasis; cranial radiation; Rathke's cleft cysts, etc.
Pituitary diseases – prolactinomas; acromegaly; thyrotropinomas; Cushing's disease; infiltrative disorders; metastasis; hypophysitis; empty sella syndrome, etc.
Stalk disorders – inflammatory (hypophysitis; granulomatosis with polyangiitis (Wegener's), sarcoidosis, Langerhans cell histiocytosis) and infectious (tuberculosis) lesions; neoplasms (germinomas); traumatic brain injury
Neurogenic – chest wall lesions (burns; breast surgery; thoracotomy; nipple rings; herpes zoster; etc.); spinal cord injury (cervical ependymoma; tabes dorsalis; extrinsic tumors; etc.), breast stimulation, etc.
Idiopathic
Ectopic prolactin production – renal cell carcinoma; ovarian teratomas; gonadoblastoma; non-Hodgkin lymphoma; uterine cervical carcinoma; colorectal adenocarcinoma, etc.
Macroprolactinemia
Pharmacologic (see Table 2)
Adapted from references [1, 7, 8, 16].

The elevation of serum PRL levels has multiple etiologies that can be divided into physiological, pharmacological, and pathological causes (Tables 1, 2) [6, 7]. A prolactinoma is the most common cause of chronic hyperprolactinemia after pregnancy, primary hypothyroidism, and drugs that increase PRL levels have been excluded [8].

When determining the etiology of hyperprolactinemia and interpreting PRL levels, clinicians need to be aware of some conditions that can lead to misdiagnosis and, consequently, to inappropriate management [7–9]. In this review article, the authors aim to comment on the most important causes of hyperprolactinemia and particularly to emphasize the main pitfalls and challenges that can be faced in the diagnostic evaluation of hyperprolactinemic subjects.

PRL Serum Isoforms

Human PRL presents important size heterogeneity in terms of its three major circulating molecular isoforms [10]. The monomeric or little PRL (molecular weight [MW] 23 kDa) results from a cleaved preprolactin molecule (MW 26 kDa), and it represents the major circulatory isoform (80–95%) of the total PRL in healthy subjects and those with prolactinomas [11]. Dimeric or big PRL

(45–60 kDa), and big-big PRL or macroprolactin (>150 kDa) correspond to less than 10% of the total PRL [10, 11].

When the serum of a patient with hyperprolactinemia contains mostly macroprolactin, the condition is termed macroprolactinemia [11, 12]. In the great majority of cases, macroprolactin is composed of a complex formed by an IgG and a monomeric PRL [10, 13, 14]. Furthermore, in cases with slightly elevated PRL levels, non-IgG-bound forms of macroprolactin including complexes with IgA or IgM, highly glycosylated monomeric PRL, covalent or noncovalent aggregates of monomeric PRL, have rarely been demonstrated [11].

Etiology

Physiological Causes

The most important physiological causes of hyperprolactinemia are pregnancy and breastfeeding [6, 15]. Stress from any source, whether psychological, induced by exercises, or due to other acute illness, leads to physiological elevation of PRL levels [6, 15, 16]. However, supine rest is not necessary prior to sampling, contrary to what was believed in the past [17]. Venipuncture stress may cause elevation in PRL level, but it is usually mild (<40–60 ng/mL) [18]. The same is true for breast stimulation [1, 6].

Table 2. Causes of drug-induced hyperprolactinemia

Antipsychotics
Typical – haloperidol, chlorpromazine thioridazine, thiothixene, flupentixol
Atypical – risperidone; paliperidone; molindone; amisulpride; quetiapine; olanzapine; aripiprazole (rarely)
Antidepressants
Tricyclic – clomipramine; amoxapine; amitriptyline; desipramine
SSRIs – fluoxetine; fluvoxamine; paroxetine; citalopram; escitalopram; sertraline
SNRIs – venlafaxine; duloxetine; reboxetine
MOA-I – pargyline; clorgyline
Antihypertensive drugs
Verapamil; α -methyldopa; reserpine; labetalol (intravenous)
Prokinetic agents
Metoclopramide; domperidone
H ₂ -receptor blocker agents
Cimetidine (?); ranitidine (?)
Others
Estrogens; anesthetics; opiates; methadone; morphine; alprazolam; apomorphine; heroin; cocaine; marijuana; alcohol abuse; etc.
SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin and noradrenaline reuptake inhibitors; MOA-I, monoamine oxidase inhibitors. Adapted from references [1, 7, 8, 19, 21].

Moreover, as PRL is secreted episodically, its levels measured during the day may possibly be beyond the upper limit of normality for a particular laboratory in healthy individuals [6, 7]. Therefore, an elevated PRL level should be confirmed at least once [6], unless PRL levels are clearly elevated (>80 – 100 ng/mL) [1].

Pharmacological Causes

The most common cause of nonphysiological hyperprolactinemia is the use of medications that act through different neuroendocrine mechanisms [19–21] (Table 2). Neuroleptics, particularly the classical antipsychotics (e.g., butyrophenones, thioxanthenes, and phenothiazines) and some atypical antipsychotics (e.g., amisulpride, risperidone, and paliperidone), are the drugs more often involved [19–25]. With chronic use of these drugs, 40–90% of patients maintain elevated PRL levels; galactorrhea, amenorrhea, and impotence are common manifestations in such patients [21, 24, 26]. Hyperprolactinemia is rarely seen in patients treated with aripiprazole as it is a partial dopamine agonist and can often reverse the hyperprolactinemia induced by other antipsychotic agents [21, 26, 27]. A meta-analysis of 5 randomized controlled trials showed a PRL level normalization rate of 79% [27]. Noteworthy, PRL levels tend to fall to normal within 48–96 h following discontinuation of oral antipsy-

chotic drug therapy [8, 21]. In our experience, this occurs in approximately half the patients 4 days after drug withdrawal.

The exact prevalence of hyperprolactinemia with selective serotonin reuptake inhibitors and serotonin and noradrenalin reuptake inhibitors is unknown [28–31]. In most series, they have been shown to cause a modest or no increase in PRL levels in most treated patients [28–31]. In a study of 80 patients with normal baseline PRL treated with fluoxetine for 12 weeks, mild hyperprolactinemia (PRL <40 ng/mL) developed in 4.5% of the men and 22.2% of the women [31]. In a more recent cross-sectional pilot study with 55 patients, mild hyperprolactinemia was found in 10.9% of patients treated with either escitalopram, paroxetine, or sertraline [32]. In the French Pharmacovigilance Database, the overall rate of hyperprolactinemia associated with the use of serotonin reuptake inhibitors was 1.6% [29]. In this study, the crude reporting odds ratio was higher with fluvoxamine (4.5), citalopram (3.9), fluoxetine (3.6), and paroxetine (3.1) [29]. Hyperprolactinemia seems to be even rarer with tricyclic antidepressants [21, 24, 28] with the likely exception of clomipramine [33]. PRL elevations have not been seen with the chronic use of nefazodone, bupropion, carbamazepine, mirtazapine, or trazodone [21, 24, 34–36]. Of note, euprolactinemic galactorrhea associated with

use of antidepressants or antipsychotics has already been described [28, 37, 38].

Hyperprolactinemia is also found in over 50% of patients taking the prokinetic drugs domperidone and metoclopramide which are dopamine D2 receptor blockers [21, 39, 40]. Verapamil [41] and methyldopa [42] may also raise PRL levels in some patients.

It is well known that high estrogen levels during pregnancy lead to lactotroph hyperplasia and hyperprolactinemia [8, 43]. Nonetheless, it is still controversial whether the amount of estrogens in oral contraceptives or menopause hormone therapy is sufficient to induce hyperprolactinemia [21]. In some studies, 12–30% of women given estrogen-containing oral contraceptives developed hyperprolactinemia, with little influence of the dose of estrogen [44, 45]. By contrast, other studies have shown either a minimal or no increase in PRL levels [46, 47]. Concerning estrogen replacement therapy for menopause, most studies have shown either no effect [48, 49] or minimal effect [50] on PRL levels with varying doses of estrogens up to 1.25 mg of conjugated estrogens or 50 µg of estradiol daily. In our experience, roughly 20% of women taking currently available combined oral contraceptives develop mild hyperprolactinemia [unpubl. data].

The evaluation of drug-induced hyperprolactinemia can be challenging. Indeed, the abuse of opiates, cocaine, marijuana, or alcohol may also increase PRL levels, and this information may be omitted by the patient during history taking [1, 7, 21]. Moreover, one should always consider the possibility of the concomitance of a pathological cause for PRL elevation in cases of moderate-severe hyperprolactinemia (>50 ng/mL), with clinical repercussions and/or prolonged hyperprolactinemia over time [52]. In this situation, it is recommended to perform repeated PRL measurement after discontinuing the medication for 3–4 days [8, 21, 51]. When drug withdrawal is unsafe, a magnetic resonance imaging (MRI) should be performed to rule out a sellar mass [8]. If drug-induced hyperprolactinemia is confirmed and the patient has hyperprolactinemia-related symptoms, one could try to reduce the dose of the PRL-raising agent or to switch to an alternative medication with a limited or neutral effect on PRL levels, such as aripiprazole, olanzapine, clozapine, or quetiapine, under the supervision of the patient's psychiatrist [8, 21, 51–53]. If dose reduction or drug withdrawal is not feasible or desirable, different treatment strategies have been recommended by recent guidelines: (1) adding aripiprazole; (2) starting estrogens/estrogens-progestogens and testosterone in women and men, respectively, with symptomatic hypogonadism and/or de-

creased bone mineral density; alternatively, a bisphosphonate could be given instead when the concern is osteopenia or osteoporosis; (3) adding a dopamine agonist, preferably cabergoline at low doses [8, 21, 51–53]. This approach, however, should be done cautiously as there have been a few reports on patients who had experienced an exacerbation of psychosis after initiation of bromocriptine [54, 55].

For patients with mild and asymptomatic hyperprolactinemia (PRL <50 ng/mL) watchful waiting is recommended, conducting regular measurement of PRL levels with at least yearly frequency [52].

Pathological Causes

Pituitary and Hypothalamic Disorders

Prolactinomas represent the most common type of pituitary adenoma (about 40%) being the main cause of pathological hyperprolactinemia [6, 8, 16]. Other tumors of the hypothalamic-pituitary region may also present hyperprolactinemia, either by increased production of PRL (mixed pituitary adenomas producing GH and PRL, TSH and PRL, or ACTH and PRL) or by compression of the pituitary stalk (e.g., clinically nonfunctioning pituitary adenomas [NFPAs] and craniopharyngiomas) [6, 8, 16]. In the latter situation, such tumors are called pseudoprolactinomas by some authors [1, 16] since they do not secrete PRL, but rather interfere with the supply of dopamine from the hypothalamus to the pituitary [16]. Infiltrating lesions, hypophysitis, aneurisms, empty sella, and radiotherapy can also result in hyperprolactinemia due to inadequate hypothalamic production of dopamine or to pituitary stalk disruption [16, 56].

Other Endocrine Disorders/Systemic Diseases

Up to 40% of patients with overt primary hypothyroidism, and up to 22% of those with subclinical hypothyroidism (defined by increased TSH with normal serum thyroid hormones) can present with usually mild elevation of PRL levels which normalize by thyroid hormone replacement [1, 7, 57, 58]. Furthermore, one should be aware of the occasional concomitance of primary hypothyroidism and prolactinomas [1, 7]. Although rare, this situation should be kept in mind whenever high PRL levels persist despite normalization of thyroid function with L-thyroxine (Fig. 1) [1, 7]. Glucocorticoids have a suppressible effect on PRL gene expression and PRL release [16, 59]. Thus, hyperprolactinemia may occasionally be observed in patients with primary adrenal insufficiency in whom PRL levels return to normal with glucocorticoid replacement [59].

Fig. 1. Microprolactinoma (0.7 cm) in a patient with primary hypothyroidism (arrow). This condition should be considered whenever PRL levels remain elevated following normalization of TSH and free T_4 with L-thyroxine.

In studies carried out in the 1980s, hyperprolactinemia was described in up to 7% of women with polycystic ovary syndrome (PCOS) [60]. However, in 2 recent studies, this association was not confirmed [61, 62]. An additional cause for the PRL elevation was found among the 15 women with PCOS and hyperprolactinemia evaluated by a Brazilian group [61].

Approximately 30% of patients with chronic renal failure, and up to 80% of those on hemodialysis have elevated PRL levels [63]. Correction of renal failure by transplantation results in normoprolactinemia, sometimes within days [63, 64]. Mild hyperprolactinemia is also found, with variable frequencies, in alcoholic cirrhosis (16–100%) and nonalcoholic cirrhosis (5–13%) [7, 65, 66].

Idiopathic Hyperprolactinemia

The term idiopathic hyperprolactinemia (IH) has been reserved for patients without an obvious cause for the disorder [5–7]. Presumably, in many such cases, small prolactinomas may be present but are too small (e.g., <3 mm) to be detected by current radiological techniques. PRL elevation could also result from hypothalamic regulatory dysfunction [8] or, very rarely, from loss-of-function mutations in the PRL receptor gene [67, 68]. It is noteworthy that in recent studies many subjects initially diagnosed with IH were later confirmed as having macroprolactinemia [1, 69, 70].

Neurogenic Hyperprolactinemia

Sexual breast stimulation and breastfeeding lead to reflex release of PRL, in part, by afferent neural pathways going through the spinal cord [6]. The same mechanism

would explain elevation of PRL levels following traumatic lesions (e.g., mastectomy, augmentation mammoplasty, thoracotomy), or irritative disorders of the chest wall (herpes zoster, burns, nipple piercings, etc.), or of the spinal cord (cervical ependymoma, syringomyelia, tabes dorsalis, extrinsic tumors) [3, 7, 16, 71–73].

Macroprolactinemia

Macroprolactinemia is mostly defined as condition where more than 60% of circulating PRL is made up of macroprolactin [1, 7, 74, 75]. In most in vitro studies, macroprolactin was shown to display low biological activity [9, 11]. This is corroborated by the finding that most macroprolactinemic patients are asymptomatic [69, 70, 76–84]. Hyperprolactinemia related to macroprolactin may be due to its lower renal clearance, longer half-life, and its lower capability to activate hypothalamic dopaminergic tone, which negatively regulates the secretion of pituitary PRL [2, 85].

Methods for Detection of Macroprolactin. The gold standard for the diagnosis of macroprolactinemia is gel filtration chromatography, but because this method is time-consuming and expensive, polyethylene glycol (PEG) serum precipitation has been widely used as a screening method [1, 11, 74–78]. Recoveries <40% are indicative of predominance of macroprolactin, whereas recoveries >60% point to the diagnosis of monomeric hyperprolactinemia [7, 74, 75]. This test enables the correct diagnosis of macroprolactinemia in at least 80% of cases [1, 6, 7, 74].

Clinical Relevance. Macroprolactinemia has been described worldwide, and its prevalence among hyperprolactinemic individuals ranged from 8 to 42% (mean, 19.6%) in 9 European series [69, 70, 75–81]. In 2 recent Brazilian clinical studies, macroprolactinemia represented the third most common cause of nonphysiological hyperprolactinemia (prevalence of ~16%) after prolactinomas and drugs [1, 82, 84]. Macroprolactinemia is therefore a common finding in endocrinological practice that usually requires no treatment. It has been mostly suspected when hyperprolactinemic patients do not present the typical symptoms and/or evidence of a pituitary tumor on MRI [1, 2, 12, 85]. However, many patients with macroprolactinemia can have hypogonadism symptoms or galactorrhea, presumably due to the concomitance of other disorders, such as PCOS, psychogenic erectile dysfunction, idiopathic galactorrhea, nonfunctioning pituitary tumors, or monomeric hyperprolactinemia [1, 69, 70, 86, 87]. This latter situation should be suspected whenever monomeric PRL levels remain elevated despite

Fig. 2. A 0.6-cm prolactinoma (arrow) in a 25-year-old woman with macroprolactinemia and polycystic ovary syndrome with a baseline PRL of 272 ng/dL. After PEG precipitation, PRL recovery was low (25%), but monomeric PRL levels remained elevated (68 ng/mL).

Fig. 3. Clinical features of 100 women with macroprolactinemia. Adapted from Vilar et al. [84].

recoveries <40% after PEG precipitation (Fig. 2) [1, 2, 86]. Moreover, neuroradiological abnormalities are also frequent (see below) [69, 70, 76, 84]. Likewise, PRL levels are highly variable and overlap with those found in patients with monomeric hyperprolactinemia [69, 70, 76, 83, 84]. So, neither of these conditions can be differentiated solely on the basis of clinical features, MRI findings, or PRL levels.

According to some studies, the detection of macroprolactin may change the initial diagnosis in a significant proportion of hyperprolactinemic patients. Indeed, in three series [1, 69, 70], macroprolactinemia was encountered in 25–68.3% (mean, 42.3%) of patients with apparent IH. Moreover, the diagnosis of PRL-secreting pitu-

itary microadenoma shifted to nonsecreting pituitary microadenoma in 10 of 49 patients (20%) from an Italian study [69]. Macroprolactinemia may also delay or hamper the diagnosis of psychogenic erectile dysfunction [87]. This situation should be considered whenever patients with erectile dysfunction and hyperprolactinemia have normal testosterone levels [7]. Thus, macroprolactinemia may occasionally represent a relevant cause of misdiagnosis, unnecessary investigation, and inappropriate treatment [1, 69, 70, 84, 87].

It is also noteworthy to point out that distinct assays recognize macroprolactin differently [88]. It has been demonstrated that some of the new assays show lower cross-reactivity with macroprolactin; however, the number of samples defined as macroprolactin is still significant [89].

In summary, the screening for macroprolactin should not be reserved for asymptomatic patients but also for those with an apparent IH, no obvious cause for the hyperprolactinemia, atypical clinical picture, conflicting PRL results in distinct assays, or delayed decline of serum PRL levels with the usual doses of dopamine agonists [1, 2, 56, 59]. Conversely, PRL should never be measured in asymptomatic patients in order to avoid the unnecessary detection of macroprolactinemia cases [1, 2, 85].

Diagnostic Evaluation

For the correct identification of the etiology of hyperprolactinemia, some parameters must be taken into account: medical history (symptoms, use of substances that may rise PRL levels, excessive breast stimulation, etc.); physical examination (galactorrhea, gynecomastia, goiter, spider angiomas, ascites, facial edema, chest wall lesions, nipple piercings, etc.), clinical features, laboratory findings, as well as imaging studies of the sella turcica.

In addition to PRL determination, TSH, free T₄, and creatinine levels should be obtained to rule out secondary causes of hyperprolactinemia [1, 5, 7, 8, 56]. Moreover, acromegaly should be investigated with measurement of IGF-1 levels in all patients with a pituitary adenoma, despite the lack of typical manifestations of this disease [1, 5, 7, 8, 56]. Finally, β -hCG measurement is mandatory in any childbearing age woman with amenorrhea, even if she categorically denies this possibility [6–8].

As previously commented, the screening for macroprolactinemia should often be considered, particularly in asymptomatic cases or subjects without an obvious cause for the hyperprolactinemia [1, 2, 6–8].

Fig. 4. Diffuse pituitary enlargement with suprasellar extension in a patient with primary hypothyroidism-induced hyperprolactinemia, before (a) and after (b) 6 months of L-thyroxine replacement.

The Importance of Symptoms for the Etiological Diagnosis

Although galactorrhea is the most characteristic clinical manifestation of hyperprolactinemia, it is not always present and may be intermittent or only detectable after nipple stimulation [16, 73]. Indeed, among patients with prolactinomas, galactorrhea has been reported in 30–80% of women and 14–33% of men [6, 16, 73]. Moreover, up to 50% of women with galactorrhea have normal PRL levels, characterizing the so-called *idiopathic galactorrhea* [62, 90].

When typical symptoms of hyperprolactinemia are absent, macroprolactinemia should always be suspected [2, 5, 8]. However, the presence of galactorrhea, menstrual disorders, or infertility *does not* exclude this diagnosis. Overall, symptoms related to hyperprolactinemia (galactorrhea, menstrual disorders, infertility, and sexual dysfunction) have been reported in up to 45% of patients with macroprolactinemia [69, 70, 76–84]. As commented, this mostly would result from the concomitance with monomeric hyperprolactinemia or other disorders [69, 70, 76–78, 84–86]. In our series of 120 macroprolactinemic patients, 42% of women (Fig. 3) and 50% of men were symptomatic [84]. Notably, the finding of both galactorrhea and menstrual disorders is much rarer in macroprolactinemia than in monomeric hyperprolactinemia [83, 84]. Approximately 10% of patients with monomeric hyperprolactinemia can also be asymptomatic [74, 83].

Pituitary adenomas are very rarely associated with diabetes insipidus (DI) [7, 91]. Thus, when a hyperprolactinemic patient presents with a sellar mass and DI, the most likely diagnosis would include other types of sellar tumors (e.g., dysgerminoma, craniopharyngioma, metastasis, etc.), hypophysitis, or other infiltrative disorders [7, 91, 92].

Finally, as many patients with primary hypothyroidism patients are asymptomatic [93], the lack of its typical

manifestations (goiter, cold intolerance, slurred speech, drowsiness, asthenia, etc.) does not exclude such diagnosis or the need to measure TSH and free T_4 [1, 7, 16, 56].

Imaging Studies

Pituitary MRI is primarily indicated after the exclusion of endocrine and nonendocrine systemic diseases, as well as drug-induced hyperprolactinemia [7, 16]. The rationale for this recommendation is the fact that at least 10% of the adult population presents a pituitary incidentaloma when submitted to a brain computed tomography (CT) scan or MRI in the investigation of headache or other neurological problems [94]. Furthermore, primary hypothyroidism may result in pituitary hyperplasia and diffuse pituitary enlargement that could lead to misdiagnosis of prolactinoma or NFPAs. This pituitary enlargement is reversible with L-thyroxine replacement and normalization of TSH and free T_4 (Fig. 4) [95, 96].

Abnormal pituitary images (microadenomas, cystic lesions, empty sella or, less frequently, macroadenomas) have been reported in 8–26% of patients with macroprolactinemia [76–79, 83, 84], but this frequency is similar to that found in the general population (6–20%) [94]. The detection of a pituitary adenoma in a patient without a previous diagnosis of macroprolactinemia may lead to misdiagnosis of prolactinomas, as well as to unnecessary and inappropriate treatment with dopamine agonists and pituitary surgery, as already reported in the literature [97]. Some years ago, we depicted a macroadenoma in a 25-year-old woman with amenorrhea and PRL levels of 280 ng/mL, which led to the initial diagnosis of a macroprolactinoma. However, serum PRL after PEG precipitation was 27.1 ng/mL (normal range, 1.8–29.2). The final diagnosis was NFPA and macroprolactinemia (Fig. 5).

Table 3. Prolactin levels (ng/mL) according to the etiology of hyperprolactinemia in the Brazilian Multicenter Study on Hyperprolactinemia

Etiology	n (%)	Mean prolactin (range)
Macroprolactinomas	250 (20.2)	1,422.9±3,134.7 (108–21,200)
Microprolactinomas	444 (36.0)	165.6±255.1 (32–525)
Idiopathic	45 (3.6)	163.9±81.8 (46–328)
Macroprolactinemia	115 (9.3)	119.5±112.9 (32.5–404)
Drugs	180 (14.6)	105.1±73.2 (28–380)
Acromegaly	40 (3.2)	99.3±57.4 (28–275)
NFPAs	82 (6.6)	80.9±54.5 (28–490)
Primary hypothyroidism	78 (6.3)	74.6±42.4 (30–253)

NFPAs, non-functioning pituitary adenomas. Adapted from reference [25].

Accuracy of PRL Levels

The magnitude of PRL elevation can be useful in determining the etiology of hyperprolactinemia because the highest values are observed in patients with prolactinomas (Table 3) [1, 6–8, 16, 25]. In fact, PRL levels >500 ng/mL almost always indicate the presence of a prolactinoma (6–8, 25). By contrast, most patients with elevation of PRL levels due to pituitary stalk compression, drug-induced hyperprolactinemia or systemic diseases present with PRL levels <100 ng/mL (Table 4). However, exceptions to these rules are not rare [1, 7, 16].

Prolactinomas

In patients with prolactinomas, circulating PRL levels usually parallel tumor size [16, 25, 73]. Indeed, microprolactinomas (diameter <10 mm) usually result in PRL levels of 100–200 ng/mL, but in up to 25% they may be <100 ng/mL, and occasionally reach 500 ng/mL or more [7, 25]. Macroprolactinomas (diameter ≥10 mm) are typically associated with PRL values >250 ng/mL, reaching 20,000 ng/mL or more [7, 16, 25]. In the vast majority of patients with giant prolactinomas (maximum diameter ≥4 cm), PRL levels will exceed 1,000 ng/mL [7, 98].

Artificially low PRL levels may result from the so-called hook effect, which should be considered in all cases of large (≥3 cm) pituitary adenomas associated with normal or mildly elevated PRL levels (≤250 ng/mL) [1, 7]. The hook effect is an assay artifact caused by an extremely high level of PRL, which saturates the detecting antibody used in the PRL assay, thus resulting in a falsely low reported value [16, 99, 100]. The hook effect may be unmasked by repeating PRL measurement after a 1:100 serum sample dilution. Indeed, this step will result in a dramatic rise in PRL levels if the patient has a macroprolactinoma, remaining low in cases of NPFA (Fig. 6) [1, 99, 100]. Cystic macroprolactinomas, which have a smaller

Fig. 5. A 2.5-cm macroadenoma (arrows) initially diagnosed as a macroprolactinoma (PRL = 280 ng/mL) in a 25-year-old patient with secondary amenorrhea. After PEG precipitation, PRL fell to 27.1 ng/mL. The final diagnosis was nonfunctioning pituitary adenoma and macroprolactinemia.

amount of lactotrophic tumor cells, may also present with modest increase in PRL levels, and tend to respond less favorably to dopamine agonist therapy [7, 8, 101]. Thus, once the possibility of hook effect is excluded, a PRL value <100 ng/mL in a patient harboring a solid pituitary macroadenoma virtually excludes a macroprolactinoma and is highly indicative of a NPFA [1, 7, 16].

NFPAs and Other Sellar Masses

NPFA and other sellar masses (GH-, ACTH-, or TSH-secreting adenomas; craniopharyngiomas; dysgerminomas; hypophysitis; metastasis; etc.) are typically associated with mild PRL elevations (usually <100 ng/mL) [6–8, 19, 21, 25]. The maximal PRL levels found in patients with

Table 4. Usual prolactin (PRL) levels in patients with hyperprolactinemia due to different etiologies

Etiology	Usual PRL levels, ng/mL	Comments
Microprolactinomas	100–250	PRL <100 ng/mL in up to 25% of cases; PRL >250 ng/mL in ~10% of cases
Macroprolactinomas (MAC)	200–1,000	PRL <100 ng/mL only in cases of cystic MAC or due to the hook effect; PRL >1,000 ng/mL is often found in patients with giant prolactinomas (>4 cm)
Non-functioning pituitary adenomas (NFPAs)	25–100	PRL between 100 and 250 ng/mL in up to 20% of cases; no report of PRL >250 ng/mL in subjects with immunohistochemically confirmed NFPAs without macroprolactinemia
Drugs	25–100	PRL between 100 and 250 ng/mL in ~30% of cases; PRL between >250 ng/mL in ~5% of cases (particularly with antipsychotics or prokinetics); PRL >500 ng/mL is very rare
Primary hypothyroidism	25–100	PRL between 100 and 250 ng/mL in up to 15% of cases; PRL between 250 and 300 ng/mL in 1–2% of cases
Macroprolactinemia	25–100	PRL >250 ng/mL in 5% of cases; PRL >500 ng/mL is exceedingly rare and usually restricted to patients with concomitant monomeric hyperprolactinemia

Adapted from references [1, 7, 8, 21, 25, 82–84].

NFPAs are still a matter of debate, and values as high as 490 ng/mL were reported in series where not all patients had been submitted to immunohistochemical evaluation [25]. By contrast, in a large series of histologically confirmed cases ($n = 226$), serum PRL ranged from 0.8 to 167 $\mu\text{g/L}$, and values >100 ng/mL were encountered only in 3 cases (1.3%) [102]. Likewise, among 64 patients with immunohistochemically confirmed NFPAs, we found that PRL levels ranged from 33 to 250 ng/dL (<100 ng/mL in 81%) [1]. Thus, PRL values >250 ng/mL are highly suggestive of prolactinomas and virtually would exclude NFPAs and other sellar masses as the etiology of the hyperprolactinemia [1, 7, 102]. Of note, patients with acromegaly harboring GH and PRL co-secreting macroadenomas may rarely present with PRL levels as high as 5,000 ng/mL or more [103].

Systemic Diseases

In patients with other endocrine or nonendocrine systemic diseases, PRL levels are usually <100 ng/mL [1, 7, 25]. However, marked hyperprolactinemia (PRL levels as high as 2,000 ng/mL) has already been reported in patients with chronic renal failure taking medications that increase PRL levels [104]. Among 78 patients with primary hypothyroidism evaluated in the Brazilian Multi-center Study on Hyperprolactinemia (BMSH), PRL levels range was 30–253 ng/mL (mean, 74.6 ± 42.4 ; <100 ng/mL in 87%) [25].

Fig. 6. A giant invasive prolactinoma with falsely low serum PRL (92 ng/mL) due to the hook effect. PRL levels rose to 21,200 ng/mL after a 1:100 serum sample dilution.

Drug-Induced Hyperprolactinemia

Although PRL elevation is usually mild (25–100 ng/mL) in cases of drug-induced hyperprolactinemia, it is also highly variable. Among 180 cases enrolled in the BMSH, PRL levels ranged from 28 to 380 ng/mL (<100 ng/mL in 64%; ≥ 250 ng/mL in 5%) [25]. PRL levels ≥ 250 ng/mL have more often been reported with classical antipsychotics and risperidone, reaching, in different series, values as high as 320 ng/mL [105], 350 ng/mL [106], or 380 ng/mL [25] in different studies. Interestingly, very

Fig. 7. Evaluation of hyperprolactinemia. NI, normal; MacroPRL, macroprolactin; IH, idiopathic hyperprolactinemia; MIC, microadenoma; MP, macroprolactinemia; MonoPRL, monomeric prolactin; MAC, macroadenoma; MicroPRLoma, microprolactinoma; ↑, high; MacroPRLoma, macroprolactinoma; NFPA, nonfunctioning pituitary adenoma; DA, dopamine agonist; –, negative; +, positive; ±, positive or negative.

high PRL levels (720 and 712 ng/mL) have recently been reported in a young woman with a pituitary microadenoma who was treated with domperidone for 3 months. Following domperidone discontinuation, PRL levels fell to the normal range [107].

Macroprolactinemia

In most patients with macroprolactinemia, PRL levels are <100 ng/mL, but they are highly variable, ranging from 20 to 663 µg/L (<100 µg/L in ~91% of cases) in a French study [76]. In our series of 120 macroprolactinemic subjects, PRL level ranged between 32.5 and 523 ng/mL (<100 ng/mL in 75%) [84]. Three patients presented with PRL >500 ng/mL, but they all concomitantly had monomeric hyperprolactinemia [84].

In most studies, PRL levels were found to be lower in macroprolactinemic patients than in those with monomeric hyperprolactinemia, but there was a great overlap between groups [69, 70, 74, 82, 83].

Conclusion

The definition of the etiology of hyperprolactinemia often represents a great challenge to clinicians. A suitable diagnostic evaluation is essential for the most appropriate treatment to be performed. Macroprolactinemia currently is the third most common cause of nonphysiological hyperprolactinemia, and its screening should be considered for all asymptomatic patients and for the symptom-

atic ones without an obvious cause for their PRL elevation, particularly those with PRL levels up to 500 ng/dL.

A proposed algorithm for the evaluation of hyperprolactinemia is illustrated in Figure 7. Before submitting patients to macroprolactin screening and pituitary MRI, one should exclude pregnancy, neurogenic hyperprolactinemia, drug-induced hyperprolactinemia, primary hypothyroidism, and renal failure. PRL levels are very useful in the differentiation between noncystic macroprolactinomas and nonfunctioning pituitary macroadenomas. However, they have limited specificity to distinguish macroprolactinomas from macroprolactinemia and drug-induced hyperprolactinemia in subjects with PRL

levels up to 500 ng/mL. The search for the hook effect is mandatory for all patients with large pituitary tumors (≥ 3 cm) associated with PRL levels in the normal range or only mildly elevated (≤ 250 ng/mL). Therefore, in any patient with a pituitary macroadenoma, monomeric PRL levels >250 ng/mL virtually confirm the diagnosis of a macroprolactinoma.

Disclosure Statement

The authors have no disclosures to declare.

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