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Biochemical diagnosis in prolactinomas: some caveats

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Abstract
Prolactinomas are the most frequently seen pituitary adenomas in clinical practice. A correct biochemical diagnosis of hyperprolactinemia is a prerequisite for further investigation but may be hampered by analytical difficulties as well as a large number of potentially overlapping conditions associated with increased prolactin levels. Suspicion should rise in patients whose symptoms and biochemical results do not match. Assay problems, macroprolactinemia, and high-dose hook effect are discussed as possible reasons for false positive or false negative prolactin levels. Physiological and pathological causes of hyperprolactinemia and their implications for interpreting prolactin results are reviewed.

Keywords Hyperprolactinemia · Macroprolactinemia · High-dose hook effect · Hypothyroidism · Chronic kidney disease · Liver disease · Pregnancy

Introduction

The diagnosis of prolactinomas may be impeded for a variety of reasons. Due to analytical problems prolactin levels may be falsely elevated or decreased. Furthermore, a variety of physiological and non-physiological conditions may lead to hyperprolactinemia, and therefore need to be considered during work-up. In the same line, a clinically irrelevant pituitary mass may be demonstrated in up to 10% of MRI scans, and not necessarily confirms the diagnosis of a prolactinoma after finding of hyperprolactinemia. The investigation of hyperprolactinemia should therefore include the assessment of clinical symptoms, the exclusion of analytical problems, and the evaluation of other causes, before proceeding to imaging procedures.

Are clinical symptoms supporting the diagnosis of clinically relevant hyperprolactinemia?

The clinical symptoms in prolactinomas can be attributed to the consequences of hyperprolactinemia, local mass effects of the underlying adenoma, and insufficiency of other pituitary axes due to compression of the surrounding pituitary tissue (Fig. 1). Prolactin has several important effects in the reproductive system [1]. It stimulates mammary gland growth and prepares the breast for postpartum lactation. Suppression of GnRH secretion probably via *Kiss1* leads to reduced LH and FSH secretion, with subsequent hypogonadotropic hypogonadism [2]. Oligo/amenorrhea and galactorrhea are observed in approximately 90% and 80% of premenopausal women, respectively [3]. Already mild degrees of hyperprolactinemia may be associated with a short luteal phase of the menstrual cycle and anovulatory infertility [4]. Estrogen deficiency may cause vaginal dryness, edema, decreased libido and mood effects. In postmenopausal women, symptoms may be limited to mass effects by the tumor, including severe headache, visual field abnormalities, and partial or complete hypopituitarism. The most common clinical symptoms in males also relate to central hypogonadism and include decreased libido, impotence, and infertility.

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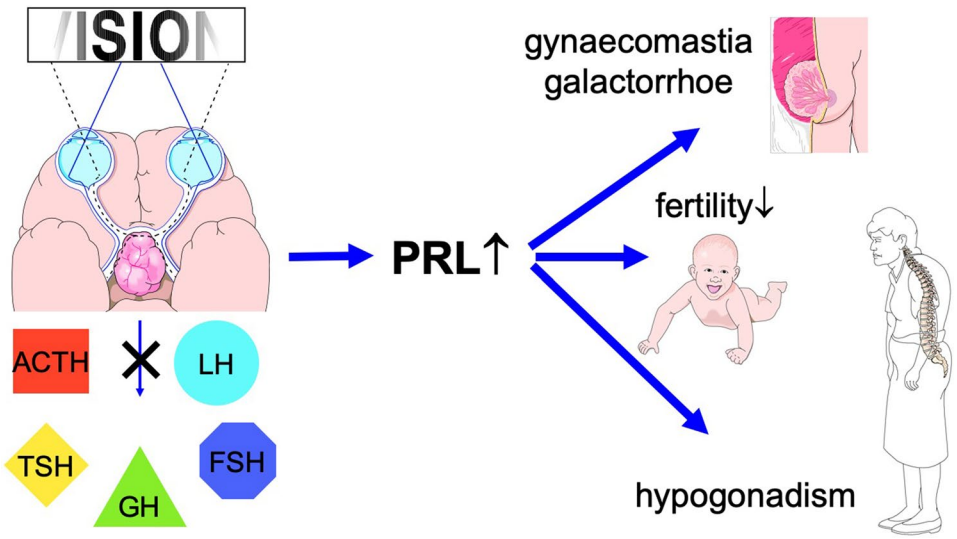

Fig. 1 Clinical consequences of prolactinoma include endocrine sequalae of hyperprolactinemia, local mass effects of the underlying adenoma, and insufficiency of other pituitary axes

Are there any analytical problems?

Physiological variations of PRL secretion

PRL secretion is influenced by a variety of physiological factors, which may not be represented in the given reference range for a particular assay. Garde et al. demonstrated both cyclic seasonal variation and within-day variation in women [5]. PRL was highest in March–May (7.3 µg/l) and lowest in September–November (4.6 µg/l), with a 44% difference based on the predicted values. During day, PRL was highest in the morning (0900–1000: 10.5 µg/l), and somehow lower at midday (1200–1400: 5.4 µg/l) and afternoon (1500–1800: 6.1 µg/l), with a with-in day variation of 55%.

PRL assays

PRL is usually measured by automated immunoassays. Despite calibration against the WHO's third international standard 84/500 containing exclusively 23 kDA monomeric prolactin from human pituitaries, there are considerable between-method differences [1]. Reference ranges for common assay platforms have been published, with upper limits lower than those presented by the majority of manufacturers [6]. Normal values are higher in women than in men. A correct diagnosis of hyperprolactinemia may therefore depend on the use of well-established assay- and sex-specific reference intervals. Clinicians should also be aware of different measurement units provided in clinical practice, with 1 µg/l equivalent to 21.2 mIU/l. Stimulation and suppression tests give non-specific results and have been largely abandoned [7].

Macroprolactinemia

In the absence of any clinical symptoms, macroprolactinemia should be considered as a potential cause of increased PRL levels [8]. The major circulating form of prolactin is little PRL with a molecular weight of 23 kDa, the remainder consisting of big PRL (MW 50 kDa) and big-big PRL (MW > 150 kDa). However, in 10–25% of hyperprolactinemic populations a high proportion of big-big prolactin is found in the serum [1]. Anti-PRL autoantibodies (mostly IgG) bound to little PRL contribute to big-big PRL and therefore macroprolactinemia. This variant is considered to be biologically inactive, with most patients with macroprolactinemia lacking typical clinical symptoms of hyperprolactinemia even during long-term follow-up [9]. Importantly, macroprolactin has been found to react in all immunoassays for prolactin (Fig. 2), albeit to a variable extent [10]. Whereas universal testing for macroprolactinemia in all patients with hyperprolactinemia is the norm in some practices and health care systems [11, 12], a case-based approach has been recommended by others [3]. The Endocrine Society Clinical Practice Guideline suggests assessing macroprolactin in all patients with asymptomatic hyperprolactinemia [7].

The diagnosis is made mainly by two methods, a polyethylene glycol method and gel chromatography. Polyethylene glycol precipitation is an inexpensive way and correlates well with gel chromatography [13]. Results are usually reported as percent total PRL recovered after PEG precipitation, using the formula: $\%R = [(PRLpeg \times 2)/PRLtot] \times 100$. A prolactin recovery < 40% is diagnostic of macroprolactinemia, 40–50% reflects macroprolactinemia in the context of an elevated prolactin and > 50% means true hyperprolactinemia [14].

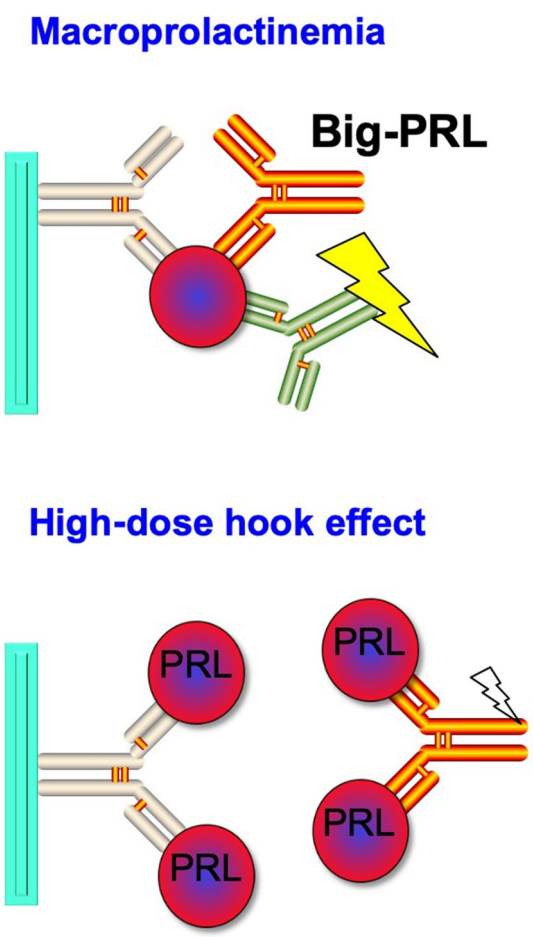

Fig. 2 Falsely elevated prolactin levels due to measurement of biologically inactive big-big PRL (upper panel) and falsely lowered prolactin levels due to saturation of assay antibodies by exceedingly high PRL levels (lower panel)

However, as patients with both macroprolactinemia and increased levels of monomeric prolactin may be misclassified, report of monomeric prolactin instead of percent total PRL has been suggested [15]. There are a number of limitations for the PEG method [11]. Due to approximately 20% of monomeric PRL co-precipitating with IgG, assay-specific reference ranges for post-PEG prolactin should be used [6, 16]. PEG may interfere in some prolactin assays [16], and very high levels of gamma globulin may result in false positive test for macroglobulin [17].

Clinicians should be aware of these potential pitfalls and verify exclusion of macroprolactinemia in their patients, especially in those without concomitant clinical symptoms. Repeat hormone or neuroradiological examinations and unnecessary treatments should thereby be avoided in patients with proven macroprolactinemia.

High-dose hook effect

A specific caution is needed when two-site immunoradiometric assays or chemiluminometric assays are used. Incubation with extremely high PRL concentrations saturates both antibodies and prevents sandwich formation ('high-dose hook effect') (Fig. 2). Patients with macroprolactinomas and very high PRL levels may seem to have only moderately elevated levels. In their initial observation, St-Jean et al. presented four patients with giant adenomas and undiluted PRL levels of 70–220 µg/l. After serial dilution, corrected PRL levels ranged 15048 to 45024 µg/l. Three of the patients had by then already been operated with the diagnosis of a non-functioning pituitary adenoma. These patients represented 5.8% of their series of macroprolactinomas, respectively 17% of their patients with giant adenomas. Petakov et al. demonstrated the high-dose hook effect in 4/28 (14.2%) of their series of patients with macroadenomas [18]. Undiluted PRL levels were 67–148 µg/l, raising to 2097–12722 µg/l after dilution. All tumors were categorized as very large adenomas (Hardy III–IV), representing 25% of all tumors in this group. Subsequently, several case reports confirmed the potential to miss the diagnosis of a macroprolactinoma due to the high-dose hook effect [19–21]. All those patients presented with giant pituitary adenomas, with corrected prolactin levels of 12266–280000 µg/l. Therefore, confusion with non-functioning macroadenomas associated with pituitary stalk disease may arise. When suspected, PRL levels should be re-measured at a 1:100 dilution.

Have other causes of hyperprolactinemia been ruled out?

Stress and exercise

In addition to prolactinomas, various other causes of a hyperprolactinemic state must be considered (Fig. 3). PRL is secreted episodically, so that some levels during the day may be above the normal range established for a given laboratory. In particular, stress may induce a two to fourfold rise in PRL levels that last less than an hour. As an example, Lennartsson et Jonsdottir investigated the influence of an acute psychological stress, applying the Trier Social Stress Test (a simulated job interview and a mental arithmetic task, both in front of a committee) to healthy subjects [22]. Prolactin levels raised by 88% (3–387%) and 85% (3–256%) in males and females, respectively, reaching its maximum after 20 min. Although a single measurement of PRL concentration is usually considered sufficient [7], a repeat test in patients with needle phobia or after traumatic venesection may be reassuring.

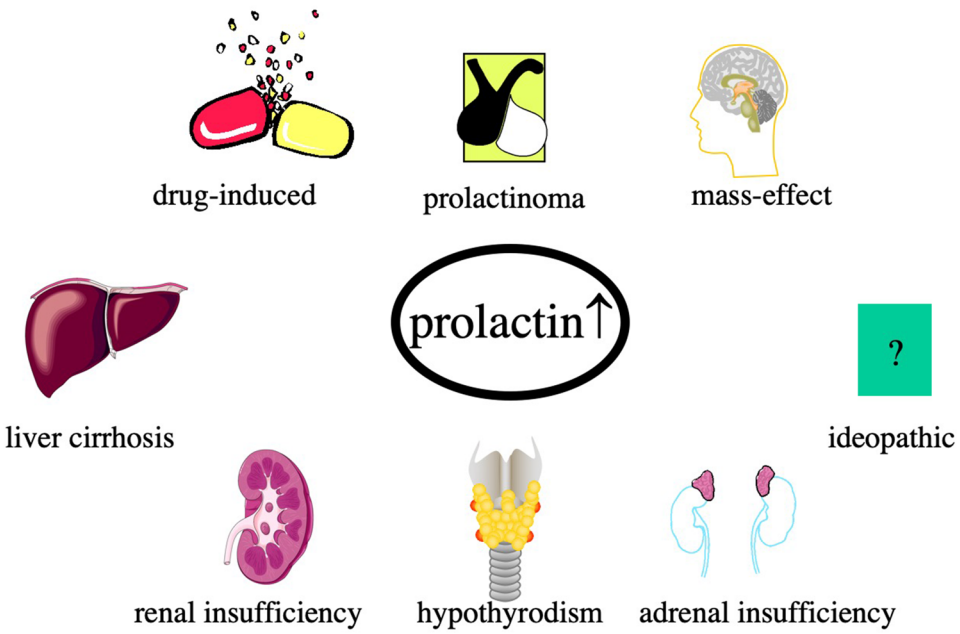

Fig. 3 Potential causes of hyperprolactinemia

Relevant increases in PRL levels may also be observed after exercise [23]. Daly et al. investigated the influence of prolonged endurance exercise in trained males [24]. PRL levels rose significantly by 375% during exercise, normalizing 90 min after stopping exercise. Of note, most studies report relative changes from baseline, which not necessarily reflect similar changes above the upper limit of normal.

Pregnancy

In pre-menopausal women with increased PRL levels, pregnancy should be excluded. Few studies have determined reference ranges for PRL during pregnancy, which may be important during follow-up of patients with prolactinomas. A recent study on pregnant women from China determined reference ranges using a modern ECLIA: first trimester 29–170 µg/l (0.8× to 4.7× ULN for healthy non-pregnant women), second trimester 68–254 µg/l (1.9× to 7.1× ULN), and third trimester 194–461 µg/l (5.4× to 12.8× ULN) [25]. Postpartum, PRL levels remain elevated in lactating women. Sexual breast stimulation and breast suckling may also cause a reflex release of PRL in non-lactating condition.

Drug-induced hyperprolactinemia

The most common causes of non-physiological hyperprolactinemia are medications that interfere with prolactin regulation [26]. The effects of antipsychotic drugs are mediated through dopamine receptors in various areas of the central nervous system. Blockade of D2 receptors in the hypothalamic tuberoinfundibular system and on pituitary lactotrophs counteracts the inhibition of PRL by dopamine. In a cross-sectional study from the UK, Smith et al. observed hyperprolactinemia in 34% and 75% of males and females, respectively, taking first generation 'typical' antipsychotic drugs (like phenothiazines, butyrophenones, and thioxanthenes) [27]. PRL levels are generally less than 100 µg/l with these drugs, although higher levels in individual patients have been described. After drug discontinuation, PRL levels usually normalize within 48–96 h, but increased levels have been found up to 3 weeks, depending on half-life of the drug and storage in fatty tissue [28]. These compounds have largely been replaced by second generation 'atypical' antipsychotic drugs. Similar binding affinity at the D2 receptor, but faster dissociation may permit sufficient antipsychotic effects, but lesser influence on prolactin levels [29]. Indeed, some of these drugs (clozapine, quetiapine, aripiprazole) do not appear to elevate prolactin levels, only transiently elevate PRL levels (ziprasidone), or increase PRL only at large doses (olanzapine), whereas others (risperidone, amisulpride) still cause marked and sustained increases in PRL levels in a relevant proportion of patients [26, 28, 30].

Tricyclic antidepressants (e.g. amitryptiline, desipramine) may cause up to twofold increases of PRL in a minority of patients, with more pronounced changes by clomipramine. Furthermore, most serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine) may cause mild hyperprolactinemia. Prokinetic dugs (metoclopramide, domperidone) may induce symptomatic hyperprolactinemia by antagonizing dopamine. Some antihypertensive drugs (alpha-methyldopa, reserpine, verapamil) may also cause moderate increase in PRL levels [31]. Galactorrhea caused by up to tenfold increases in PRL levels was observed in patients treated with protease inhibitors, possibly due

to either direct effects or more likely by inhibition of the cytochrome P450 system, thereby potentiating the dopamine antagonizing effects of other drugs [32]. Chronic abuse of cocaine or opiates has been associated with mild hyperprolactinemia. There is conflicting data on the effects of estrogens contained in oral contraceptives, with hyperprolactinemia found in 12% [33] and 30% [34], but minimal or absent effects in other studies [26, 31]. Estrogens used for hormone replacement therapy have shown minimal or no effects on PRL levels. In contrast, estrogens used in male to female transsexuals were associated with hyperprolactinemia in 63–100%, with PRL levels more than 3-fold ULN in 14–21% of patients [35].

Kidney disease

Hyperprolactinemia is also found in a number of medical conditions. Patients with chronic kidney disease may demonstrate raised PRL levels. Increased PRL secretion in those patients may be linked to primary pituitary abnormalities and reduced responsiveness to inhibiting signals [36]. Slightly reduced PRL clearance by the kidneys probably plays a minor role. Hou et al. found hyperprolactinemia in 27% of patients with creatinine levels between 1.5 to 12 mg/dl [37]. However, as some patients were taking medications known to increase prolactin levels, a clear association with chronic kidney disease was only confirmed for 18% of patients. PRL levels in these patients were all below 100 µg/l and correlated significantly with serum creatinine levels. Moreover, 81% of patients with end-stage renal disease were found to have PRL levels > 30 µg/l, and 27% had PRL levels even higher than 100 µg/l [38]. PRL levels differed significantly between both sexes, with median PRL concentrations of 53 µg/l and 90 µg/l in males and females, respectively. In contrast, patients with successful renal transplantation will rapidly normalize their PRL levels [39]. Elevated levels of PRL in patients on renal replacement therapy were not found to be due to increased presence of macroprolactin [40].

Liver disease

Basal PRL levels may also be increased in patients with alcoholic or nonalcoholic liver cirrhosis. Hyperprolactinemia has been demonstrated in 12–14% of patients with liver disease [41, 42], but may be more frequent with severe disorders. In a study by McClain et al., two third of patients with liver cirrhosis presented with moderately elevated prolactin levels (all below 40 µg/l) [43]. Patients with additional portal systemic encephalopathy demonstrated significantly higher PRL levels (> ULN in more than 85% of patients, > 40 µg/l in ~ 43%). As the metabolic clearance of PRL is not altered in those patients, increased PRL levels are most likely due to increased secretion, probably caused by impaired central neurotransmission of dopamine [44]. A more recent study questioned the relevance of liver cirrhosis as a cause of hyperprolactinemia, as raised PRL levels in that cohort were mostly due to medication or comorbidities, leaving less than 2% with a clear association with liver disease [45].

Hypothyroidism

Hyperprolactinemia may also be seen in primary hypothyroidism. A compensatory rise in hypothalamic TRH [46], alleviated prolactin clearance [47], reduced sensitivity to the inhibitory action of dopamine [48], and unrestrained PRL synthesis with lower thyroid hormone levels [49] may all contribute to the raise in PRL levels. Hekimsoy et al. observed significantly increased PRL levels in 36% and 22% of patients with overt and subclinical hypothyroidism, respectively [50]. PRL levels were positively correlated with TSH concentrations, rarely exceeded 60 µg/l, and decreased to normal levels after normalization of thyroid function with thyroid hormone substitution. In another large study of 2848 individuals, hyperprolactinemia was found in 43% and 40% of females and males with overt hypothyroidism, respectively, and 36% and 32% of patients with subclinical hypothyroidism [51]. In contrast, Raber et al. described hyperprolactinemia in only 8% of 1003 unselected outpatients consecutively referred with newly diagnosed hypothyroidism [52]. PRL levels did not exceed 4.5 × ULN, when excluding patients on medication potentially increasing PRL levels. The reasons for the discrepant results are currently unclear, but may be due to different degrees of hypothyroidism, cofounding medication, and undetected macroprolactinemia.

Others

Adrenal insufficiency has rarely been reported as a cause of hyperprolactinemia. Elevated PRL levels have also been found after chest wall [53] and cervical cord lesions, after mastectomy and thoracotomy, and after spinal cord injuries. Ectopic production of PRL is exceedingly rare.

Conclusions

Diagnosis of hyperprolactinemia and subsequent determination of the underlying cause are usually straight forward. If clinical symptoms and prolactin levels do not match, analytical problems should be considered. A careful history and physical examination, blood chemistry, thyroid function test, and a pregnancy test will help to exclude other potential causes of hyperprolactinemia.

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Compliance with ethical standards

Conflict of interest Author SP declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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