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Pituitary Disorders

Prolactinomas

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ABSTRACT

Hyperprolactinemia, defined by a level of serum prolactin above the standard upper limit of normal range, is a common finding in clinical practice and prolactinomas are the main pathological cause. Prolactinomas lead to signs and symptoms of hormone oversecretion, such as galactorrhea and hypogonadism, as well as symptoms of mass effect, including visual impairment, headaches and intracranial hypertension. Diagnosis involves prolactin measurement and sellar imaging, but several pitfalls are involved in this evaluation, which may difficult the proper management. Treatment is medical in the majority of cases, consisting of dopamine agonists, which present high response rates, with a very favorable safety profile. Major adverse effects that should be monitored consist of cardiac valvulopathy and impulse control disorders. Other treatment options include surgery and radiotherapy. Temozolomide may be used for aggressive or malignant carcinomas. Finally, pregnancy outcomes are similar to general population even when dopamine agonist treatment is maintained.

1. Introduction

Hyperprolactinemia, defined by a level of serum prolactin (PRL) above the standard upper limit of normal range, is a common finding in clinical practice and has several physiological, pharmacological and pathological causes. Among pathological causes, PRL secreting adenomas, or prolactinomas, are the most frequent etiology [1]. They occur more frequently in women, in the third to fifth decades of age, in whom they are usually smaller than 1 cm (microprolactinomas) [2]. On the other hand, older women and men more frequently present with macroprolactinomas [3]. Clinical picture is characterized by signs and symptoms of hyperprolactinemia, such as hypogonadism and galactorrhea, and/or adenoma mass effects, mainly visual field loss [4].

They respond well to pharmacological therapy and primary treatment is usually with dopamine agonists (DA) [2]. These drugs, specially cabergoline, are well tolerated and safe, with high efficacy rates both in terms of biochemical and tumor control [4]. However, a long-term treatment, sometimes life-long, is commonly necessary. Despite its safety, DA may present potentially serious side-effects, specially impulsive control disorders (ICD) [5].Therefore, the role of surgical treatment as a primary option is currently being discussed [6].

In this article, we discuss the epidemiology and clinical presentation of prolactinomas, some caveats in its diagnosis and current treatment options.

2. Hyperprolactinemia

Hyperprolactinemia is present in a diversity of clinical settings. It can be found in 30% of women with galactorrhea or infertility, in 10–25% of women with secondary amenorrhea or oligomenorrhea and in 75% of those with both amenorrhea and galactorrhea [7]. Moreover, in a large series with 1370 participants presenting with erectile dysfunction, hyperprolactinemia was present in 1.5% [8].

The causes of hyperprolactinemia can be divided into physiologic, pharmacologic and pathologic (Box 1) [4]. The most common cause of hyperprolactinemia and amenorrhea is pregnancy, with 10-fold increase in PRL serum levels during the third trimester. But other physiological conditions also can elevate PRL levels, such as exercise, physical and emotional stress and nipple stimulation. Except from pregnancy, in physiologic conditions PRL levels rarely exceed 40 mcg/L [9,10]. The main cause of non-physiological

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hyperprolactinemia is pharmacological, whereas among the pathological causes prolactinomas are the most common.

2.1. Hypothalamus/Pituitary diseases

Prolactinomas are the most common cause of pathological hyperprolactinemia. In a Brazilian study, with 1234 patients with hyperprolactinemia, prolactinomas were responsible for 56.2% of cases [11]. Other pituitary adenomas may co-secrete prolactin and GH, TSH or ACTH, also leading to hyperprolactinemia.

Prolactin secretion is constantly inhibited by dopamine secreted by the hypothalamus, that reaches anterior pituitary gland through pituitary stalk. Therefore, any condition interrupting this influx leads to hyperprolactinemia, what is called "stalk effect" [12]. Other pituitary adenomas, in particular clinically nonfunctioning pituitary adenomas (NFPA), with suprasellar expansion are a common cause of non-tumoral hyperprolactinemia [11]. Pituitary stalk section, empty sella syndrome or infiltrative diseases may also lead do hyperprolactinemia due to interruption of dopamine supply to the pituitary gland. Recently, Devuyst et al. [13] evaluated patients with pituitary stalk thickening and central diabetes insipidus and found that the presence of elevated prolactin levels increased the likelihood of a tumoral disease. In cases of "stalk effect", prolactin levels rarely exceed 100 mcg/L [14].

2.2. Systemic diseases

Hyperprolactinemia may be found in 8% to 43% of patients with hypothyroidism [15–17]. Hekimsoy et al. [17] described a frequency of prolactin elevation of 36% in patients with overt hypothyroidism and 22% in patients with subclinical hypothyroidism. After TSH normalization, prolactin levels decreased to normal in all patients [17]. Glucocorticoids suppress prolactin gene expression and prolactin release, so hyperprolactinemia may be found in patients with adrenal insufficiency [18].

Chronic renal failure may lead to hyperprolactinemia both due to increased prolactin secretion and reduced prolactin clearance [19]. In patients with cirrhosis, hyperprolactinemia is caused by decreased prolactin secretion inhibition and increased estrogen levels, and prolactin levels may be correlated with severity degree [20]. However, some data suggest that hyperprolactinemia may be found in a small percentage of patients [21]. In both cases, prolactin levels rarely exceed 100 mcg/L.

2.3. Neurogenic

Breast stimulation lead to reflex prolactin release, in part, by afferent neural pathways going through the spinal cord. This may explain prolactin increase associated with chest wall and spinal cord lesions [18]. Also, nipple piercing may increase prolactin levels.

2.4. Seizures

Hyperprolactinemia following seizures may occur due to propagation of epileptic activity from the temporal lobe to the hypothalamo-pituitary axis, occurring most commonly after generalized tonic-clonic seizures [12].

2.5. Others

Ectopic prolactin secretion is exceedingly rare and should be considered in cases with prolactin levels > 200 mcg/L, normal sella MRI and combined secondary causes excluded [22]. In 2013, Newey et al. [23] described mutation in the prolactin receptor gene in a family with hyperprolactinemia of non-identified cause. A heterozygous A-to-G substitution at c.635 in *PRLR* was identified, which results in a His188Arg substitution, leading to a loss of function of the prolactin receptor. The patients in this family presented different clinical presentations, two sisters presenting oligo-amenorrhea with normal fertility and the other sister with infertility. The ratio of wild-type or mutated PRL-R homodimers or heterodimers in different tissues may vary between patients, what can partially explain this variability of clinical presentation [24].

2.6. Pharmacologic agents

The most common cause of non-physiologic hyperprolactinemia is pharmacological [15]. Therefore, use of drugs that cause prolactin increase must be rule out before proceeding with investigation.

Drug-induced hyperprolactinemia can reach PRL levels up to 150 mcg/L [25]. Antipsychotic drugs increase prolactin levels by blockade of D2 receptors in the hypothalamic tuberoinfundibular system and on pituitary lactotrophs. Haloperidol and risperidone cause marked prolactin elevation, whereas other atypical antipsychotics such as quetiapine and aripiprazole may have prolactin lowering effects [26]. Prokinetic agents also antagonize D2 receptor and may induce symptomatic hyperprolactinemia [15].

Antidepressants (tricyclics and serotonin reuptake inhibitors), antihypertensive, estrongens protease inhibitors and narcotics are usually associated with mild hyperprolactinemia.

When the patient is taking one of these drugs, it is suggested to withdraw it for at least 72 h, if this can be done safely, and then proceed to new serum test of prolactin to confirm or exclude hyperprolactinemia [7]. If the drug cannot be stopped, sella turcica imaging should be performed [27].

If no cause is identified, the patient is considered as having idiopathic hyperprolactinemia.

3. Epidemiology

Pituitary adenomas are benign neuro-endocrine tumors and represents 10% of all intracranial tumors [28]. Epidemiological studies on pituitary adenomas have shown a higher prevalence than previously thought, but by definition it represents a rare disease with incidence of 4–7 cases per 100,000 per year and prevalence of 75–115 cases per 100000 per year, varying with age and gender. Prolactinomas are the most common type of pituitary adenomas and correspond to 53% (41–66%) of them [29].

Typically, this condition affects women between 20 and 50 years old, with a gender ratio of 10:1 [30]. In this population, microprolactinomas are more common. On the other hand, men generally present with larger tumors [3]. One possible explanation to this difference could be the clinical presentation, which is more evident in female patients, what would make women seek medical evaluation earlier. However, Fernandez et al. [31] found a median duration of symptoms until diagnosis shorter in men than in women (1.0 *vs* 1.8 years – clinical significance not reported). Additionally, prolactinomas in men present higher Ki-67, cellular atypia and proliferative features, as well as invasion and drug resistance [3,32]. In fact, in the last WHO classification of tumours of endocrine organs, prolactinomas in men were classified amongst tumors with higher risk of recurrence [33].

After the fifth decade of life, the prevalence of prolactinomas is similar in both genders. The diagnosis and treatment of prolactinomas in elderly has received less attention over the years maybe due to an apparently lower impact of hyperprolactinemia in this group. Kovacs et al. [34] found prolactin-staining microadenomas in 13% of patients aged over 80, but clinical series showed a clear prevalence of NFPA, with prolactinomas corresponding to only 4–8% of the pituitary adenomas [35–37].

Unlike adults, in childhood and adolescence, pituitary adenomas are not the most common sellar lesions, accounting for <3% of

childhood supratentorial tumors, but prolactinomas are the most frequent adenoma subtype [38]. Also, macroprolactinomas are more common both in boys and girls [39]. Arya et al. [39] described a series of 22 patients aged < 20 years. It was more frequent in female patients, but with a ratio of 1.4:1, and 12 (55%) had macroprolactinomas [39].

4. Inherited prolactinomas

Most frequently, prolactinomas occur sporadically, but they may present in familial settings, such as in multiple endocrine neoplasia type 1 (MEN-1), MEN-4, familial isolated pituitary adenomas (FIPA), Carney complex and rarely in the familial pheochromocytoma/paraganglioma/pituitary adenoma syndrome (3PAs) [40,41]. Our group evaluated the frequency of familial disease in 262 patients with functioning pituitary adenomas, including 65 with prolactinomas. Familial syndromes were found in 5% of the 262 patients and 3% of the 65 prolactinoma patients [40].

MEN-1 is caused by mutation in the *MEN1* gene located on chromosome 11q13, that encodes the protein Menin, and 22% of patients develop prolactinoma, that are generally large, with invasive behavior and resistant to conventional treatment [42,43]. MEN-4 presents with the same phenotype, but mutations are found in the *CDKN1B* gene, located on chromosome 12p13 [44]. Patients with Carney complex may develop mild hyperprolactinemia and subclinical acromegaly due to multifocal hyperplasia of somatomammotropic cells of anterior pituitary [45].

Other familial condition is FIPA, that implies the occurrence of at least two cases of pituitary adenomas in a family that does not exhibit any other syndromic feature, such as MEN1, MEN4 or Carney complex [46]. Germline mutation in the aryl hydrocarbon receptor-interaction protein (AIP) gene can be present in 20% of these patients and is associated with young or childhood onset of growth hormone and/or PRL-secreting adenomas [46]. Our group searched for *AIP* mutations in patients with apparently sporadic pituitary adenomas, including 38 prolactinomas, among which mutation was found in solely one patient (2.6%) [47]. The 3PAS is a rare syndrome characterized by the combination of pituitary adenomas and pheochromocytoma/parangliomas, and is associated with mutations in the in the genes of the succinate dehydrogenase family (SDHx) [40].

5. Clinical presentation

Clinical presentation of prolactinomas may be due to hyperprolactinemia and/or tumor mass effects over structures near sella turcica [11]. In premenopausal women, signs and symptoms of hyperprolactinemia predominate; whereas in men, tumoral effects are more important [3]. They may also present as a pituitary incidentaloma, from which prolactinomas correspond to 18% [48].

In women, as mentioned above, the presenting symptoms are more commonly those secondary to hyperprolactinemia, which are galactorrhea, menstrual disorders (oligomenorrhea, primary or secondary amenorrhea), pubertal delay, and infertility. Decreased libido and dyspareunia may also be present. Long term estrogen deficiency may lead to osteoporosis (Table 1) [49].

Table 1
Prolactinoma: clinical presentation.

Hyperprolactinemia	Mass effects	Comorbidities
Galactorrhea	Visual disturbance	Osteoporosis
Oligoamenorrhea	Hypopituitarism	Dyslipidemia*
Erectile disfunction	Headache	Glucose metabolism impairment*
Infertility	Cranial hypertension	
Decreased libido	Coma	
Weight gain *		

* Not classically associated with prolactinomas. Several studies demonstrate such association, but it is yet to be fully determined.

Box 1
Etiology of non-physiological hyperprolactinemia.

Pathological
Pituitary diseases
Prolactinomas, Acromegaly, Cushing's disease, Empty Sella syndrome, Lymphocytic hypophysitis
Hypothalamic diseases
Tumors: Craniopharyngiomas, Meningiomas, Dysgerminomas, Gliomas
Infiltrative diseases: Sarcoidosis, Histiocytosis X, Tuberculosis
Neuroaxis irradiation
Vascular
Pituitary stalk diseases
Pituitary stalk section
Pituitary stalk compression (nonfunctioning pituitary adenomas, Rathke cleft cyst, carotid aneurism, metastasis)
Systemic diseases
Endocrine: Hypothyroidism, Adrenal insufficiency
Non-endocrine: Chronic renal failure, Cirrhosis, Pseudocyesis
Neurogenic
Chest wall lesions (herpes zoster, burns, mastectomy), Spinal cord lesions
Ectopic prolactin secretion
Renal cell carcinoma, Gonadoblastoma, Ovarian teratoma, Perivascular epithelioid tumor
Prolactin receptor gene mutation
Seizures
Pharmacologic
Antipsychotics (haloperidol, phenotiazines, risperidone)
Anti-depressants (tricyclics, monoamine-oxidase inhibitors, serotonin reuptake inhibitors)
Prokinetics (metoclopramide, domperidone)
Anti-hypertensives (reserpine, verapamil, methyldopa)
Estrogen
Protease inhibitors
Narcotics (cocaine, opiates)
Idiopathic

Men may present with signs of hypogonadism, such as decreased libido and erectile disfunction. Oligo-azoospermia may be found, leading to infertility. Also, osteoporosis may be present in patients with prolonged hypogonadism [49]. However, men usually present with symptoms of mass effect, which may vary from visual disturbances (bitemporal hemianopsia to amaurosis, strabismus) to intracranial hypertension (Table 1) [3].

Apoplexy may also be the presenting clinical picture, although not common [49,50]. Classically, pituitary apoplexy presents with acute onset of a severe headache along with visual disturbances [51]. But the clinical picture may vary significantly, it may present with headache, visual disturbances, including severe cases with amaurosis, intracranial hypertension and coma [51].

Association between hyperprolactinemia and metabolic alterations has gained attention lately but is still neglected [52,53]. Prolactin has effects on the orexigenic–anorexigenic systems that regulate appetite, so patients with hyperprolactinemia may develop hyperphagia, with consequent weight gain and metabolic disturbances. Our group evaluated metabolic syndrome in 22 patients with prolactinoma [54]. Of these 22 patients, 27% were overweight (body mass index – BMI - 25–29.9 Kg/m^2) and 45% were obese (BMI > 30 Kg/m^2), with a median BMI of 29.5 kg/m^2 (18.6–39.2). Metabolic syndrome was found in 27% of patients, whereas insulin resistance (defined by a HOMAIR index >2.7) was present in 18%. However, there was no correlation between PRL levels and BMI, leptin, insulin, HOMAIR index or lipid profile [54]. Similarly, Auriemma et al. [55] found normal weight, overweight and obesity in 36, 39 and 25% of patients with prolactinoma, respectively. Metabolic syndrome was present in 28% of patients and was significantly more frequently in patients with prolactin levels above the median (129 mcg/L) than in the ones below the median (34.5% *vs* 12.5% - $p = 0.03$). It was found higher insulin and HOMA in 40 premenopausal women with

hyperprolactinemia when compared with 41 age-matched healthy controls, as well as a direct correlation between prolactin and fasting glucose levels [56]. Hyperprolactinemia has been associated with decreased HDL cholesterol and increased total or LDL cholesterol, triglycerides and post-prandial hyperinsulinemia [52]. Erem et al. [57] found higher total and LDL cholesterol in 22 newly diagnosed prolactinoma patients in comparison to 20 age-matched healthy controls.

6. Biochemical diagnosis

In patients with clinical features suggestive of hyperprolactinemia, diagnosis is made by basal prolactin measurement [2]. Prolactin levels usually correlated with prolactinoma tumor size, as shown by Chanson and Maiter [58]. After confirming elevated prolactin levels, and excluding other causes, sellar imaging should be performed. Some pitffals in the evaluation of prolactin levels should be taken into consideration [15].

6.1. Macroprolactinemia

The predominant circulating form of prolactin is monomeric (little prolactin) with a molecular mass of 23 kDa. Two other forms may be found, including a dimeric (big prolactin), with a molecular mass of 48−56 kDa, and a polymeric complex of prolactin and IgG autoantibodies (big-big prolactin − also known as macroprolactin), with molecular mass >100 kDa [59]. These complexes have minimal biological activity and no pathological function, but prolactin assays may detect them in varying degrees [24]. Precipitation with polietilenoglicol (PEG) can be used to detect macroprolactin, since these complexes precipitate with PEG, leaving only monomeric prolactin to be recovered in the supernatant. In patients with predominance of macroprolactin present recoveries < 40%, whereas recoveries > 60% indicate the presence of monomeric hyperprolactinemia [4].

A meta-analysis found a prevalence of 18.9% (0−55.6%) of macroprolactinemia among patients with hyperprolactinemia [59]. In the study by Vilar et al. [11], macroprolactin was responsible by hyperprolactinemia in 9.3% of cases. The authors point out that macroprolactin was not routinely evaluated in all centers involved in the study. Another Brazilian study specifically designed to investigate the frequency of macropolactin among hyperprolactinemic patients found it to be 16.5% [60].

Macroprolactin is typically associated with elevated prolactin levels in asymptomatic patients. The Endocrine Society guideline for diagnosis and treatment of hyperprolactinemia suggests that macroprolactin should be assessed in asymptomatic patients with elevated prolactin levels [2]. However, studies have shown that patients with macroprolactinemia may present with symptoms compatible with hyperprolactinemia, which may be due to causes other than the macroprolactinemia. Vilar et al. [11] reported presence of symptoms in 51.5% of patients with elevated prolactin levels due to macroprolactin. Another study with 2089 hyperprolactinemic patients found that more than half of patients with macroprolactin had symptoms [61]. The Pituitary Society recommends that macroprolactin should be investigated in patients with moderately elevated prolactin levels (up to 150 mcg/L) and atypical symptoms (headache, reduced libido) [27]. The American Association of Clinical Endocrinology and the American College of Endocrinologists suggest that macroprolactin should be tested in: asymptomatic patients; absence of galactorrhea in the absence or presence of menstrual disturbances; appropriate gonadotropin and/or sex hormone levels; poor or no clinical or biochemical response to DA treatment; and negative pituitary imaging [62]. Finally, the Brazilian Society of Endocrinology and Metabolism indicates screening for macroprolactin in asymptomatic hyperprolactinemic patients, subjects with idiopathic hyperprolactinemia and patients without an apparent cause for prolactin elevation [4]. These strategies should avoid unnecessary repeated hormone evaluation, neuroradiological examination and, more importantly, treatment.

6.2. Hook effect

When two-site immunoradiometric assays or chemiluminometric assays are used, the incubation with remarkably high prolactin concentrations may saturate both antibodies and consequently prevent sandwich formation. This phenomenon is called hook effect, meaning that patients with exceptionally large macroprolactinomas may present with moderately elevated prolactin levels (30−220 mcg/L) [58,63]. As previously mentioned, prolactin levels function as a tumor marker, having direct correlation with tumor diameter (specially in macroprolactinomas) [58,64]. So, the presence of a large macroadenoma (3 cm) associated with moderately elevated prolactin levels may lead to a misdiagnose of a NFPA [18]. To circumvent this limitation, a 1:100 dilution should be performed [15]. To avoid the need for repeated measurement, we order diluted prolactin for all patients with tumors larger than 3 cm.

6.3. Stalk effect

Stalk effect was defined earlier in the differential diagnosis of hyperprolactinemia. Any sellar/suprasselar lesion causing compression of pituitary stalk and interrupting dopamine influx to anterior pituitary may lead to mild prolactin increase (typically < 100 mcg/L). A large series with 226 histologically confirmed NFPA, with suprasellar extension, found prolactin values varying from 0.8 to 154 mcg/L, with hyperprolactinemia present in 38.5% of patients [65]. Only three patients presented prolactin higher than 100 mcg/L and two of them were on oestrogen therapy. A recent study evaluated 76 patients with prolactinoma and 217 with NFPA, comparing prolactin levels and tumor size. They found that prolactin level was strongly correlated with tumor volume in prolactinomas ($r = 0.831$, $p < 0.001$), but not in NFPA. A prolactin cut-off point of 248.15 mcg/L distinguished prolactinomas and NFPA with more than 4.0 cm^3 with an area under the curve (AUC) of 1.0 [64]. In conclusion, prolactin levels > 250 mcg/L are virtually only encountered in macroprolactinomas, whilst levels higher than 100 mcg/L seldom have etiology other than a prolactinoma [65,66]. Attention should be taken for adenomas with large cystic areas. Cystic macroprolactinomas may not present highly elevated prolactin levels, what can hinder differentiation with NFPA [18].

7. Imaging

After confirmation of pathological hyperprolactinemia and exclusion of other causes, a sellar imaging is required, preferentially a magnetic resonance imaging (MRI) [27]. Prolactinomas usually present as hypointense on T1-weighted image, while it is hyperintense on T2-weighted image in the majority of cases [67]. Burlacu *et al* [68] evaluated 80 patients with prolactinoma in respect to T2 weighted MRI characterization and found that 80% were hyperintense and 40% were heterogeneous. There was no difference between hyper and hypo/isointense tumors regarding sex, age, tumor volume or degree of prolactin secretion. On the other hand, heterogeneous tumors were more frequent in men, larger and more secretive (higher prolactin/tumor area) tumors. Kreutz *et al* [69] also found men to exhibit a more heterogeneous pattern of T2 intensity, whereas women had higher signal intensity. Patients with low signal intensity were almost exclusively male.

8. Treatment

The goal of treatment of prolactinomas consist in restoration of gonadal function and tumor mass control. Microprolactinomas

natural history shows that the minority of them (< 10%) tend to grow during long -term follow up [70]. So, in such cases, tumor mass control is not a concern and gonadal function preservation is the main focus of the treatment. In this sense, do all microprolactinoma patients need to be treated? For premenopausal women with normal menstrual cycles and postmenopausal women, in both cases without bothersome galactorrhea, a watchful waiting approach may be considered, with PRL level monitoring [71]. Premenopausal women not seeking fertility may also be treated with estrogen plus progestogen replacement therapy [72]. Serial MRI is not necessary since a tumor growth would be detected by increases in PRL levels [73].

8.1. Medical treatment

Three DA are currently available for the treatment of prolactinomas: bromocriptine, cabergoline and quinagolide. The Endocrine Society recommends the use of cabergoline due to its higher efficacy and lower frequency of adverse effects [2]. Treatment with DA should be started with low dose, usually cabergoline 0.5−1.0 mg weekly, with dose escalation every two to three months according to prolactin levels response and reduction in tumor size [4,9,27]. Patients with macroprolactinomas may request higher doses and faster dose escalation [74]. However, in a comparative prospective randomized study intensive treatment with cabergoline was not superior to the conventional dosage schedule in respect to the time necessary to normalize prolactin levels and to reduce tumor in 50% [75].

A systematic review evaluated 8 randomized and 178 non-randomized studies, including 3000 patients [76]. Compared with no treatment, DAs were able to reduce PRL levels and the risk of persistent hyperprolactinemia. Prolactin normalization was obtained in approximately 70% of patients, whereas tumor reduction was observed in approximately 60% [76]. In a Brazilian study, including 694 patients with prolactinoma, cabergoline normalized prolactin levels in 81.9% of patients (85.9% of micro- and 77.8% of macroprolactinomas), with a mean dose of 1.2 ± 0.7 mg/week (0.2−3.5) for micro- and 1.7 ± 0.7 mg/week (1.0−3.5) for macroprolactinomas. Resolution of galactorrhea was found in 100% of women and menstrual cycles normalization in 79%. Among men, hypogonadism symptoms improvement occurred in 60.3%. Tumor shrinkage was observed in 80% of patients, whereas complete tumor disappearance was found in 57.5% [11].

In respect to metabolic alterations, dos Santos Silva et al. [54] demonstrated significant reduction of triglycerides, HDL cholesterol, fasting glucose and HOMAIR index after 6 months of treatment with cabergoline. Frequency of metabolic syndrome reduced from 23% to 14% after six months of treatment. Among 158 patients with hyperprolactinemia, treatment with DA (six to 60 months) decreased metabolic syndrome from 32% to 10% [52]. Also, total and LDL cholesterol significantly reduced ($p < 0.001$ and $p = 0.005$, respectively) after 9 months of cabergoline treatment in 53 prolactinoma patients [77].

8.2. Adverse effects

DA are usually well tolerated, with minimal adverse effects. The most common are headaches, dizziness, nasal stuffiness, postural hypotension and nausea [11]. But the last two adverse effects can be ameliorated by proper water intake and medication administration right after last meal, respectively. Less commonly, patients may present with Raynaud's phenomenon and pleuropulmonary inflammatory-fibrotic syndrome [78,79]. Two potentially serious DA side-effects are cardiac valve involvement and psychiatric disorders [5].

In 2007, Zanettini et al. [80] reported a significantly higher frequency of clinically important valve regurgitation in patients with Parkinson's disease using ergot-derived dopamine agonists, with relative risks for patients under cabergoline treatment varying from 4.6 to 7.3. Subsequently, Colao et al. [81] demonstrated a higher frequency of moderate tricuspid regurgitation in treated patients (54%) when compared to *de novo* patients (0%) and to sex- and age-matched control subjects (18% - $p < 0.001$). After that, several studies addressed the subject, most of them with negative results, including one from the same authors as the previously cited where such association was not found [82−84]. A meta-analysis including 13 case-control studies where patients received at least 6 months of cabergoline for treatment of hyperprolactinemia found an odd-ratio of 3.74 (95% CI, 1.79−7.8; $p < 0.001$) for tricuspid regurgitation when compared with controls [84]. On the other hand, a recent population-based cohort study using data from over 1.5 million patient's primary records and considering as endpoint significant valvulopathy, characterized by cardiac valve surgery or heart failure diagnosis, was performed [85]. They identified 646 prolactinoma patients treated with cabergoline for at least 6 months who were matched to age, sex, ethnicity, location, diabetes, hypertension, and smoking status controls. The hard endpoint was similar between patients and controls (2.8% *vs* 2.33%). Uni and multivariate analysis failed to demonstrate association between treatment with cabergoline and cardiac endpoints. In 2019, the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology published a joint position statement recommending that standard transthoracic echocardiogram should be performed before a patient starts long-term DA therapy for hyperprolactinemia and at 5 years interval if no change is observed if the total weekly dose remains 2 mg or lower. In those taking more than 2 mg weekly, echocardiogram should be performed yearly [86].

Other important adverse effects of DA treatment, that are somewhat overlooked, are their psychological effects. Psychosis, mania, anxiety, depression, confusion, auditory hallucinations, hyperactivity, insomnia, nightmares, paranoia and impulse control disorders (ICDs) may develop after starting DA therapy or it can be exacerbated in patients with previously known psychiatric disease [87]. Among these disorders, ICDs are the most associated with DA treatment. These disorders are characterized by failure to resist an impulse to realize a determined activity that will offer an immediate reward, ignoring future potential harms [88]. Five conditions are formally recognized in the DSM as ICDs: pathological gambling, kleptomania, trichotillomania, intermittent explosive disorder, and pyromania. Pathological skin picking, compulsive sexual behavior, compulsive buying and others are currently classified under ICDs not otherwise specified [89]. DA exert their function through interaction with dopamine receptor 2 (D2) specially, but also may interact with D3. This receptor is highly expressed within the limbic system, in the frontal cortex and the thalamus, and it is thought that DA induce ICDs via excessive stimulation of D3 receptors [88]. Several ICD types have been reported in DA treated patients with prolactinomas, including compulsive gambling, shopping, eating, punding and hypersexuality, but their frequency is not well determined. Bancos et al. [90] evaluated 77 patients with prolactinoma (with current or past DA treatment) and 70 patients with NFPA (no history of DA treatment) and found increased hypersexuality in the prolactinoma patients group. Men with prolactinoma had higher ICD frequency than those with NFPA (27.7 vs 3.7%, $p = 0.01$), what was not found for female patients. A study with 10 patients with hyperprolactinemia treated with DA, 10 untreated hyperprolactinemic patients and 10 normoprolactinemic controls found higher degree of impulsivity in DA treated hyperprolactinemic as compared to both untreated hyperprolactinemic patients and to normoprolactinemic controls [91]. Celik et al. [92] identified two cases of hypersexuality associated with DA use among 25 prolactinoma patients who were prospectively evaluated, which resolved after drug withdraw. After drug was restarted with lower dose, patients presented milder symptoms or none. A higher number of DA treated patients screened positive on obsession, interpersonal sensitivity, paranoid ideation when compared to healthy controls ($p < 0.05$). Other psychiatric disorders may also develop. A study

evaluating 76 DA-treated and 27 naïve patients found moderate and moderately severe depression to be more frequent in DA-treated patients, whereas severe depression was only found in DA-treated patients [93]. In this study, patients with higher scores in the Barratt Impulsivity Scale-11 (BIS-11 >60) had higher treatment duration and cabergoline cumulative dosage. The implications of ICDs for the patients may be devastating, but it is reversible with drug withdraw, therefore clinicians and patients´ awareness is crucial for an early identification and management of such adverse effects. Hinojosa-Amaya et al. [93] suggest that the self-assessment tools BIS-11 and 9-item Patient Health Questionnaire (PHQ-9) are acceptable for routine screening of ICD and depression in clinical practice, however a formal recommendation is still lacking. Management of psychiatric adverse effects includes initially to reduce or stop DA treatment whenever possible. This procedure alone will lead to cessation or significant improvement of behavioral symptoms. For those who it is not possible, alternative treatment with surgery, radiotherapy or sex hormone replacement may be necessary. Non-pharmacological treatment, such as psychotherapy, may be of help, whereas the use of antipsychotic medications may be challenging. The use of aripiprazole may be preferable due to its partial agonist effect over DR [87].

8.3. Follow up

As previously mentioned, DA is usually started with low dose, with progressive increase every two to three months until prolactin normalization is reached. Therapy should aim to normalize prolactin levels, but it has been suggested to obtain the lowest prolactin levels to increase chances of tumor reduction (particularly in macroprolactinomas) [27]. Although, evidences indicate that fertility is more commonly restored in patients with normal prolactin levels than in the ones with suppressed [27].

In patients with microprolactinoma, after prolactin normalization, annual prolactin assessment should be performed [27]. In women with macroprolactinoma, DA therapy may be interrupted after menopause. In such cases, tumor increase surveillance should be performed [2]. In patients with macroprolactinoma, a MRI should be performed 2–3 months after DA start and then with longer intervals, whereas prolactin levels may be evaluated every three months [27]. Eroukhmanoff *et al* [94] questioned the necessity of serial MRI assessment in patients with DA controlled prolactin levels, since no significant tumor increase was observed in their series. Patients with macroprolactinomas with optic chiasm compression should also be monitored with visual perimetry.

The Endocrine Society guideline recommends continuing DA therapy, at least, for two year after adjusting the minimum dosage adequate to control PRL levels and reduction of tumor volumes [2]. Treatment withdrawal is attempted after this period [2].

8.4. Dopamine agonist withdrawal

It has been shown that the complete withdrawal of DA can be possible in the right conditions, without recurrence of hyperprolactinemia [95]. Colao et al. [96] evaluated cabergoline withdraw in a study with 200 patients (25 patients with nontumoral hyperprolactinemia, 105 with microprolactinomas and 70 with macroprolactinomas). Inclusion criteria were extremely strict: (1) normal prolactin levels, (2) no tumor evidence on MRI (or tumor reduction ≥ 50%, with the tumor at more than 5 mm from the optic chiasm, and no invasion of the cavernous sinuses or other critical areas), (3) possibility of follow-up for at least 24 months after withdrawal. Moreover, cabergoline dose had to be tapered to 0.5 mg/week with maintenance of normal prolactin levels and treatment was maintained for 12 months after fulfilling inclusion criteria. After two to five years of follow up, recurrence was observed in 24% of patients with nontumoral hyperprolactinemia, 31% with microprolactinomas, and 36% with macroprolactinomas.

Since then, it has been evaluated by several studies, confirming the possibility of long-term remission, although with less impressive results [97–99]. Dekkers et al. [97] presented a meta-analysis with 743 patients from 19 studies showing remission rate of 21% of all prolactinomas after DA withdrawal. More recently, Xia et al. [99] reviewed 24 studies evaluating DA (bromocriptine or cabergoline) withdraw, including 1106 patients. Remission rate after DA withdrawal was 36.6% (95% CI 29.4–44.2%) and varied from 0% to 85% in different studies. Proportion of patients in remission was higher in patients with low cabergoline dose (0.5 mg/week) before withdrawal than in those with higher doses (51.5% *vs* 21.5% - $p = 0.007$). This was not observed for bromocriptine. A dramatic tumor shrinkage (>50%) before withdrawal was associated with withdrawal success ($p = 0.032$). Patients treated for more than 24 months had better results (41.3% *vs* 20.8% – $p = 0.037$). And finally, the chance of persisting with normal prolactin levels was not related to the length of follow up.

Most studies addressing DA withdrawal point that the most effective predictor of long-term remission is absence of tumor in the pre-withdrawal MRI [58]. However, it has been suggested for microprolactinomas not to use MRI as a criterion for withdrawal based on the fact that up to 59% of patients with microprolactinoma remnant on MRI may not present recurrence after DA withdrawal [73].

Recently, Hage and Salvatori [100] evaluated clinical, radiological, or biochemical features that may predict the likelihood of reaching withdrawal conditions (significant decrease in prolactin level and tumor size after 2 years of treatment, assessed by the treating physician) in 213 prolactinoma patients. Of these, 78 (37%) reached withdrawal conditions after a mean follow-up 79.9 months (±47.6). In 56 patients, medication was withdrawn, with sustained normoprolactinemia in 14 (25%). Patients who reached withdrawal conditions showed lower median prolactin levels at diagnosis (144.4 *vs* 289 mcg/L – $p = 0.0213$), higher prolactin decline in the first check after DA start (91.8 vs 75.2 – $p < 0.001$) and smaller tumors (1.27 cm *vs* 1.69 cm – $p = 0.0182$) with less frequent cavernous sinuses invasion (23% *vs* 50% - $p < 0.001$). The authors found that for every 1% increase percent prolactin drop after DA start withdrawal chance increased 5%, whereas for every 1 cm increase in the maximal diameter size, it decreased 28%. Finally, if there was suprasellar extension or optic chiasm compression, the odds of reaching withdrawal conditions were 69% lower.

In summary, DA withdraw should be attempt after 2 years of treatment in patients who maintained normoprolactinemia after medication was tapered (to 0.5 mg/week if possible) and whose tumor reduced > 50%. At diagnosis, patients with lower prolactin levels, smaller and non-invasive tumors, who responded well in the first months of treatment, have higher chances of achieving the withdrawal criteria.

Evidence suggests that recurrence occurs early after drug discontinuation. Therefore, the Endocrine Society guideline proposed to monitor prolactin levels every 3 months for the first year and then annually [2]. An MRI should be performed if prolactin levels raise above normal range. In patients who present recurrence, a second attempt may be tried, which presents efficacy rates similar to those found in first attempt [101]. A recent study by Espinosa-Cárdenas et al. [102] evaluated the necessity of restart treatment after recurrence in 50 patients. In this series, recurrence was found in 34 (68%) of patients, but cabergoline was only restarted in eight. Drug was not restarted in the other 26: 14 premenopausal women without biochemical hypogonadism, five asymptomatic men under 65 without biochemical hypogonadism, five asymptomatic postmenopausal women and 2 asymptomatic men over 65. It may be inferred that, although recurrence rates after DA withdrawal may be elevated, drug restart should be individualized based on clinical parameters.

8.5. Dopamine agonists resistance

Some points must be taken into consideration to define DA resistance, which is still lacking, what have direct impact in the determination of both response rates and predictors of response. First point is whether only biochemical response should be considered or if tumor response should also be included in the criteria. Second, the maximum dose that should be reached before considering the patient resistant. Third point is the length of treatment necessary to define resistance. Finally, the clinical response must also be taken into consideration since prolactin levels reduction necessary to restore gonadal function may vary among individuals [79]. It may be defined as failure to achieve normal prolactin levels and/or failure to achieve tumor size reduction > 50%, after at least six months of treatment at standard dose (7.5 mg/day of bromocriptine or 2.0 mg/week of cabergoline) [103]. The mechanism of resistance to DA is not clear. It may involve reduced D2 receptor density in resistant prolactinomas, alteration in short and long D2 isoform ratio, changes in downstream cascades (e.g. in G protein subunit) or disruptions in the autocrine growth factor signaling pathway [79,104].

Resistance to DA treatment has been reported in 20% to 30% of patients treated with bromocriptine, and in approximately 10% of those treated with cabergoline [104]. Maiter [105] compiled 15 studies evaluating cabergoline effects on prolactinomas. Prolactin normalization was reached in 90% of micro- and in 83% of macroprolactinomas, whereas significant tumor reduction was observed in 71% of both micro- and macroprolactinomas. Delgrange et al [106] characterized cabergoline resistance in 122 patients. In this study, 94% of patients had prolactin levels normalized, 83% of them with low dose (≤ 1.5 mg/week). Of the 26 patients that were not controlled with this low dose, 73% responded to dose increase up to 3.5 mg/week (no benefit was observed beyond this dose). Significant tumor reduction (30% reduction in craniocaudal diameter) was found in 83% of patients. Vroonen et al. [107] characterized a series of 92 resistant prolactinomas. Fifty (46%) were male, with a mean age at diagnosis of 32.0±16.1 years. Macroadenomas were found in 82.6% of patients, with 51.7% invasive tumors. The mean maximal weekly cabergoline dose was 4.1±1.7 mg (median 3.5, range 2.0−10.5). Eight (8.7%) patients presented late resistance, after initial response. Five patients presented with clinical MEN1 and three with FIPA.

The approaches for patients with resistance to DA therapy include switching to another DA; increasing the dose of the DA if the patient continues to respond and tolerate, surgery, radiotherapy and experimental treatments [2,4,27]. In the study by Vroonen et al. [107], 19 patients were treated with high cabergoline doses (> 3.5 mg/week), 56 were operated on (either as first-line or debulking surgery) and 13 received radiotherapy. After multimodal treatment, prolactin normalization was achieved in 28% of patients and tumor disappearance in 19.9%.

8.6. Dose increase

Dose escalation may be beneficial for patients with partial resistance to DA, after it was switched to a more efficient drug (usually cabergoline). Ono et al. [108] evaluated prospectively high dose cabergoline treatment in 150 patients, who were divided in three groups: group U (60 previously untreated patients), group I (64 patients intolerant to other DA) and group R (26 patients resistant to other DA). Doses used in the study varied from 0.5 mg/week to 12 mg/week. Most patients in the groups U and I were controlled with doses up to 2.0 mg/ week (81.7% and 94%, respectively), whereas none of the patients in the group R was controlled with these doses. In this group, prolactin normalization rates gradually increased to 34.6%, 73.1%, 88.5% and 96.2% at 3, 6, 9 and 12 mg/week doses, respectively. Adverse effects were similar to previously described, mild and transient, and there were no dropouts during the study. Another study followed prospectively 20 patients refractory to cabergoline 3.0 mg/week with progressive dose increase up to 9 mg/week [4]. Normal prolactin levels were obtained in 12%, 36% and 24% with the doses of 4, 5 and 6-7 mg/week. No benefit was found in doses higher than 7 mg/week. So, in patients resistant to standard cabergoline doses, it may be progressively increased, provided that there is continued benefit with no adverse effects.

8.7. Surgery

Surgical treatment of prolactinoma has mostly been considered as an adjuvant treatment after DA failure. Other indications are pituitary apoplexy, cerebrospinal fluid (CSF) leakage and symptomatic tumor expansion during pregnancy [58]. It may also be considered in female patients with desire to be pregnant, in young patients who are not willing to maintain a long-term treatment and in patients with cystic prolactinomas [109]. In this situation, it should be taken into consideration that DA therapy has proven efficacy in cases of cystic prolactinomas, with prolactin normalization, tumor reduction and improvement in optic chiasm compression [110].

In the study by Vroonen et al. [107], 56/92 (60.9%) patients were operated, 15 (16.3%) as first-line treatment. Although prolactin levels significantly decreased after surgery (540 mcg/l to 161 mcg/L $p < 0.0001$), normalization occurred in only 7.8%. Nevertheless, a significant effect of debulking surgery was observed in 14 patients who received cabergoline before and after surgery, evidenced by lower prolactin levels with lower cabergoline doses.

Another study found significantly better results. It were evaluated 63 patients (13 DA intolerant, 26 DA resistant, 14 due to patient's choice and 10 due to acute complications) submitted to transsphenoidal surgery, with post-operative remission in in 63% of microprolactinomas, 60% of noninvasive macroprolactinomas, but none of the invasive macroprolactinomas [111]. Remission rate was significantly lower (10%) in patients operated due to acute complications and slightly, but not significantly, higher (71%) in patients operated due to personal choice. In multiple logistic regression, the factors associated with post-operatory remission were prolactin levels at diagnosis and absence of tumor residue after surgery, but only diagnostic prolactin levels predicted remission at last visit. However, 34% presented relapse after a follow up of seven to 164 months (median 36 months). Prolactin normalization was obtained in 63% of patients treated with DA after surgery, including 7 out of 15 DA resistant patients, with significantly lower cabergoline dose (1.4 *vs* 2.4 − p =< 0.01). In respect to complications, it occurred in 14% and consisted of: partial pituitary insufficiency, permanent diabetes insipidus, CSF leak in two patients with one case of secondary meningitis, and severe epistaxis requiring hemostatic intervention.

Gillam et al. [79] summarized results from 50 studies evaluating surgery efficacy, including 2137 patients with micro- and 2226 with macroprolactinomas. Remission was identified in 74.7% (38% to 100%) of patients with microadenomas and 33.9% (6.7 to 80%) of patients with macroadenomas. Although these success rates are encouraging, one of the downfalls of surgical management is the likelihood of recurrence in patients initially considered in remission. Among these studies, recurrence was described up to 50% of cases (median 18.2% for micro- and 22.8% for macroprolactinomas), however many factors may influence these rates, including short follow up period, drop-outs, definition of remission/recurrence, what may be underestimating it. After all, long-term remission rates were 61.1% and 26.2% for micro- and macroprolactinomas, respectively.

Transsphenoidal surgery, performed in reference centers by experienced surgeons, is safe and presents low complications rates. In a very large series of pituitary adenomas operated by a single surgeon, including 208 prolactinomas, mortality rate was very low (0.2%), mostly occurring in patients with NFPA, which are usually older [112]. Major complications occurred in 2.1% of patients and minor in

1.35%. However, mortality and complication rates, as well as length of hospital stay, are significantly higher in hospitals and surgeons with lower volumes of surgery [113].

Recent studies suggest the value of surgical treatment as first line therapy [114]. A recent meta-analysis, including 55 studies on medical treatment and 25 on surgical therapy, compared clinical outcomes after DA withdrawal and transsphenoidal surgery [6]. It was found that long term remission was higher in patients submitted to surgical treatment than medical (67% *vs* 34%), which was even more significant for microprolactinomas (83% *vs* 36%). During DA treatment, 81% of patients reached biochemical control, with side-effects in 26%. In respect to transsphenoidal surgery complications, permanent diabetes insipidus was found in 2% and cerebrospinal fluid leakage in 3%, with 0% mortality.

These data suggest that surgery, performed in referral centers by experienced surgeons, is a safe and efficient therapy for DA resistant patients, as well as it is a viable first-line treatment, especially considering the need for long-term treatment and DA associated adverse effects.

8.8. Radiotherapy

Radiotherapy in the management of prolactinoma is usually reserved for those patients refractory to medical and surgical therapies, usually highly aggressive or malignant tumors [66]. An international multicenter study evaluated the efficacy of stereotactic radiosurgery in 289 patients with prolactinoma [115]. They found remission rates of 28%, 41%, and 54% at 3, 5, and 8 years after treatment. Complications included new hormone deficit in 25% of patients and new visual complication in 3%.

Another study evaluated the effect of gamma-knife radiosurgery [116]. This study included 28 patients followed for a median of 140 months. Prolactin normalization was obtained in 82.1% of patients, 46.4% without adjuvant DA and 35.7% with DA. Tumor increase was not observed in any patient, but one patient developed a cystic transformation with tumor expansion.

A previous compilation of studies, including 300 patients treated with single dose stereotactic radiosurgery, found a median prolactin normalization of 31.4%, with follow-up varying from 6 to 55 months [79]. The short follow-up time may have influenced these results since stereotactic radiotherapy have a latency of 2 years for full effect.

Radiotherapy is associated with a significant incidence of major side effects, including new pituitary disfunction, optic nerve damage, neurologic deficit and increased risks of stroke and secondary brain tumors [117]. Complication rates for stereotactic radiotherapy seem lower than what is found for conventional radiotherapy. New pituitary hormone deficit may be found in 10–40% of patients, whereas optic and other cranial nerves deficits occur in up to 7%. The risk of stroke or secondary malignancies seem low, but the short follow-up period may be underestimating this risk [118].

8.9. Other pharmacological treatments

Temozolomide is an oral DNA alkylating agent with the lipophilic property of passing the blood–brain barrier that has been used in the treatment of aggressive pituitary adenomas and pituitary carcinomas. It has been used in more than 30 invasive prolactinomas/carcinomas and approximately 50% of patients exhibited more than 30% tumor volume reduction [104]. There are reports showing dramatic improvements including substantial primary tumor reduction, disappearance of metastases, and prolactin normalization [104]. Temozolomide treatment in 38 patients with aggressive prolactinoma/carcinoma showed completed regression in 5%, partial regression in 45%, stable disease in 26% and progression in 24% [119]. Clinically relevant adverse effects from temozolomide were reported in 33/157 (21%) patients with aggressive pituitary adenomas/carcinomas, most commonly development of cytopaenias (n = 14; thrombocytopaenia n = 7, leukopaenia n= 2 or combination n = 5), fatigue (n = 11) and nausea/vomiting (n = 10) [119].

The use of first-generation somatostatin receptor ligands for the treatment of prolactinomas has been proven ineffective, with just one report of successful combination of octreotide and cabergoline in a DA resistant macroprolactinoma [120,121]. On the other hand, there are some promising reports of efficacy of pasireotide, a second-generation somatostatin receptor ligands, in the management of prolactinoma, suggesting that a therapeutic trial in selected patients with aggressive and DA-resistant prolactinomas could be considered [104,120].

Estrogen modulators have shown limited and conflicting results, whereas metformin have anecdotal reports [104]. Future perspectives include tyrosine kinase inhibitors, VEGF targeted therapy, immunotherapy and peptide receptor radionuclide therapy [120].

9. Giant prolactinomas

A precise definition of giant prolactinoma is still lacking, but it can be considered as a prolactinoma > 4 cm with PRL levels higher than 250 mcg/L [66]. Precise frequency is not determined, but estimatives range from 0.5% to 4.4% [66]. Unlike prolactinomas in general, giant prolactinomas are more common in men in a 9:1 ratio, with a mean age of 41 years old [122]. Iglesias *et al* [123] compared giant and non-giant prolactinomas in men. Age distribution was similar, even though mean age was lower in giant prolactinoma group (not statistically significant). Visual deficit was more common in patients with giant prolactinomas (65.2% *vs* 25.6% - $p = 0.004$); without differences in other symptoms, such as headaches, impotence, decreased libido, and gynecomastia. Some degree of hypopituitarism at diagnosis was found in similar proportion in both groups, without significant differences in the type of hormonal axis affected or in the prevalence of complete hypopituitarism. Delgrange *et al* [124] described a series of giant prolactinomas in women. Women were diagnosed at older age than men (44 *vs* 35 years old – $p < 0.05$), but presented a bimodal distribution with a peak at 25 years and a second one at 49 years. Symptoms were mostly similar to what is found in women with smaller tumors, including amenorrhoea, galactorrhoea, visual disturbances and headache; but less frequent symptoms related to the mass effects, such as new onset of seizures, nasal congestion and exophthalmos, were alto present.

Therapeutic approach is similar to patients with smaller tumors due to the high response rates, even in patients with visual impairment (Fig. 1) [66]. In both series previously described, DA was used in all patients, prolactin normalization reached in 66.7% of men (similar to men with non-giant prolactinomas – 65.6%) and in 56% of women [123,124]. Tumor reduction > 30% was found in 79% of women treated with cabergoline [124]. Maiter and Delgrange reviewed 13 studies with 97 patients with giant prolactinomas and primary DA treatment improved visual field in 97% of cases, normalized prolactin levels in 60% and reduced tumor volume in 74% [122].

DA treatment usually offers quick relief of symptoms of mass effect, including visual impairment and hydrocephalus, avoiding the need for urgent surgery. But on the other hand, this rapid response, eventually with massive tumor reduction, may lead to CSF leakage [122]. Methods to detect CSF leakage include chemical analysis of the discharge fluid, intrathecal fluorescein application and surgical exploration. Glucose and protein evaluation in the discharge fluid have been used, but they are present in several body fluids. B2-transferrin is a transferrin isoform found in CSF, ocular fluid and perilymph (not in nasal mucus) and its evaluation in the discharge fluid has similar high sensitivity and specificity compared with the aforementioned invasive methods [125]. Other complications of DA treatment in giant prolactinomas include herniation of the frontal lobe and optic chiasm

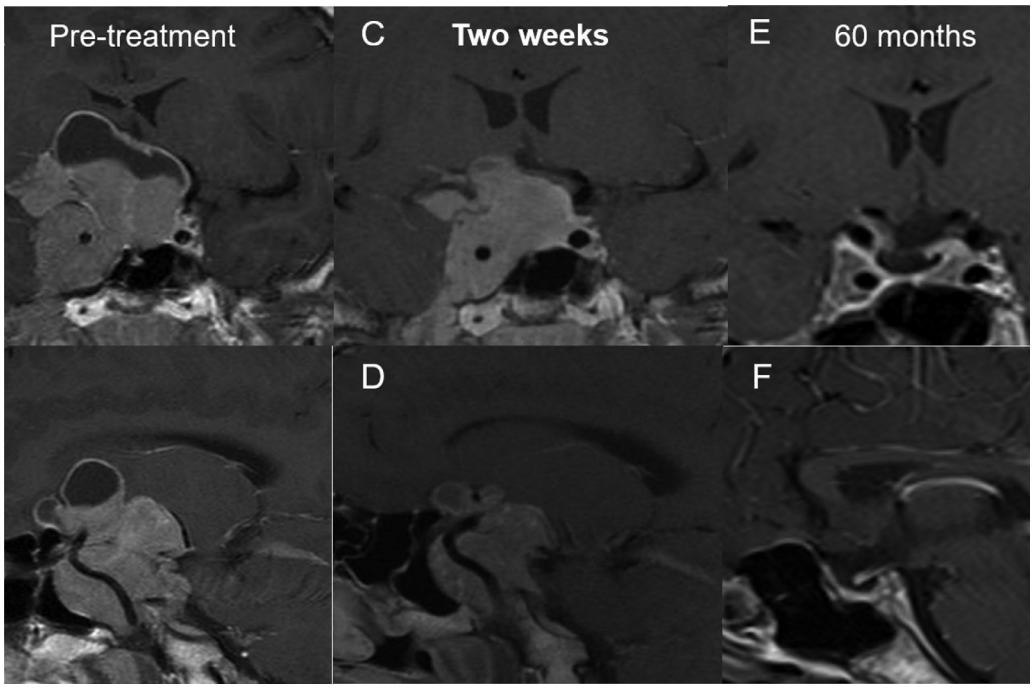

Fig. 1. MRI showing tumor reduction of a giant prolactinoma following cabergoline treatment. A 12-year-old boy with amaurosis at right eye and temporal hemianopsia at left eye, presenting a 4.1 × 5.1 × 4.4 cm (volume: 47.7 cm^3- A and B) macroprolactinoma and prolactin levels 7.674 mcg/L (NR: 2–15.2). After two weeks of treatment, prolactin levels reduced to 159 mcg/L and tumor showed a 52% reduction (volume 22.9 cm^3 – C and D). Prolactin normalized (9.4 mcg/L) after two months and visual field improved progressively. After 60 months, patient is controlled with cabergoline 0.5 mg/week (prolactin 15.3 mcg/L – E and F) and with normal visual field.

into the pituitary sella, pneumocephalus and apoplexy [66]. Although, Möller-Goede *et al* [126] did not find DA treatment to be associated with apoplexy.

In patients with giant prolactinomas, alternative treatment with cytoreductive surgery and/or radiotherapy may be necessary, as well as temozolomide. In a series with 71 patients with giant prolactinomas, 30 patients were operated on, with total resection obtained in 3 (10%) [127]. Radiotherapy was used in 10 patients. In this series, multimodal treatment involving DA treatment, surgery and radiotherapy was able to normalize prolactin levels in 55% of patients. Alternatively, in patients not biochemically controlled, but with residual tumors without mass effect, hypogonadism treatment may be an option [66]. It is important to stress out that it can induce tumor growth, so this decision should be taken on individual basis and tumor volume closely monitored.

10. Prolactinoma in pregnancy

Two major concerns are present in the management of prolactinomas during pregnancy, the concern that the high levels of estrogen may induce tumor growth and the potential risk of fetal malformations due to DA use [4]. Tumor growth was identified in 2.5% of 800 microprolactinomas, 18% of 288 macroprolactinomas without previous surgery or radiotherapy and 4.7% of 148 macroprolactinomas submitted to surgery and/or radiotherapy [128]. It is unclear whether tumor growth is secondary to the high estrogen levels or to DA withdrawal. In patients with microprolactinomas and intrasellar macroprolactinomas, DA may be withdrawn and patients should be clinically monitored in a trimester basis (prolactin measurement not indicated) [4]. Patients with invasive/expansive macroprolactinomas, DA (preferentially bromocriptine) may be maintained at the physician discretion [129]. If symptoms related to mass effect appear, an MRI without contrast should be performed and, if tumor growth is confirmed, DA should be reintroduced [129]. If patient is near term, delivery may be considered.

In respect to pregnancy outcomes, bromocriptine was not associated with adverse outcomes in more than 6000 reported pregnancies and cabergoline in more than 1000 pregnancies [128]. However, Hurault-Delarue et al. [130] found an increased risk of pregnancy loss and preterm birth in women who used at least one DA dose (183 women) compared to a matched control group, but no increase in risk of fetal malformation or difference in psychomotor development at 9 and 24 months.

A study evaluated safety of cabergoline during pregnancy [131]. At total, 233 pregnancies in 194 women were evaluated. In 89% of them, cabergoline was withdrawn after confirmation of pregnancy. Symptomatic tumor growth was evidenced in 25 patients, which were more frequent in older patients with shorter cabergoline treatment duration before pregnancy. Miscarriage rate was higher in patients using cabergoline (38% *vs* 7.5%), but all other maternal and fetal outcomes were found in frequencies similar to general population [131].

In pre-conception counseling, due to higher amount of evidence of safety, in women with prolactinomas expressing desire to be pregnant it is recommended to use bromocriptine, although there are increasing data indicating cabergoline safety [129].

11. Conclusion

In conclusion, hyperprolactinemia is a very common endocrine disorder and prolactinomas are the main pathological cause of this alteration. Its diagnosis may be difficulted by some pitfalls in PRL levels evaluation and by the diversity of causes of PRL elevation. The treatment of prolactinomas is medical in the majority of cases, including patients with giant prolactinomas, with high remission rates, but with frequent relapse. DA treatment is safe and well tolerated, but potentially serious adverse effects, such as cardiac valve involvement and ICD, should be monitored. In this sense, primary surgical treatment may be considered in selected cases. Other treatment options for DA resistant prolactinomas include surgery and radiotherapy. For aggressive giant prolactinomas and carcinomas, temozolomide can be used. Finally, pregnancy outcomes in patients with prolactinoma seem similar to general population, even if DA must be maintained during gestation, but some studies found a higher rate of miscarriage and premature birth.

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