Clinics of Oncology

Case Report ISSN: 2640-1037 | Volume 8

Diagnosis and Management of Male Prolactinoma: Similarities and Differences

Sumita Cholekho[1], Yuke Liu[1], Deepa Kumari Acharya[3] and Huiwen Tan[1,2*]

[1]Division of Endocrinology and Metabolism, West China Hospital, Sichuan University

[2]Center of Pituitary Adenoma and Related Diseases. West China Hospital, Sichuan University (Chengdu 610041), China

[3]Shahid Gangalal National Heart Center, Bansabhari, 44606 Kathamandu, Nepal

***Corresponding author:**

Huiwen Tan,
Division of Endocrinology and Metabolism, West China Hospital of Sichuan University, No.37 Guo Xue Road, Chengdu, Sichuan Province, 610041, P. R China

Received: 12 Aug 2024
Accepted: 20 Sep 2024
Published: 26 Sep 2024
J Short Name: COO

Citation:

Huiwen T, Diagnosis and Management of Male Prolactinoma: Similarities and Differences. Clin Onco. 2024; 8(1): 1-9

Abbrevations:

PRL: Prolactin; Pit-NETs: Pituitary Neuroendocrine Tumors; BMI: Body-Mass Index; BMD: Bone Mineral Density; IGT: Impared Glucose Tolerance; MRI: Magnetic Resonance Imaging; TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxine; FT3: Free Triiodothyronine; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; T: Testosterone; GnRH: Gonadotropin-Releasing Hormone; GH: Growth Hormone; GHD: Growth Hormone Deficiency; IGF-1: Insulin-Like Growth Factor-1; ACTH: Adrenocorticotropic Hormone; PTC: Plasma Cortisol; E2: Estradiol; CAB: Cabergoline; DA: Dopamine Agonists; CVD: Cardiovascular Disease; ER: Estrogen Receptor; ICDs: Impulse Control Disorders

1. Abstract

Prolactinoma is the most prevalent type of functional pituitary adenoma or pituitary neuroedocrine tumor (PiNETs), and its clinical presentation can vary depending on the patient's age, gender, and the progression of the tumor. In male prolactinoma, the condition typically starts gradually, and they often present with larger adenomas when treatment begins, which can sometimes be more aggressive. In comparison to women, male prolactinoma tend to be older, with higher levels of prolactin, and experience more pronounced complications. Consequently, early diagnosis and treatment of prolactinoma in male patients presents unique difficulties. Timely diagnosis and the application of standardized treatments for prolactin-secreting adenomas are of paramount importance for preserving normal pituitary function, preventing tumor recurrence, and enhancing the quality of life for patients with prolactinoma. This review systematically outlines the primary clinical characteristics, complications, pathological features, and treatment therapeutic strategy for male prolactinoma. It aims to equip clinicians with a comprehensive understanding of diagnosing prolactinomas in males by combining current insights and highlighting recent advancements.

2. Introduction

Prolactinomas, or prolactin-secreting pituitary adenomas are benign adenomas that primarily produce prolactin and originate from lactotroph cells, accounting more than 50% of all functioning (hormonally active) pituitary adenomas in both women and men [1]. Male prolactinoma, characterized by the secretion of prolactin, typically exhibits common hyperprolactinemia symptoms, such as sexual dysfunction and infertility [2]. Furthermore, prolactinoma can give rise to localized mass effects, leading to headaches and visual field disturbances [3]. Women with prolactinoma often receive early diagnoses due to irregular menstruation, galactorrhea, and infertility, whereas male sexual dysfunction is more easily overlooked. Typically, male prolactinoma tends to have large and aggressive tumor growth. Some male patients with giant prolactinomas (defined as prolactinoma with a tumor >4 cm) may even experience pituitary apoplexy while undergoing hige-dose dopamine agonist(DA) therapy [4]. Hence, early diagnosis and treatment of male prolactinoma is significant important and clinically challenging. Data on the characteristics of male prolactinoma are limited. This review primarily focuses on the analysis and summarization of the clinical characteristics, pathological features, recent challenges in diagnosis, and therapeutic strategy for male

prolactinoma. This review aims to equip clinicians with a comprehensive understanding of diagnosing prolactinomas in males by combining current insights and highlighting recent advancements.

3. Epidemiology

The prevalence and annual incidence of prolactinomas are roughly 50 cases per 100,000 people and 3 to 5 new cases per 100,000 individuals each year, respectively [5]. It is a significant contributor to hyperprolactinemia [6]. Epidemiologic studies have revealed the incidence of prolactinoma in men compared to women stands at approximately 1:10 for individuals aged between 18 and 50 years, and this ratio remains similar for both men and women beyond the age of 50 [7, 8]. These tumors are rare and account for around 19% of of all PiNETs diagnosed in male patients [9]. Importantly, the median age of men who was diagnosed (47 years) is notably higher than in women (32 years) [8]. This difference may be attributed to the fact that the clinical symptoms of hyperprolactinemia in men are generally less specific than those in women. A higher percentage of men, around 80%, with a diagnosis of macroprolactinoma in comparison to women [10-13].

4. Diagnosis of Male Prolactinoma

4.1. Main Clinical Features of Male Prolactinoma

The diagnosis of male prolactinoma primarily depends on clinical features of hypogonadism and tumor- related compression of surrounding tissues, markedly increased serum prolactin level, and pituitary space- occupying lesions in the sellar region on imaging, such as MRI. Other pituitary disorders and factors leading to elevated prolactin levels are ruled out [1]. The primary clinical symptoms in male patients with prolactinoma result from hypogonadism induced by hyperprolactinemia. In general, about half of men with prolactinomas exhibit symptoms related to the tumor mass, such as headaches, visual problems, and neurological issues resulting from the compression or invasion of nearby structures. The other half experience symptoms associated with hypogonadism, which include libido decrease, erectile dysfunction, decreased vitality, weakness, reduced sperm count, gynecomastia, infertility, and osteopenia [14, 15]. It's worth noting that previous studies have indicated that 23 to 42% of male patients with prolactinoma exhibit normal or nearly normal testosterone levels before treatment [16]. The diagnosis of prolactinoma in older men poses greater challenges, primarily due to the often-asymptomatic nature of hyperprolactinemia in older patients. In addition, age-related ocular conditions, such as cataracts or macular degeneration, can conceal visual field defects resulting from compression of the optic chiasm.

4.2. Laboratory Examinations

Prolactinomas generally lead to increased serum prolactin levels, which serve as a crucial diagnostic indicator. Elevated prolactin levels inhibit the secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus, subsequently reducing the secretion of gonadotropins and testosterone. Prolactin levels exceeding 250 ng/ml are primarily associated with macroprolactinomas, while levels surpassing 100 ng/ml are rarely attributed to causes other than prolactinomas [17, 18]. Male prolactinoma can also exhibit other forms of pituitary-target gland hypofunction. These may include growth hormone deficiency (GHD), central hypothyroidism (involvement of the pituitary-thyroid axis dysfunction), and central adrenocortical hypofunction (pituitary-adrenal axis involvement) [19]. Hypopituitarism can arise due to either direct compression of the pituitary or, more frequently, dysfunction of the hypothalamus or pituitary stalk. Individuals with larger adenomas are at a higher risk of exhibiting one or multiple hormonal deficiencies. Therefore, it is important to assess all patients with pituitary macroadenomas for potential anterior pituitary insufficiency. Furthermore, the characteristics of hypopituitarism in older patients may be misconstrued as symptoms of multiple chronic illnesses, side effects of complex medication regimens, or even as natural consequences of the aging process. Hence, in older male patients with hyperprolactinemia and hypogonadism, the awareness of their hypogonadism may only emerge after their prolactinoma has already shown clinical improvement through medical treatment [20].

4.3. Magnetic Resonance Imaging

Male prolactinoma often manifest as large tumors, frequently categorized as macroadenomas (with a maximum diameter of ≥10mm) or even giant adenomas (with a diameter > 40mm), which tend to exhibit a certain level of invasiveness. MRI is the preferred imaging method for diagnosing lesions in the pituitary and parasellar regions, as well as for monitoring PiNETs before and after treatment. It helps to evaluate the response to medical treatment and establish baseline conditions post-surgery, typically within 3–6 months [21, 22]. Prolactinomas typically appear slightly hyperintense on T2-weighted MRI scans [23]. In men, there may be variations in T2 signal intensity indicating necrosis and hemorrhage, often associated with higher prolactin levels and a less effective response to dopamine agonists compared to more uniform adenomas [24, 25]. Kreutz et al. [24] has shown that men with prolactinoma tend to have a her erogenous T2 intensity pattern, whereas women usually exhibit higher signal intensity. Enhanced MRI features of sagittal, transverse and coronal sellar region in male patient with giant prolactinoma in Figure 1(A, B, and C) respectively. However, diagnosing prolactinoma in men should follow the same criteria as in women, which include: (i) consistent elevation of prolactin levels in multiple tests, (ii) ruling out other potential causes solely responsible for hyperprolactinemia (such as macroprolactin), (iii) definitive identification of a pituitary adenoma, and (iv) excluding a mixed GH-PRL adenoma associated with acromegaly. (21, 26, 27).

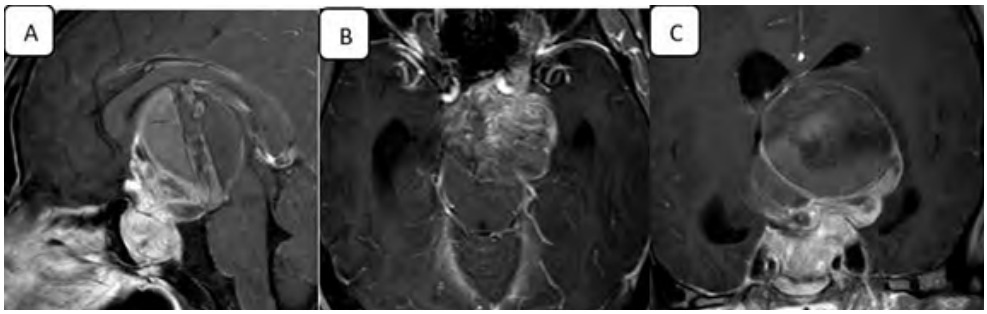

Figure 1: Enhanced MRI features of the sellar region in male patients with giant prolactinoma.

5. Comorbidities and Complications of Male Prolactinoma

5.1. Abnormal Bone Metabolism

Pituitary hormones play an important role in maintaining bone health. Abnormal or inadequate secretion of pituitary hormones can lead to alterations in bone structure and strength [28]. Hyperprolactinemia or alterations in other hormone levels in prolactinoma could lead to a reduction in bone mineral density (BMD) and an increased risk of fractures. The research studies found that 55.6% of male patients with prolactinoma exhibited osteopenia or osteoporosis in one or more sites. The lumbar spine was the most commonly affected site, with 29.6% having osteopenia and 14.8% having osteoporosis, a condition associated with hyperprolactinemia and hypogonadism [28]. Osteopenia and osteoporosis are prevalent complications in individuals with prolactinoma, particularly in elderly male patients. Furthermore, a cross-sectional study indicated a considerably higher occurrence of vertebral fractures in men with prolactinoma (37.5%) compared to age-matched controls with normal prolactin levels (7.8%), regardless of their serum testosterone levels [29]. The prevalence of vertebral fractures was reduced in patients who received treatment for prolactinoma compared to untreated patients. Hence, it has been proposed that the elevated fracture risk in patients with prolactinoma is not linked to hypogonadism.

5.2. Anemia

Mild anemia is a frequent occurrence in male pituitary prolactin-secreting macroadenomas. A retrospective cohort study of individuals with prolactin-secreting macroadenomas revealed that nearly 83% of 36 male patients had hemoglobin levels below the reference range at the time of diagnosis, a condition associated with larger pituitary adenomas [30]. In a cross-sectional analysis of 22 cases of macroadenoma and 4 cases of microadenoma, it was found that 34.6% of the patients had anemia, and all of these cases were associated with prolactin-secreting macroadenomas [31]. It is widely recognized that androgens, particularly testosterone, play a role in promoting erythropoiesis in men. Hemoglobin levels are comparable in men and women before puberty, but they increase in men after puberty, coinciding with the elevation of testosterone levels. Testosterone is responsible for a 12.2% difference in hemoglobin concentrations between adult men and women. Consequently, men with prolactinoma and hypogonadism often experience anemia. Anemia also tends to improve in hypogonadal male prolactinoma following successful treatment and the restoration of normal prolactin and testosterone levels [30].

5.3. Metabolic Disorders

Hyperprolactinemia and hypogonadism have been linked to impaired metabolic functioning. Hyperprolactinemia have been demonstrated to disordor of glucose and lipid metabolism, resulting in impared glucose tolerance (IGT) and hyperinsulinemia [32]. A recent study observed substantial increases in body fat content and low-density lipoprotein cholesterol levels, along with significant reductions in total cholesterol and low-density lipoprotein cholesterol, in untreated male patients with prolactinoma following treatment with cabergoline. These effects were not observed in female patients with prolactinoma when compared to healthy men [16]. Auriemma et al. reported that among 32 male patients with prolactinoma, 50% were diagnosed with metabolic syndrome, 59.5% were obese, and 25% had IGT [32]. The treatment with dopamine receptor agonists (DA) can enhance the metabolic parameters in these patients with prolactinoma. This includes improvements in body weight, waist circumference, body mass index (BMI), blood lipid profiles, and plasma glucose levels, as well as a reduction in the prevalence of metabolic syndrome. Moreover, the administration of suitable androgen replacement therapy can further ameliorate issues related to visceral obesity and insulin resistance in male hyperprolactinemia patients with testosterone deficiency [2, 32].

5.4. Others

Considerable extra-sellar expansion has been documented in numerous patients with giant prolactinomas, potentially resulting in a range of distinctive neurological symptoms. Table 1 describes the common clinical manifestations, mass effects, and comorbidities of male prolactinoma. These symptoms may encompass temporal epilepsy, reversible dementia, disorientation, hemiplegia, olfactory hallucinations, cranial nerve paralysis (III, IV, V, VI) associated with ophthalmoplegia, or even obstructive hydrocephalus [33]. Additional symptoms that may be associated with giant prolactinomas include epistaxis, exophthalmos, nasal obstruction, and cerebrospinal fluid rhinorrhea etc. [34].

Table 1: Common clinical presentations, mass effects and comorbidities of male prolactinoma.

Male prolactinoma	Mass effects	Comorbidities
Decreased libido	Decreased vision	Osteoporosis
Erectile dysfunction	Vision field defects	Osteopenia
Infertility	Hypopituitarism	Anemia
Gynecomastia	Headache	Dyslipidemia
Galactorrhea	Cranial hypertension	Metabolic Disorder
		Others: Cranial nerve palsy (III, IV. V, VI),temporal epilepsy, reversible dementia, hemiplegia, olfactory hallucinations

6. Pathological Features of Male Prolactinoma

Male prolactinomas are often characterized by rapid growth and aggressiveness, leading to compression of neighboring structures. While most prolactinomas exhibit sparse and granular characteristics, the more aggressive and resistant dense granular tumors are primarily observed in men [35]. The tumor grade of male prolactinomas is typically higher than that of females, primarily falling into the middle and high-grade categories. This is associated with a poor prognosis of male prolactinomas. The greater tumor size and more aggressive characteristics seen in men are primarily attributed to gender-related disparities in tumor behavior and these differences may involve the estrogen-receptor pathway. This is not primarily linked to a delay in diagnosis [10, 36, 37].

6.1. Proliferation Markers

Ki-67 has served as the proliferation marker for human tumor cells for decades. Most prolactinomas typically exhibit low proliferative activity as indicated by the Ki-67 proliferative index [38]. Despite analyzing tumors likely resistant to medical therapy or those presenting with clinical complications such as visual disturbances or apoplexy, most reported clinico-pathological series still indicate a prevalent trend of low proliferative activity in lactotroph adenomas. Studies have indicated a positive correlation between higher Ki-67 levels and factors such as tumor size, PRL levels, and resistance to dopamine agonists (DA). Consequently, macroprolactinomas and invasive tumors typically exhibit significantly higher Ki-67 levels compared to micro- prolactinomas [37, 39]. In particular, a mitotic count exceeding 2 and a Ki-67 index of 3% or higher have been identified as correlates with DA-resistant and invasive lactotroph tumors, particularly noteworthy in male patients [40].

6.2. Estrogen Receptor Expression

The gender-based variation in estrogen receptor (ER) expression in prolactinomas remains a topic of debate, although numerous studies have indicated that ER α and certain growth factors, like basic fibroblast growth factor and transforming growth factor, have a substantial impact on the onset and progression of prolactinomas. The level of ER expression is significantly associated with tumor size, proliferation activity, and prolactin levels [41]. Aromatase is an enzyme responsible for synthesizing estrogen. In rodent models, it has been confirmed that aromatase expression in the pituitary gland has sex dimorphism, with males showing higher aromatase expression in the pituitary compared to females. Androgens have also been shown to promote pituitary aromatase expression in animals, while estrogen inhibits it [42, 43]. In summary, aromatase plays a significant role in mediating the occurrence and invasive development of male prolactinomas. Consequently, the expression level of ERs within the tumor may be one of the potential factors contributing to the distinct biological characteristics of male prolactinomas.

6.3. Mutations in the SF3B1 Gene

More recently, Li et al. identified hotspot mutations in the splice factor 3B subunit 1 (SF3B1) gene in as many as 19.8% of prolactinoma cases. Patients with these mutations exhibited higher prolactin levels and shorter progression-free survival compared to patients without such mutations [44]. Even more intriguingly, this mutation was more prevalent in men compared to women (24.34% versus 10.67%, respectively), indicating a substantial association between SF3B1 mutations and a poorer prognosis. Among other findings, Guo et al. [44]. Conducted transcriptomic analysis on human prolactinomas mutated by SF3B1R625H and heterozygous mutated GH3 cells. Their analysis revealed that the SF3B1R625H mutation can lead to abnormal splicing, reducing the maintenance of cell polarity and the expression of the tumor suppressor Discs large 1 (DLG1). This reduction in DLG1 expression promotes cell migration and invasion through the PI3K/Akt pathway and epithelial-mesenchymal transformation. In summary, when SF-3B1R625H mutation is present in male prolactinomas, it induces abnormal splicing of ERRγ and DLG1, leading to increased proliferative activity and invasiveness in male prolactinomas.

6.4. The TGFβ1-TGFβRII Signaling Pathway

Dopamine agonists work by binding to dopamine receptors on tumor cell membranes, leading to the exertion of their anti-proliferative effects and the inhibition of prolactin secretion [45]. In recent years, TGFβ1, among the growth factors involved in regulating pituitary prolactin function, has garnered attention. The TGFβ1 system plays a role in dopamine and estradiol regulation in lactin cells: dopamine binds to the dopamine D2 receptor (D2DR), which upregulates various components of the TGFβ1 system (such as TGFβ1 mRNA, potential TGFβ-binding proteins, LTBPs, active TGFβ1, TGFβ receptor II, and phosphorylated Smad 2/3). Additionally, it promotes the expression of local activators of TGFβ1, including platelet reactive protein TSP1 and tissue kinin release. This is further facilitated by the expression of KLK1 and matrix metalloproteinases MMP2 and MMP9. The TGFβ1-TGFβRII signaling pathway inhibits the proliferation of lactating cells. On the other hand, estradiol down-regulates various components of the TGFβ1 system and certain local activators (like TSP1), thereby inhibiting the TGFβ1-TGFβRII signal and consequently increasing PRL levels.The study of animal models suggest that males may have a more robust TGFβ1 system than females in the pituitary [46]. In summary, TGFβ1 is a crucial molecule in regulating sexual differences, with implications for therapeutic interventions of prolactinomas.

7. Treatment of Male Prolactinoma

7.1. Medical Therapy

The primary objectives of hyperprolactinemia treatment are to alleviate the adverse effects of excessive pituitary hormone production, normalize serum prolactin levels to restore gonadal and sexual function, safeguard any remaining pituitary function, and prevent the recurrence or advancement of the condition [47, 48]. For the majority of patients with prolactinoma, the preferred treatment option continues to be medical therapy, primarily represented by DA. Currently, available DA options encompass bromocriptine, cabergoline, and quinagolide. Both bromocriptine and cabergoline effectively normalize prolactin levels and reduce tumor volume in most male prolactinoma cases. However, cabergoline is often favored due to its superior efficacy and tolerability, making it the current treatment of choice [33]. A meta-analysis involving 88 male patients with prolactinomas, including 15 with microadenomas and 73 with macroadenomas, demonstrated that DA therapy successfully restored prolactin levels in 73.3% of microadenoma cases and 65.2% of macroadenoma cases. Additionally, approximately 78.7% of patients experienced a reduction in tumor volume. After the follow-up period, MRI scans revealed complete tumor disappearance in 53.3% of microadenomas and 28.3% of macroadenomas. Furthermore, serum testosterone levels returned to normal in 73.3% of microadenomas and 56.2% of macroadenoma [4]. While testosterone levels are frequently reduced, they can remain within the normal range in men who have prolactinomas. Nevertheless, effective treatment of hyperprolactinemia leads to the normalization or a significant increase in testosterone levels in 60-80% of patients [49-51]. Once normal testosterone levels are restored, probably, sperm volumes and counts will also normalize, although this process may take a while, usually around 2 years [49, 52]. Giant prolactinomas, frequently observed in men, are typically aggressive; however, the majority of these tumors are benign and exhibit positive responses to DA treatment. It is currently advised that regardless of the tumor size or the extent of neurological and ophthalmic complications, cabergoline should be considered as the initial treatment choice for prolactinomas, subject to thorough clinical and laboratory monitoring to promptly ameliorate neuro-ophthalmic symptoms. It's worth highlighting that partial resistance is a frequent occurrence, and the gradual escalation of DA doses may assist in normalizing prolactin levels or reducing tumor size.

7.2. Surgical Treatment

Transsphenoidal surgery (TSS) serves as a secondary treatment option for individuals with prolactinoma who cannot tolerate DA therapy, are unresponsive to drug treatment, or experience spontaneous or DA-induced cerebrospinal fluid (CSF) leakage. The success rate of surgical treatment for male prolactinoma is contingent on factors including aggressiveness, tumor size, and prolactin levels. A recent systematic review and meta- analysis demonstrated that 38% of patients with prolactinoma who underwent surgery after DA therapy failure achieved a favorable response. Furthermore, when multiple therapies were combined, approximately 62% of patients with prolactinomas achieved a response [53]. Hence, while surgery may not be the primary treatment choice for prolactinoma, it serves as a crucial option in cases where medical therapy proves ineffective.

7.3. Radiation Therapy

The primary objective of radiotherapy is to manage tumor growth, with the normalization of prolactin secretion being an ancillary goal. This goal is reported to be attained in only around one-third of cases [54, 55]. The most frequently employed radiation therapy methods for pituitary tumors include stereotactic radiation therapies such as gamma knife, cyberknife, and proton beam therapy. The stereotactic radiosurgery is a secure and efficient treatment option for individuals with recurrent or remaining pituitary adenomas. Radiotherapy is primarily employed in patients who still have DA-resistant tumor remnants or experience uncontrolled tumor growth following unsuccessful surgical procedures. A multicenter study evaluating the long-term outcomes of 289 patients with prolactinoma who underwent stereotactic body radiation therapy revealed that 95% of patients achieved control of adenoma growth, with only 5% experiencing tumor progression at their last follow-up, which had a mean duration of 60-267 months. Endocrine

response rates, defined as normal prolactin levels without the need for DAs, were observed in 28% at 3 years, 41% at 5 years, and 54% at 8 years [56]. This implies that stereotactic body radiation therapy is a valuable treatment option for patients with refractory or residual/recurrent prolactinoma who are not suitable candidates for surgical resection. The primary adverse effect of radiotherapy is the development of new pituitary-target hormone deficiencies. These deficiencies can be managed and rectified through hormone replacement therapy [57]. According to the literature, new pituitary hormone deficiencies are documented in 25% of patients with prolactinoma following radiotherapy, and new visual complications are experienced by approximately 3% of patients with prolactinoma [56].

7.4. Combination Therapy and Other Potential Treatment Options

For patients dealing with drug-resistant, aggressive, or vision-threatening tumors, as well as those who experience severe adverse reactions to DA treatment, a multifaceted approach is advised. This approach may encompass surgery, radiotherapy, and ongoing drug therapy. Temozolomide, an oral alkylating agent, is considered a fourth-line treatment for prolactinoma cases that remain unresponsive to DA therapy, transsphenoidal surgery, and radiotherapy. It is a viable option for specific invasive, resistant, or malignant giant prolactinomas in clinical practice [33, 55]. In certain cases of resistant prolactinoma, particularly those with somatostatin receptor expression (mainly type 5 and type 2), combination therapy involving cabergoline and octreotide/pasireotide may be effective in managing tumor size and prolactin levels [57, 58]. Metformin, in addition to its antidiabetic properties, has been discovered to possess anti-tumor effects in recent research. There are reports of two patients with bromocriptine-resistant prolactinoma who experienced a reduction in prolactin levels and a significant decrease in tumor size when bromocriptine was combined with metformin [59]. Furthermore, potential treatment approaches like anti-vascular endothelial growth factor therapy, targeted therapy, and immunotherapy have displayed promise in the management of prolactinoma. Additional research is necessary to elucidate the underlying mechanisms of refractory prolactinoma and establish the most effective treatment strategies.

7.5. Follow Up

For individuals who have shown a favorable response to DA treatment and achieved normal or near-normal prolactin levels, the current recommendation is to monitor prolactin levels every 3-6 months during the first year and then at intervals of 6-12 months. If an MRI reveals a reduction in tumor size, it's safe to extend the intervals to one year or longer for MRI scans. In cases where prolactin levels remain normal, there may be no need for pituitary-enhanced MRI, as it is exceedingly rare for a tumor to increase in size without a significant rise in prolactin levels. Visual field assessment should be repeated until it returns to normal or remains stable [60]. Discontinuing DA therapy is feasible under specific conditions, offering favorable prospects of remission as follows: (a) the patient has received continuous treatment for at least 2 to 3 years, potentially longer for macroprolactinomas; (b) achieving low prolactin levels with a minimal DA dosage (<0.5 mg/week of cabergoline); (c) observing either disappearance or more than a 50% reduction in the maximal tumor size; and (d) absence of cavernous sinus invasion. When these criteria are fulfilled, sustained remission is observed in approximately one-third of patients, particularly following cabergoline use in microprolactinomas (50%) compared to bromocriptine or in cases of macroprolactinomas [61]. Consequently, it is advisable to include follow-up echocardiography for men who are undergoing high-dose cabergoline treatment. Apart from the typical side effects like nausea, vomiting, orthostatic hypotension, and headaches, nasal obstruction, as well as psychiatric symptoms, such as depression, anxiety, and insomnia. Certain clinical studies have indicated that some male prolactinoma may develop impulse control disorders (ICDs) involve behaviors like gambling addiction, hypersexuality, compulsive eating, and impulsive buying following DA treatment [5, 62].

8. Challenges in Prolactinoma Treatment

8.1. Resistance to DA Treatment

Various treatment options can be explored for cases of resistance to dopamine agonists (DAs) [63, 64]. While a decrease in the expression of D2 receptors has been observed in resistant prolactinomas, the underlying mechanisms are not fully understood [64]. Approximately 70–80% of patients resistant to bromocriptine may achieve normalization of prolactin (PRL) levels with cabergoline (CAB) treatment [21]. This presents a therapeutic dilemma, defined by the inability to achieve normal PRL levels with the highest tolerated doses of DAs and/or a failure to achieve a 50% reduction in tumor size [26, 63]. Resistance is uncommon in microadenomas, more prevalent in macroprolactinomas (3–5%), and often associated with invasive tumors [63]. Subsequently, the dosage of CAB may be incrementally increased to the maximum tolerated level [63]. Additionally, resistant prolactinomas may warrant transsphenoidal neurosurgery to debulk large tumors and enhance postoperative medical management [65]. Radiation therapy should be considered only for rare cases where surgical treatment fails and aggressive prolactinomas are present [62]. It may take up to 20 years to see maximum effects, and normalization of hyperprolactinemia is achieved in only one-third of cases [26].

8.2. Invasive Giant Prolactinomas

Giant prolactinomas that are invasive often infiltrate nearby tissues and pose significant challenges for complete removal. Nonetheless, cytoreductive surgery (CRS) can mitigate symptoms caused by compression, improve visual field, reduce excessive prolactin production, and alleviate systemic effects of hyperprolactinemia

[55]. Additionally, CRS can enhance the effectiveness of other treatment approaches such as medication and radiation therapy. By enabling better control of tumor biochemistry with lower doses of DA, it reduces the risk of long-term side effects associated with their use [54]. Therefore, despite the limited efficacy of surgery alone, its ability to promptly relieve compression symptoms and mitigate DA side effects is highly valuable. Current guidelines advise a thorough assessment by experienced specialists including pituitary surgeons, ophthalmologists, and endocrinologists. This evaluation aims to determine the suitability of adenoma removal for patients who do not respond quickly to DA therapy (within 2 weeks), those who are resistant to or cannot tolerate DA treatment, or those who choose not to pursue DA therapy.

8.3. Cardiovascular Risk

It's essential to be aware of the potential risk of heart valve disease associated with high doses of cabergoline. The primary mechanism possibly involves the stimulation of serotonin receptors by DA, leading to fibroblast proliferation [66]. Men diagnosed with PRLoma face a heightened likelihood of developing cardiovascular disease (CVD), whereas this correlation was not observed among female patients with the same condition [4]. In a recent meta-analysis comprising 13 case-control studies, patients with prolactinoma received cabergoline treatment for over 6 months due to hyperprolactinemia were revealed an elevated incidence of tricuspid regurgitation among these patients. However, there were no significant disparities detected in the functioning of other cardiac valves [67]. Patients with prolactinoma undergoing cabergoline treatment should receive annual clinical cardiovascular assessments, and those with a heart murmur should undergo color Doppler echocardiography.

8.4. Pathological Impulse Control Disorder

Impulse control disorders (ICDs) associated with dopamine agonists encompass behaviors such as pathological gambling, compulsive shopping, hypersexuality, binge eating, and the repetitive engagement in purposeless mechanical activities, known as "punding" [68]. Potential risk factors for these disorders include male gender and younger age. The underlying cause of this intricate disorder is believed to involve a hyperdopaminergic state in specific brain regions [69]. Despite its infrequency, when it does manifest, the severity of symptoms can lead to significant economic or social repercussions for patients and their families, depending on the nature of the behavioral manifestation. Discontinuation of the dopamine agonists typically leads to a rapid cessation of these unwanted compulsions. Endocrinologists should maintain heightened awareness regarding the potential for ICDs, and interactions with patients in clinical settings present opportunities to discuss this rare but significant side effect of an otherwise well-tolerated therapy.

9. Conclusion

Male prolactinomas are typically large and aggressive tumors characterized by elevated prolactin levels and hypogonadism. Primary medical treatment is recommended for most male patients with prolactinoma. Long- term dopamine agonist treatment has proven effective. It can normalize or nearly normalize prolactin levels and restore testosterone to normal in the majority of cases, leading to significant tumor shrinkage or even complete disappearance. Surgery can be particularly beneficial for male patients with rapidly growing prolactinomas and can enhance the effectiveness of adjuvant therapies by alleviating the mass effect of the tumor and/or reducing the tumor burden. The management of male prolactinoma often necessitates a multifaceted approach involving various medical specialties including endocrinology, neurosurgery, and radiotherapy. For male prolactinoma, long-term follow-up is essential to track their response to therapy and general health monitoring.

References

1. Chanson P, Maiter D. The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new. Best Pract Res Clin Endocrinol Metab. 2019;33(2):101290.
2. Duskin-Bitan H, Shimon I. Prolactinomas in males: any differences? Pituitary. 2020;23(1):52-7.
3. Webster J. Clinical management of prolactinomas. Best Practice & Research Clinical Endocrinology & Metabolism. 1999;13(3):395-408.
4. Iglesias P, Bernal C, Villabona C, Castro JC, Arrieta F, Díez JJ. Prolactinomas in men: a multicentre and retrospective analysis of treatment outcome. Clin Endocrinol (Oxf). 2012;77(2):281-7.
5. Fukuhara N, Nishiyama M, Iwasaki Y. Update in Pathogenesis, Diagnosis, and Therapy of Prolactinoma. Cancers (Basel). 2022;14(15);3604.
6. Wildemberg LE, Fialho C, Gadelha MR. Prolactinomas. Presse Méd. 2021;50(4):104080.
7. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf). 2010;72(3):377-82.
8. Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab. 1997;82(7):2102-7.
9. Maiter D. Prolactinomas in Men. In: Tritos NA, Klibanski A, editors. Prolactin Disorders: From Basic Science to Clinical Management. Cham: Springer International Publishing; 2019. p. 189-204.
10. Nishioka H, Haraoka J, Akada K. Growth potential of prolactinomas in men: is it really different from women? Surg Neurol. 2003;59(5):386-90.
11. Ramot Y, Rapoport MJ, Hagag P, Wysenbeek AJ. A study of the clinical differences between women and men with hyperprolactinemia. Gynecol Endocrinol. 1996;10(6):397-400.

12. Di Somma C, Colao A, Di Sarno A, Klain M, Landi ML, Facciolli G, et al. Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab. 1998;83(3):807-13.

13. Noel GL, Suh HK, Frantz AG. Prolactin Release During Nursing and Breast Stimulation in Postpartum and Nonpostpartum Subjects. J Clin Endocrinol Metab. 1974;38(3):413-23.

14. Shimon I, Benbassat C. Male prolactinomas presenting with normal testosterone levels. Pituitary. 2014;17(3):246-50.

15. Karavitaki N, Thanabalasingham G, Shore HC, Trifanescu R, Ansorge O, Meston N, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. Clin Endocrinol (Oxf). 2006;65(4):524-9.

16. Moraes AB, Silva CM, Vieira Neto L, Gadelha MR. Giant prolactinomas: the therapeutic approach. Clin Endocrinol (Oxf). 2013;79(4):447-56.

17. Tirosh A, Benbassat C, Lifshitz A, Shimon I. Hypopituitarism patterns and prevalence among men with macroprolactinomas. Pituitary. 2015;18(1):108-15.

18. Shimon I, Hirsch D, Tsvetov G, Robenshtok E, Akirov A, Fraenkel M, et al. Hyperprolactinemia diagnosis in elderly men: a cohort of 28 patients over 65 years. Endocrine. 2019;65(3):656-61.

19. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273-88.

20. Melmed S. Pituitary-Tumor Endocrinopathies. N Engl J Med. 2020;382(10):937-50.

21. Hinojosa-Amaya JM, Varlamov EV, McCartney S, Fleseriu M. Chapter 32 - Pituitary magnetic resonance imaging use in the post-treatment follow-up of secreting pituitary adenomas. In: Honegger J, Reincke M, Petersenn S, editors. Pituitary Tumors: Academic Press; 2021. p. 447-55.

22. Kreutz J, Vroonen L, Cattin F, Petrossians P, Thiry A, Rostomyan L, et al. Intensity of prolactinoma on T2-weighted magnetic resonance imaging: towards another gender difference. Neuroradiology. 2015;57(7):679-84.

23. Burlacu MC, Maiter D, Duprez T, Delgrange E. T2-weighted magnetic resonance imaging characterization of prolactinomas and association with their response to dopamine agonists. Endocrine. 2019;63(2):323-31.

24. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485-534.

25. Maiter D, Chanson P. Prolactin, Prolactinoma, and Pregnancy. In: Petraglia F, Di Tommaso M, Mecacci F, editors. Hormones and Pregnancy: Basic Science and Clinical Implications. Cambridge: Cambridge University Press; 2022. p. 73-86.

26. Mazziotti G, Frara S, Giustina A. Pituitary Diseases and Bone. Endocr Rev. 2018;39(4):440-88.

27. Mazziotti G, Porcelli T, Mormando M, De Menis E, Bianchi A, Mejia C, et al. Vertebral fractures in males with prolactinoma. Endocrine. 2011;39(3):288-93.

28. Shimon I, Benbassat C, Tzvetov G, Grozinsky-Glasberg S. Anemia in a cohort of men with macroprolactinomas: increase in hemoglobin levels follows prolactin suppression. Pituitary. 2011;14(1):11- 5.

29. Iglesias P, Castro JC, Díez JJ. Clinical significance of anaemia associated with prolactin-secreting pituitary tumours in men. Int J Clin Pract. 2011;65(6):669-73.

30. Auriemma RS, Galdiero M, Vitale P, Granieri L, Lo Calzo F, Salzano C, et al. Effect of chronic cabergoline treatment and testosterone replacement on metabolism in male patients with prolactinomas. Neuroendocrinology. 2015;101(1):66-81.

31. Shimon I. Giant Prolactinomas. Neuroendocrinology. 2018;109(1):51-6.

32. Hamidi Ok, Van Gompel J, Gruber L, Kittah NE, Donegan D, Philbrick KA, et al. Management and Outcomes of Giant Prolactinoma: A Series of 71 Patients. Endocrine Practice. 2019;25(4):340-52.

33. Saeger W, Honegger J, Theodoropoulou M, Knappe UJ, Schöfl C, Petersenn S, et al. Clinical Impact of the Current WHO Classification of Pituitary Adenomas. Endocr Pathol. 2016;27(2):104-14.

34. Delgrange E, Duprez T, Maiter D. Influence of parasellar extension of macroprolactinomas defined by magnetic resonance imaging on their responsiveness to dopamine agonist therapy. Clinical Endocrinology. 2006;64(4):456-62.

35. Trouillas J, Delgrange E, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P, et al. Clinical, Pathological, and Molecular Factors of Aggressiveness in Lactotroph Tumours. Neuroendocrinology. 2019;109(1):70-6.

36. Lopes MBS. Pathology of prolactinomas: any predictive value? Pituitary. 2020;23(1):3-8.

37. Delgrange E, Sassolas G, Perrin G, Jan M, Trouillas J. Clinical and histological correlations in prolactinomas, with special reference to bromocriptine resistance. Acta Neurochirurgica. 2005;147(7):751-8.

38. Lv H, Li C, Gui S, Zhang Y. Expression of estrogen receptor α and growth factors in human prolactinoma and its correlation with clinical features and gender. J Endocrinol Invest. 2012;35(2):174-80.

39. García-Barrado MJ, Blanco EJ, Iglesias-Osma MC, Carretero-Hernández M, Catalano-Iniesta L, Sanchez-Robledo V, et al. Relation among Aromatase P450 and Tumoral Growth in Human Prolactinomas. Int J Mol Sci. 2017;18(11).

40. García-Barrado MJ, Blanco EJ, Catalano-Iniesta L, Sanchez-Robledo V, Iglesias-Osma MC, Carretero-Hernández M, et al. Relevance of pituitary aromatase and estradiol on the maintenance of the population of prolactin-positive cells in male mice. Steroids. 2016;111:121-6.

41. Li C, Xie W, Rosenblum JS, Zhou J, Guo J, Miao Y, et al. Somatic SF3B1 hotspot mutation in prolactinomas. Nat Commun. 2020;11(1):2506.

42. Pivonello C, Patalano R, Negri M, Pirchio R, Colao A, Pivonello R, et al. Resistance to Dopamine Agonists in Pituitary Tumors: Molecular Mechanisms. Front Endocrinol (Lausanne). 2021;12:791633.

43. Recouvreux MV, Faraoni EY, Camilletti MA, Ratner L, Abeledo-Machado A, Rulli SB, et al. Sex differences in the pituitary TGFβ1 system: The role of TGFβ1 in prolactinoma development. Front Neuroendocrinol. 2018;50:118-22.
44. Halperin Rabinovich I, Cámara Gómez R, García Mouriz M, Ollero García-Agulló D. Guía clínica de diagnóstico y tratamiento del prolactinoma y la hiperprolactinemia. Endocrinología y Nutrición. 2013;60(6):308-19.
45. Martin N. Prolactin disorders. Medicine. 2009;37(8):411-3.
46. Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, et al. Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. J Clin Endocrinol Metab. 2004;89(4):1704-11.
47. Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A. Primary medical therapy of micro- and macroprolactinomas in men. J Clin Endocrinol Metab. 2000;85(9):3053-7.
48. Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab. 1999;84(7):2518-22.
49. De Rosa M, Zarrilli S, Vitale G, Di Somma C, Orio F, Tauchmanova L, et al. Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. J Clin Endocrinol Metab. 2004;89(2):621-5.
50. Yagnik KJ, Erickson D, Bancos I, Atkinson JLD, Choby G, Peris-Celda M, et al. Surgical outcomes of medically failed prolactinomas: a systematic review and meta-analysis. Pituitary. 2021;24(6):978-88.
51. Cozzi R, Ambrosio MR, Attanasio R, Battista C, Bozzao A, Caputo M, et al. Italian Association of Clinical Endocrinologists (AME) and International Chapter of Clinical Endocrinology (ICCE). Position statement for clinical practice: prolactin-secreting tumors. Eur J Endocrinol. 2022;186(3):P1-33.
52. Maiter D. Management of Dopamine Agonist-Resistant Prolactinoma. Neuroendocrinology. 2019;109(1):42-50.
53. Hung YC, Lee CC, Yang HC, Mohammed N, Kearns KN, Nabeel AM, et al. The benefit and risk of stereotactic radiosurgery for prolactinomas: an international multicenter cohort study. J Neurosurg. 2019:1-10.
54. Fusco A, Lugli F, Sacco E, Tilaro L, Bianchi A, Angelini F, et al. Efficacy of the combined cabergoline and octreotide treatment in a case of a dopamine-agonist resistant macroprolactinoma. Pituitary. 2011;14(4):351-7.
55. Sosa-Eroza E, Espinosa E, Ramírez-Rentería C, Mendoza V, Arreola R, Mercado M. Treatment of multiresistant prolactinomas with a combination of cabergoline and octreotide LAR. Endocrine. 2018;61(2):343-8.
56. Liu X, Liu Y, Gao J, Feng M, Bao X, Deng K, et al. Combination Treatment with Bromocriptine and Metformin in Patients with Bromocriptine-Resistant Prolactinomas: Pilot Study. World Neurosurg. 2018;115:94-8.
57. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. Jama. 2017;317(5):516- 24.
58. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM. Recurrence of Hyperprolactinemia after Withdrawal of Dopamine Agonists: Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2010;95(1):43-51.
59. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2011;96(2):273-88.
60. Delgrange E, Daems T, Verhelst J, Abs R, Maiter D. Characterization of resistance to the prolactin- lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. Eur J Endocrinol. 2009;160(5):747-52.
61. Molitch ME. The cabergoline-resistant prolactinoma patient: new challenges. J Clin Endocrinol Metab. 2008;93(12):4643-5.
62. Primeau V, Raftopoulos C, Maiter D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. Eur J Endocrinol. 2012;166(5):779-86.
63. Castinetti F, Albarel F, Amodru V, Cuny T, Dufour H, Graillon T, et al. The risks of medical treatment of prolactinoma. Ann Endocrinol (Paris). 2021;82(1):15-9.
64. Stiles CE, Tetteh-Wayoe ET, Bestwick J, Steeds RP, Drake WM. A meta-analysis of the prevalence of cardiac valvulopathy in hyperprolactinemic patients treated with Cabergoline. J Clin Endocrinol Metab. 2018.
65. Weintraub D, David AS, Evans AH, Grant JE, Stacy M. Clinical spectrum of impulse control disorders in Parkinson's disease. Mov Disord. 2015;30(2):121-7.
66. Vriend C. The neurobiology of impulse control disorders in Parkinson's disease: from neurotransmitters to neural networks. Cell Tissue Res. 2018;373(1):327-36.