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Review

Update on prolactinomas. Part 1: Clinical manifestations and diagnostic challenges

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ABSTRACT

The authors provide an update on the clinical manifestations and diagnostic challenges of prolactinomas. Prolactinomas are the most common pituitary adenoma seen in clinical practice. Secondary causes of hyperprolactinemia should be ruled out by assessment of the clinical history, including current medications, physical examination, pregnancy test, routine biochemical analysis with a thyroid function test, and neuroimaging, before a confirmatory diagnosis of prolactinoma is made. Prolactinomas are associated with endocrine dysfunction, affecting gonadal function and causing neurological deficits due to mass effect. The progress in elucidating the pathogenesis of prolactinomas and advances in diagnostic methods, including more sensitive diagnostic hormone assays and neuroimaging, have enriched the current diagnostic approach and management. Making the correct diagnosis is crucial to implementing the appropriate therapy. Dopamine agonist therapy remains the first line of treatment for prolactinomas, as it is effective in normalizing serum prolactin levels and reducing tumor size. Surgery is typically indicated for patients who are resistant to medical therapy or intolerant of its adverse side effects, or for those experiencing progressive neurological deficits. Nevertheless, curative surgical resection as a primary mode of treatment for smaller prolactinomas has recently gained attention as an alternative to lifelong dopamine agonist treatment.

1. Introduction

Prolactinomas are prolactin-secreting adenomas derived from lactotroph cells in the pituitary gland [1]. They are the most common pituitary adenoma, accounting for approximately 40% of all pituitary tumors and 50–60% of all functional pituitary tumors. Most of these are small, intrasellar, and slow growing tumors, and are found predominantly in females [2–4]. Larger prolactinomas do occur, but are more often found in men and younger patients. Further up the spectrum are giant prolactinomas (>4 cm), which are rare and invasive, contributing to only 2–3% of all prolactin-secreting adenomas [3]. These larger tumors may cause symptomatic mass effect by compressing the surrounding structures, resulting in visual loss and extraocular motor palsies [3,4]. Prolactinomas commonly induce endocrine effects, causing reproductive and sexual dysfunction due to prolactin hypersecretion [5,6]. A variety of other conditions can also cause hyperprolactinemia. Therefore, it is of critical importance to properly and accurately diagnose prolactinomas in order to develop an appropriate treatment plan and achieve optimal patient outcomes. In this paper, we discuss the clinical presentation and diagnosis of prolactinomas, including how to navigate the diagnostic dilemmas and challenges.

2. Clinical presentation

Prolactinoma patients predominantly present with clinical manifestations of hyperprolactinemia. The primary function of prolactin is to stimulate milk production, but it also has secondary effects on gonadal function [2,7]. Hyperprolactinemia interrupts the hypothalamic production of gonadotrophin-releasing hormone, inhibiting the release of luteinizing hormones and follicle-stimulating hormone. This impairs gonadal steroidogenesis, resulting in hypogonadism and infertility [7–9]. Other manifestations include clinical sequelae of endocrine dysfunction, local mass effect on neurologic structures and rarely, pituitary tumor apoplexy [5].

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The most common symptoms of hyperprolactinemia in women are galactorrhea, amenorrhea, and infertility. Approximately 90% of premenopausal women exhibit oligo/amenorrhea, with galactorrhea seen in about 80% [2,7]. Amenorrhea may often be masked by the use of oral contraceptives and, therefore, may not be detected until after discontinuation of use, or until after pregnancy [1]. Women usually present in the earlier stages of the disease with smaller tumors (microprolactinomas) due to more readily detected symptoms of galactorrhea and amenorrhea, as illustrated in a Figure 1 with a young woman who presented with a microprolactinoma [1,6,8]. However, postmenopausal women do not present with these classic clinical features and, therefore, they often present later, with larger adenomas and symptomatic mass effect [7,10]. Nevertheless, postmenopausal women on estrogen replacement therapy may present with galactorrhea [10].

Conversely, 80% of prolactinomas in men are macroadenomas and, therefore, display neurological manifestations and clinical signs due to mass effect on the neighboring structures [11]. These include headaches, visual symptoms, cranial neuropathies, impedance of cerebrospinal fluid flow, or hypopituitarism due to compression of the pituitary gland and stalk [6]. Visual field defects and hypopituitarism are seen in approximately 45 and 35% of patients with macroprolactinomas, respectively [1]. Galactorrhea and gynecomastia are very uncommon in men [1]. The more subtle presentation of symptoms such as decreased libido and erectile dysfunction may delay diagnosis and intervention in adult men [1,10]. The larger tumor size seen in men presumably reflects this diagnostic delay, but may also be due to biological differences in tumor growth and mitotic activity [7,12–14]. Long term hypogonadism may lead to reduced bone mineral density in both men and women due to the inhibitory effect of prolactin on sex steroids, leading to testosterone and estrogen deficiencies [10,12,15]. A typical clinical presentation of a macroprolactinoma is illustrated in Figure 2.

Although rare, prolactinomas do occur in children and adolescents. They predominantly present as macroadenomas (~60–80%) rather than microadenomas, and are accompanied with symptoms of mass effect [5,12,13]. Primary hypogonadism and delayed puberty are seen in both sexes, and primary amenorrhea and galactorrhea in girls [7,8].

3. Causes of hyperprolactinemia

Physiological causes of hyperprolactinemia include exercise, diet, stress (physical and psychological), neurogenic stimulation (such as those created by chest wall stimulation and nipple stimulation), sexual intercourse, or pregnancy (Table 1) [10,16]. Psychological stress may slightly elevate prolactin levels, but no association has been seen between any chronic psychiatric state and chronic hyperprolactinemia [16]. However, some antipsychotic medications can serve as a potential pharmacologic cause of hyperprolactinemia. Medications are the most common cause of non-tumoral hyperprolactinemia [17]. Any drug that disturbs the dopamine system or mechanism of its receptor can potentially increase prolactin levels. These include drugs that inhibit dopamine reuptake (monoamine oxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors), deplete dopamine (reserpine, methyldopa), increase transcription of the prolactin (PRL) gene (estrogens), or antagonize the dopamine receptor on lactotrophs (risperidone, metoclopramide, haloperidol; Table 2) [1,5,16]. In a study of 106 patients on antipsychotics, 81% of those on risperidone, 35% of those on olanzapine, 39% of those on ziprasidone, and 38% of those on typical antipsychotics presented with hyperprolactinemia [16,17]. Most individuals on the newer, more efficacious atypical antipsychotics (except risperidone, amilsulpride and molindone) do not usually present with a hyperprolactinemic state [16]. In instances of drug-induced hyperprolactinemia, prolactin levels increase slowly with oral administration, but the elevation is usually mild with prolactin levels less than 100 ng/mL [1]. These levels should return to normal within a few days to weeks of drug cessation [5].

When elevated prolactin levels are seen, it is critical to rule out pregnancy first in women. Rising estrogen concentrations, secreted by the placenta during pregnancy, stimulate prolactin synthesis and induce lactotroph hyperplasia, which may lead to pituitary enlargement and prolactin levels as high as 10 times the normal range. During pregnancy, serum prolactin levels can rise to around 200–500 ng/mL [7,15]. Prolactin levels decrease after delivery in postpartum women, and normalize within approximately 6 months after delivery in those who breast feed, and within weeks in those who do not breast feed [5,8].

Chronic renal failure and liver cirrhosis can increase circulating prolactin concentrations due to decreased clearance [1]. About one third of patients with kidney disease develop hyperprolactinemia [17]. Prolactin levels have been shown to return to normal shortly after renal transplantation [16]. Primary hypothyroidism may cause moderate hyperprolactinemia due to the increased synthesis of thyrotropin-releasing hormone [5,10,18]. In patients with inadequately treated or long term primary hypothyroidism, pituitary hyperplasia may occur, mimicking a pituitary tumor [17]. This may lead to a misdiagnosis of prolactinoma and, therefore, it is critical to evaluate thyroid function to rule out primary

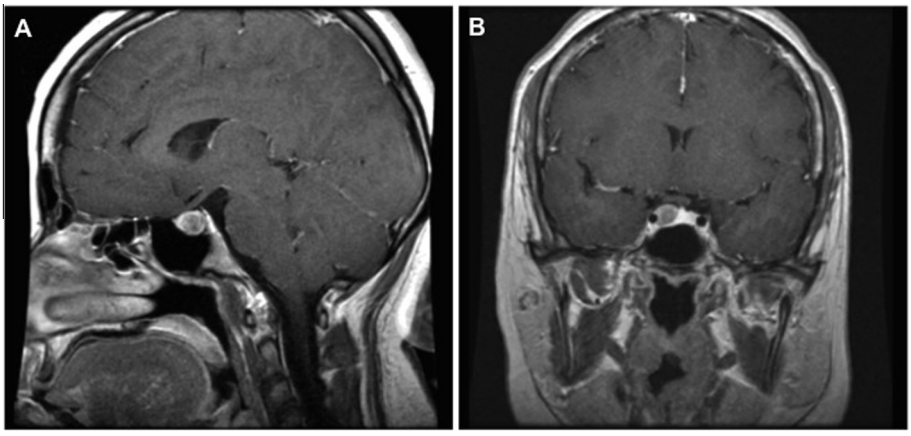

Fig. 1. Post-gadolinium T1-weighted MRI (A: sagittal; B: coronal) of a 22-year-old woman with a microprolactinoma on the right side of the sella, who presented with amenorrhea and galactorrhea. Her serum prolactin was 89 ng/mL.