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PROLACTINOMA - THE MOST COMMON PITUITARY TUMOR. A LITERATURE REVIEW

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Abstract

The most common neoplastic change in the pituitary gland is a prolactinoma. Its presence leads to an increase in prolactin levels in the body, known as hyperprolactinemia. This tumour is most frequently diagnosed in young women due to menstrual disorders and the fertility issues it causes, although hyperprolactinemia affects both genders. Diagnosis is not complicated, but certain issues, such as the "hook effect" and macroprolactinemia, can pose challenges to establishing an accurate diagnosis. The primary treatment method involves the use of dopamine agonists, most commonly cabergoline. However, cases of resistance to this method of normalizing prolactin levels, despite using the highest, well-tolerated patient doses, do occur. Other treatment techniques include surgical methods and radiotherapy, but they may also prove ineffective at times. A literature review indicates a continuous increase in researchers' interest in new treatment methods for cases resistant to standard therapeutic approaches or highly invasive pituitary tumours. An example of this is the use of temozolomide in treatment. Research is also underway on other groups of drugs, but there is still insufficient data about them to incorporate them into standard procedures. Therefore, it is crucial to deepen knowledge in this area and conduct further observations.

Key words: sprolactinoma, dopamine agonists, temozolomide, fertility issues, hypogonadism

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Introduction

Prolactinoma is the most common pituitary gland tumour originating from lactotroph cells, causing autonomous secretion of prolactin. The incidence of this tumour between the ages of 20 and 50 varies between men and women, while after the sixth decade of life, it becomes similar in both sexes [1]. This difference may be attributed to the fact that in young women, symptoms related to hyperprolactinemia-induced hypogonadism (infertility, amenorrhea) motivate them to seek prompt medical consultation. In contrast, in older age, the frequency is similar in both sexes because the diagnosis is typically based on the mass effect of the tumour [2].

Predisposing Factors

Despite the fact that a significant portion of pituitary tumours occurs sporadically, prolactinoma may also have a genetic basis and be associated with certain hereditary syndromes. These syndromes include multiple endocrine neoplasia type 1 and 4 (MEN-1, MEN-4), familial isolated pituitary adenomas (FIPA), and Carney's syndrome [3,4,5].

A genetic defect in the case of prolactinoma may lead to a more aggressive tumour development and a weaker response to standard dopamine agonist (DA) treatment [3]. Therefore, it can be concluded that genetic counselling may be valuable for individuals with a family history of the condition.

Prolactinoma and Fertility

Elevated prolactin levels in the blood are one of the most common causes of secondary hypogonadism and infertility in both sexes [6]. Prolactin excess affects reproductive function centrally and peripherally. Centrally, it inhibits the release of gonadotropin-releasing hormone (GnRH), leading to reduced gonadotropin secretion, promoting hypogonadism and infertility [6]. Peripherally, it acts to suppress the synthesis and secretion of sex hormones, specifically oestrogens and progesterone in women. In men, prolactin receptors are present on epithelial cells of ducts, Leydig cells, and Sertoli cells. Through these receptors, prolactin inhibits the activity of these cells, negatively impacting steroidogenesis, spermatogenesis, and the secretory functions of male reproductive organs [6,7].

Symptoms

A pituitary adenoma can have a mass effect, resulting in headaches, pituitary insufficiency, or visual disturbances. Elevated

prolactin (PRL) levels in the blood in both sexes lead to hypogonadism, infertility, galactorrhoea, weight gain, delayed puberty, osteoporosis, and osteopenia. Additionally, in men, there may be erectile dysfunction, decreased libido, or gynecomastia, but these symptoms are sometimes mild and can be underestimated, leading to delayed diagnosis [8]. Menstrual irregularities or galactorrhoea in women typically prompt them to seek prompt medical consultation.

Prolactin also directly influences pancreatic β cells and adipocytes, negatively affecting metabolic profiles. This results in an unfavourable lipid profile, insulin resistance, impaired glucose tolerance, and ultimately abdominal obesity and metabolic syndrome in over 30% of patients [9].

Hyperprolactinemia, by influencing the pituitary and the release of gonadotropins, leads to reduced oestrogen secretion in women. This causes accelerated bone turnover, particularly affecting trabecular bone more than cortical bone. The skeletal system is also weakened in men under the influence of elevated prolactin levels, but it is not yet known whether this is due to a deficiency of testosterone or oestradiol. In both sexes, there is a reduction in bone mineral density (BMD), especially in the lumbar spine, and to a lesser extent in the femoral neck. Moreover, the duration of the disease is strongly correlated with the severity of bone loss, thus untreated prolactinoma is associated with a significant increase in the risk of fractures, especially in the lumbar spine [10,11].

Symptoms in women after the menarche and in women before menopause may vary depending on prolactin levels in the blood:

Moderate increase in prolactin levels (<2.3 mmol/l; up to 50 µg/l) – decreased libido, sometimes galactorrhoea, infertility, corpus luteum insufficiency, or menstrual irregularities.

Prolactin levels within the range of 2.3-4.5 nmol/l (50-100 µg/l) – often galactorrhoea, infrequent menstruation, or sometimes amenorrhea, or decreased libido.

Markedly elevated prolactin levels (>4.5 nmol/l; >100 µg/l) – hypogonadism, amenorrhea, or galactorrhoea [12].

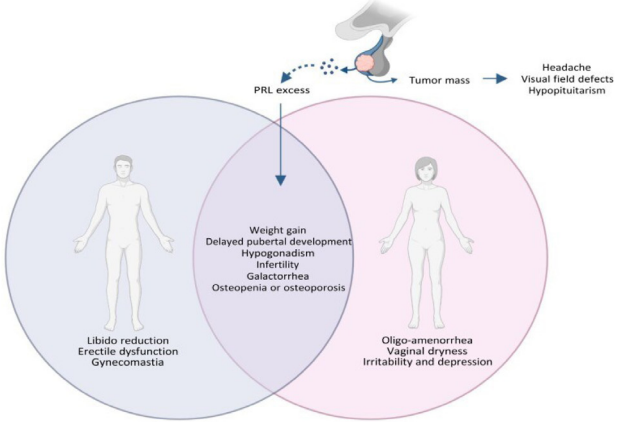

Fig. 1 Clinical Symptoms of Hyperprolactinemia [13].

Diagnosis

Various physiological, pathological states, and certain medications can influence the elevation of prolactin levels in the blood (Figure 2), so it is essential to exclude them before establishing a diagnosis [14]. To identify a pituitary tumour, the concentration of PRL in the serum should be examined. Breast examination should not be performed on patients complaining of galactorrhoea before the PRL test, as nipple stimulation can result in increased PRL levels [14,15]. A concentration slightly above the upper limit of normal can be challenging in diagnosis. In such cases, the test can be repeated after a night of sleep deprivation, taking 2 to 3 samples at intervals of 15-20 minutes to minimize pulsatile PRL secretion [15].

When the prolactin concentration is >9 nmol/l (200 µg/l), the likelihood of a prolactinoma is very high, and it is quite substantial at concentrations within the range of 150-200 µg/l. An imaging study of the pituitary gland is then recommended, preferably using magnetic resonance imaging (MRI) [12, 14,15]. In the case of a concentration exceeding 500 µg/l, a macroprolactinoma (pituitary tumour larger than 10 mm) can likely be diagnosed. Confirmation of the diagnosis must be preceded by an imaging study. Currently, the gold standard is gadolinium-enhanced pituitary magnetic resonance imaging. Computed tomography (CT) is reserved only for individuals with contraindications to MRI, as it is less effective, especially for small tumours [14,16]. Contraindications to MRI include patients with implanted heart defibrillators, clips in brain aneurysms, carotid arteries, aorta, cochlear implants, Swan-Ganz catheters, or pregnant women. MRI in pregnant women is justified only when there is a sudden impairment of the visual field due to tumour growth and is performed in the second trimester of pregnancy [15]. For patients with a tumour larger than 10 mm (macroprolactinoma) compressing the optic chiasm, a visual field examination is recommended.

Physiological	Pharmacological	Pathological
Stress	Neuroleptics	Prolactinoma
Sleep	Selective serotonin reuptake inhibitor	Non-functioning pituitary tumors
Lunch or dinner	Histamine H_2 receptor blocker	
Chest wall stimulation	Methyldopa	Empty sella syndrome
Pregnancy	Verapamil	Infiltrative disorders or CNS masses
	Reserpine	
	Metoclopramide	Hypothyroidism
	Protease inhibitors	Renal failure, idiopathic

Fig.2 Causes of hyperprolactinemia [17].

The diagnostic criteria include the presence of symptoms such as amenorrhea-galactorrhoea, erectile dysfunction in men, a significant increase and lack of variability in PRL levels

in the serum, as well as the presence of a pituitary adenoma in MRI or CT scans. Other causes of hyperprolactinemia and the occurrence of macroprolactinemia should be ruled out before establishing the diagnosis [13].

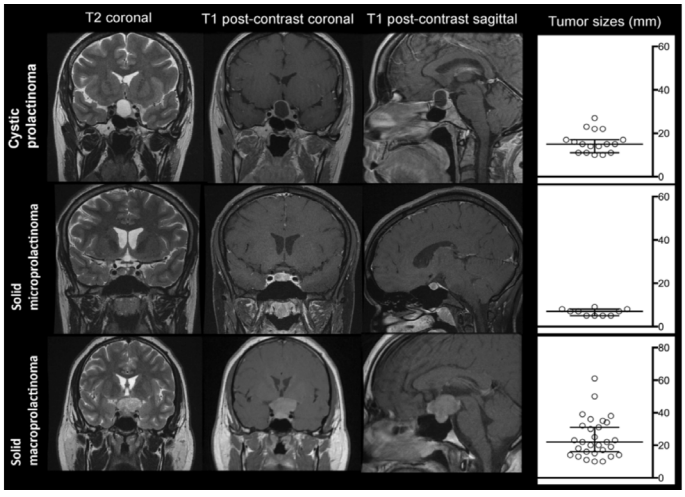

Fig. 3 MRI Characteristics of the Prolactinoma Subgroups Characteristic MRI-findings for cystic-, solid micro-, and solid macroprolactinomas in coronal (T2 and T1 postcontrast sequences) and sagittal (T1 postcontrast sequence) planes. The right-most panel demonstrates median tumour sizes in each group, with interquartile range [18].

Macroprolactin

Macroprolactin is an isoform of prolactin with a higher molecular mass and lower biological activity than monomeric Prolactin. The majority of Prolactin in the blood exists in a monomeric form (23 kDa), but occasionally dimers ("big Prolactin" – 50 kDa) and larger polymeric forms ("big-big Prolactin" – 150 kDa) may be present [19]. Macroprolactin, on the other hand, is a complex of IgG with monomeric prolactin. As a result, hyperprolactinemia is the consequence of low renal clearance of prolactin and reduced dopaminergic tone. Although symptoms occur much less frequently in the case of macroprolactin, they resemble those present in monomeric hyperprolactinemia [20]. Determining macroprolactin levels is therefore helpful in patients with asymptomatic hyperprolactinemia as it aids in excluding true hyperprolactinemia, which requires appropriate treatment [14,21].

"Hook Effect"

The diameter of a prolactinoma correlates with the prolactin concentration. In cases where there is a significant discrepancy between a large pituitary tumour and a moderate elevation of prolactin levels, sample dilution in a 1:100 ratio can be applied. This helps identify an artifact present in laboratory results that lowers the prolactin level, known as the "hook effect" [12,14]. It occurs when using certain immunological tests, such as the ELISA test. The "hook effect" is associated with a characteristic binding curve that increases with the analyte concentration in the sample, but at a certain point, exceeding the test components' capacity, the curve drops. This effect can mask the correct diagnosis and erroneously lead to the conclusion of the presence of an inactive pituitary tumour [22].

Menopause – Diagnostic Challenges

During menopause, oestrogen secretion significantly decreases, resulting in less stimulating influence on prolactin secretion and lactotroph cell proliferation. This may pose a challenge in underestimating the frequency of prolactinoma occurrence because in postmenopausal women, fertility is not the primary concern, and the absence of menstruation or galactorrhoea is not prevalent [23]. In postmenopausal patients diagnosed with a prolactinoma, macroprolactinoma or even giant pituitary tumours are most commonly encountered. These tumours, causing a mass effect, can lead to headaches, vision disturbances, and occasionally pituitary apoplexy [24]. Biologically, these tumours are likely similar to those occurring in men, characterized by a relatively rapid growth rate and increased cell proliferation indices [2,24].

Treatment

The goal of treatment is to restore prolactin levels to normal. Effective treatment leads to the alleviation of prolactinoma effects, including visual field disturbances, headaches, cranial nerve paralysis, pituitary insufficiency, hypogonadism, infertility, osteoporosis, and osteopenia [2,14,15]. Since tumours below 10mm rarely grow over the years [25], asymptomatic hyperprolactinemia usually does not require treatment [15]. However, appropriate treatment should be initiated for small symptomatic tumours [25]. Macroprolactinomas, due to their susceptibility to growth and tendency to invade neighbouring structures like the optic chiasm or pituitary stalk, are indications for treatment [19,21].

Dopamine Agonists (DA)

Dopamine agonists (DA) are the first-line treatment. They act similarly to dopamine on dopamine type 2 receptors (D2DR), the activation of which blocks PRL secretion in pituitary cells, inhibits the expression of the PRL gene, and inhibits lactotroph cell proliferation [26]. Cabergoline and bromocriptine are commonly used preparations. Others, such as quinagolide or pergolide, are less commonly used due to their inferior efficacy. Cabergoline is preferred in the first line because of its greater effectiveness [27,28]. In the majority of patients, the normalization of PRL and a reduction in tumour size are achieved through their use [27]. Cabergoline also reduces the intensity of symptoms such as amenorrhea, infertility, sexual dysfunction, or galactorrhoea. Occasionally, even with DA use, hypogonadism persists, necessitating replacement therapy with caution using oestrogen and progesterone. In men, cabergoline positively impacts symptoms like erectile dysfunction, reduced libido, and abnormal semen parameters. In some cases, testosterone replacement therapy may be necessary for correcting hypogonadism [29]. Care should be taken in testosterone replacement therapy since testosterone can be converted to oestrogen through aromatase, stimulating the proliferation of lactotroph cells, potentially leading to resistance to DA. In the past, to improve fertility and semen quality in persistent hypogonadism, clomiphene citrate was tried, but its effectiveness is still under debate [30].

Impact on Metabolic Disorders

Long-term use of cabergoline in individuals with hyperprolactinemia has a beneficial impact on their metabolic profile. It alleviates or even restores to physiological norms metabolic effects such as insulin resistance, unfavourable lipid profiles, abnormal glucose tolerance, consequently reducing visceral obesity and metabolic syndrome symptoms [31]. Cabergoline leads to weight and waist circumference reduction. Improvement in glucose tolerance and reduced insulin resistance occurs after 6 months of treatment [32]. In cases of resistance to standard cabergoline doses requiring significantly higher doses (around 2-7mg/week), treatment is not futile, even if PRL normalization is not achieved in about 50% of patients. This is because significant improvements are observed in insulin secretion, peripheral sensitivity, fasting glucose levels, and body mass index [33].

Tolerance and Adverse Effects

Among all available drugs reducing PRL levels, cabergoline exhibits the fewest side effects. Common adverse effects include nausea, vomiting, headache, dizziness, and hypotension [34]. Compulsive disorders and psychoses are very rarely observed. Studies have shown that even low doses of bromocriptine can induce mania in postpartum women and psychotic reactions in women with pre-existing mental disorders, but this has not been observed with cabergoline [34].

Resistance to Treatment

Treatment resistance occurs when, despite using maximum tolerated doses, PRL normalization and at least a 50% reduction in tumour size do not occur. The definition is not uniform, as there is ongoing discussion about the specific drug dose at which treatment resistance can be determined [35]. Fortunately, primary resistance is relatively rare. In case of resistance, either increasing the dose to a well-tolerated one or switching to cabergoline from another DA is an option. Studies have shown that despite resistance to quinagolide or bromocriptine, cabergoline caused PRL normalization in over half of the patients.

Pregnancy Considerations

DA use rapidly and effectively restores fertility. Therefore, it is important to advise patients not planning pregnancy to use mechanical contraception along with starting DA treatment [14,15]. For women planning pregnancy, it is recommended to attempt conception after PRL normalization and a clear reduction in tumour mass to minimize the risk of tumour compression on the optic chiasm during pregnancy [14,15]. The risk of tumour enlargement during pregnancy is very low, so once pregnancy is confirmed, DA should be discontinued. Evidence indicates that DA use in the first 6 weeks of foetal development does not increase the risk of adverse effects for the mother nor the foetus, including ectopic pregnancies, spontaneous abortions, trophoblastic diseases, congenital anomalies, or multiple pregnancies [38]. In cases where the mass effect of the tumour and symptoms affecting the visual system occur during pregnancy, resuming treatment is recommended, with bromocriptine being the first choice. There are no contraindications to breastfeeding; however, caution is required in patients with a large residual tumour adjacent to the optic chiasm [39,40].

Surgery and Radiotherapy

In aggressive or malignant prolactinomas, surgical treatment, sometimes combined with radiotherapy, may be required [41]. Surgical treatment involves selectively removing the tumour through the sphenoid sinus. Surgical and medical treatments yield similar results in normalizing PRL; however, for macroprolactinomas, surgical methods are favoured [41]. Radiotherapy is a third-line treatment dedicated to patients for whom pharmacotherapy and surgical treatment have been ineffective. It is not widely used due to the long waiting time for a response and complications such as pituitary insufficiency [42].

Failure of Conventional Treatments

When all treatment lines fail, particularly in aggressive and malignant prolactinomas, an oral alkylating agent, temozolomide, may be used. It has allowed approximately 40% of patients to control tumour growth. Temozolomide is currently recommended as first-line chemotherapy for tumours showing growth [43,44]. If there is a radiological progression of the disease after three treatment cycles, therapy should be discontinued [45]. If temozolomide proves effective, treatment can be continued for a minimum of 6 months or even longer if therapeutic benefit is consistently observed. During treatment, haematological parameters and liver function should be monitored, and attention should be paid to side effects such as fatigue, vomiting, or nausea. An interesting property of temozolomide is its ability to sensitize the tumour to radiation, which may be another option for patients with aggressive and malignant prolactinomas [43,45].

Summary

Diagnosing and treating the majority of prolactinomas cases usually do not present significant challenges. Characteristic clinical symptoms, such as hypogonadism in both sexes, visual disturbances due to the mass effect of the tumour, MRI changes, and elevated prolactin levels in serum, guide the physician to the correct diagnosis. However, certain difficulties may arise, such as the "hook effect" or macroprolactinemia, which can complicate the diagnosis. Treatment typically relies on dopamine agonists, and in more challenging cases, surgical methods or radiotherapy may be necessary. However, these approaches may sometimes prove insufficient, necessitating alternative therapeutic methods, such as the use of temozolomide. Occasionally, these methods fail, highlighting the need for further research into other new drugs or therapeutic approaches that could improve the effectiveness of treatment in highly complicated cases. Currently, there is insufficient data on alternative treatment methods, such as other cytostatic drugs, radionuclides of peptide receptors, mTOR inhibitors, or tyrosine kinase inhibitors to introduce them as standard treatments.

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