Endotext

PROLACTINOMA MANAGEMENT

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ABSTRACT

Prolactinomas comprise nearly 40% of all pituitary tumors. Patients with prolactinomas usually come to medical attention as a result of symptoms caused by elevated prolactin levels, such as hypogonadism, menstrual irregularities, infertility or galactorrhea, or due to mass effects. Sometimes these patients can present as an emergency, either due to a visual field defect or loss of vision, or due to acute severe headache caused by pituitary apoplexy associated with hypopituitarism. Most patients with hyperprolactinemia do not have prolactinomas. A number of physiological conditions as well as several medications can also cause prolactin elevations; in these instances, prolactin levels are usually < 150 ng/mL (3000 mIU/L). Hyperprolactinemia can also result from reduced dopamine reaching the lactotrophs due to stalk compression. Furthermore, when evaluating patients with only modestly elevated prolactin levels and large macroadenomas, one should be aware of the “hook effect”, caused by saturation of antibodies of a two-site immunoassay by very high prolactin levels. A dopamine agonist is the treatment of choice in the vast majority of cases. Dopamine agonists can normalize prolactin levels, restore the function of the gonadal axis, stop galactorrhea, and significantly decrease tumor size in most of the patients, with cabergoline generally being more efficacious and better tolerated than bromocriptine. Indeed, cabergoline is first-line therapy even in patients with visual field defects, as long as visual acuity is not threatened by rapid progression or recent tumor hemorrhage. Cerebrospinal fluid leakage is a rare complication of dopamine agonists if they cause rapid tumor shrinkage and there is disruption of the sellar floor by the tumor. Transsphenoidal surgery is an alternative treatment in cases of dopamine agonist resistance or intolerance. Radiation therapy is reserved for those rare patients with macroadenomas not responding to either medical or surgical treatment. Symptomatic growth during pregnancy may occur in about 20-25% of macroprolactinomas, and therefore visual field testing is indicated each trimester in such patients. MRI scans (without gadolinium) are done in those patients who develop visual field defects or severe headaches when a therapeutic intervention is contemplated. Prolactinoma is the most common pituitary tumor subtype in children and adolescents and macroprolactinomas are more frequent in this age group compared to adults. In addition to typical symptoms of hyperprolactinemia, pediatric patients may present with delayed or arrested puberty, growth failure, and weight gain. Many aspects of the care for children and adolescents with prolactinomas are similar to that in adults; however, key differences exist,

particularly in presentation and etiology. For that reason, children and adolescents with pituitary adenomas, including prolactinomas, should be treated by a pituitary specific multidisciplinary team.

CLINICAL RECOGNITION

Patients with prolactinomas come to clinical recognition because of the effects of elevated prolactin levels or tumor mass effects. The most typical symptoms of hyperprolactinemia in premenopausal women are oligo/amenorrhea (approximately 90%) and galactorrhea (approximately 80%) (1). Hyperprolactinemia is a cause of amenorrhea in 10%-20% of nonpregnant women (2), while non-puerperal galactorrhea may occur in 5-10% of normally menstruating, normoprolactinemic women, and therefore is suggestive, but not definitive, of hyperprolactinemia. However, when oligo/amenorrhea is associated with galactorrhea, about 75% of women will be found to have hyperprolactinemia. Galactorrhea is reported in ~10% of cases in men with prolactinomas and is virtually pathognomonic of a prolactinoma. Hyperprolactinemia inhibits the pulsatile secretion of gonadotropin releasing hormone via interfering with hypothalamic kisspeptin-secreting cells via the prolactin receptor, and may involve an opioid link (3).

Table 1. Etiology of Hyperprolactinemia
Pituitary Disease
Prolactinomas
Acromegaly
Clinically nonfunctioning pituitary adenomas
Empty Sella syndrome
Hypophysitis
Rathke's pouch cyst
Metastases (breast, lung)
Hypothalamic Disease
Craniopharyngiomas
Meningiomas
Germinomas
Other tumors
Sarcoidosis
Langerhans cell histiocytosis
Neuroaxis irradiation
Vascular
Tuberculosis
Pituitary Stalk Section
Medications
Phenothiazines
Butyrophenones
Atypical Antipsychotics
Tricyclic Antidepressants
Serotonin Reuptake Inhibitors
Serotonin Noradrenaline Reuptake inhibitors

Sibutramine
MAO inhibitors
Reserpine
Methyldopa
Verapamil
Metoclopramide
Domperidone
Opioids
Estrogens
GnRH agonists
Other
Neurogenic
Chest wall/Breast lesions
Spinal Cord lesions
Other
Pregnancy
Breast-feeding
Hypothyroidism
Renal Insufficiency
Severe liver disease
Adrenal Insufficiency
Polycystic ovary syndrome
Ectopic prolactin production
Familial hyperprolactinemia (mutated prolactin receptor)
Untreated phenylketonuria and tetrahydrobiopterin deficiencies
Idiopathic

EPIDEMIOLOGY

Prolactinomas comprise 25 to 50% of all pituitary adenomas (4). Prolactinomas are roughly three times more common in women than in men; prior to menopause, prolactinomas predominantly affect women in a ratio of 5:1 to 10:1, while the ratio equalizes afterwards, mainly reflecting the decline in circulating estrogen levels. Microprolactinomas (<10 mm in maximal diameter) are the most frequent type and very rarely grow into macroprolactinomas (≥ 10 mm in maximal diameter). Macroprolactinomas, on the other hand, have a different clinical prognosis (higher risk of invasiveness, higher rates of resistance to medical therapy as well as a higher frequency of other anterior pituitary hormone deficiencies) and require closer follow-up, particularly in men (5). Prolactinomas measuring > 40 mm in diameter are named giant prolactinomas.

PATHOPHYSIOLOGY

The vast majority of prolactinomas are sporadic. Familial cases of prolactinomas are very rare and occur usually in association with Multiple Endocrine Neoplasia type 1 or the Familial Isolated Pituitary Adenoma (FIPA) syndrome and more rarely due to MEN4, MEN5 or associated with paragangliomas (6-8). Genetic testing for young-onset macroprolactinomas should include the MEN1 and AIP genes. Similar to other types of pituitary adenomas, prolactinomas arise from a single

transformed cell (lactotroph) with monoclonal proliferation.

A number of candidate somatic genetic alterations involved in the genesis and progression of prolactinomas have been investigated, among which a somatic mutation in the splicing factor 3 subunit B1 (SF3B1) gene stands out. A mutational hotspot (SF3B1R625H) was described in approximately 20% of over 200 surgically resected prolactinomas from a cohort of Chinese patients (9). A recent study by the same group suggests that the SF3B1R625H allele, by promoting aberrant splicing and suppression of Human Disc Large (DLG1), a tumor suppressor protein, may stimulate cell migration, invasion, and epithelial-mesenchymal transition (10). A recent retrospective, multicenter study involving 282 patients from 8 European centers detected SF3B1 variants (including a new variant SF3B1R625C) in seven patients with lactotroph tumors, including 3 metastatic and 3 aggressive tumors (11). The overall prevalence of likely pathogenic SF3B1 variants in lactotroph tumors was 2.5%, but when considering only metastatic cases, it reached the 50%. Furthermore, SF3B1 variants correlated with significantly larger tumor size, higher Ki67 proliferation index, multiple treatments, including radiotherapy and chemotherapy, increased disease-specific death, and shorter postoperative survival.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The majority of patients with hyperprolactinemia do not actually have prolactinomas (Table 1) (2,12,13). Drug-induced hyperprolactinemia is the most common cause, and a number of physiological conditions, including stress (psychological or associated with acute illness), exercise and sleep can also cause prolactin elevation. The hyperprolactinemia caused by drugs and other non-prolactinoma causes is usually <150 ng/mL (3000 mIU/L). Many medications block dopamine release or action, the most common being antipsychotic medications, verapamil, and metoclopramide (14,15). The best way to determine whether hyperprolactinemia is drug-induced or not is to discontinue the drug or switch to another drug in a similar class that is not known to cause hyperprolactinemia and see if the prolactin levels return to normal within 72 hours. The best example is the partial dopamine receptor agonist aripiprazole, which has been shown to be effective in attenuating antipsychotic medication-induced hyperprolactinemia (16).

A variety of suprasellar lesions cause hyperprolactinemia because of compression of the hypothalamus or pituitary stalk with decreased dopamine reaching the lactotrophs. These can be mass lesions, such as craniopharyngiomas or meningiomas, or infiltrative disease, such as sarcoidosis and Langerhans cell histiocytosis. Cystic prolactinomas, which are prolactin secreting tumors in which the cystic component accounts for more than 50% of the tumor volume, may offer a diagnostic challenge since the prolactin levels are usually lower (50-150 ng/mL) than their solid counterparts. The diagnostic evaluation should exclude other pituitary cystic lesions with hyperprolactinemia caused by stalk compression, such as cystic non-functioning pituitary adenomas (NFPAs), craniopharyngiomas, and Rathke's cleft cysts. It should be noted that cystic prolactinomas might respond to dopamine agonist therapy, which should be considered a viable option, particularly in patients without urgent need of optic chiasm decompression (5). The rapidity and degree of response to dopamine agonist therapy could be a possible way to differentiate the two scenarios with the idea that hyperprolactinemia due to lack of dopamine release would respond more rapidly and markedly to dopamine agonist therapy than prolactinomas. Nevertheless, a recent descriptive study on 68 prolactinomas presenting with prolactin levels between 50 and 200 ng/mL described a median prolactin percent change of 87% by 2 months with more than 25% of the patients having a percent drop >95% (17).

The high estrogen levels of pregnancy cause lactotroph hyperplasia and hyperprolactinemia, so pregnancy must always be excluded. The estrogen levels produced by oral contraceptives or post-menopausal hormonal replacement therapy generally do not cause hyperprolactinemia. The prevalence of hyperprolactinemia in patients with polycystic ovary syndrome is variable and should be a diagnosis of exclusion. Notably, prolactin values above 60-80 ng/mL suggest another underlying cause of hyperprolactinemia that should be actively investigated (2,18). Hypothyroidism and renal failure (serum creatinine >2 mg/dL (176 µmol/L) can also cause hyperprolactinemia (19). Thus, the initial laboratory evaluation involves repeat measurement of prolactin, a TSH, a serum creatinine, and a pregnancy test. Unless there is very good evidence for these conditions or drug-induced hyperprolactinemia, even patients with mild hyperprolactinemia should be evaluated with radiological methods, preferably MRI, to distinguish among idiopathic hyperprolactinemia, microprolactinomas, and large mass lesions. Measurement of IGF-1 is recommended for patients presenting with hyperprolactinemia and pituitary adenomas (19,20) as prolactin may be elevated in up to 50% of patients with GH-secreting tumors (21).

Special caution is needed when two-site ('sandwich') prolactin assays are used, as patients with large prolactinomas and very high prolactin levels may appear to have prolactin levels that are normal or only modestly elevated, thus mimicking a large NFPA. This "hook effect" is due to saturation of the assay antibodies and prolactin levels should always be remeasured at 1:10 or 1:100 dilution in patients with larger macroadenomas (> 2-3 cm) and normal to modestly elevated prolactin levels (20,22-24).

Sometimes prolactin levels are elevated due to increased amounts of macroprolactin. Macroprolactin consists of high molecular weight prolactin variants that are either aggregates with immunoglobulins or dimers, and have diminished biologic potency. Macroprolactin can be detected in the serum by precipitating the complex with polyethylene glycol. In normal individuals, macroprolactin comprises < 30% of circulating prolactin; therefore, if after precipitation with polyethylene glycol the prolactin levels in the supernatant are > 70% of the upper limit of normal for the assay, the patient can be assumed to have true hyperprolactinemia and not an elevation due simply to macroprolactin. Macroprolactinemia has usually been found in patients with equivocal symptoms and not those typically due to hyperprolactinemia. A lack of recognition of the presence of macroprolactin can lead to unnecessary laboratory investigations, imaging, and pharmacologic or surgical treatment.

When no pituitary lesions are seen by radiological studies and other known causes have been excluded, the diagnosis of idiopathic hyperprolactinemia is made; in long term follow-up, although prolactin levels may rise to over 50% of the baseline in 10-15% of the patients, only about 10% develop detectable microadenomas, one-third resolve their hyperprolactinemia without specific intervention and prolactin levels remain stable in most patients (25).

TREATMENT

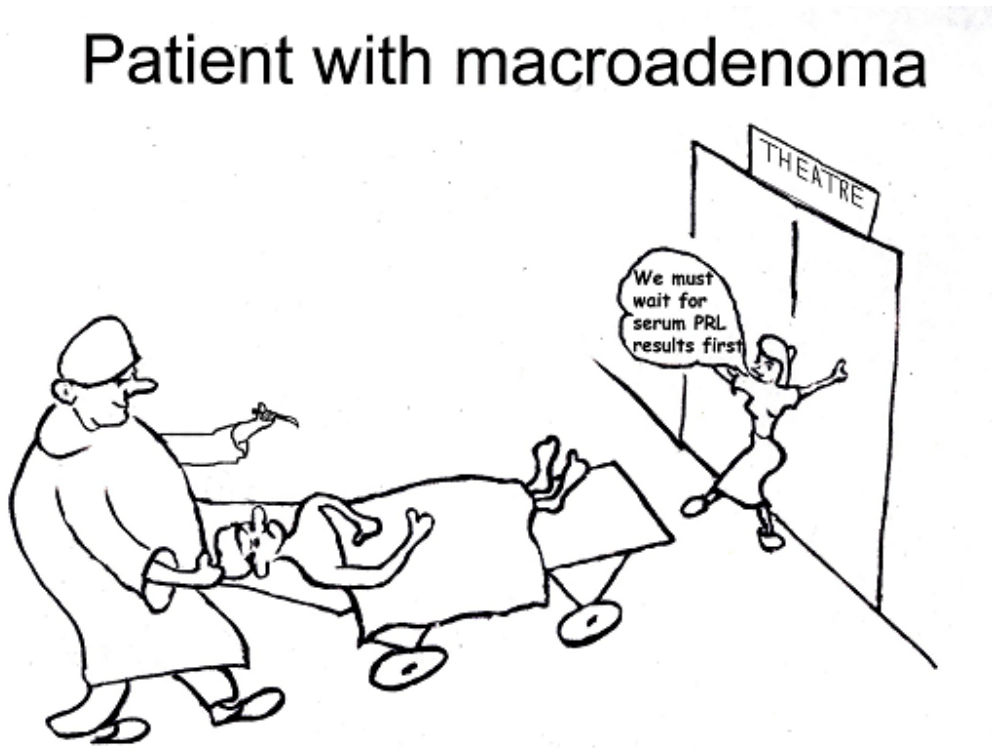

Figure 1. Serum prolactin measurement is required in all patients presenting with hypothalamic-pituitary lesions before surgery (Figure courtesy of D. Korbonits)

Not all patients require treatment. If a patient with a microadenoma or idiopathic hyperprolactinemia presents with non-bothersome galactorrhea and has normal estrogen/testosterone levels, they can simply be followed with periodic prolactin levels. Similar patients who may have amenorrhea but are not interested in fertility may be treated with estrogen replacement. However, for most symptomatic patients, a dopamine agonist is the therapy of choice. Dopamine agonists normalize prolactin levels, correct amenorrhea-galactorrhea, and decrease tumor size by more than 50% in 80-90% of patients, with cabergoline generally being more efficacious and better tolerated than bromocriptine (19,26). Thus, defining whether a pituitary tumor is a prolactinoma is crucial for optimal patient management since it is reasonable to use cabergoline as first-line therapy even in patients with visual field defects, unless visual acuity is threatened by rapid progression or recent tumor hemorrhage, in which cases, surgery is indicated (Figure 2). Starting dose in patients with large tumors threatening vision could be somewhat higher than usual, as illustrated by a retrospective case series of 14 patients with giant prolactinomas and visual field defects who received cabergoline starting doses of 0.5 mg twice or three times a week with visual improvement in 85% of the cases (27). Rapid escalation of cabergoline dose seems to be safe but not more effective than conventional treatment for the achievement of normoprolactinemia and significant tumor shrinkage as shown by a prospective randomized trial including 38 newly diagnosed patients with macroprolactinomas, 68% of them presenting with visual field defects (28). The drop in prolactin levels may be seen as early as 24 hours after initiation of medical treatment, as illustrated by the case of a 16-year old male patient presenting with a giant invasive prolactinoma whose

prolactin levels fell from 1,238,960 mIU/L (58,441 ng/mL) to 307,500 mIU/L (14,505 ng/mL) after a single dose of cabergoline 0.25 mg (29,30). Vision often starts to improve within days after the initiation of dopamine agonist therapy and should be preferentially monitored with serial Goldman perimetry tests.

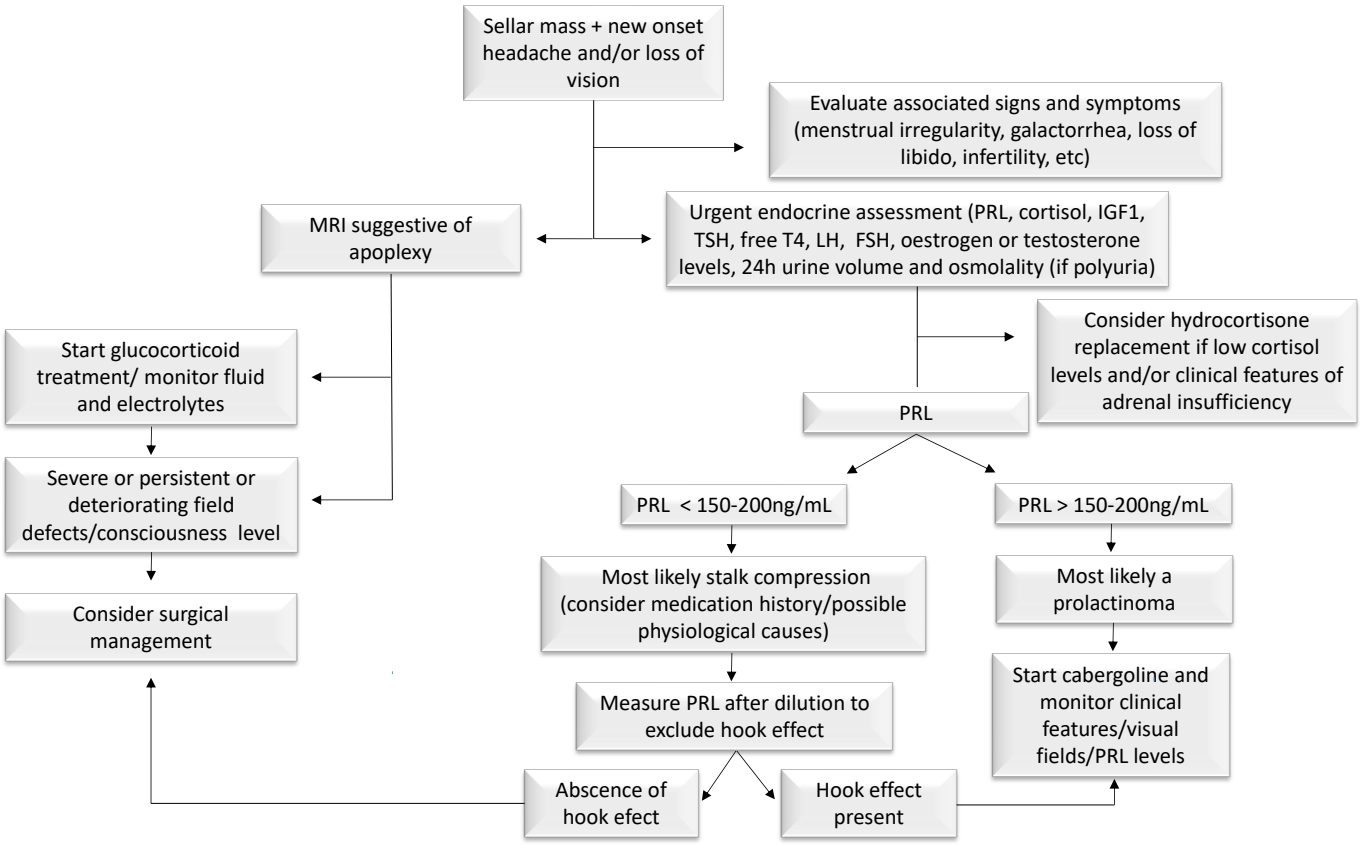

Figure 2. Suggested management in patients presenting with a pituitary mass and new onset compressive symptoms.

In non-emergent situations cabergoline is usually initiated at 0.25-0.5 mg/week (taken initially carefully with meal just before bedtime, to reduce nausea and improve compliance), whereas the initial dose of bromocriptine is 1.25 mg/day. About 40-50% of patients, whose prolactin levels normalize and tumors shrink to the point of non-visualization, can be tapered off cabergoline after 1-2 years without tumor re-expansion. Favorable predictors of successful withdrawal include low maintenance doses of cabergoline, treatment duration >2 years, and substantial adenoma size reduction (5) Factors associated with greater risk of recurrence are the presence of pituitary deficits at diagnosis and higher prolactin levels, at diagnosis and before withdrawal (31)

A rare but significant side-effect of dopamine agonist treatment is cerebrospinal fluid leakage (CSF) leak, due to the rapid shrinkage of a large prolactinoma allowing CSF to escape if significant damage is present at the fossa floor (32). According to a retrospective series of 38 patients with medically induced CSF leaks (97% of them associated with dopamine agonists), the average time from initialization of medical treatment to onset of rhinorrhea was 3.3 months (range 3 days-17 months), but this adverse effect can also occur during long term treatment (33). Patients should be advised to seek

medical assistance if clear fluid appears and this should be tested for beta-2 transferrin (20,34) or beta-trace-protein (35), If positive, patients need urgent neurosurgical input. Discontinuing dopamine agonist therapy is not usually recommended as it may cause recurrence of the tumor (36).

Dopamine agonist therapy has been implicated as a precipitating factor for pituitary apoplexy in patients with prolactinomas (37,38). Nonetheless, prolactinomas are, by themselves, more prone to bleeding, and the reported prevalence of pituitary apoplexy in macroprolactinomas treated with dopamine agonists, ranging from 1% to 6%, is not significantly different from the rate recorded in untreated prolactinomas (39). As opposed to the normal pituitary, the vascularization of pituitary adenomas is predominantly supported by a direct arterial blood supply rather than the portal system (40). Indeed, abnormal terminal arterioles have been described in prolactinomas suggesting reduced blood supply (41). Further precipitating factors which have been associated with pituitary apoplexy are cerebral angiography, surgical procedures, head trauma, dynamic tests, anticoagulation therapy, and pregnancy (40,42).

Pituitary apoplexy is a medical emergency and treatment must be tailored to each patient after a thorough evaluation by a multidisciplinary team, including an endocrinologist, a neuroradiologist, an ophthalmologist, and a neurosurgeon with expertise in pituitary pathology. The optimal management of pituitary apoplexy is still controversial, as some patients recover normal visual and endocrine function after conservative steroid-based management. However, prolactinomas with an important bleeding component may not significantly shrink under conservative management and close surveillance is mandatory. Surgical decompression is the most rapid treatment to improve symptoms and relieve compression of local structures and is indicated in case of significant neuro-ophthalmic signs or reduced levels of consciousness (43).

Rarely, vision deterioration may occur during dopamine agonist treatment despite normalization of prolactin levels and tumor shrinkage. An under recognized complication of dopamine agonist therapy in macroprolactinomas is optic chiasm herniation (the optic chiasm which is pulled down into a partially empty sella) which can be diagnosed by MRI (44,45). Multidisciplinary team evaluation is indicated, and treatment approaches include reduction/interruption of dopamine agonist therapy or neurosurgery (chiasmopexy).

A well-described side-effects of dopamine agonists include psychiatric complications, such as depression, anxiety, insomnia, hallucinations, and mania. More recently impulse control disorders have also been described in pituitary adenoma patients (20,46-49). The underlying mechanism is related to an interaction between the dopamine agonists and the D3 receptor in the mesolymbic system (50). Impulse control disorders can manifest as hypersexualism, gambling, compulsive eating, compulsive shopping, and “punding” (compulsive performance of and fascination with repetitive mechanical tasks, for example assembling and disassembling household objects or collecting or sorting various items) (48), with hypersexualism and gambling being the most commonly observed in pituitary patients. Hypersexualism has also been described in teenage children (30). Although impulse control disorders are infrequent, they have the potential to cause devastating consequences on patients’ life and clinicians should be sensitive to these potential side-effects discussing it with the patient and patient´s partner and/or family members at the start of treatment and during long-term follow-up (48). Discontinuation of the dopamine agonists usually reverses these side-effects (47).

In some cases, prolactinomas appear to be resistant to a dopamine agonist, but it is important to ensure compliance and to be certain that the underlying lesion is a prolactinoma and not some other cause of

hyperprolactinemia. About 50% of patients resistant to bromocriptine will then respond to cabergoline. Most patients resistant to standard doses of cabergoline respond to larger doses (51). T2-weighted MRI intensity may aid as a tool for predicting response to dopamine agonists. Prolactinomas showing T2-weighted MRI signal heterogeneity are more common in males, are usually larger, more secreting, and may show poorer hormonal response to dopamine agonists as compared with homogeneous prolactinomas (52). In females, T2-weighted MRI tumor hypointensity has been associated with higher prolactin levels at diagnosis and dopamine agonists resistance (53).

Previous reports in patients taking cabergoline for Parkinson's disease have shown that doses >3 mg/day may be associated with cardiac valvular abnormalities. Whether similar valvular changes occur in patients receiving low-dose cabergoline for treatment of hyperprolactinemia is still debatable; common practice has been to perform periodic echocardiograms every 12 to 24 months in patients taking >2 mg/week (54). However, a clinically significant association between low-dose cabergoline and cardiac valvulopathy is not supported by a large multicenter follow-up study (55). A meta-analysis of case-control studies evaluating patients who had received ≥6 months cabergoline treatment for hyperprolactinemia reported an increased risk of mild tricuspid regurgitation in the cabergoline-treated patients compared to controls (56). Nevertheless, these results were mainly influenced by the results from a single center (57) and in the majority of the reviewed studies there were no cases of moderate-severe tricuspid regurgitation in either group. Furthermore, neither cumulative dose nor treatment duration was associated with an increased risk of moderate-severe valve lesions (56) and none of these lesions were found as a result of cardiac symptoms.

According to the cross-sectional CATCH study conducted among 174 community-based adults (mean age of 49 years) receiving dopamine agonists for >12 months for hyperprolactinemia and no cardiac-related symptoms, cabergoline use and greater cumulative cabergoline exposure (>115 mg) were associated with a higher prevalence of valvular regurgitation, i.e., ≥2 valves with grade 2+ regurgitation, compared with bromocriptine (58). According to a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology (59), a standard transthoracic echocardiogram should be performed before a patient starts dopamine agonist therapy for hyperprolactinemia in order to detect any pre-existing valve alterations. Repeat transthoracic echocardiography should then be performed at 5 years after starting cabergoline in patients taking a total weekly dose less than or equal to 2 mg. If there has been no change on the 5-year scan, repeat echocardiography could continue at 5-yearly intervals. If a patient is taking more than a total weekly dose of 2 mg, then annual echocardiography is recommended. Patients treated with ≤2.0 mg/week of cabergoline who develop clinical signs or symptoms potentially suggestive of valvular abnormalities should undergo annual echocardiography if treatment is continued. Decisions regarding discontinuation of dopamine agonist therapy should only be made after review of serial imaging by a cardiologist experienced in analyzing drug induced valvopathy or carcinoid heart disease. These recommendations diverge to some extent from a recently published international consensus statement of the Pituitary Society (5) which recommends baseline echocardiography only if long-term treatment with a weekly dose > 2 mg is anticipated, echocardiographic monitoring every 2-3 years in patients taking more than a total weekly dose of 2 mg, instead of annual cardiac examination, and, in patients treated with < 1 mg per weak who have no clinical signs of valvular dysfunction, some experts suggested repeated examinations would not be necessary.

An alternative approach is transsphenoidal surgery, which has initial remission rates of approximately 75% for microprolactinomas and 40% for macroadenomas, and long-term recurrence rates of nearly 20% and

35%, respectively, when performed by expert neurosurgeons (60). Transsphenoidal surgery has been usually reserved for patients with resistance or intolerance to dopamine agonists, macroprolactinomas with chiasmal compression and visual deficits without rapid improvement on medical treatment, or with acute tumor complications, such as symptomatic apoplexy or cerebrospinal fluid leakage (20). Complications of hypopituitarism, infections, and bleeding are minimal, but increase proportionately with tumor size. Nevertheless, reappraisal of the position of surgery as a viable first line option alongside dopamine agonists in the treatment algorithm of adult patients with microprolactinomas and well circumscribed macroprolactinomas (Knosp grade 0 and 1) has been recently advocated by some experts (5) based on the advance of surgical techniques over the years, improved remission and low complication rates of current transsphenoidal surgery performed by experienced neurosurgeons (61,62). Craniotomy for large tumors is rarely curative and is fraught with much higher complication rates. Radiation therapy is reserved for those patients with macroadenomas not responding to either medical or surgical treatment. Radiation therapy in all forms is associated with a high rate of hypopituitarism that develops gradually over many years. Temozolomide, an orally-active alkylating chemotherapeutic agent, is reserved for the treatment of aggressive prolactinomas refractory to other treatment modalities (63). Despite current limited experience, alternative medical approaches for uncontrolled patients with aggressive tumors include cytotoxic drugs, mTOR/Akt inhibitors, tyrosine kinase inhibitors, anti-VEGF monoclonal antibody, peptide receptor radionuclide therapy, and immunotherapy (64).

FOLLOW-UP

The goals of treatment are to normalize prolactin levels or at least bring them to levels at which gonadal/reproductive/sexual function is normalized and to decrease tumor size. As noted, according to different series, nearly 80% of patients treated with dopamine agonists will reach these prolactin goals and achieve significant tumor size reduction (65-67). Once prolactin levels have reached normal or near-normal level, they can just be monitored every 3-6 months for the first year and then every 6-12 months thereafter. Macroadenoma tumor size can be monitored by serial MRI scans and once maximal size reduction has been documented, further scans may not be necessary as long as prolactin levels are being monitored. Whether a second MRI scan is necessary in patient with microadenomas is debatable if prolactin levels are regularly monitored. It is extremely rare for a tumor to increase in size without there being a significant increase in prolactin levels. Visual field testing should be repeated until the visual fields normalize or remain stable and then do not need to be repeated.

PREGNANCY

Dopamine agonists have to be given to allow ovulation to occur and then are usually stopped once pregnancy is diagnosed. In this fashion, the developing fetus has been exposed to the drug for about 4-6 weeks. There do not appear to be any risks for fetal malformations or other adverse pregnancy outcomes with either bromocriptine or cabergoline. A comprehensive review confirms no impairments in maternal–fetal outcomes in bromocriptine-induced pregnancies (6272 cases) as well as in cabergoline-induced pregnancies (1061 cases) regarding premature labor, abortions, and fetal malformations (68). In a recent multicenter study including 194 women (233 pregnancies) with prolactinomas the miscarriage rate among women who discontinued cabergoline shortly after pregnancy diagnosis was lower (7.5%) than in those who maintained the medication by medical advice or inadvertently (38%) (69). Despite the potential effect of cabergoline on abortion rates, no associations were observed between maintaining cabergoline after the first trimester and preterm birth, congenital malformations, or neurodevelopmental changes. Dopamine agonists should be reinstituted when breast-feeding is completed.

Pregnancy is a risk factor for prolactinoma enlargement, especially for macroprolactinomas, and risk is increased in patients without prior surgery (5). Symptomatic growth occurs in about 23% of macroprolactinomas and about 3% of microprolactinomas in the second or third trimester due both to the stimulatory effect of the high estrogen levels of pregnancy and the withdrawal of the dopamine agonist that may have been restraining tumor growth. In patients with growing or invasive macroadenomas, pregnancy can be recommended once the gonadotrophic axis is restored and the tumor is reduced within the sellar boundaries (68). Maintenance of dopamine agonist therapy during pregnancy is an option, particularly in patients who have not had prior surgical or radiation therapy of if the tumor is abutting the optic chiasm (5,19).

A recent joint position statement from the Brazilian Societies of Endocrinology and Gynecology recommends dopamine agonists for at least one year to reduce tumor dimension to less than 10 mm in patients with macroprolactinomas who wish to become pregnant. If the tumor reduces in size, discontinuation of the medication once pregnancy is confirmed may be discussed (45). Otherwise, pituitary surgery should be considered. Pre-pregnancy adenoma debulking could increase the chance to avoid symptoms from tumor enlargement during pregnancy. If transsphenoidal surgery is performed prior to pregnancy, the risk of symptomatic macroprolactinoma enlargement is reduced from 21% to 4.7% (5,70).Nevertheless, patients undergoing pituitary surgery before pregnancy should be informed of the potential risk of hypopituitarism and its impact on fertility. Most experts recommend surgery in women with macroprolactinomas who wish to become pregnant if the tumor is close to optic structures and do not experience pituitary tumor shrinkage during dopamine agonist therapy or who cannot tolerate dopamine agonist therapy (5,19).

Visual field testing should be carried out each trimester in patients with macroadenomas but in those with microadenomas only when they develop visual symptoms or progressive headaches. MRI scans (without gadolinium) are done in those patients who develop visual field defects or severe headaches when a therapeutic intervention is contemplated. Prolactin levels may rise during pregnancy when there is no tumor size change and some tumors enlarge without an associated rise in prolactin; therefore, measurement of prolactin during pregnancy need not be carried out, as the results can be misleading. When there is evidence of significant symptoms and tumor growth, the patient should be restarted on the dopamine agonist that was discontinued at conception (71). Again, there are fewer data with cabergoline than bromocriptine but there is no particular reason to favor one versus the other in this context. Transsphenoidal surgical decompression can be performed if there is an unsatisfactory response to the dopamine agonist. Delivery of the baby and placenta can also be initiated if the pregnancy is sufficiently advanced.

Pituitary apoplexy during pregnancy is a rare event, estimated to occur in about 1 in 10,000 term pregnancies and, on numerous occasions, it can be the first clinical manifestation of a pituitary tumor (43). The pathogenesis of pituitary apoplexy during pregnancy is suggested to include compromised blood supply to the pituitary gland due to the physiological gestational growth of the lactotroph cells and the compression of blood vessels which, in combination with a prothrombotic state of pregnancy may predispose to infarction or hemorrhage. According to a recent review of 25 cases of prolactinomas complicated by apoplexy during pregnancy (72), pituitary apoplexy mostly occurred during the second or third trimester. The main presenting symptom was sudden severe headache, followed by visual disturbances. Dopamine agonists had been discontinued at the diagnosis of pregnancy in all cases. Microadenomas accounted for 9 out of 25 cases. Half of the prolactinomas, whether microprolactinomas or not, were managed

conservatively, with dopamine agonist therapy and hormone replacement when necessary. In the other half of patients, surgery was performed. Healthy babies were born at term in most of the cases.

CHILDREN AND ADOLESCENTS

Despite the rarity of pituitary adenomas in this age group, prolactinoma is the most common adenoma type in children and adolescents, affecting approximately 100,000 patients every year (73). Although prolactinomas may be diagnosed before puberty, an adolescent presentation is more typical (74). Many aspects of the care for children and adolescents with prolactinomas are similar to those in adults; however, key differences exist, particularly in presentation and etiology. For that reason, children and adolescents with pituitary adenomas, including prolactinomas, should be treated by a pituitary specific multidisciplinary team, with experts from both pediatric and adult practice aiming to achieve optimal care, improved quality of live and reducing potentially serious life-changing and life-limiting sequelae (15,75).

Pediatric patients with hyperprolactinemia may display delayed or arrested puberty, growth failure, menstrual disturbances, including primary or secondary amenorrhea (in post-menarche girls), galactorrhea, and gynecomastia (in boys). Of course, gynecomastia is very common in adolescent boys even in the absence of hyperprolactinemia. Of note, up to 50% of children or adolescents with macroprolactinomas may present with overweight or obesity at diagnosis and weight gain may be the main complaint in some patients (76). As macroprolactinomas, including giant prolactinomas, are more common in this age group compared to adults (77), mass effects, such as headaches and visual field loss, are frequently observed and are more common in boys than in girls. Visual assessment in children and adolescents should be done with age-specific tests, including assessment of visual acuity (ideally with logarithm of the minimum angle of resolution measurement), visual fields (ideally Goldmann perimetry), fundoscopy (with or without color vision) and, in patients with potentially severe deficits, optical coherence tomography (75). Pituitary hemorrhage resulting in apoplexy seems to be more common within prolactinomas in children than in adults. (78). Therefore, the level of suspicion for potential apoplexy in children with prolactinoma and new headache, visual loss or other sudden symptoms should be high.

Genetic testing should be offered to all children and adolescents with prolactinomas. In a retrospective series of 77 patients with macroprolactinomas diagnosed before the age of 20, 14% had a genetic etiology (5% MEN 1 and 9% AIP) (76). Further rare germline abnormalities described include MEN-1 like due to MAX variants and pheochromocytoma-paraganglioma gene related pituitary disease (3PA) due to SDHx variants, as previously mentioned. In regards to biochemical evaluation, serum prolactin concentrations need to be interpreted according to pubertal status and sex. Pediatric cohort studies of prolactinomas report diagnostic serum PRL concentrations above 4,000 mIU/L (188 mcg/L), although lower levels may be seen in patients with microprolactinomas (74,76). As in adults, IGF-1 should be also evaluated to rule out mixed GH and prolactin hypersecretion and should be interpreted according to age and sex-specific reference ranges. Few cases of macroprolactinemia have been reported in the pediatric population (79,80), so assessment of baseline macroprolactin levels should be performed where serum prolactin is found to mildly or incidentally elevated. As with the adult population, serial dilutions of serum for prolactin measurement should be ordered in patients with large lesions and normal or mildly elevated PRL levels to exclude a “high dose hook-effect”.

Medical treatment with a dopamine agonist is first line treatment in children and adolescents with prolactinomas. Several studies conducted in the pediatric population have shown that dopamine agonists reduce clinical symptoms and prolactin levels

as well as induce tumor shrinkage (73,81). Cabergoline is the agonist of choice due to its superior effectiveness and lower adverse effect profile, even in the presence of visual disturbance and pituitary apoplexy, while carefully monitoring for any deterioration in vision, pituitary function, or general status. Dopamine agonist therapy is initiated at low doses (for example, 0.25 mg per week of cabergoline), with slow dose increases due to increased probability of adverse effects in children. The frequency of dose-independent psychological intolerance, including mental disorders and behavioral problems, seems to be higher in children and adolescents than in adults (82). Maintenance doses do not differ from the adult population, with most patients achieving treatment goals with conventional doses (up to 2 mg/week). For resistant cases, the dose may be increased to 3.5 mg/week or up to 7 mg in exceptional cases. Although successful dopamine agonist discontinuation has been achieved in children and adolescents, younger patients and those with high serum prolactin concentrations at diagnosis are less likely to achieve complete remission (81). To date, cardiac valvopathy in children and adolescents treated with dopamine agonists for hyperprolactinemia has not been reported. Nevertheless, considering potential longer treatment duration and larger cumulative doses in the pediatric population, surveillance for cardiac valvopathy with echocardiography is recommended such as in the adult population.

In children and adolescents with prolactinomas, neurosurgical intervention should be considered if vision deteriorates or does not improve on medical therapy or if dopamine agonist resistance, escape or intolerance occurs. Pediatric series report lower surgical remission rates than in adults, most likely due to the higher incidence of proportionately larger prolactinomas in children and adolescents, as well as a possible higher frequency of new and permanent pituitary hormone deficiencies after surgery (83,84). If surgery is indicated, it should be performed by experienced pituitary surgeons in age-appropriate neurosurgical units. Endoscopic rather than microscopic transsphenoidal surgery should be considered for its potentially superior efficacy in preserving pituitary function in this age group (85,86). Radiotherapy is reserved for exceptional patients who need control of tumor growth where other treatment modalities are not available or have been exhausted (75).

For follow-up imaging, particularly in macroadenomas, gadolinium-containing contrast agents should be used judiciously since low-level gadolinium deposits in the dentate nucleus and globus pallidus have unknown neurological impact. Unenhanced T1-weighted and T2-weighted MRI sequences should be considered during follow-up in pediatric patients, especially if good quality enhanced images have been obtained at diagnosis (87,88). If gadolinium-containing contrast agents are necessary, macrocyclic or newer linear contrast agents are preferred until further studies clarify possible long-term retention risks.

GUIDELINES

Korbonits M, Blair JC, Boguslawska A, Ayuk J, Davies JH, Druce MR, Evanson J, Flanagan D, Glynn N, Higham CE, Jacques TS, Sinha S, Simmons I, Thorp N, Swords FM, Storr HL, Spoudeas HA. Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 1, general recommendations. Nat Rev Endocrinol. 2024 Feb 9. doi: 10.1038/s41574-023-00948-8. Epub ahead of print. PMID: 38336897.

Korbonits M, Blair JC, Boguslawska A, Ayuk J, Davies JH, Druce MR, Evanson J, Flanagan D, Glynn N, Higham CE, Jacques TS, Sinha S, Simmons I, Thorp N, Swords FM, Storr HL, Spoudeas HA. Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 2, specific diseases. Nat Rev Endocrinol. 2024 Feb 9. doi: 10.1038/s41574-023-00949-7. Epub ahead of print. PMID: 38336898.

Treatment of hyperprolactinemia in women: A Position Statement from the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Brazilian Society of Endocrinology and Metabolism (SBEM). Benetti-Pinto CL, Prestes Nácul A, Rosa-E-Silva ACJS, Maciel GAR, Dos Santos Nunes Nogueira V, Condé Lamparelli Elias P, Martins M, Kasuki L, Mendes Garmes H, Glezer A.Arch Endocrinol Metab. 2024 Apr 5;68:e230504. doi: 10.20945/2359-4292-2023-0504.PMID: 38578473.

Diagnosis of hyperprolactinemia in women: A Position Statement from the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Brazilian Society of Endocrinology and Metabolism (SBEM). Glezer A, Mendes Garmes H, Kasuki L, Martins M, Condé Lamparelli Elias P, Dos Santos Nunes Nogueira V, Rosa-E-Silva ACJS, Maciel GAR, Benetti-Pinto CL, Prestes Nácul A.Arch Endocrinol Metab. 2024 Apr 5;68:e230502. doi: 10.20945/2359-4292-2023-0502.PMID: 38578472.

Petersenn, S., Fleseriu, M., Casanueva, F.F.et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society International Consensus Statement. Nat Rev Endocrinol 19, 722–740 (2023).

Shlomo Melmed, Felipe F. Casanueva, Andrew R. Hoffman, David L. Kleinberg, Victor M. Montori, Janet A. Schlechte, John A. H. Wass. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, 2011;96(2): 273–288.

REFERENCES

1. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006;65(2):265-273.
2. Glezer A, Mendes Garmes H, Kasuki L, Martins M, Condé Lamparelli Elias P, Dos Santos Nunes Nogueira V, Rosa ESA, Maciel GAR, Benetti-Pinto CL, Prestes Nácul A. Diagnosis of hyperprolactinemia in women: A Position Statement from the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Brazilian Society of Endocrinology and Metabolism (SBEM). Arch Endocrinol Metab. 2024;68:e230502.
3. Sonigo C, Bouilly J, Carre N, Tolle V, Caraty A, Tello J, Simony-Conesa FJ, Millar R, Young J, Binart N. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. J Clin Invest. 2012;122(10):3791-3795.
4. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485-534.
5. Petersenn S, Fleseriu M, Casanueva FF, Giustina A, Biermasz N, Biller BMK, Bronstein M, Chanson P, Fukuoka H, Gadelha M, Greenman Y, Gurnell M, Ho KKY, Honegger J, Ioachimescu AG, Kaiser UB, Karavitaki N, Katznelson L, Lodish M, Maiter D, Marcus HJ, McCormack A, Molitch M, Muir CA, Neggers S, Pereira AM, Pivonello R, Post K, Raverot G, Salvatori R, Samson SL, Shimon I, Spencer-Segal J, Vila G, Wass J, Melmed S. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nat Rev Endocrinol. 2023;19(12):722-740.
6. Subasinghe CJ, Somasundaram N, Sivatharshya P, Ranasinghe LD, Korbonits M. Giant prolactinoma of young onset: a clue to diagnosis of MEN-1 syndrome. Case Rep Endocrinol. 2018;2018:2875074.
7. Iacovazzo D, Hernandez-Ramirez LC, Korbonits M. Sporadic pituitary adenomas: the role of germline mutations and recommendations for genetic screening. Expert Rev Endocrinol Metab. 2017;12(2):143-153.
8. Srirangam Nadhamuni V, Korbonits M. Novel Insights into Pituitary Tumorigenesis: Genetic and Epigenetic Mechanisms. Endocr Rev. 2020;41(6).
9. Li C, Xie W, Rosenblum JS, Zhou J, Guo J, Miao Y, Shen Y, Wang H, Gong L, Li M, Zhao S, Cheng S, Zhu H, Jiang T, Ling S, Wang F, Zhang H, Zhang M, Qu Y, Zhang Q, Li G, Wang J, Ma J, Zhuang Z, Zhang Y. Somatic SF3B1 hotspot mutation in prolactinomas. Nat Commun. 2020;11(1):2506.
10. Guo J, Li C, Fang Q, Liu Y, Wang D, Chen Y, Xie W, Zhang Y. The SF3B1R625H mutation promotes prolactinoma tumor progression through aberrant splicing of DLG1. Journal of Experimental & Clinical Cancer Research. 2022;41(1):26.
11. Simon J, Perez-Rivas LG, Zhao Y, Chasseloup F, Lasolle H, Cortet C, Descotes F, Villa C, Baussart B, Burman P,

Maiter D, von Selzam V, Rotermund R, Flitsch J, Thorsteinsdottir J, Jouanneau E, Buchfelder M, Chanson P, Raverot G, Theodoropoulou M. Prevalence and clinical correlations of SF3B1 variants in lactotroph tumours. Eur J Endocrinol. 2023;189(3):372-378.
12. Soto-Pedre E, Newey PJ, Bevan JS, Greig N, Leese GP. The epidemiology of hyperprolactinemia over 20 years in the Tayside region of Scotland: the Prolactin Epidemiology, Audit and Research Study (PROLEARS). Clin Endocrinol (Oxf). 2017;86(1):60-67.
13. Newey PJ, Gorvin CM, Cleland SJ, Willberg CB, Bridge M, Azharuddin M, Drummond RS, van der Merwe PA, Klenerman P, Bountra C, Thakker RV. Mutant prolactin receptor and familial hyperprolactinemia. N Engl J Med. 2013;369(21):2012-2020.
14. Kolnikaj TS, Musat M, Salehidoost R, Korbonits M. Pharmacological Causes of Hyperprolactinemia. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, eds. Endotext. South Dartmouth (MA): MDText.com, Inc.
Copyright © 2000-2024, MDText.com, Inc.; 2000.
15. Korbonits M, Blair JC, Boguslawska A, Ayuk J, Davies JH, Druce MR, Evanson J, Flanagan D, Glynn N, Higham CE, Jacques TS, Sinha S, Simmons I, Thorp N, Swords FM, Storr HL, Spoudeas HA. Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 2, specific diseases. Nat Rev Endocrinol. 2024;20(5):290-309.
16. Chen JX, Su YA, Bian QT, Wei LH, Zhang RZ, Liu YH, Correll C, Soares JC, Yang FD, Wang SL, Zhang XY. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose-response study. Psychoneuroendocrinology. 2015;58:130-140.
17. Hage C, Salvatori R. Speed of response to dopaminergic agents in prolactinomas. Endocrine. 2022;75(3):883-888.
18. Kyritsi EM, Dimitriadis GK, Angelousi A, Mehta H, Shad A, Mytilinaiou M, Kaltsas G, Randeva HS. The value of prolactin in predicting prolactinoma in hyperprolactinaemic polycystic ovarian syndrome. Eur J Clin Invest. 2018;48(7):e12961.
19. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273-288.
20. Vilar L, Abucham J, Albuquerque JL, Araujo LA, Azevedo MF, Boguszewski CL, Casulari LA, Cunha Neto MBC, Czepielewski MA, Duarte FHG, Faria MDS, Gadelha MR, Garmes HM, Glezer A, Gurgel MH, Jallad RS, Martins M, Miranda PAC, Montenegro RM, Musolino NRC, Naves LA, Ribeiro-Oliveira Junior A, Silva CMS, Viecceli C, Bronstein MD. Controversial issues in the management of hyperprolactinemia and prolactinomas - An overview by the Neuroendocrinology Department of the Brazilian Society of Endocrinology and Metabolism. Arch Endocrinol Metab. 2018;62(2):236-263.
21. Kleinberg DL, Noel GL, Frantz AG. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med. 1977;296(11):589-600.
22. Glezer A, Bronstein MD. Hyperprolactinemia. Endotext. South Dartmouth (MA)2000.
23. Fleseriu M, Lee M, Pineyro MM, Skugor M, Reddy SK, Siraj ES, Hamrahian AH. Giant invasive pituitary prolactinoma with falsely low serum prolactin: the significance of 'hook effect'. J Neurooncol. 2006;79(1):41-43.
24. Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. Neurosurgery. 1998;42(4):913-915; discussion 915-916.
25. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. Pituitary. 2002;5(2):55-65.
26. Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab. 1999;84(7):2518-2522.
27. Shimon I, Sosa E, Mendoza V, Greenman Y, Tirosh A, Espinosa E, Popovic V, Glezer A, Bronstein MD, Mercado M. Giant prolactinomas larger than 60 mm in size: a cohort of massive and aggressive prolactin-secreting pituitary adenomas. Pituitary. 2016;19(4):429-436.
28. Rastogi A, Bhansali A, Dutta P, Singh P, Vijaivergiya R, Gupta V, Sachdeva N, Bhadada SK, Walia R. A comparison between intensive and conventional cabergoline treatment of newly diagnosed patients with macroprolactinoma. Clin Endocrinol (Oxf). 2013;79(3):409-415.
29. Gan HW, Bulwer C, Jeelani O, Levine MA, Korbonits M, Spoudeas HA. Treatment-resistant pediatric giant prolactinoma and multiple endocrine neoplasia type 1. Int J Pediatr Endocrinol. Vol 2015. England2015:15.
30. Bulwer C, Conn R, Shankar A, Ferrau F, Kapur S, Ederies A, Korbonits M, Spoudeas HA. Cabergoline-related impulse control disorder in an adolescent with a giant prolactinoma. Clin Endocrinol (Oxf). 2017;86(6):862-864.
31. Sala E, Bellaviti Buttoni P, Malchiodi E, Verrua E, Carosi G, Profka E, Rodari G, Filopanti M, Ferrante E, Spada A, Mantovani G. Recurrence of hyperprolactinemia following dopamine agonist withdrawal and possible predictive factors of recurrence in prolactinomas. J Endocrinol Invest. 2016;39(12):1377-1382.

32. Cesak T, Poczos P, Adamkov J, Nahlovsky J, Kasparova P, Gabalec F, Celakovsky P, Choutka O. Medically induced CSF rhinorrhea following treatment of macroprolactinoma: case series and literature review. Pituitary. 2018.
33. Lam G, Mehta V, Zada G. Spontaneous and medically induced cerebrospinal fluid leakage in the setting of pituitary adenomas: review of the literature. Neurosurg Focus. 2012;32(6):E2.
34. Mantur M, Lukaszewicz-Zajac M, Mroczko B, Kulakowska A, Ganslandt O, Kemona H, Szmitkowski M, Drozdowski W, Zimmermann R, Kornhuber J, Lewczuk P. Cerebrospinal fluid leakage--reliable diagnostic methods. Clin Chim Acta. 2011;412(11-12):837-840.
35. Almela MT, Navarro-Zaragoza J, Laorden ML, Sánchez-Celemín F, Almela P. Cut-off value for β-trace protein (β-TP) as a rapid diagnostic of cerebrospinal fluid (CSF) leak detection. Laryngoscope Investig Otolaryngol. 2023;8(5):1233-1239.
36. de Lacy P, Benjamin S, Dixon R, Stephens JW, Redfern R, Price DE. Is surgical intervention frequently required for medically managed macroprolactinomas? A study of spontaneous cerebrospinal fluid rhinorrhea. Surg Neurol. 2009;72(5):461-463; discussion 463.
37. Balarini Lima GA, Machado Ede O, Dos Santos Silva CM, Filho PN, Gadelha MR. Pituitary apoplexy during treatment of cystic macroprolactinomas with cabergoline. Pituitary. 2008;11(3):287-292.
38. Chng E, Dalan R. Pituitary apoplexy associated with cabergoline therapy. J Clin Neurosci. 2013;20(12):1637-1643.
39. Carija R, Vucina D. Frequency of pituitary tumor apoplexy during treatment of prolactinomas with dopamine agonists: a systematic review. CNS Neurol Disord Drug Targets. 2012;11(8):1012-1014.
40. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. Endocr Rev. 2015;36(6):622-645.
41. Schechter J, Goldsmith P, Wilson C, Weiner R. Morphological evidence for the presence of arteries in human prolactinomas. J Clin Endocrinol Metab. 1988;67(4):713-719.
42. Grand'Maison S, Weber F, Bedard MJ, Mahone M, Godbout A. Pituitary apoplexy in pregnancy: A case series and literature review. Obstet Med. 2015;8(4):177-183.
43. Iglesias P. Pituitary Apoplexy: An Updated Review. J Clin Med. 2024;13(9).
44. Jones SE, James RA, Hall K, Kendall-Taylor P. Optic chiasmal herniation--an under recognized complication of dopamine agonist therapy for macroprolactinoma. Clin Endocrinol (Oxf). 2000;53(4):529-534.
45. Benetti-Pinto CL, Prestes Nácul A, Rosa ESA, Maciel GAR, Dos Santos Nunes Nogueira V, Condé Lamparelli Elias P, Martins M, Kasuki L, Mendes Garmes H, Glezer A. Treatment of hyperprolactinemia in women: A Position Statement from the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) and the Brazilian Society of Endocrinology and Metabolism (SBEM). Arch Endocrinol Metab. 2024;68:e230504.
46. Davie M. Pathological gambling associated with cabergoline therapy in a patient with a pituitary prolactinoma. J Neuropsychiatry Clin Neurosci. Vol 19. United States2007:473-474.
47. Bancos I, Nannenga MR, Bostwick JM, Silber MH, Erickson D, Nippoldt TB. Impulse control disorders in patients with dopamine agonist-treated prolactinomas and nonfunctioning pituitary adenomas: a case-control study. Clin Endocrinol (Oxf). 2014;80(6):863-868.
48. Noronha S, Stokes V, Karavitaki N, Grossman A. Treating prolactinomas with dopamine agonists: always worth the gamble? Endocrine. 2016;51(2):205-210.
49. Hamblin R, Karavitaki N. Impulse Control Disorders in Patients with Pituitary Tumors Treated with Dopamine Agonists: A Systematic Review. Arch Med Res. 2023;54(8):102910.
50. Ahlskog JE. Pathological behaviors provoked by dopamine agonist therapy of Parkinson's disease. Physiol Behav. 2011;104(1):168-172.
51. Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, Kubo O, Hori T, Takano K. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. J Clin Endocrinol Metab. 2008;93(12):4721-4727.
52. 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):323-331.
53. Dogansen SC, Yalin GY, Tanrikulu S, Tekin S, Nizam N, Bilgic B, Sencer S, Yarman S. Clinicopathological significance of baseline T2-weighted signal intensity in functional pituitary adenomas. Pituitary. 2018;21(4):347-354.
54. Molitch ME. Management of medically refractory prolactinoma. J Neurooncol. 2014;117(3):421-428.
55. Drake WM, Stiles CE, Bevan JS, Karavitaki N, Trainer PJ, Rees DA, Richardson TI, Baldeweg SE, Stojanovic N, Murray RD, Toogood AA, Martin NM, Vaidya B, Han TS, Steeds RP, group UKCvs, Baldeweg FC, Sheikh UE, Kyriakakis N, Parasuraman SK, Taylor L, Butt N, Anyiam S. A Follow-Up Study of the Prevalence of Valvular Heart Abnormalities in Hyperprolactinemic Patients Treated With Cabergoline. J Clin Endocrinol Metab. 2016;101(11):4189-4194.
56. 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.
57. Colao A, Galderisi M, Di Sarno A, Pardo M, Gaccione M, D'Andrea M, Guerra E, Pivonello R, Lerro G, Lombardi G. Increased prevalence of tricuspid regurgitation in patients

with prolactinomas chronically treated with cabergoline. J Clin Endocrinol Metab. 2008;93(10):3777-3784.
58. Budayr A, Tan TC, Lo JC, Zaroff JG, Tabada GH, Yang J, Go AS. Cardiac valvular abnormalities associated with use and cumulative exposure of cabergoline for hyperprolactinemia: the CATCH study. BMC Endocr Disord. 2020;20(1):25.
59. Steeds RP, Stiles CE, Sharma V, Chambers JB, Lloyd G, Drake W. Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinemia: a joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology. Echo Res Pract. 2019;6(1):G1-g8.
60. Colao A. Pituitary tumours: the prolactinoma. Best Pract Res Clin Endocrinol Metab. 2009;23(5):575-596.
61. Giese S, Nasi-Kordhishti I, Honegger J. Outcomes of Transsphenoidal Microsurgery for Prolactinomas - A Contemporary Series of 162 Cases. Exp Clin Endocrinol Diabetes. 2021;129(3):163-171.
62. Honegger J, Nasi-Kordhishti I, Aboutaha N, Giese S. Surgery for prolactinomas: a better choice? Pituitary. 2020;23(1):45-51.
63. Chen C, Yin S, Zhang S, Wang M, Hu Y, Zhou P, Jiang S. Treatment of aggressive prolactinoma with temozolomide: A case report and review of literature up to date. Medicine (Baltimore). 2017;96(47):e8733.
64. Auriemma RS, Pirchio R, Pivonello C, Garifalos F, Colao A, Pivonello R. Approach to the Patient With Prolactinoma. J Clin Endocrinol Metab. 2023;108(9):2400-2423.
65. Vilar L, Freitas MC, Naves LA, Casulari LA, Azevedo M, Montenegro R, Jr., Barros AI, Faria M, Nascimento GC, Lima JG, Nobrega LH, Cruz TP, Mota A, Ramos A, Violante A, Lamounier Filho A, Gadelha MR, Czepielewski MA, Glezer A, Bronstein MD. Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. J Endocrinol Invest. 2008;31(5):436-444.
66. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G. Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. J Clin Endocrinol Metab. 2000;85(6):2247-2252.
67. Berinder K, Stackenas I, Akre O, Hirschberg AL, Hulting AL. Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. Clin Endocrinol (Oxf). 2005;63(4):450-455.
68. Glezer A, Bronstein MD. Prolactinomas in pregnancy: considerations before conception and during pregnancy. Pituitary. 2020;23(1):65-69.
69. Sant' Anna BG, Musolino NRC, Gadelha MR, Marques C, Castro M, Elias PCL, Vilar L, Lyra R, Martins MRA, Quidute ARP, Abucham J, Nazato D, Garmes HM, Fontana MLC, Boguszewski CL, Bueno CB, Czepielewski MA, Portes ES, Nunes-Nogueira VS, Ribeiro-Oliveira A, Jr., Francisco RPV, Bronstein MD, Glezer A. A Brazilian multicentre study evaluating pregnancies induced by cabergoline in patients harboring prolactinomas. Pituitary. 2020;23(2):120-128.
70. Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. Eur J Endocrinol. 2015;172(5):R205-213.
71. Molitch ME. Prolactinoma in pregnancy. Best Pract Res Clin Endocrinol Metab. 2011;25(6):885-896.
72. Kuhn E, Weinreich AA, Biermasz NR, Jorgensen JOL, Chanson P. Apoplexy of microprolactinomas during pregnancy: report of five cases and review of the literature. Eur J Endocrinol. 2021;185(1):99-108.
73. Hoffmann A, Adelmann S, Lohle K, Claviez A, Müller HL. Pediatric prolactinoma: initial presentation, treatment, and long-term prognosis. Eur J Pediatr. 2018;177(1):125-132.
74. Acharya SV, Gopal RA, Bandgar TR, Joshi SR, Menon PS, Shah NS. Clinical profile and long term follow up of children and adolescents with prolactinomas. Pituitary. 2009;12(3):186-189.
75. Korbonits M, Blair JC, Boguslawska A, Ayuk J, Davies JH, Druce MR, Evanson J, Flanagan D, Glynn N, Higham CE, Jacques TS, Sinha S, Simmons I, Thorp N, Swords FM, Storr HL, Spoudeas HA. Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 1, general recommendations. Nat Rev Endocrinol. 2024;20(5):278-289.
76. Salenave S, Ancelle D, Bahougne T, Raverot G, Kamenicky P, Bouligand J, Guiochon-Mantel A, Linglart A, Souchon PF, Nicolino M, Young J, Borson-Chazot F, Delemer B, Chanson P. Macroprolactinomas in children and adolescents: factors associated with the response to treatment in 77 patients. J Clin Endocrinol Metab. 2015;100(3):1177-1186.
77. Arya VB, Aylwin SJB, Hulse T, Ajzensztejn M, Kalitsi J, Kalogirou N, Bodi I, Thomas N, Hampton T, Kapoor RR, Buchanan CR. Prolactinoma in childhood and adolescence-Tumour size at presentation predicts management strategy: Single centre series and a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021;94(3):413-423.
78. Culpin E, Crank M, Igra M, Connolly DJA, Dimitri P, Mirza S, Sinha S. Pituitary tumor apoplexy within prolactinomas in children: a more aggressive condition? Pituitary. 2018;21(5):474-479.
79. Fideleff HL, Ruibal G, Boquete H, Pujol A, Sequera A, Sobrado P. Macroprolactinemia in childhood and adolescence: a cause of asymptomatic hyperprolactinemia. Horm Res. 2000;53(1):16-19.
80. Tütüncüler F, Darendeliler F, Aygün M, Hekim N. Macroprolactinemia in childhood and adolescence: a

cause of hyperprolactinemia. Turk J Pediatr. 2006;48(2):143-147.
81. Breil T, Lorz C, Choukair D, Mittnacht J, Inta I, Klose D, Jesser J, Schulze E, Bettendorf M. Clinical Features and Response to Treatment of Prolactinomas in Children and Adolescents: A Retrospective Single-Centre Analysis and Review of the Literature. Horm Res Paediatr. 2018;89(3):157-165.
82. Brichta CM, Wurm M, Krebs A, Schwab KO, van der Werf-Grohmann N. Start low, go slowly - mental abnormalities in young prolactinoma patients under cabergoline therapy. J Pediatr Endocrinol Metab. 2019;32(9):969-977.
83. Abe T, Lüdecke DK. Transnasal surgery for prolactin-secreting pituitary adenomas in childhood and adolescence. Surg Neurol. 2002;57(6):369-378; discussion 378-369.
84. Yang A, Cho SY, Park H, Kim MS, Kong DS, Shin HJ, Jin DK. Clinical, Hormonal, and Neuroradiological Characteristics and Therapeutic Outcomes of Prolactinomas in Children and Adolescents at a Single Center. Front Endocrinol (Lausanne). 2020;11:527.
85. Massimi L, Rigante M, D'Angelo L, Paternoster G, Leonardi P, Paludetti G, Di Rocco C. Quality of postoperative course in children: endoscopic endonasal surgery versus sublabial microsurgery. Acta Neurochir (Wien). 2011;153(4):843-849.
86. Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC, Gardner PA, Tyler-Kabara EC. Endoscopic endonasal skull base surgery in the pediatric population. J Neurosurg Pediatr. 2013;11(3):227-241.
87. Bonneville JF. A plea for the T2W MR sequence for pituitary imaging. Pituitary. Vol 22. United States2019:195-197.
88. Shah R, D'Arco F, Soares B, Cooper J, Brierley J. Use of gadolinium contrast agents in pediatric population: Donald Rumsfeld meets Hippocrates! Br J Radiol. 2019;92(1094):20180746.