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Review Article

A Rational Approach to the Evaluation and Management of Patients with Hyperprolactinemia

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Abstract

Prolactin has multiple biological functions. Hyperprolactinemia is a common condition in clinical practice both in women and men. It has multiple etiologies and may present with variable symptoms to different health-care providers. Therefore, a rational and systematic approach is paramount when evaluating patients with hyperprolactinemia to arrive at the correct diagnosis and institute the appropriate therapy. We here review the etiology, clinical presentation, and differential diagnosis of hyperprolactinemia and present a practical plan for further evaluation and management. It is most essential to establish the diagnosis and need for the treatment of patients with micro- and macro-prolactinomas and identify when only observation may be warranted. The biological, medical, and social contexts have to be considered to make the appropriate management decisions on an individual basis.

Keywords: Cabergoline, hyperprolactinemia, pituitary tumors, prolactin

Introduction

Prolactin is an important hormone primarily produced by lactotroph cells in the anterior pituitary with multiple biological functions.[1] Prolactin secretion is regulated by several factors in health and disease [Figure 1]. However, dopamine is the main regulatory factor with its prolactin-release inhibiting activity. Hyperprolactinemia denotes serum prolactin level above the laboratory gender-specific normal range, is a relatively common endocrine disorder worldwide.[2-4] It is more common in females, and its prevalence has increased over the past two decades.[5]

The prevalence of hyperprolactinemia is 20 and 90 cases per 100,000 for males and females

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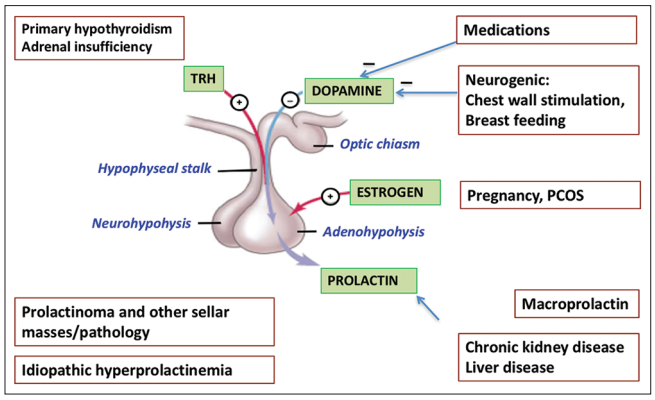

Figure 1: Regulation of prolactin secretion and mechanisms of hyperprolactinemia in different clinical conditions

respectively. The annual incidence in women aged 25–34 years is about 23.9/100,000 person-years.[6] Hyperprolactinemia can cause menstrual disorders, gynecomastia, decreased libido, impotence, and infertility.[7] Hyperprolactinemia may result from physiological changes, pathological conditions, medications, macroprolactin excess, or it can be idiopathic. The leading physiological causes are pregnancy, lactation, and stress, whereas common pathological causes include prolactinomas, other sellar masses, polycystic ovarian syndrome (PCOS), chronic kidney disease, and hypothyroidism [Table 1].[8] Antipsychotics, antidepressants, and anti-emetics are among the most common medications causing hyperprolactinemia.[4,7,8] Macroprolactin is a large molecule of prolactin mostly attached to immunoglobulins and can result in hyperprolactinemia due to reduced renal clearance.[9] As patients with hyperprolactinemia may present to different medical specialties, a practical review on the clinical presentations, etiologies, workup, and management will be discussed in this article.

Clinical Presentations

Patients with hyperprolactinemia generally present with symptoms related to hypogonadism (irregular periods, amenorrhea in premenopausal women or decreased libido, erectile dysfunction in men). Galactorrhea and infertility are other common symptoms in hyperprolactinemia.[10] Galactorrhea either spontaneously or after nipple stimulation, may be observed in up to 80% of female patients while it is uncommon in males (8%).[11]

Table 1: Physiological and pathological causes of hyperprolactinemia

Physiological: (*usually mild, transient or self-evident*), Pregnancy; lactation; stress; nipple stimulation, sexual intercourse and exercise, sleep, pain
Pathological: (*usually moderate or very high, persistent, and associated with reproductive dysfunction, or underlying pathology*)
Systemic diseases - Primary hypothyroidism; adrenal insufficiency; PCOS; renal insufficiency; liver cirrhosis
Hypothalamic diseases: Tumors (craniopharyngiomas, dysgerminomas, meningiomas, etc.); infiltrative disorders (histiocytosis, sarcoidosis, etc.), metastasis; cranial radiation; Rathke's cleft cysts, etc.
Pituitary diseases: Prolactinomas; acromegaly; thyrotropinomas; Cushing's disease; infiltrative disorders; metastasis; lymphocytic hypophysitis; etc.
Stalk disorders: TBI
Neurogenic: Chest wall lesions -burns; breast surgery; thoracotomy; nipple rings; herpes zoster; etc.), Spinal cord injury - cervical ependymoma; tabes dorsalis; extrinsic tumors; etc.)
Idiopathic: No cause is found.

TBI: Traumatic brain injury, PCOS: Polycystic ovarian syndrome

Long-standing hyperprolactinemia may result in osteoporosis in both sexes and is linked to weight gain.[12-14] In postmenopausal women, hyperprolactinemia may present with the disappearance of hot flushes, as a result of the suppression of luteinizing hormone and follicle-stimulating hormone secretion. Furthermore, hyperprolactinemia is often detected during sellar masses evaluation, screening individuals on high-risk medications or rarely when assessing seizure in the emergency department.[4]

Etiology

Causes of hyperprolactinemia usually fall into three categories physiologic, pharmacologic, and pathologic. The physiologic and pathologic causes are listed in Table 1. Recognized physiological states, including exercise, diet, stress, neurogenic stimulation such as chest wall stimulation and nipple stimulation, sexual intercourse, or pregnancy, can cause various degrees of serum prolactin elevation.[15,16] Another important cause is the intake of some medications.[6] Hyperprolactinemia has been recognized in association with several classes and individual pharmacological agents [Table 2]. Medications that block the central dopaminergic system can potentially increase prolactin levels. These include a group of drugs that antagonize the dopamine receptor on lactotrophs (risperidone, metoclopramide, haloperidol), inhibit dopamine reuptake (serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants), deplete

Table 2: Classes and examples of pharmacological agents recognized to cause hyperprolactinemia*

Antipsychotics
Typical - Phenothiazines; butirophenones; thyoxanthenes
Atypical - Risperidone; molindone; amisulpride; quetiapine; olanzapine
Antidepressants
Tricyclics - Amitriptyline; desipramine; clomipramine
MAO inhibitors - Pargyline; clorgyline
SSRIs - Fluoxetine; citalopram; paroxetine
Antihypertensive drugs
Verapamil; alpha-methyldopa; reserpine; labetolol
Anticonvulsants
Phenytoin
Prokinetic agents
Metoclopramide; domperidone
Others
Estrogens; anesthetics; cimetidine; ranitidine; opiates; methadone; morphine; apomorphine; heroin; cocaine; marijuana; alcohol; sibutramine, etc.

*History of current or recent intake of medications may not be forthcoming and may need to be sought and ascertained by careful drug history.
MAO: Monoamine oxidase inhibitors, SSRIs: Selective serotonin reiptake inhibitors

dopamine (reserpine, methyldopa), or increase transcription of the prolactin gene (estrogens).[16-18] Other drugs, such as opiates, can cause hyperprolactinemia through the opioid receptor in the hypothalamus. The mechanism by which verapamil and protease inhibitors elevate prolactin is unclear. Detailed drug history is essential in the diagnostic evaluation of hyperprolactinemia.

Pathological causes of hyperprolactinemia include a wide range of disorders [Table 1]. Naturally, the most important cause is a prolactin-secreting pituitary adenoma (prolactinoma), which accounts for 30%–40% of all pituitary tumors.[19] Furthermore, any pathology in the hypothalamic-pituitary region such as craniopharyngiomas, granulomatous infiltration of the hypothalamus, and other hypothalamic tumors can cause hyperprolactinemia through interference with the normal dopaminergic inhibitory effect on prolactin secretion stalk effect.[11]

Chronic illness such as chronic renal failure and liver cirrhosis can increase circulating prolactin levels due to decreased clearance.[17] Hypothyroidism can cause moderate hyperprolactinemia by the enhanced release of thyrotropin-releasing hormone (TSH) and reduced prolactin clearance.[18,20] It is more frequent in overt than subclinical hypothyroidism.[21] One study suggested that a TSH of >7.5 IU/ml may predict the presence of hyperprolactinemia.[22] Cases of adrenal insufficiency-associated hyperprolactinemia have been described.[23] Mild hyperprolactinemia is reported in about 30% of patients with polycystic (PCOS) ovary syndrome.[24,25] It remains controversial whether any prolactin elevation should trigger a pituitary imaging in PCOS patients. However, serum prolactin of >85.2 ng/ml predicted pituitary abnormality on magnetic resonance imaging (MRI) in one small retrospective study.[26] Chest wall or spinal cord lesions or trauma may increase circulating prolactin levels through stimulation of afferent neural pathways.[11] Finally, idiopathic hyperprolactinemia should be considered when imaging shows normal hypothalamic-pituitary anatomy, and there is no plausible cause of hyperprolactinemia.[27]

Further Evaluation

Clinical history is paramount in evaluating a patient with hyperprolactinemia. History of acute illness, stress, or pain at the time of blood extraction is important to obtain as prolactin might be transiently elevated in such conditions. Similarly, it is essential to document symptoms related to the effect of prolactin on the reproductive system, namely, menstrual irregularities, infertility, galactorrhea in women, and decreased libido and infertility in men.

Symptoms of potential causes of hyperprolactinemia should be elicited, such as headache, vision loss (sellar mass), cold intolerance, constipation, muscle weakness, and weight gain (hypothyroidism). One should focus on medication history, especially those known to elevate prolactin not only at the time of clinic visit but also at the time of prolactin measurement as time may lapse between the first detection of hyperprolactinemia and the visit to health-care physician [Table 2 and Figure 2].[28] Patients should be asked about any history of renal and liver diseases or their related risk factors.

A single measurement of serum prolactin is usually adequate to document an abnormally high serum prolactin level and establish the diagnosis of hyperprolactinemia.[11] Typical normal range is slightly higher in women than in men. Repeat

prolactin to confirm the presence of persistent hyperprolactinemia is recommended in patients with mild hyperprolactinemia, especially if asymptomatic. In general, serum prolactin levels below 200 µg/L may be seen in cases with all causes of hyperprolactinemia [Figure 3]. In contrast, serum prolactin levels >250 µg/L indicate the presence of a prolactinoma.[29-33]

Once persistent hyperprolactinemia is confirmed, additional laboratory investigations aim to rule out the common causes of hyperprolactinemia. The decision to consider routine evaluation for the presence of macroprolactin largely depends on the prolactin assay and may need to be discussed with local laboratory specialists. If no obvious cause of hyperprolactinemia is evident, MRI of the pituitary region is recommended to rule out other sellar masses or pathologies. Examples of a microprolactinoma, a macroprolactinoma and an invastive giant prolactinolma are shown in Figure 4. In certain patients, no obvious cause of hyperprolactinemia is detected and those are labeled as idiopathic hyperprolactinemia. Small microprolactinomas (below the level of MRI detection) might be present in such patients. Figure 5 provides an algorithm for practical workup hyperprolactinemia.

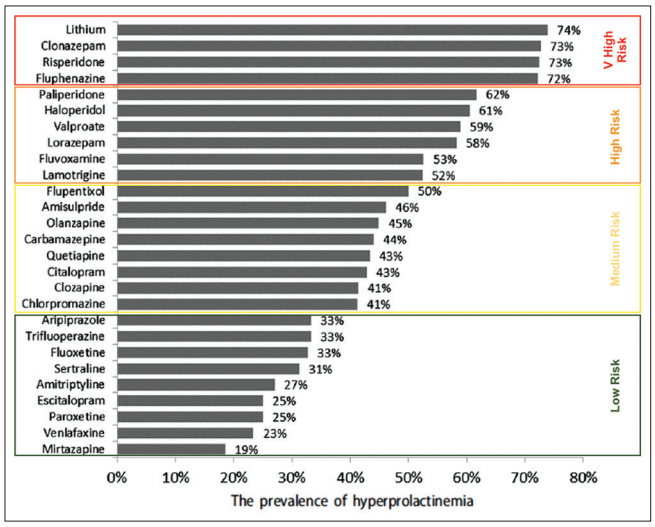

Figure 2: The relative frequency of psychotropic drug-induced hyperprolactinemia. Frequency of drug-induced hyperprolactinemia is represented as percentages and categorized high, medium and low probabilities (modified from ref 28)

Rational Management

The main aim of hyperprolactinemia management is to treat the underlying cause when possible. If

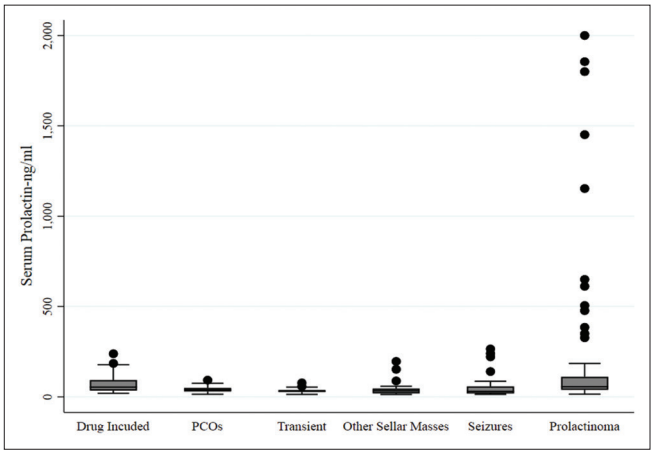

Figure 3: The degree of hyperprolactinemia and history can help focus the differential diagnosis in the real world. (Data are based on ref 4) Multiply by 21.7 to convert from mcg/l to mIU/L

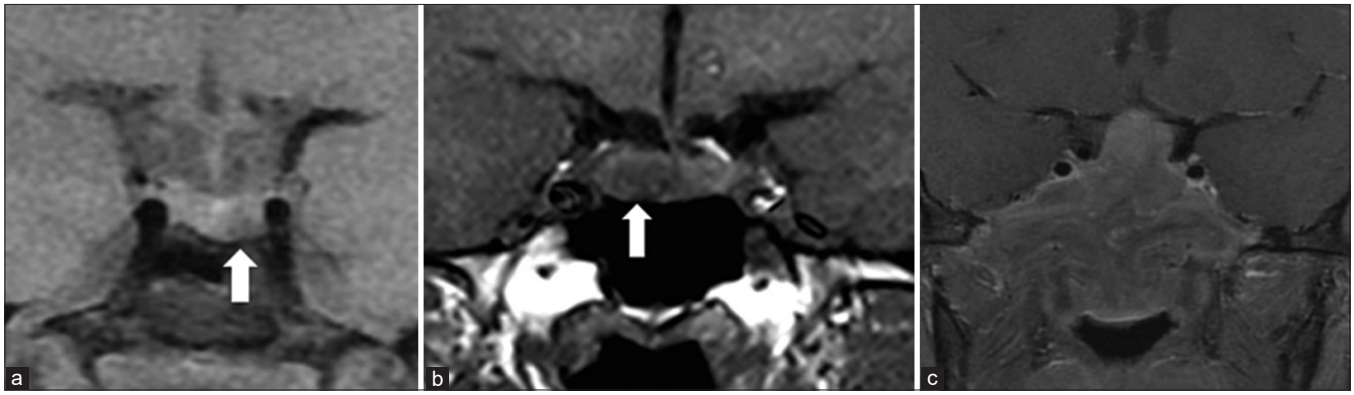

Figure 4: MRI coronal sections of the pituitary without contrast demonstrating the three different categories of prolactinomas. (a) Microprolactinoma: A small (6 × 6 mm) hypointense lesion within the left pituitary gland associated with mild depression of the sellar floor in keeping with pituitary microadenoma. The pituitary stalk is located in the midline and the suprasellar optic pathway is unremarkable. (b) Macroprolactinoma: A small (1.1 × 0.9 cm) hypointense lesion within the right pituitary gland in keeping with pituitary macroadenoma. The pituitary stalk is deviated to the left side. (c) Giant invasive prolactinoma with suprasellar extension and compression and upward displacement defect over the optic chiasm. The stalk could not be identified

hyperprolactinemia is drug induced, the medication should be stopped when possible. Otherwise, one should consider switching to other drugs with a lesser prolactin-enhancing effect [Figure 2]. It is noteworthy that such modification, especially the psychotropic medications, need to be discussed with the treating specialist to avoid worsening of the underlying clinical condition.

The management of prolactinomas is in the remit of clinical endocrine practice and should be undertaken by the appropriately qualified endocrinologist. For patients with prolactinoma, the primary goals of treatment are the reduction of tumor mass and normalization of prolactin levels, the restoration of gonadal function and fertility and the reduction pressure symptoms such as headaches and visual field defects.[29-33]

In the decision to treat or not, tumor size and symptoms are important factors to consider. In patients with asymptomatic micorprolactinoma (<10 mm), treatment is not indicated as 90% of the cases do not enlarge during follow-up. Instead, a regular follow-up should be maintained.[31,32] Therefore, treatment is always indicated for symptomatic patients with microprolactinoma and all macroprolactinoma (≥10 mm) due to a high propensity to grow.[33]

A recent survey of physicians managing prolactinoma in the Middle East and North Africa region revealed that 40% of them would treat microprolactinoms regardless of symptoms.[34] Therefore, it is important to highlight that not all patients with micrporlactinoma need treatment, as the risk of the progression of untreated microprolactinoma is small, and oral contraceptive pill might be an alternative in women with symptoms of estrogen deficiency.[35]

Dopamine agonists (DAs) are the treatment of choice for prolactinoma. An illustrative case of the hormonal and mass responses of a macroprolactinoma to DA therapy is shown in Figure 6. Compared to bromocriptine (BRC), cabergoline (CAB) is better tolerated, more convenient, and is more efficacious.[6] The dose of CAB varies with most patients achieving normal prolactin with a dose of 0.25–2 mg weekly. Nausea and dizziness are among the most commonly reported side effects. Hence, patients are advised to take the medication at night after a light snack. Thickening of cardiac valves has been reported mostly in those requiring higher doses of DAs like in Parkinson's disease but not in those treated for prolactinoma. Nonetheless, we suggest

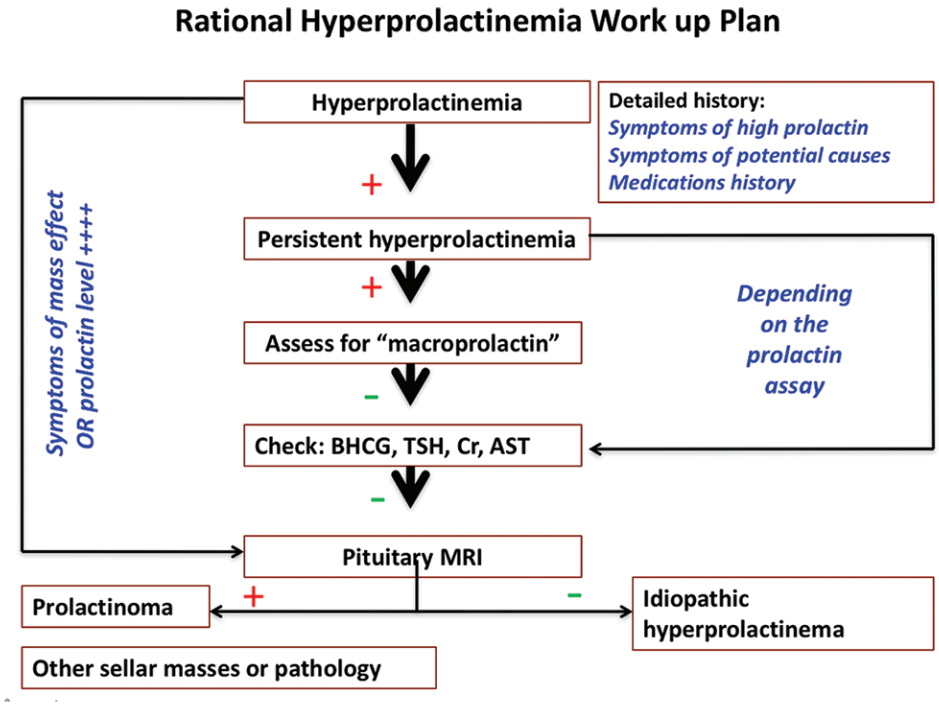

Figure 5: Algorithm for a rational evaluation of hyperprolactinemia

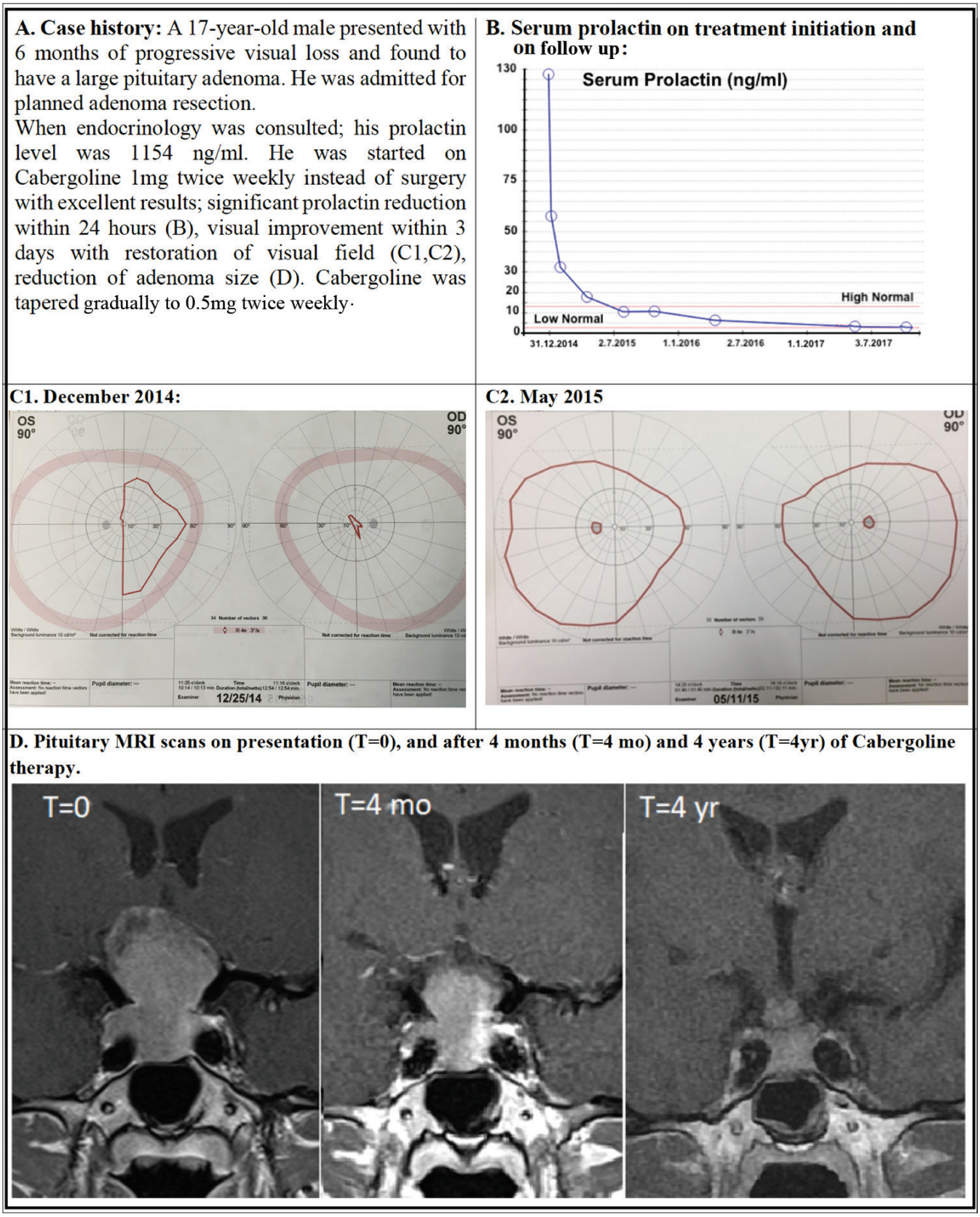

Figure 6: An illustration of the hormonal and mass effect responses of a macroprolactinoma to medical therapy

that cardiac auscultation is routinely performed on patients receiving DA therapy while considering periodic Echocardiogram in patients on higher doses (CAB ≥ 2 mg/week, BRC ≥ 15 mg/wk). Impulse

control disorders such as hypersexuality, impulsive shopping, pathologic gambling, and punding are now increasingly recognized adverse effects of DAs in prolactinoma patients.[35] These behaviors should be explored with all patients and their close family members during the follow-up visits as prompt recognition, and early management may help to avoid serious consequences.

Dopamine agonist withdrawal might be considered in patients treated for idiopathic hyperprolactinemia or microprolactinoma with a success rate of about 22%–31%.[37] Factors predicting favorable results include 2–3 years of DA therapy, normal prolactin level before withdrawal, low dose of DA and no or minimal residual tumor on imaging.[6]

Surgical resection of the pituitary adenoma, usually by the transsphenoidal route, is a treatment option in patients with resistance or intolerance to DA, macroprolactinoma with chiasmal compression and visual defect without marked improvement by DA, symptomatic apoplexy or cerebrospinal fluid leak.[38] According to recent data from 50 published series, the remission post surgery occurred on average in 74.7% of microadenomas and 34% of macroprolactinomas, with a recurrence rate of 18% and 23%, respectively.[39] In addition, tumor debulking in patients with partial resistance to DA may help in prolactin normalization with lower doses of DA.[40,41] Complications from transsphenoidal surgery are limited in the experienced hand, with mortality of <1%.[42] Radiotherapy is rarely needed in the management of prolactinoma and generally reserved for tumors that progress despite combined medical and surgical treatment. Radiation is usually applied as conventional fractionated therapy or stereotactic radiosurgery. The response to treatment is slow with complete normalization of prolactin in 30%–70%.[42,43] However, local tumor control can be achieved in the majority of patients regardless of the radiotherapy modality.[45,46] Complications of radiotherapy include the development of hypopituitarism (up to 100% after 10 years), optic nerve injury, cerebrovascular disease, and rarely development of secondary tumors.[47,48]

Conclusions

Hyperprolactinemia is a frequent encounter in clinical practice with symptoms of abnormal sexual and reproductive function, galactorrhea, and mass effect. The diagnosis can be confirmed with single serum measurement of prolactin level. If the serum prolactin is >250 μg/L, macroprolactinoma should be seriously considered. The majority of patients with hyperproteinemia, including prolactinomas, can be successfully treated with dopaminergic medications as first-line resulting in, restoration of gonadal function, and marked tumor shrinkage in a large proportion of prolactinoma cases. Several studies suggest that DA therapy may be safely withdrawn in many prolactinoma patients after an adequate period of treatment, provided that recommended criteria are applied. In patients with resistant prolactinoma, additional treatment modalities will be needed.

Authors contributions

The authors were assigned specific sections to draft, these were developed into a single manuscript which was reviewed and approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

Not applicable. None of the authors reported human or animal studies.

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