Prolactinomas

Andrea Glezer, MD, PhD, Marcello D. Bronstein, MD, PhD*

KEYWORDS

• Hyperprolactinemia • Prolactinoma • Pituitary tumors
• Hypogonadotropic hypogonadism • Infertility • Prolactin • Dopaminergic agonists

KEY POINTS

- Hyperprolactinemia is an important cause of infertility.
- Prolactinomas are the main pathologic cause of hyperprolactinemia.
- Medical treatment with dopamine agonists is effective and safe in most cases.
- Many current and potential future treatments may overcome the burden of aggressive and resistant prolactin-secreting tumors.

INTRODUCTION

Hyperprolactinemia is an important cause of galactorrhea, irregular menses, and infertility, especially among young women. The prolactin (PRL)-secreting pituitary adenoma (prolactinoma) is the most common pathologic cause of hyperprolactinemia. In patients harboring macroprolactinomas, besides hypogonadism-related symptoms, mass effect symptoms, such as other pituitary deficiencies and headache and visual disturbances, can also be found.

Besides prolactinomas, physiologic (pregnancy and lactation), pharmacologic (especially antipsychotics), systemic diseases (renal and hepatic failure), endocrine diseases (hypothyroidism, Cushing disease), other pituitary or sellar region tumors causing pituitary stalk disconnection, and macroprolactinemia can be the cause of hyperprolactinemia. More recently, PRL receptor mutation was described as a cause of hyperprolactinemia. Idiopathic hyperprolactinemia is diagnosed after ruling out all referred causes.

The identification of the correct cause of hyperprolactinemia is crucial for treatment. For example, in pharmacologic hyperprolactinemia, this can be achieved by discontinuing or switching the suspected drug. Concerning prolactinomas, dopamine agonist (DA) is the specific treatment of choice in most cases.

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Neuroendocrine Unit, Laboratory of Cellular and Molecular Endocrinology LIM-25, Division of Endocrinology and Metabolism, Hospital das Clinicas, University of São Paulo Medical School, Rua Enéas de Carvalho Aguiar, São Paulo CEP 05403-000, Brazil
* Corresponding author. Rua Enéas de Carvalho Aguiar, 155 8 Andar Bloco 03, São Paulo CEP 05403-000, Brazil.
E-mail address: mdbronstein@uol.com.br

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EPIDEMIOLOGY

Prolactinoma is the most common pituitary tumor. Its estimated prevalence is 500 cases per million and incidence of 27 cases per million per year. Microadenomas correspond to 60% of the cases prevailing in women. Adolescents and men usually harbor macroadenomas. PRL-secreting carcinomas are extremely rare.[1]

PATHOPHYSIOLOGY

PRL is under dopaminergic inhibitory tonus coming from tuberoinfundibular-pituitary neurons. Dopamine acts through dopamine receptor type 2, especially the short isoform, reducing PRL transcription and secretion, and reducing lactotroph proliferation.[2] However, various factors stimulate PRL secretion by inhibiting dopamine tonus, such as opioids, cholecystokinin, bombesin, neurotensin, and neuropeptide Y; or by directly stimulating PRL secretion, such as vasoactive intestinal peptide, breastfeeding, and stress.[3] Estrogens stimulate PRL secretion acting directly in the lactotrophs and also reducing dopaminergic activity by increasing expression of the less active long isoform of the D_2 receptor.[2] Hyperprolactinemia causes hypogonadism mainly by inhibiting pulsatile gonadotropin-releasing hormone secretion, in addition to direct inhibition of gonadal steroidogenesis.[4] It was recently demonstrated in rodents that PRL directly acts on hypothalamic neurons by inhibiting the expression of the gene Kiss1 kisspeptin, and this could be the possible mechanism responsible for reducing secretion of gonadotropin-releasing hormone.[5] Signs and symptoms related to hyperprolactinemia are present in physiologic states, such as pregnancy and breastfeeding, and in pharmacologic and pathologic cases.

CLINICAL FEATURES

Signs and symptoms found in patients with hyperprolactinemia are related to hypogonadotropic hypogonadism and galactorrhea. Galactorrhea is not a specific signal and may be present in individuals with normal PRL levels.[6] Hypogonadism can cause menstrual irregularity and amenorrhea in women, sexual dysfunction, infertility, and loss of bone mineral mass in both genders. Hyperprolactinemia is an important cause of infertility in clinical practice. In women, it can be characterized by short luteal phase, anovulatory cycles, oligomenorrhea, and amenorrhea, whereas in men, changes in viability and quantity of sperm can occur.[7] Hyperprolactinemia can also reduce libido independently of testosterone levels.[8,9] Patients with hyperprolactinemia often have reduced bone mineral density,[10] which may lead to fractures in both sexes. In patients with macroprolactinomas, besides the implications related to hormonal hypersecretion, tumor mass effect symptoms, such as headache, visual changes, and hydrocephalus, can also occur. Hypopituitarism beyond hypogonadism can occur if there is compression of the pituitary stalk or destruction of normal pituitary tissue.[11,12]

DIAGNOSIS

In patients with signs and symptoms related to hyperprolactinemia, evaluation of serum PRL is required. Usually, in prolactinomas, PRL level is proportional to the tumor mass: 50 to 300 ng/mL in microprolactinomas and 200 to 5000 ng/mL in macroprolactinomas (normal range, 2–23 ng/mL). However, disproportion between PRL levels and tumor mass can be found in cystic prolactinomas and giant prolactinomas because of “hook effect” (discussed later). Provocative tests, such as thyrotropin-releasing hormone and metoclopramide, or even suppression test with L-dopa are