

## Evaluation of Patients with Hyperprolactinemia

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### ABSTRACT

*Hyperprolactinemia is characterized by the elevation of prolactin levels in circulation. It is the most common disorder of the hypothalamic–pituitary axis. Proper evaluation of the etiology in these patients is extremely important for the accurate follow-up and treatment. This review study aimed to discuss differential diagnoses and key points in patients with hyperprolactinemia.*

*Key words: Hyperprolactinemia, macroprolactinemia, prolactinoma*

### INTRODUCTION

Prolactin (PRL) is one of the anterior pituitary hormones that plays an important role in reproductive functions. Besides its role in milk production during lactation, it also affects gonadal function by suppressing the action of luteinizing and follicle-stimulating hormones.

Hyperprolactinemia is characterized by increased PRL levels in the blood. It is the most common endocrine disorder of the hypothalamo–hypophyseal–adrenal axis (1).

Prolactinoma is the most common cause of hyperprolactinemia after excluding pregnancy primary hypothyroidism and the use of drugs, which can also lead to hyperprolactinemia (2). Menstrual disturbances, infertility, and galactorrhea in women, sexual dysfunction and infertility in men, as well as functional evaluation of pituitary tumors are frequent areas of PRL measurement in the clinic.

While investigating the etiology of hyperprolactinemia, clinicians should be aware that some situations may lead to false diagnosis. This review study focused on the differential diagnosis of hyperprolactinemia and the signs leading to the correct diagnosis.

### EPIDEMIOLOGY

The frequency of hyperprolactinemia may vary according to the population studied. Various studies in the general population have reported the prevalence of 0.4%–17% (3). As expected, it is higher in endocrinology or gynecology outpatient clinics. The incidence of hyperprolactinemia can be as high as 9% in amenorrhoeic women, 25% in women with galactorrhea, 16%–30% in women with infertility, and 70% in women with both amenorrhea and galactorrhea (2, 4, 5).

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## PROLACTIN REGULATION

The primary function of PRL is to promote breast development and lactation during pregnancy. Dopamine is the main physiological inhibitor in prolactin release. Its effect has been demonstrated through binding to dopamine D2 receptors in lactotrophic cells. On the contrary, the main stimulant in PRL synthesis is thyrotropin-releasing hormone (TRH). The balance between dopamine and TRH determines the amount of PRL release from the pituitary gland (6).

## PROLACTIN MOLECULE AND MACROPROLACTINEMIA

Although the predominant form of PRL is monomeric PRL (molecular weight 23 kDa), dimeric or large PRL (45–60 kDa) and macroprolactin (150–170 kDa) constitute less than 20% of the total PRL (7). It is called macroprolactinemia when more than 60% of circulating serum PRL consists of macroprolactin (8). Although the exact prevalence of macroprolactinemia in the population with hyperprolactinemia is unknown, it has been reported to be 10%–25% in various studies [9,10]. Macroprolactin is formed by decreased clearance of PRL in chronic renal failure or more complex formation of immunoglobulin G and monomeric PRL (11). These

PRL forms have an immunogenic effect and are included in PRL measurement using many PRL kits (3). The gold standard method for measuring macroprolactin is gel filtration chromatography. However, precipitation with polyethylene glycol (PEG) has more commonly been used in clinical practice due to the laborious and expensive procedure of gel filtration (12). PEG reduces the level of macroprolactin in the supernatant by precipitation, and a decrease of less than 60% allows the diagnosis of monomeric hyperprolactinemia. Macroprolactin has low bioactivity and bioavailability, which explains why typical symptoms do not occur in many patients with macroprolactinemia (13).

## ETIOLOGY

The causes of hyperprolactinemia can be categorized into three main categories, apart from the macroprolactinemia mentioned earlier: physiological, pharmacological, and pathological (Table 1). The presence of a secondary cause for hyperprolactinemia and fluctuations in PRL levels in follow-up patients suggests other causes besides prolactinoma. Precisely focusing on such situations has been of great importance in terms of preventing unnecessary examination and treatment.

TABLE 1: Causes of hyperprolactinemia.

Physiological	Pregnancy and lactation
	Sleep
	Physical activity
	Stress
Pharmacological	Dopamine receptor blockers: phenothiazines, haloperidol, metoclopramide
	Dopamine reducing agents: reserpine, alpha-methyl dopamine, opiates
	Histamine receptor antagonists: cimetidine, ranitidine
	Serotonin reuptake inhibitors: paroxetine
	Calcium channel blockers: verapamil
	Estrogen and antiandrogens
Pathological	Hypophasic disease: prolactinoma, acromegaly, Cushing's disease, lymphocytic hypophysitis, empty sella
	Hypothalamo–hypophyseal damage: tumors (craniofarniation, and meningioma), nonfunctional pituitary adenomas, trauma, radiation
	Inflammatory/granulomatous: sarcoidosis, and histiocytosis
	Systemic diseases: hypothyroidism, chronic renal insufficiency, cirrhosis, adrenal insufficiency
	Idiopathic

## PHYSIOLOGICAL CAUSES

The most important physiological causes of hyperprolactinemia are pregnancy and lactation (14). PRL levels during pregnancy vary from patient to patient but can range up to 600 ng/mL depending on estrogen concentration (15). With a decrease in estradiol concentration at 6 weeks of birth, the PRL concentration returns to normal even if the mother is breastfeeding. Nipple warnings lead to PRL elevation in women who are lactating, especially in the first weeks of the postpartum (16). A number of stress-related factors (physical, exercise, hypoglycemia, myocardial infarction, surgery), coitus, and sleep can also contribute to increased PRL release (17).

## PHARMACOLOGICAL CAUSES

Drugs can cause hyperprolactinemia via various mechanisms. Increased transcription in the PRL gene (estrogens), antagonist effect on dopamine receptor (risperidone, haloperidol, metoclopramide, domperidone, and sulpiride), decrease in dopamine level (reserpine and methyl dopa), reduction of hypothalamic dopamine production (verapamil and morphine), dopamine reuptake inhibition (tricyclic antidepressants, amphetamines and monoamine inhibitors), and serotonin reuptake inhibition (opiates and paroxetine) are the most important of these mechanisms. Some studies demonstrate that risperidone can increase PRL levels by more than 200 ng/mL; however, PRL levels in drug-associated hyperprolactinemia are generally in the range of 25–100 ng/mL (18). A study has shown that antidepressants (tricyclic antidepressants) and antipsychotics (haloperidol, phenothiazines, and risperidone) are responsible for the majority of cases with drug-associated hyperprolactinemia (19). Serum PRL level increases within hours after antipsychotic use and returns to normal within 2–4 days after discontinuation of chronic therapy (20).

The new generation of atypical antipsychotics has been characterized by increased antipsychotic activity and less neurological and endocrine side effects. Unlike the drugs with high hyperprolactinemia-causing effects (such as risperidone, amyl sulpiride, and molindone), atypical antipsychotics rarely cause hyperprolactinemia (21). Furthermore, hyperprolactinemia

has been reported to be recovered by the addition of atypical antipsychotics such as quetiapine and aripiprazole to other antipsychotics (22).

In a study of paroxetine, a selective serotonin reuptake inhibitor, a slight increase in PRL levels was reported in the long term (23). In another study using fluoxetine, no significant difference in PRL concentration was observed in the group using and not using the drug (24).

## PATHOLOGICAL CAUSES

Prolactinoma constitutes 25%–30% of functional pituitary adenomas. It has been the most common functional pituitary adenoma and the main cause of pathologic hyperprolactinemia (25). Although microadenomas (<1 cm) are more common in premenopausal women, macroadenomas ( $\geq 1$  cm) are more common in both men and postmenopausal women. Pituitary tumors other than prolactinoma [growth hormone (GH)–PRL, thyroid-stimulating hormone–PRL, or ACTH–PRL-producing tumors] may also increase PRL production (6). Moreover, functional or nonfunctional pituitary tumors can cause hyperprolactinemia by preventing dopamine to reach from hypothalamus to the pituitary gland by pressing the gland. Infiltrative lesions, hypophysitis, aneurysms, and radiotherapy are the other lesions that can cause hyperprolactinemia by compressing the pituitary gland (26).

Pathological hyperprolactinemia may also be caused by nonpituitary endocrine causes. It has been reported that mild hyperprolactinemia may develop in patients with obvious and subclinical primary hypothyroidism (40% and 22%, respectively) (27). However, PRL levels are determined to be normal in many hypothyroid patients (28). The main cause of the increase in PRL in hypothyroidism is the stimulation of prolactin by TRH. A reduction in prolactin clearance and decreased PRL sensitivity to dopamine effects are other mechanisms involved. Thyroid function tests should be evaluated in patients with PRL elevation because pituitary hyperplasia (with thyroid hormone replacement) and hypophyseal MRI (magnetic resonance imaging) can be confused with prolactinoma. Adrenal insufficiency is another endocrine disorder in which PRL elevation may develop. Since glucocorticoids

TABLE 2: Key points in diagnosis of hyperprolactinemia.

Diseases other than prolactinoma that can cause hyperprolactinemia should be carefully examined.
The possibility of macroprolactinemia should be kept in mind in patients who do not report symptoms associated with hyperprolactinemia.
The presence of macroprolactinemia in a patient does not exclude prolactinoma.
The patient's prolactin level is indicative. A prolactin level greater than 250 ng/mL suggests macroprolactinoma, while prolactin level is generally less than 100 ng/mL in microprolactinoma, pituitary stalk pressure, and drug-dependent or systemic disease.
The hook effect should be considered in patients who have prolactin level not as high as expected and are macroadenomic. Another possibility might be the stalk pressure.
Some patients with prolactinomas may not be able to display adenomas on pituitary MRI, and some displayed adenomas may also be nonfunctional.

have a suppressive effect on PRL release, an increase in PRL levels (which is normalized by steroid replacement) may be observed in adrenal insufficiency (29).

The most important cause of nonendocrine-associated hyperprolactinemia is chronic renal failure (CRF) and dialysis. It has been found that PRL levels return to normal after renal transplantation in the patients with CRF (30). It has been associated with decreased clearance of PRL and increased production related to hypothalamic dysregulation. Although the etiology has not been elucidated yet, alcoholic and nonalcoholic cirrhosis is another illness known to cause mild prolactinemia.

Chest wall and spinal cord lesions (mastectomy, herpes zoster, tabes dorsalis, and cervical ependymoma) may also cause PRL elevation, similar to breast stimulation and lactation causing PRL release reflex. More rarely, tumors that produce ectopic PRL have been reported. These tumors include renal cell carcinoma, gonadoblastoma, uterine carcinoma, colorectal carcinoma, and ovarian teratoma. However, ectopic foci scanning is not recommended unless clinically strong evidence is determined since these ectopic tumors are quite rare.

When the cause of hyperprolactinemia is not found, the terminology of idiopathic hyperprolactinemia is used and, in many patients, it is due to lactotrophic adenomas that cannot be detected by radiological techniques (31).

## CLINICAL FEATURES OF HYPERPROLACTINEMIC PATIENTS

Hyperprolactinemia is a typical gonadal finding in premenopausal women and men. However, symptoms are eradicated in postmenopausal women, and these patients may be hospitalized with complaints of direct lactotrophic adenomatous mass effect. The classic findings of hyperprolactinemia are hypogonadism-related symptoms such as oligomenorrhea, amenorrhea, and infertility in women as well as decreased libido and erectile dysfunction in men in addition to galactorrhea. Extracted hypogonadism may cause decreased bone density. The most characteristic finding of hyperprolactinemia is galactorrhea; however, it may be absent or intermittent in most patients. Moreover, macroadenomas are more frequent due to late diagnosis, especially in postmenopausal female and male patients, and these patients may present with mass effect and neuro-ophthalmic complaints (headache and visual field defect) (17). Rarely, cases of prolactinomas with hydrocephalus and trigeminal neuralgia have been reported (32).

## APPROACH TO PATIENTS WITH HYPERPROLACTINEMIA

Key points in approaching patients with hyperprolactinemia are given in Table 2. First, pregnancy should be excluded in a patient with amenorrhea and hyperprolactinemia. Thyroidectomy history or thyroid disease in the family suggests primary hypothyroidism. The drugs, which can induce elevations in PRL levels, should be used with caution. As mentioned earlier, macroprolactinemia should be kept in mind in the absence of typical symptoms.

Finally, the elevation in the PRL level may give a clue for determining the etiology of hyperprolactinemia. Stress due to blood drawing may cause a slight increase in prolactin levels (<40 ng/mL). PRL is generally found to be less than 100 ng/mL in drug-related or systemic diseases (19). PRL is expected to be <100 ng/mL as a result of pressure to the pituitary stalk caused by nonfunctional hypophyilous tumors (33). GH- and PRL-secreting adenomas may cause extremely high PRL levels >2000 ng/mL (34).

In prolactinoma, the level of circulating PRL is often correlated with the tumor size. PRL levels are predicted to be <100 ng/mL in microprolactinoma and frequently >250 ng/mL in macroprolactinoma (35). However, if the PRL level is found to be slightly elevated in a large macroadenoma, the "hook effect" should be considered. This is due to the circulation of excessively high amounts of PRL, saturating the antibodies in the PRL measurement and resulting in false low results (36). The hook effect can be corrected with a 1:100 dilution of serum, and a dramatic increase in PRL level is expected after this procedure (36).

Pituitary MRI is the preferred method for both microprolactinoma and macroprolactinoma imaging (37). Pituitary MRI is superior to computed tomography and can demonstrate optic chiasm and cavernous sinus involvement. Since nonfunctional pituitary adenomas are quite frequent in the general population (even if pituitary adenomas are found in patients with hyperprolactinemia), this situation might be due to etiologic factors other than prolactinoma. Various studies have shown that up to 25% of macroprolactinemic patients may have abnormal findings in pituitary imaging (microadenomas, cystic lesions, and empty sella) (38). This situation is of great importance since hyperprolactinemia can be misinterpreted as microprolactinoma and treated unnecessarily.

## CONCLUSIONS

Proper identification of the etiology of hyperprolactinemia is of great importance for proper follow-up and treatment. Therefore, patients with hyperprolactinemia should be cautiously questioned for etiologies except prolactinoma. Although the level of PRL provides important clues in making this decision, the clinician

should be careful with measurements that incorrectly reflect the PRL level, such as macroprolactinemia or the "hook effect." Since some lactotrophic adenomas cannot be visualized with pituitary MRI and some displayed adenomas might be nonfunctional, the findings should be evaluated by correlating clinical parameters.

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