



HAL
open science

The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new

Philippe Chanson, Dominique Maiter

► **To cite this version:**

Philippe Chanson, Dominique Maiter. The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new. *Best Practice and Research: Clinical Endocrinology and Metabolism*, 2019, 33, pp.101290 -. 10.1016/j.beem.2019.101290 . hal-03487649

HAL Id: hal-03487649

<https://hal.science/hal-03487649>

Submitted on 21 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

THE EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OF PROLACTINOMAS: THE OLD AND THE NEW

Philippe Chanson, Professor of Endocrinology^{a,b,c,*}

Dominique Maiter, Professor of Endocrinology^d

^aAssistance Publique-Hôpitaux de Paris (AP-HP), Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, Hôpital de Bicêtre, F-94276 Le Kremlin-Bicêtre, France;

^bUMR-S1185 Université Paris-Sud, Univ Paris-Saclay, F-94276 Le Kremlin-Bicêtre, France;

^cInstitut National de la Santé et de la Recherche Médicale (Inserm) U1185, F-94276 Le Kremlin Bicêtre, France

^dService d'Endocrinologie et Nutrition, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

* Corresponding author: Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre, Paris, France.

E-mail address: philippe.chanson@bct.aphp.fr (P. Chanson).

Keywords: prolactin, pituitary adenoma, dopamine agonist

ABSTRACT

Prevalence and incidence of prolactinomas are approximately 50 per 100,000 and 3-5 new cases/100,000/year. The pathophysiological mechanism of hyperprolactinemia-induced gonadotropic failure involves kisspeptin neurons. Prolactinomas in males are larger, more invasive and less sensitive to dopamine agonists (DAs). Macroprolactin, responsible for pseudohyperprolactinemia is a frequent pitfall of prolactin assay.

DAs still represent the primary therapy for most prolactinomas, but neurosurgery has regained interest, due to progress in surgical techniques and a high success rate in microprolactinoma, as well as to some underestimated side effects of long-term DA treatment, such as impulse control disorders or impaired quality of life. Recent data show that the suspected effects of DAs on cardiac valves in patients with prolactinomas are reassuring. Finally, temozolomide has emerged as a valuable treatment for rare cases of aggressive and malignant prolactinomas that do not respond to all other conventional treatments.

1 – Introduction

Prolactinomas are the most common types of pituitary adenomas. They are well known to endocrinologists and neurosurgeons, as well as to gynecologists and general practitioners, due to their effects on fertility, particularly in women. Their management has been transformed by the use of dopamine agonists (DAs) that were introduced in the seventies. Even if medical practice in the field of prolactinomas is now well established, our objective in this article was to highlight some data that, although they are older, are still relevant, and to provide insights into the epidemiology, diagnosis and treatment of prolactinomas in 2019. We will not describe the pathophysiology, histology or specific aspects of prolactinomas during pregnancy, because these topics have recently been reviewed in detail [1-5].

2- Epidemiology

Prolactinomas represent the most common type of pituitary adenomas, accounting for approximately 50% of all pituitary tumors requiring medical attention [6, 7]. Previous radiological and autopsy studies have revealed a high prevalence of pituitary adenomas (10-20%), and the vast majority (>99%) are small microadenomas with a predominance (25-60%) of lactotroph tumors, based on immunohistochemistry [7-9]. In clinical settings, microadenomas are approximately four- to five-fold more frequent than macroadenomas, and a net predominance of PRL-secreting tumors (and of hyperprolactinemia in general) is observed in women aged 25–44 years compared to men (a male to female ratio of 1:5 to 1:10), while this difference disappears after menopause [2, 10-12].

Several epidemiological studies performed in different countries over the past few years have shown a much higher prevalence of pituitary adenomas requiring medical attention than previously predicted, and prolactinomas were always the most frequent tumor subtype (**Table**

1) [13-20]. Overall, the prevalence of PRL-secreting tumors ranged from 25 per 100,000 to 63 per 100,000. The prevalence of symptomatic microprolactinomas and macroprolactinomas is approximately 40 and 10 per 100,000, respectively.

Important gender differences in both the age at diagnosis and tumor size have been observed. The peak age of occurrence in women occurs at approximately 30 years, while most men are diagnosed after age 50 [15]. The ratio between macro- and microprolactinomas is approximately 1:8 in women, whereas it is inverted in men (macroadenomas in 80% of cases) [14].

The standard annual incidence rate of prolactinomas ranged from 2 to 5 new cases/100,000, and the value is 3-times higher in women than in men [14, 17, 19, 20]. Most studies also reported an increase in this incidence rate over time, possibly indicating improved disease recognition.

3- Diagnosis

3-1 Clinical consequences of hyperprolactinemia

3-1-1 Women

Most women with a prolactinoma have a microadenoma, and therefore endocrine symptoms are much more prevalent than mass effects, at least before menopause. Classic symptoms of prolactinomas in women include oligo- or amenorrhea (which is present in almost all patients, 85-90%), galactorrhea, (present in 84% of patients, according to a recent meta-analysis [21]) and infertility [21-24]. Conversely, in nearly 15% of women who experience secondary amenorrhea or oligomenorrhea hyperprolactinemia is found, and in more than half of those, this is due to a prolactinoma [22, 25]. Although the prevalence of mild hyperprolactinemia in an unselected, asymptomatic population with infertility is approximately 5%, the finding of a pituitary adenoma at MRI is rather low in the absence of oligoamenorrhea and/or galactorrhea

[26]. The mechanism by which hyperprolactinemia induces gonadotropic failure has recently been elucidated [27]: hyperprolactinemia does not directly inhibit GnRH neurons but acts *via* kisspeptin neurons, as an infusion of kisspeptin reverses gonadotropic failure in both mice [27] and humans [28].

Postmenopausal women with prolactinomas usually do not present with functional symptoms. They present with mass effects related to large tumors, although prolactinomas may also be discovered incidentally or because of a history of “premature” menopause [29-32].

3-1-2 Men

Compared to women, a greater proportion of men (approximately 80%) are diagnosed with a macroprolactinoma [33-36]. The larger tumor size and more aggressive features observed in men are not primarily related to a diagnostic delay, but rather to gender-related differences in tumor behavior [35, 37, 38] and may involve the estrogen-receptor pathway [39].

Overall, approximately half of men with prolactinomas typically present with symptoms caused by the tumor mass and the other half with symptoms of hypogonadism, including a loss of libido, erectile dysfunction, gynecomastia, infertility, and/or osteopenia [40, 41].

Although testosterone concentrations are often decreased, these levels may be normal in men with prolactinomas [42]. However, the successful treatment of hyperprolactinemia leads to a normalization or significant increase in testosterone levels in 60-80% of patients [43-45]. When normal testosterone levels are achieved, sperm volumes and counts are also likely to normalize, although sometimes after a prolonged (~2 years) duration [43, 46].

3-2 Mass Effects

Macroadenomas may exert local mass effects. Visual field defects due to chiasmal compression depend on the extent of suprasellar extension. Headaches are a frequent

symptom which is often associated with the lateralization of the tumor, and cluster-like headache may also occur as a major manifestation.

Hypopituitarism may result from direct pituitary compression or more commonly from hypothalamic/stalk dysfunction. Patients with larger tumors are more likely to present with one or more hormonal deficits. All patients with macroadenomas should be evaluated for possible deficits in pituitary function.

Macroprolactinomas may invade one or both cavernous sinuses, but cavernous sinus syndrome is rare and is generally observed in the context of pituitary apoplexy [47], which is characterized by headache with a sudden and severe onset that is generally associated with visual disturbances or ocular palsy.

Giant prolactinomas are associated with endocrine symptoms (75%), visual symptoms (70%) and headaches (60%), but they are also responsible for unique manifestations related to the extensive invasion of surrounding structures [48]. The extensive invasion of the skull floor with bony destruction occasionally occurs and may cause spontaneous cerebrospinal fluid (CSF) rhinorrhea, exophthalmos and optic nerve compression at the orbital apex, nasal stuffiness and epistaxis, or cranio-cervical junction instability [49]. Extrasellar extension in other directions may cause hydrocephalus, hearing impairments, unilateral hemiparesis, temporal epilepsy or dementia due to frontal lobe extension [48].

Malignant prolactinomas are rare tumors defined by the presence of distant cerebrospinal, meningeal and/or systemic metastases. Indeed, a reliable distinction between carcinoma and adenoma is rarely achieved based on standard histological criteria [50-53]. Pituitary carcinomas differ from invasive pituitary tumors that remain contiguous with the primary tumor site. Their precise incidence is not precisely known but, overall, they account for only 0.1-0.2% of all pituitary tumors, and prolactinomas correspond to approximately one-third of these tumors. Detailed descriptions of approximately 65 cases of malignant prolactinoma (45

men and 20 women) have been published, and the characteristics of most of these tumors have been reviewed [2]. Briefly, these tumors occur at any age but mostly develop in the fifth or sixth decade of life in patients with a preexisting prolactinoma. Typically, the primary tumor has been diagnosed many years before metastasis (the latent period between initial diagnosis and detection of metastases may persist for up to 22 years) and has been treated with high-dose DAs, repeated surgery and radiotherapy before the tumor becomes completely resistant to treatment and metastases become apparent [50-52]. Once metastases are diagnosed, the median survival time is approximately 18 months, but the outcome of these tumors has improved over the past few years and prolonged, asymptomatic survival has now been reported in several patients [50].

3-3 Biochemical diagnosis

3-3-1 PRL levels correlate with prolactinoma size.

The diagnosis of hyperprolactinemia is determined by measuring basal PRL levels, which generally correlate well with the prolactinoma size [54, 55]. Patients with large macroprolactinomas have PRL levels that exceed 250 $\mu\text{g/l}$, virtually all patients with macroprolactinomas have levels greater than 100 $\mu\text{g/l}$ and most patients with microprolactinomas present levels ranging from 50 to 150 $\mu\text{g/L}$ [56, 57] (Figure 1).

3-3-2 Pitfalls in the PRL assay.

When two-site immunoradiometric assays (IRMA) or immunochemiluminometric (ICMA) assays are used, patients with very high PRL levels may appear to have normal or only moderately elevated PRL levels, i.e., on the order of 30–200 $\mu\text{g/L}$, due to the so-called “hook effect” [58-60]. Under these circumstances, a prolactinoma may be misclassified as a clinically nonfunctioning macroadenoma, which may cause a similar moderate increase in PRL levels due to interference with stalk dopamine transport to normal lactotrophs. This

confusion can be avoided by repeating the measurements of PRL levels in these patients after diluting the samples 1:100 or using an assay that does not induce this hook effect.

Another pitfall of the PRL assay is macroprolactin interference, which is more common with the current generation of PRL immunoassays [60]. High molecular weight forms of PRL (150 kDa, big-big PRL) pose a major problem due to their interference with PRL assays. These forms may result in a false diagnosis of hyperprolactinemia that is not or is rarely accompanied by the usual signs of hyperprolactinemia, i.e., amenorrhea and galactorrhea [59, 61-64]. Macroprolactin is recognized by immunoassays for PRL but has no biological activity *in vivo*. High concentrations of macroprolactin appear to be due to reduced clearance of IgG-PRL aggregates [65] and to their interference with the reactivity between PRL and the capture and detection antibodies involved in the sandwich reaction of PRL immunoassays [66]. All available immunoassays detect macroprolactin, but the variability is quite surprising, with 2.3- to 7.8-fold differences in detection levels [67]. False hyperprolactinemia related to macroprolactin is an important clinical issue because it may lead to misdiagnosis, mismanagement of patients, including unnecessary pituitary explorations, a waste of healthcare resources and unnecessary concerns for both patients and clinicians [68-75]. The prevalence of macroprolactinemia in hyperprolactinemic samples obtained in clinical practice has been evaluated in different studies and reported to range from 15 to 46% [76]. When hyperprolactinemia is detected in the first assay, clinicians are advised to obtain a control test from another laboratory that uses a different assay kit. If a major discrepancy is observed between the two results, particularly if one is normal, then macroprolactinemia is the most likely explanation [63]. The current recommendation for best practices in clinical chemistry laboratories when hyperprolactinemia is detected is to sub-fractionate the serum using 12.5% (w/v) polyethylene glycol (PEG). This procedure removes the higher molecular weight forms of PRL through precipitation, and the monomeric forms

remain in the supernatant [63]. Residual PRL levels measured after precipitation with PEG correspond closely to monomeric PRL levels obtained after gel filtration chromatography (GFC) [77], which is the reference method for fractionating the various isoforms of PRL, including macroprolactin, in serum, but this method is cumbersome and costly.

3-3-3 Differential diagnosis

Hyperprolactinemia is the hallmark of prolactinomas, but may also be a consequence of a large variety of other disorders that must be excluded before prolactinoma is diagnosed.

Polycystic ovary syndrome (PCOS) is often associated with hyperprolactinemia and was long considered one of its causes. In fact, this association of two disorders that are both very common in the general population is more likely due to random chance. Indeed, an etiological investigation of women with both PCOS and hyperprolactinemia (11 to 16% of women with PCOS) showed that 50-70% had a prolactinoma, while hyperprolactinemia was drug-induced or related to assay artefacts (macroprolactin) in the remaining cases [78, 79]. Prolactinomas are the cause of hyperprolactinemia in approximately 12% to 70% of patients, depending on the level of PRL considered the diagnostic value and the type of population studied [10, 26, 78, 80].

Many physiological and pathological conditions may be associated with hyperprolactinemia [2]. They are generally excluded by a careful review of the history and physical examination, as well as routine blood chemistry and thyroid function tests **(Table 2)**.

4- Imaging

All patients with hyperprolactinemia in whom obvious non-hypothalamic–pituitary disorders have been excluded should undergo a pituitary MRI including at least T2-weighted coronal sections and T1-weighted coronal sections before and after gadolinium enhancement [81, 82, 83]. A challenge in evaluating patients with mild hyperprolactinemia is the finding of a false-

positive CT or MRI mass (pituitary incidentaloma). Because these techniques detect incidental non-secreting tumors, cysts, infarcts, or even normal focal heterogeneity in the pituitary gland [7], the finding of a visible pituitary nodule on images from a patient with elevated PRL levels may not always be synonymous with the presence of a prolactinoma.

On T1-weighted MRI, micro- and macroprolactinomas are usually hypointense and occasionally isointense, but are rarely hyperintense (hemorrhagic transformation) [81] (Figures 2 and 3). The T2 MRI is more variable: 80% of prolactinomas are hyperintense and approximately half are heterogeneous [83, 84]. Physiological conditions, such as puberty and the post-pubertal period in girls [85], as well as pregnancy or spontaneous intracranial hypotension (which induces an increase in pituitary height) [86], and morphological abnormalities leading to container-content mismatch [83] may result in misleading images.

Pituitary macroadenomas generally exhibit extrasellar extension that usually extends upwards towards the optochiasmatic cistern (Figure 3). Downward extension into the sphenoid sinus or lateral extension towards the cavernous sinus may also be observed [37]. Hemorrhagic transformation occurs in approximately 20% of macroprolactinomas, but is usually asymptomatic [87]. Acute intra-adenomatous bleeding in the setting of pituitary apoplexy [47] results in heterogeneous T1 hyperintensity. In the subacute stage, the sedimentation of blood and hemoglobin derivatives (deoxyhemoglobin and methemoglobin) can lead to the appearance of fluid-fluid levels within the hemorrhage.

Visual field testing should be performed in patients whose tumors are adjacent to or abut the optic chiasm, as visualized on an MRI scan. If a clear distance of >2 mm is seen, this testing is unnecessary.

A CT scan of the pituitary region is useful for detecting skull base bone erosion in patients with large invasive macroprolactinomas (Figure 4), particularly in men, which, in

combination with subsequent tumor shrinkage following treatment with DAs, may result in spontaneous CSF rhinorrhea [49].

5- Treatment

5-1 Surveillance

Studies of the natural history of untreated microprolactinomas have shown that significant or persistent growth of these tumors is uncommon [87, 88]. Therefore, as recommended by the most recent guidelines for the treatment of prolactinomas [55], symptomatic eugonadal patients with microprolactinomas do not require active therapy and can be monitored with regular measurements of PRL levels. A prolactinoma is unlikely to show significant growth without a concomitant increase in hormone levels. Likewise, amenorrheic premenopausal women with a microadenoma who do not wish to become pregnant may be treated with oral contraceptives instead of DA therapy, if PRL levels do not increase substantially and evidence of tumor enlargement is not observed [55, 56].

For patients with macroprolactinomas, therapy is usually advisable as these tumors have shown a propensity to grow and eventually become aggressive, particularly in males, in whom cavernous sinus invasion is frequently observed [35]. Moreover, most macroprolactinomas are associated with symptoms related to significantly increased PRL levels or tumor compression (see the preceding sections).

5-2 Medical treatment

Medical therapy with DAs represents the primary therapy for almost all prolactinomas, including microadenomas that require treatment, macroprolactinomas and giant prolactinomas. The well-documented high efficacy of DA therapy for decreasing hyperprolactinemia and the tumor volume applies to both female and male patients, in whom DA therapy will usually normalize PRL levels, regardless of the tumor size [44, 89, 90]. The three drugs currently that

are available for this indication in most countries are bromocriptine, cabergoline and quinagolide.

5-2-1 Efficacy of the different DAs

5-2-1-1 The “old” agent bromocriptine

Bromocriptine is an ergot derivative that functions as both a D₁R and D₂R agonist. It was the first DA introduced into clinical practice more than 40 years ago [91]. Although its use has largely been supplanted by cabergoline, some patients may continue to use this drug in specific situations (e.g., patients whose symptoms have been well controlled by this drug for many years, in young women who are planning a pregnancy and reside in countries where the use of cabergoline has not been approved for this indication, or patients with severe cardiac valve disease). Most patients are successfully treated with daily doses of 7.5 mg or less. However, doses as high as 20–40 mg/day may be necessary for patients who display DA resistance. Bromocriptine normalizes serum PRL levels in 78% and 72% of patients with microprolactinomas and macroprolactinomas, respectively [56, 92]. The resumption of ovulatory cycles occurred in approximately 80% of women.

A significant decrease in tumor size is achieved in approximately 77% of patients, with a reduction in tumor size greater than 50%, between 25 and 50%, and less than 25%, in 40%, 30% and in the remainder of patients, respectively [93]. Importantly, some patients experience an extremely rapid decrease in tumor size with a significant improvement in visual fields noted within 24–72 hours, and changes are already apparent on images within 2 weeks [94]. Improvements in the visual field generally parallel the changes observed on pituitary images, whereas the reduction in PRL levels usually precedes any detectable change in tumor size.

5-2-1-2 The “new” agent cabergoline

Cabergoline is an ergot derivative that is more (but not strictly) selective for D₂R and has a long duration of action, which permits once or twice weekly administration. Most patients are successfully treated with weekly doses of 0.5 or 1 mg, but a few will require doses of ≥ 3.5 mg to control their symptoms [95].

In a compilation of 14 prospective studies of the effects of cabergoline treatment on patients with hyperprolactinemic disorders, the hormonal response rate was 73-96% and the tumor size was reduced by 50 to 100% [56] (Figure 5). Approximately 80–90% of patients present a rapid response (within 3 months) to low doses of cabergoline (less than 2.0 mg/week) and exhibit good tolerability [95, 96]. However, some patients require higher doses, and approximately 10–15% of patients respond to each dose increase with a step-wise reduction in their PRL levels. Thus, cabergoline is certainly the most effective compound to treat prolactinomas, and provides good patient compliance with long-term treatment regimens.

3-2-1-3 Quinagolide

Quinagolide is a non-ergot dopamine agonist with selective D₂R activity. Therapeutic doses range from 0.075 to 0.600 mg once daily. Its efficacy in normalizing PRL levels and reducing tumor size is similar to bromocriptine and pergolide [56, 97]. Furthermore, approximately 40% of patients who are resistant to bromocriptine respond to quinagolide [98], and adverse effects occur less frequently than with bromocriptine [56, 97], likely because of the more specific D₂R affinity and no intrinsic agonist activity towards 5-HT_{2B} receptors.

This drug is currently unavailable in the US, but is approved for use in Europe.

3-2-2 Management of medical treatment

Usually, the DA is initiated at a low dose (typically 0.25–0.5 mg of cabergoline once or twice weekly), and the dose is escalated at 1–3 monthly intervals according to PRL levels and the reduction in tumor size [2, 11, 54-56]. In patients with macroprolactinomas, more intensive

treatment with higher doses of cabergoline and a more rapid increase in the dose has been suggested to achieve a more rapid reduction in PRL levels and tumor volumes [99]. In fact, a comparative prospective randomized study showed that intensive treatment with cabergoline was not superior to the conventional recommended dosage schedule with respect to the time needed to normalize PRL levels and to achieve 50% tumor shrinkage [100]. According to Endocrine Society guidelines, once the PRL level has been normalized and tumor volume has decreased, DA therapy (sometimes at high doses) should be continued for a minimum of two years [55] before attempting treatment withdrawal. Another strategy is to gradually taper the DA dose to the minimum concentration required to maintain both a normal PRL level and control the tumor volume [55]. In a large retrospective study of cabergoline-treated patients with macroprolactinomas, a strategy in which the cabergoline dose was maintained (fixed-dose group) and a strategy in which the cabergoline dose was tapered (de-escalation group) until the minimal effective dose required to maintain a normal PRL level was established were compared once the PRL levels were normalized [101]. Cabergoline de-escalation was successful in 91.7% of patients. The mean cabergoline dose was reduced from 1.52 ± 1.17 to 0.56 ± 0.44 mg/week at the last visit. De-escalation was also possible in patients requiring high doses of cabergoline (≥ 2 mg/week) to normalize PRL levels. Cabergoline de-escalation had no negative long-term effects on the tumor size [101].

3-2-3 Discontinuation of DA treatment

While the medical treatment of prolactinoma is generally considered a lifelong therapy in most patients [102], many studies have now shown that withdrawal of DA may be successful under well-defined conditions without recurrence of hyperprolactinemia. A meta-analysis reported by Dekkers *et al.* in 2010, which included 19 studies and 743 patients, showed a global remission rate of 21% of all prolactinomas after DA withdrawal [103]. Slightly better

results were observed in patients with a microprolactinoma, in patients who were treated for at least 2 years, and in patients treated with cabergoline rather than bromocriptine. In addition, the absence of cavernous sinus invasion, a longer treatment duration, and lower PRL levels, residual tumor diameter and cabergoline doses at the time of withdrawal were all associated with a higher likelihood of remission [104, 105].

Recent studies using strictly defined criteria to eventually stop DA treatment (strict PRL normalization with the lowest dose of the DA (i.e., 0.25 mg/week of cabergoline), no cavernous sinus invasion, at least 2 or 3 years of treatment, and tumor disappearance or a greater than 50% reduction in size on MRI) have indeed shown a substantial proportion of patients with persistent normoprolactinemia after drug withdrawal (**Table 3**) [105-111]. In these studies, remission rates observed for microprolactinomas range from 23 to 78% (overall: 47%) and remission rates for macroprolactinomas range from 7 to 73% (overall: 41%). In most of these studies, the most effective predictor of long-term remission appeared to be the observation of no visible tumor remnant on MRI at the time of drug withdrawal. Notably, a second attempt at cabergoline withdrawal after two additional years of therapy may be successful, particularly in patients with low PRL levels after treatment and no visible tumor on pituitary MRI [112, 113].

The precise mechanisms underlying the post-treatment remission of prolactinomas are still unclear but may involve prolactin cell necrosis or apoptosis, and tumor hemorrhage or fibrosis that may occur in response to DA therapy [87, 114, 115].

3-2-4 Side effects of DAs

3-2-4-1 Short-term side effects

All currently available DAs – even when administered at low doses – may produce several side effects, including nausea and vomiting, other gastrointestinal symptoms, postural

hypotension, dizziness, headache, nasal stuffiness and Raynaud's phenomenon [55, 56]. These short-term side effects are related to a parallel activation of 5-HT₁R and D₁R receptors, and are much more common with bromocriptine than with cabergoline or quinagolide [116, 117], likely because of a shorter half-life and a less specific D₂R agonist activity. In most patients, these side effects are moderate and subside with time. They can be minimized by introducing the drug at a low dose at bedtime, taking it with food, and then escalating the dose very gradually. However, intolerance persists in some patients, the quality of life deteriorates and therapy withdrawal is required. Fortunately, this scenario is uncommon and occurs in less than 3–4% of cabergoline-treated patients [45, 56, 116, 118]. When intolerance to all available DAs is observed, an alternative treatment such as neurosurgery must be considered. Nonsurgical CSF rhinorrhea has been reported during treatment of a large invasive macroprolactinoma with bromocriptine or cabergoline. This complication is due to rapid tumor shrinkage, partially removing the “cork” that was formed by the adenoma to cover the tumor-induced defect in the skull base [48, 119]. A reduction in the dose but not discontinuation of the DA is advocated in these patients to achieve mild reexpansion of the adenoma and obturation of the breach.

3-2-4-2 Long-term side effects

Regarding long-term side effects, constrictive pericarditis and pleuropulmonary fibrosis have been reported in patients who are chronically treated with high doses of bromocriptine or cabergoline for Parkinson's disease [120-122], but rather exceptionally in patients treated with lower doses for a prolactinoma [123, 124].

A more concerning issue that has been identified over the last few years has been the possible association between the long-term use of bromocriptine or cabergoline and cardiac valve disease. Indeed, while occasionally reported in previous studies, a significant risk of cardiac

valve regurgitation in patients treated with some ergot-derived DAs was reinforced by two reports published in 2007 of data from patients who were chronically treated with high doses of DAs for Parkinson's disease [125, 126]. Valve abnormalities typically included fibrotic thickening and stiffening of the leaflets and chordae and a reduction of the valve tenting area (an index of valve closure ability), and involved mainly the tricuspid, mitral and aortic valves. The risk is mainly related to the variable intrinsic agonist properties of some DAs for the serotonergic 5-HT_{2B} cardiac receptors present in heart valves [127]. Higher risks were observed for patients treated with cabergoline and pergolide than bromocriptine, and the risks appeared to be negligible for patients treated with quinagolide [127].

Since 2007, many cross-sectional and prospective studies were initiated to identify an increased prevalence of cardiac valve complications in patients treated with DAs (mainly cabergoline) for hyperprolactinemic disorders, and most of these data were summarized in a review published by Caputo *et al.* in 2015 [128]. The authors concluded that the probability of clinically significant cabergoline-associated valvular heart disease was very low, as only two of 1 811 patients (prevalence: 0.11%) had a confirmed typical cabergoline-associated valvulopathy, as defined by the triad of moderate or severe valve regurgitation associated with a thickened and restricted valve (notably, a third case has since been reported based on a new-onset cardiac murmur [129]).

A large follow-up multicenter study performed in the UK confirmed the lack of association between the cumulative dose of DA treatment for prolactinoma and the age-corrected prevalence of any valvular abnormality [130], while a new meta-analysis only identified an association between "low-dose" cabergoline treatment for hyperprolactinemia and an increased prevalence of mild to moderate tricuspid regurgitation, without any clinical consequences [131]. Thus, a definite conclusion has not been reached, but the risk of clinically significant changes in valve morphology and dysfunction associated with DAs

administered at doses used to manage hyperprolactinemia appear to be extremely limited. Based on all these data, Steeds *et al.* recommend, in a recent joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology, a standard transthoracic echocardiogram before a patient starts long-term DA therapy for hyperprolactinemia at 5 years after starting cabergoline if the total weekly dose remains ≤ 2 mg and annually if the patient is taking more than 2 mg weekly [132].

Much more worrisome are neuropsychiatric symptoms such as psychosis (or exacerbation of pre-existing psychosis) [133] and impulse control disorders (ICDs), including pathological gambling, hypersexuality, compulsive shopping or eating, and punding (repetitive performance of tasks), which can have devastating effects on the patient and his/her social environment. These side effects have long been underestimated until recent studies showed that ICDs are associated with both chronic bromocriptine and cabergoline treatments [134-137]. The true prevalence of ICDs specifically related to DAs in hyperprolactinemic patients remains unclear. A cross-sectional study found a non-significant increase in the prevalence of ICDs in 77 patients with prolactinomas with current or past use of DAs (24.7%) compared to 70 patients with non-functioning adenomas (17.1%). Another recent cross-sectional study performed in 308 patients observed the presence of any ICD in one of six hyperprolactinemic patients who were treated with DA [138]. Interestingly, men had a higher frequency of ICDs associated with DAs, and hypersexuality was the most commonly reported side effect [134, 138]. A recent literature review concluded that despite the lack of randomized controlled studies, a consistent association exists between a wide variety of ICDs and DA treatment in patients with prolactinoma [139], and for the authors recommended that endocrinologists increase their awareness of this potential adverse event to facilitate early detection and subsequent drug cessation. Risk factors include the dosage of DA, male gender, younger age and being unmarried [140].

3-2-4-3 Quality of life of patients receiving chronic DA treatment

Most studies on treatment of functioning pituitary adenomas, particularly prolactinomas, have focused on clinical and biochemical outcomes rather than on functional and mental wellbeing. Recently, this important outcome has received increasing attention, and researchers recommend that it should now be considered when deciding the appropriate treatment strategy [141, 142]. A specific chapter of this issue will be devoted to the psychological burden of pituitary diseases and their treatment (see Biermacz N, Best Pract Res Clin Endocrinol Metab. 2019 in this issue)

In the study by Kars *et al*, the quality of life (QoL) was significantly impaired in female patients with microprolactinoma after several years of treatment with DAs compared with control subjects. This impairment was due to increased anxiety, depression and fatigue scores, but the authors failed to show an association with current use of DAs [143]. Similar results were reported by other authors who also observed an inverse relationship between the QoL and both the PRL level and free androgen index [144]. Although not found in all studies, negative effects of the chronic use of DAs on some dimensions of QoL, such as mood or sexual activity, have been reported [145, 146]. These adverse effects do not appear to be related to gender, personal history of psychiatric disorders, type of DA, dose and duration of therapy, and, importantly, they are usually reversible after DA discontinuation [145]. Clearly, this important issue deserves greater medical attention and further studies, including comparisons with surgical treatment.

5-3 Surgical treatment

5-3-1 Indications for surgery

Although DAs remain the primary treatment for prolactinomas in current guidelines, indications for neurosurgery have been expanding over the last few years due to several advances in imaging and surgical techniques and better surgical outcomes [147]. For many years, classical indications for neurosurgery have been restricted to a few indications, including (i) acute complications such as pituitary apoplexy or CSF leakage, (ii) resistance or intolerance to DAs, resulting in doses that are insufficient to sufficiently reduce PRL levels or tumor size, and, rarely, (iii) symptomatic pregnancy-related tumor expansion that is refractory to medical therapy [55]. Neurosurgery should be also considered for women with worrisome macroadenomas that are planning a pregnancy.

Other indications are now being reconsidered, such as young patients with a high likelihood of complete tumor resection and who do not wish to undergo prolonged medical treatment, or patients with predominantly cystic tumors [148]. Individuals who require higher than standard doses of cabergoline to control PRL levels (the “partially resistant” patients) might also benefit from surgery, although tumor resection is incomplete. Surgical debulking may indeed improve their hormonal control with lower postoperative doses of the DA [149, 150]. Other potential indications for surgery emerge, as the patients in whom drug withdrawal might become mandatory due to rare cardiac valve complications with chronic dopamine agonist therapy or, more frequently, unacceptable ICDs (see the preceding section).

5-3-2. Neurosurgical techniques

With the exception of the rare giant tumors with large suprasellar extension beyond the midline, the transsphenoidal approach still represents the standard of care. Recent technological advances include endonasal endoscopy, intraoperative MRI and neuronavigation [147, 151-154]. Immediate surgical results obtained using the endonasal endoscopic approach are comparable to the results obtained using the traditional operating

microscope, but overall complication rates appear to be slightly lower, and the operative duration and hospitalization stays may be reduced [147, 151-154]. More important for a successful outcome is the pituitary expertise of the neurosurgeon and his familiarity and expertise with the technique used, regardless of the operative route and imaging modalities [155].

5-3-3 Neurosurgical outcome

Surgical results from a very large number of published series have been summarized in two comprehensive reviews using the same inclusion criteria (cure or remission rates according to the size of the tumor (microadenoma vs. macroadenoma) and defined by postoperative normalization of PRL levels), with documented follow-up. The first review analyzed results from 50 series published between 1980 and 2005 with a total of 4 363 patients (2 137 with a microprolactinoma and 2 226 with a macroprolactinoma) [56] and the second focused on 12 more recent series published between 2005 and 2015, including a total of 1 583 patients (741 with a micro- and 842 with a macroprolactinoma) [2]. In the review by Gillam et al [56], average estimated rates of remission were 75% and 34% for micro- and macroprolactinomas, respectively, while in the review by Chanson and Maiter [2], slightly better rates were obtained (81% for PRL-secreting microadenomas and 41% for macroadenomas). Surgical success rates were highly variable across the series, ranging from 60% to 93% for microadenomas and from 10% to 74% for macroadenomas, depending on surgeon's expertise and different selected indications.

The absence of cavernous sinus invasion and the initial magnitude of PRL hypersecretion were identified as the two best factors predicting surgical success [147]. Indeed, a preoperative PRL concentration less than 200 µg/l is associated with a higher likelihood of long-term remission [156]. The remission rate is higher for patients with prolactinomas

enclosed by the pituitary gland (87%) than for patients with adenomas located laterally (45%) due to the possible invasion of the cavernous sinus [157]. When visual deficits are present preoperatively, they are improved by surgery in the vast majority of patients [158].

The immediate success rates of surgery should be tempered by the rather high risk of recurrence of hyperprolactinemia after initial remission. Based on 30 studies published between 1985 and 2010 including 3 152 patients, a median recurrence rate of 18% was observed after a median follow-up period of 4.9 ± 0.6 years [159]

When performed by a very experienced surgeon, the overall mortality rate for transsphenoidal surgery is very low, less than 0.5%, and major complications (CSF leakage, meningitis, stroke, intracranial hemorrhage, and vision loss) occur in 1 to 3% of patients, with similar rates observed for the microscopic and endoscopic approaches [160, 161]. However, these risks are much greater in less experienced centers, reaching greater than 1.0% and between 6 and 15% for mortality and severe morbidity, respectively [162]. As observed for patients with other types of pituitary adenomas, these risks are lower for patients with microadenomas, while larger invasive tumors and giant adenomas are associated with a higher morbidity rate. Minor local postoperative complications (such as sinusitis, nasal bleeding or nasal septal perforations) are observed in approximately 5% of patients, regardless of the size of the tumor [161].

Complications of surgery may also include anterior hypopituitarism, permanent diabetes insipidus, and hyponatremia due to transient inappropriate secretion of vasopressin. Most patients with intact pituitary hormonal axes preoperatively retain normal function after surgery, except for diabetes insipidus, which can occur in up to 10% of patients, even in hospitals with a high caseload [162]. Researchers have not clearly determined what proportion of patients with preoperative pituitary deficits regain or experience a further deterioration of their pituitary function after neurosurgical treatment of macroprolactinomas.

Finally, the impact of preoperative DA treatment on surgical outcomes is still a matter of debate, with studies showing a negative effect [163 , 164], a neutral effect [165, 166], or a positive effect of preoperative bromocriptine administration [167, 168]. Unfortunately, no randomized study has addressed this issue.

5-3-4 Cost effectiveness analyses

A few studies have compared the relative cost effectiveness of transsphenoidal surgery (either microsurgical or endoscopic) and medical therapy (either bromocriptine or cabergoline) with decision analysis modeling [169, 170]. Both studies concluded that surgery (either microscopic or endoscopic) appeared to be more cost-effective than life-long medical therapy in young patients with a life expectancy greater than 10 years, if neurosurgery is performed only in select patients by experienced pituitary surgeons at high-volume centers with high biochemical cure rates and low complication rates.

5-4 Radiotherapy

Due to high effectiveness of medical treatment to control the symptoms of most patients and of surgery to rapidly relieve most acute complications, radiotherapy (RT) has become exceptionally rarely used in patients with prolactinomas. It should be reserved for the rare large tumors that do not respond to DAs, recur or progress after surgery, and are highly aggressive or malignant [2, 53]. Recent advances in radiation techniques employed in the treatment of pituitary adenomas are reviewed elsewhere in another chapter of the same issue (Minniti G Best Pract Res Clin Endocrinol Metab 2019). These techniques currently facilitate much more accurate treatments by delivering higher radiation doses to the target volume and sparing the normal surrounding tissues. These technical improvements include intensity-modulated radiotherapy, volumetric modulated arc therapy, and stereotactic techniques, either

stereotactic radiosurgery (SRS) using a gamma knife, linear accelerator-based systems or proton units, or fractionated stereotactic radiotherapy.

In most patients, RT (whether stereotactic or not) is administered following non-curative surgery of macroprolactinomas. In these patients, and despite progresses in irradiation techniques, this treatment is still disappointing regarding the normalization of PRL levels, which occurs in approximately 25–40% of patients after a median delay of 44 to 120 months after fractionated external beam RT (EBRT) and in 16 to 46% of patients after a median follow-up of 30 to 96 months after SRS [2, 171-175]. For example, in one large series, the reported remission rate of hyperprolactinemia was 31.4% in 455 patients with prolactinomas who were treated with gamma knife and the median time to PRL normalization ranged from 2 to 8 years [175]. With the addition of medical therapy, however, the normalization of PRL levels was observed in approximately 80–100% of patients [174]. In contrast, local tumor control is usually excellent, with rates of 80–100% reported in recent series, regardless of whether EBRT or SRS was used [2].

The choice of the mode of irradiation will mainly depend on the characteristics of the tumor remnant and technique and the experience available at the site at which the patient is being managed. When available, SRS is preferred if the tumor is well delineated and located at least 5 mm distant to the optic structures. In other patients, particularly in patients with large tumors presenting with suprasellar extension, EBRT is preferred [174-176].

Regardless of the technique used, the most frequent long-term complication of pituitary irradiation is anterior hypopituitarism. Indeed, technological advances in the more focused delivery of radiation are unlikely to significantly reduce this complication, as irradiated prolactinoma residues are usually invasive and located in close proximity to the adjacent normal pituitary and hypothalamic tissues. Not surprisingly, the cumulative actual risk of

hypopituitarism is similar, approximately 50% at 10 years, for both EBRT and SRS [2, 174, 175, 177].

Other reported risks of irradiation occur at a far lower frequency and include optic nerve damage, cerebrovascular accidents, neurological dysfunction, and secondary intracranial benign and malignant tumors [171]. These risks will likely be significantly reduced in the future with the application of modern RT techniques, but further studies are needed. To date, no cases of secondary brain malignancy following SRS for pituitary adenomas have been reported, and only a few cases of benign brain tumors have been identified [175].

5-4 Treatment of malignant prolactinomas

Resistance to dopamine agonists is a key feature of prolactin-secreting carcinomas [2, 50, 53, 178] and effective therapeutic options are limited when craniospinal or systemic metastases are present. Palliative debulking surgery is generally used and eventually repeated with the aim of relieving local compressive effects [50, 53]. Radiotherapy may help slow tumor growth to some extent, but with the exception of a single case study [179], evidence that RT prolongs survival is not available [2].

A major advance in the treatment of these pituitary carcinomas has been reported in recent years with the use of temozolomide (TMZ), an oral alkylating agent that was first approved for the treatment of glioblastomas [50, 180-182]. Recently, Raverot *et al.* reviewed the existing literature and established ESE guidelines for the management of pituitary carcinomas and aggressive pituitary tumors, emphasizing the central role of this drug in the treatment algorithm [53]. To date, long-term results of TMZ treatment have been reported in detail in 15 patients with malignant prolactinomas, with a complete response observed in two patients and a partial (hormonal and tumor) response in 7, along with substantial reductions in the primary tumor volume, size of metastases, and prolactin levels (see [2] for a review). In most of these

studies, a TMZ dose between 150 and 200 mg/m² was administered for 5 days every 4 weeks. Furthermore, as also reported for other aggressive and malignant pituitary tumors, low MGMT expression in the tumor correlates with a good treatment response in some but not all studies [2, 50, 53, 178].

Conclusions

Several advances in the epidemiology, diagnosis and treatment of prolactinomas have been reported in recent years. The prevalence (approximately 50 per 100 000) and the incidence (3-5 new cases/100,000/year) have been specified by recent epidemiological studies. The mechanisms by which hyperprolactinemia induces hypogonadotropic hypogonadism have been elucidated and the substantial gender differences in the natural evolution, consequences and complications of prolactinomas are now well recognized.

Improvements in PRL assay methods and imaging now allow clinicians to diagnose prolactinoma with a higher accuracy and to avoid pitfalls such as macroprolactinemia or the hook effect.

Medical therapy with DAs still represents the primary treatment for most PRL-secreting tumors, but neurosurgery has regained interest as a treatment strategy, due to advances in surgical techniques and a high success rate in patients with microprolactinomas, as well as to some underestimated side effects of long-term DA treatment, such as ICDs, which might affect up to one in six patients. Finally, temozolomide has emerged as a valuable treatment for aggressive and malignant prolactinomas that do not respond to all other conventional treatments. Future treatments should aim at upregulating or bypassing the D₂R and modulating downstream pathways involved in either PRL secretion or cell proliferation.

Practice points

- Prolactinomas remain the most common types of pituitary adenomas.
- Their prevalence is approximately 50 per 100 000 and incidence is 3-5 new cases/100,000 individuals/year
- In males prolactinomas are larger, more invasive and less sensitive to DAs
- High molecular weight forms of PRL (macroprolactin) pose a major problem due to their interference with PRL assay and may lead to misdiagnosis, mismanagement of patients, a waste of healthcare resources and unnecessary concerns for both patients and clinicians.
- Medical therapy with DAs still represents the primary treatment for most prolactinomas.
- If suspected effects of DAs on cardiac valves in patients with prolactinomas seem to be not substantiated by recent data which are reassuring, attention has recently be drawn to underestimated side effects, such as impulse control disorders that might affect a substantial number of patients or impaired quality of life.
- Thus, neurosurgery has regained interest as a treatment strategy, due to progress in surgical techniques and a high success rate in microprolactinoma, as well as to DAs side effects or intolerance.
- Temozolomide has emerged as a valuable treatment for rare cases of aggressive and malignant prolactinomas that do not respond to all other conventional treatments.

Research agenda.

- More research needs to be made to understand pathophysiological mechanisms leading to the development of prolactinomas.
- Define if microprolactinomas and macroprolactinomas which have a very different behavior in terms of proliferation correspond to two distinct diseases.

- Develop future treatments aiming at upregulating or bypassing the D₂R and modulating downstream pathways involved in either PRL secretion or cell proliferation.

Legends of Figures

Figure 1. Correlation between pretreatment serum PRL concentration and maximal tumor size at diagnosis in 504 patients with a prolactinoma (□ : 108 men with a micro (n=29) or a macroadenoma (n=79) and ● : 396 women with a micro (n=293) or a macroadenoma (n=103). Note the Log10 scale for both axes. The inserted graph gives a larger view of the weaker correlation ($R^2=0.331$) between hormone levels and size in microprolactinomas only (□ : 29 men and ● : 293 women) (D. Maiter, personal communication).

Figure 2. Microprolactinoma. The microprolactinoma is not visible (isointense) (white arrow) on MRI T1W coronal section (A) and becomes visible as an hyperintense lesion (white arrow) in the left part of the pituitary on T2W coronal section (B).

Figure 3. Macroprolactinoma. MRI sagittal (A) and coronal (B) T1W sections after injection of gadolinium showing a macroprolactinoma with suprasellar extension (white arrow).

Figure 4. Giant macroprolactinoma in a 35y-old male patient. T1-weighted MRI coronal section after gadolinium injection and sagittal section; CT scan, coronal section showing erosion of the skull base by the macroprolactinoma (reproduced by permission from ref [2]).

Figure 5. Sagittal (upper pannels) and coronal (lower pannels) T1W MRI sections illustrating the shrinkage of a giant macroprolactinoma under treatment with dopamine agonist.

References

- [1] Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, Ezzat S, et al. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. *Endocr Relat Cancer*. 2017;24:C5-C8.
- [2]* Chanson P, Maiter D. Prolactinoma. In: Melmed S, editor. *The Pituitary*. 4th ed. London, UK: Elsevier; 2017. p. 467-514.
- [3] Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. *Endocr Pathol*. 2017;28:228-43.
- [4] Molitch M. Prolactin and pregnancy. In: Tritos NA, Klibanski A, editors. *Prolactin disorders From basic science to clinical management*. Springer Nature Switzerland AG: Humana Press; 2019. p. 161-74.
- [5] Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. *Eur J Endocrinol*. 2015;172:R205-13.
- [6] Daly AF, Tichomirowa MA, Beckers A. The epidemiology and genetics of pituitary adenomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23:543-54.
- [7] Molitch ME. Pituitary tumours: pituitary incidentalomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23:667-75.
- [8] Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. *Cancer*. 2004;101:613-9.
- [9] Buurman H, Saeger W. Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. *Eur J Endocrinol*. 2006;154:753-8.

- [10] Kars M, Souverein PC, Herings RM, Romijn JA, Vandebroucke JP, de Boer A, et al. Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. *J Clin Endocrinol Metab.* 2009;94:2729-34.
- [11] Schlechte JA. Clinical practice. Prolactinoma. *N Engl J Med.* 2003;349:2035-41.
- [12] Soto-Pedre E, Newey PJ, Bevan JS, Greig N, Leese GP. The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland: the Prolactin Epidemiology, Audit and Research Study (PROLEARS). *Clinical Endocrinology.* 2017;86:60-7.
- [13] Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab.* 2006;91:4769-75.
- [14] Raappana A, Koivukangas J, Ebeling T, Pirila T. Incidence of pituitary adenomas in Northern Finland in 1992-2007. *J Clin Endocrinol Metab.* 2010;95:4268-75.
- [15] Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf).* 2010;72:377-82.
- [16] Fontana E, Gaillard R. [Epidemiology of pituitary adenoma: results of the first Swiss study]. *Rev Med Suisse.* 2009;5:2172-4.
- [17] Gruppeta M, Mercieca C, Vassallo J. Prevalence and incidence of pituitary adenomas: a population based study in Malta. *Pituitary.* 2013;16:545-53.
- [18] Tjornstrand A, Gunnarsson K, Evert M, Holmberg E, Ragnarsson O, Rosen T, et al. The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. *Eur J Endocrinol.* 2014;171:519-26.

- [19] Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, et al. The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. *Eur J Endocrinol*. 2015;173:655-64.
- [20] Day PF, Loto MG, Glerean M, Picasso MF, Lovazzano S, Giunta DH. Incidence and prevalence of clinically relevant pituitary adenomas: retrospective cohort study in a Health Management Organization in Buenos Aires, Argentina. *Arch Endocrinol Metab*. 2016;60:554-61.
- [21] Lamba N, Noormohamed N, Simjian T, Alsheikh MY, Jamal A, Doucette J, et al. Fertility after transsphenoidal surgery in patients with prolactinomas: A meta-analysis. *Clin Neurol Neurosurg*. 2019;176:53-60.
- [22] Touraine P, Plu-Bureau G, Beji C, Mauvais-Jarvis P, Kuttenn F. Long-term follow-up of 246 hyperprolactinemic patients. *Acta Obstet Gynecol Scand*. 2001;80:162-8.
- [23] 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;63:450-5.
- [24] Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: Clinical manifestations and diagnostic challenges. *J Clin Neurosci*. 2015;22:1562-7.
- [25] Lee DY, Oh YK, Yoon BK, Choi D. Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems. *Am J Obstet Gynecol*. 2012;206:213 e1-5.
- [26] Souter I, Baltagi LM, Toth TL, Petrozza JC. Prevalence of hyperprolactinemia and abnormal magnetic resonance imaging findings in a population with infertility. *Acta Obstet Gynecol Scand*. 2010;94:1159-62.
- [27]*Sonigo C, Bouilly J, Carre N, Tolle V, Caraty A, Tello J, et al. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. *J Clin Invest*. 2012;122:3791-5.

- [28] Millar RP, Sonigo C, Anderson RA, George J, Maione L, Brailly-Tabard S, et al. Hypothalamic-Pituitary-Ovarian Axis Reactivation by Kisspeptin-10 in Hyperprolactinemic Women With Chronic Amenorrhea. *J Endocr Soc.* 2017;1:1362-71.
- [29] Maor Y, Berezin M. Hyperprolactinemia in postmenopausal women. *Fertil Steril.* 1997;67:693-6.
- [30] Shimon I, Bronstein MD, Shapiro J, Tsvetov G, Benbassat C, Barkan A. Women with prolactinomas presented at the postmenopausal period. *Endocrine.* 2014;47:889-94.
- [31] Santharam S, Tampourlou M, Arlt W, Ayuk J, Gittoes N, Toogood A, et al. Prolactinomas diagnosed in the postmenopausal period: Clinical phenotype and outcomes. *Clin Endocrinol (Oxf).* 2017;87:508-14.
- [32] Pekic S, Medic Stojanoska M, Popovic V. Hyperprolactinemia / Prolactinomas in the post-menopausal period:

challenges in diagnosis and management

. *Neuroendocrinology.* 2018.
- [33] Nishioka H, Haraoka J, Akada K. Growth potential of prolactinomas in men: is it really different from women? *Surg Neurol.* 2003;59:386-90; discussion 90-1.
- [34] Ramot Y, Rapoport MJ, Hagag P, Wyszynski AJ. A study of the clinical differences between women and men with hyperprolactinemia. *Gynecol Endocrinol.* 1996;10:397-400.
- [35] Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. *J Clin Endocrinol Metab.* 1997;82:2102-7.
- [36] Maiter D. Prolactinomas in men. In: Tritos NA, Klibanski A, editors. *Prolactin disorders From basic science to clinical management.* Springer Nature Switzerland AG: Humana Press; 2019. p. 189-204.

- [37] Delgrange E, Duprez T, Maiter D. Influence of parasellar extension of macroprolactinomas defined by magnetic resonance imaging on their responsiveness to dopamine agonist therapy. *Clin Endocrinol (Oxf)*. 2006;64:456-62.
- [38] Trouillas J, Delgrange E, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P, et al. Clinical, pathological and molecular factors of aggressiveness in lactotroph tumours. *Neuroendocrinology*. 2019.
- [39] Wierinckx A, Delgrange E, Bertolino P, Francois P, Chanson P, Jouanneau E, et al. Sex-Related Differences in Lactotroph Tumor Aggressiveness Are Associated With a Specific Gene-Expression Signature and Genome Instability. *Front Endocrinol (Lausanne)*. 2018;9:706.
- [40] Di Somma C, Colao A, Di Sarno A, Klain M, Landi ML, Faccioli G, et al. Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. *J Clin Endocrinol Metab*. 1998;83:807-13.
- [41] Noel GL, Suh HK, Frantz AG. Prolactin release during nursing and breast stimulation in postpartum and nonpostpartum subjects. *J Clin Endocrinol Metab*. 1974;38:413-23.
- [42] Shimon I, Benbassat C. Male prolactinomas presenting with normal testosterone levels. *Pituitary*. 2014;17:246-50.
- [43] Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, et al. Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J Clin Endocrinol Metab*. 2004;89:1704-11.
- [44] Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A. Primary medical therapy of micro- and macroprolactinomas in men. *J Clin Endocrinol Metab*. 2000;85:3053-7.

- [45] Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J Clin Endocrinol Metab.* 1999;84:2518-22.
- [46] De Rosa M, Zarrilli S, Vitale G, Di Somma C, Orio F, Tauchmanova L, et al. Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. *J Clin Endocrinol Metab.* 2004;89:621-5.
- [47] Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary apoplexy. *Endocr Rev.* 2015;36:622-45.
- [48] Maiter D, Delgrange E. Therapy of endocrine disease: the challenges in managing giant prolactinomas. *Eur J Endocrinol.* 2014;170:R213-27.
- [49] Cesak T, Poczos P, Adamkov J, Nahlovsky J, Kasparova P, Gabalec F, et al. Medically induced CSF rhinorrhea following treatment of macroprolactinoma: case series and literature review. *Pituitary.* 2018;21:561-70.
- [50] Heaney AP. Clinical review: Pituitary carcinoma: difficult diagnosis and treatment. *J Clin Endocrinol Metab.* 2011;96:3649-60.
- [51] Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB. Clinical review: Diagnosis and management of pituitary carcinomas. *J Clin Endocrinol Metab.* 2005;90:3089-99.
- [52] Kars M, Roelfsema F, Romijn JA, Pereira AM. Malignant prolactinoma: case report and review of the literature. *Eur J Endocrinol.* 2006;155:523-34.
- [53]* Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, et al. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol.* 2018;178:G1-G24.

- [54] Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)*. 2006;65:265-73.
- [55]* Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:273-88.
- [56]* Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. *Endocr Rev*. 2006;27:485-534.
- [57] Delgrange E, Donckier J, Maiter D. Hyperprolactinaemia as a reversible cause of weight gain in male patients? *Clin Endocrinol (Oxf)*. 1999;50:271.
- [58] Delgrange E, de Hertogh R, Vankrieken L, Maiter D. Potential hook effect in prolactin assay in patients with giant prolactinoma. *Clin Endocrinol (Oxf)*. 1996;45:506-7.
- [59]* Fahie-Wilson M, Smith TP. Determination of prolactin: the macroprolactin problem. *Best Pract Res Clin Endocrinol Metab*. 2013;27:725-42.
- [60] Binart N, Young J, Chanson P. Prolactin assays and regulation of secretion: animal and human data. In: Tritos NA, Klibanski A, editors. *Prolactin disorders From basic science to clinical management*. Springer Nature Switzerland AG: Humana Press; 2019. p. 55-78.
- [61] Fahie-Wilson MN, Soule SG. Macroprolactinaemia: contribution to hyperprolactinaemia in a district general hospital and evaluation of a screening test based on precipitation with polyethylene glycol. *Ann Clin Biochem*. 1997;34 (Pt 3):252-8.
- [62] Leslie H, Courtney CH, Bell PM, Hadden DR, McCance DR, Ellis PK, et al. Laboratory and clinical experience in 55 patients with macroprolactinemia identified by a simple polyethylene glycol precipitation method. *J Clin Endocrinol Metab*. 2001;86:2743-6.
- [63] Smith TP, Kavanagh L, Healy ML, McKenna TJ. Technology insight: measuring prolactin in clinical samples. *Nat Clin Pract Endocrinol Metab*. 2007;3:279-89.

- [64] Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange S, Enjalbert A, et al. Macroprolactinemia revisited: a study on 106 patients. *J Clin Endocrinol Metab.* 2002;87:581-8.
- [65] Hattori N, Inagaki C. Anti-prolactin (PRL) autoantibodies cause asymptomatic hyperprolactinemia: bioassay and clearance studies of PRL-immunoglobulin G complex. *J Clin Endocrinol Metab.* 1997;82:3107-10.
- [66] Hattori N, Nakayama Y, Kitagawa K, Ishihara T, Saiki Y, Inagaki C. Anti-prolactin (PRL) autoantibody-binding sites (epitopes) on PRL molecule in macroprolactinemia. *J Endocrinol.* 2006;190:287-93.
- [67] Smith TP, Suliman AM, Fahie-Wilson MN, McKenna TJ. Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. *J Clin Endocrinol Metab.* 2002;87:5410-5.
- [68] Cattaneo FA, Fahie-Wilson MN. Concomitant occurrence of macroprolactin, exercise-induced amenorrhea, and a pituitary lesion: a diagnostic pitfall. Case report. *J Neurosurg.* 2001;95:334-7.
- [69] Fahie-Wilson M. In hyperprolactinemia, testing for macroprolactin is essential. *Clin Chem.* 2003;49:1434-6.
- [70] Gibney J, Smith TP, McKenna TJ. The Impact on clinical practice of routine screening for macroprolactin. *J Clin Endocrinol Metab.* 2005;90:3927-32.
- [71] Guay AT, Sabharwal P, Varma S, Malarkey WB. Delayed diagnosis of psychological erectile dysfunction because of the presence of macroprolactinemia. *J Clin Endocrinol Metab.* 1996;81:2512-4.
- [72] Heaney AP, Laing I, Walton L, Seif MW, Beardwell CG, Davis JR. Misleading hyperprolactinaemia in pregnancy. *Lancet.* 1999;353:720.

- [73] Olukoga AO, Kane JW. Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. *Clin Endocrinol (Oxf)*. 1999;51:119-26.
- [74] Schlechte JA. The macroprolactin problem. *J Clin Endocrinol Metab*. 2002;87:5408-9.
- [75] Suliman AM, Smith TP, Gibney J, McKenna TJ. Frequent misdiagnosis and mismanagement of hyperprolactinemic patients before the introduction of macroprolactin screening: application of a new strict laboratory definition of macroprolactinemia. *Clin Chem*. 2003;49:1504-9.
- [76] Gibney J, Smith TP, McKenna TJ. Clinical relevance of macroprolactin. *Clin Endocrinol (Oxf)*. 2005;62:633-43.
- [77] Kavanagh L, McKenna TJ, Fahie-Wilson MN, Gibney J, Smith TP. Specificity and clinical utility of methods for the detection of macroprolactin. *Clin Chem*. 2006;52:1366-72.
- [78] Filho RB, Domingues L, Naves L, Ferraz E, Alves A, Casulari LA. Polycystic ovary syndrome and hyperprolactinemia are distinct entities. *Gynecol Endocrinol*. 2007;23:267-72.
- [79] Kyritsi EM, Dimitriadis GK, Angelousi A, Mehta H, Shad A, Mytilinaiou M, et al. The value of prolactin in predicting prolactinomicronma in hyperprolactinaemic polycystic ovarian syndrome. *Eur J Clin Invest*. 2018;48:e12961.
- [80] Miyai K, Ichihara K, Kondo K, Mori S. Asymptomatic hyperprolactinaemia and prolactinoma in the general population--mass screening by paired assays of serum prolactin. *Clin Endocrinol (Oxf)*. 1986;25:549-54.
- [81] Bonneville JF, Bonneville F, Cattin F. Magnetic resonance imaging of pituitary adenomas. *Eur Radiol*. 2005;15:543-8.
- [82] Bayrak A, Saadat P, Mor E, Chong L, Paulson RJ, Sokol RZ. Pituitary imaging is indicated for the evaluation of hyperprolactinemia. *Fertil Steril*. 2005;84:181-5.

- [83] Bonneville F, Cattin F, Bonneville J-F. Imagerie de l'hypophyse et de la tige pituitaire. In: Chanson P, Young J, editors. *Traité d'Endocrinologie*. Paris: Flammarion; 2007. p. 978-94.
- [84] 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;63:323-31.
- [85] Chanson P, Daujat F, Young J, Bellucci A, Kujas M, Doyon D, et al. Normal pituitary hypertrophy as a frequent cause of pituitary incidentaloma: a follow-up study. *J Clin Endocrinol Metab*. 2001;86:3009-15.
- [86] Schievink WI, Nuno M, Rozen TD, Maya MM, Mamelak AN, Carmichael J, et al. Hyperprolactinemia due to spontaneous intracranial hypotension. *J Neurosurg*. 2015;122:1020-5.
- [87] Sarwar KN, Huda MS, Van de Velde V, Hopkins L, Luck S, Preston R, et al. The prevalence and natural history of pituitary hemorrhage in prolactinoma. *J Clin Endocrinol Metab*. 2013;98:2362-7.
- [88] Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. *J Clin Endocrinol Metab*. 1989;68:412-8.
- [89] Colao A, Sarno AD, Cappabianca P, Briganti F, Pivonello R, Somma CD, et al. Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. *Eur J Endocrinol*. 2003;148:325-31.
- [90] Verhelst JA. Toward the establishment of a clinical prediction rule for response of prolactinomas to cabergoline. *J Clin Endocrinol Metab*. 1999;84:4747.
- [91] Thorner MO, McNeilly AS, Hagan C, Besser GM. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine. *Br Med J*. 1974;2:419-22.
- [92] Colao A, di Sarno A, Pivonello R, di Somma C, Lombardi G. Dopamine receptor agonists for treating prolactinomas. *Expert Opin Investig Drugs*. 2002;11:787-800.

- [93] Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev.* 1992;13:220-40.
- [94] Thorner MO, Martin WH, Rogol AD, Morris JL, Perryman RL, Conway BP, et al. Rapid regression of pituitary prolactinomas during bromocriptine treatment. *J Clin Endocrinol Metab.* 1980;51:438-45.
- [95] Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, et al. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J Clin Endocrinol Metab.* 2008;93:4721-7.
- [96]* Delgrange E, Daems T, Verhelst J, Abs R, Maiter D. Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. *Eur J Endocrinol.* 2009;160:747-52.
- [97] Brownell J. Quinagolide in hyperprolactinemia. *Rev Contemp Pharmacother.* 1998;9:1-75.
- [98] Barlier A, Jaquet P. Quinagolide--a valuable treatment option for hyperprolactinaemia. *Eur J Endocrinol.* 2006;154:187-95.
- [99] Ono M, Miki N, Amano K, Kawamata T, Seki T, Makino R, et al. Individualized High-Dose Cabergoline Therapy for Hyperprolactinemic Infertility in Women with Micro- and Macroprolactinomas. *J Clin Endocrinol Metab.* 2010.
- [100] Rastogi A, Bhansali A, Dutta P, Singh P, Vijaivergiya R, Gupta V, et al. A comparison between intensive and conventional cabergoline treatment of newly diagnosed patients with macroprolactinoma. *Clin Endocrinol (Oxf).* 2013;79:409-15.
- [101] Paepegaey AC, Salenave S, Kamenicky P, Maione L, Brailly-Tabard S, Young J, et al. Cabergoline tapering is almost always successful in patients with macroprolactinomas. *J Endocr Soc.* 2017;1:221-30.

- [102] Schlechte JA. Long-term management of prolactinomas. *J Clin Endocrinol Metab.* 2007;92:2861-5.
- [103] Dekkers OM, Lagro J, Burman P, Jorgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2010;95:43-51.
- [104] Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med.* 2003;349:2023-33.
- [105] Kharlip J, Salvatori R, Yenokyan G, Wand GS. Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. *J Clin Endocrinol Metab.* 2009;94:2428-36.
- [106] Huda MS, Athauda NB, Teh MM, Carroll PV, Powrie JK. Factors determining the remission of microprolactinomas after dopamine agonist withdrawal. *Clin Endocrinol (Oxf).* 2010;72:507-11.
- [107] Anagnostis P, Adamidou F, Polyzos SA, Efstathiadou Z, Karathanassi E, Kita M. Long term follow-up of patients with prolactinomas and outcome of dopamine agonist withdrawal: a single center experience. *Pituitary.* 2012;15:25-9.
- [108] Barber TM, Kenkre J, Garnett C, Scott RV, Byrne JV, Wass JA. Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma. *Clin Endocrinol (Oxf).* 2011;75:819-24.
- [109] Watanabe S, Akutsu H, Takano S, Yamamoto T, Ishikawa E, Suzuki H, et al. Long-term results of cabergoline therapy for macroprolactinomas and analyses of factors associated with remission after withdrawal. *Clinical Endocrinology.* 2017;86:207-13.
- [110] Ji MJ, Kim JH, Lee JH, Lee JH, Kim YH, Paek SH, et al. Best candidates for dopamine agonist withdrawal in patients with prolactinomas. *Pituitary.* 2017;20:578-84.

- [111] Teixeira M, Souteiro P, Carvalho D. Prolactinoma management: predictors of remission and recurrence after dopamine agonists withdrawal. *Pituitary*. 2017;20:464-70.
- [112] Kwacharoen R, Auriemma RS, Yenokyan G, Wand GS, Colao A, Salvatori R. Second attempt to withdraw cabergoline in prolactinomas: a pilot study. *Pituitary*. 2014;17:451-6.
- [113] Vilar L, Albuquerque JL, Gadelha PS, Rangel Filho F, Siqueira AM, da Fonseca MM, et al. Second attempt of cabergoline withdrawal in patients with prolactinomas after a failed first attempt: Is it worthwhile? *Front Endocrinol (Lausanne)*. 2015;6:11.
- [114] Esiri MM, Bevan JS, Burke CW, Adams CB. Effect of bromocriptine treatment on the fibrous tissue content of prolactin-secreting and nonfunctioning macroadenomas of the pituitary gland. *J Clin Endocrinol Metab*. 1986;63:383-8.
- [115] Stefanescu L, Kovacs K, Scheithauer BW, Kontogeorgos G, Riehle DL, Sebo TJ, et al. Effect of Dopamine Agonists on Lactotroph Adenomas of the Human Pituitary. *Endocr Pathol*. 2000;11:341-52.
- [116] Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Saf*. 1996;14:228-38.
- [117] Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group [see comments]. *N Engl J Med*. 1994;331:904-9.
- [118] Rains CP, Bryson HM, Fitton A. Cabergoline: a review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinemia and inhibition of lactation. *Drugs*. 1995;49:255-79.
- [119] Suliman SG, Gurlek A, Byrne JV, Sullivan N, Thanabalasingham G, Cudlip S, et al. Nonsurgical cerebrospinal fluid rhinorrhea in invasive macroprolactinoma: incidence, radiological, and clinicopathological features. *J Clin Endocrinol Metab*. 2007;92:3829-35.

- [120] McElvaney NG, Wilcox PG, Churg A, Fleetham JA. Pleuropulmonary disease during bromocriptine treatment of Parkinson's disease. *Arch Intern Med.* 1988;148:2231-6.
- [121] Guptha SH, Promnitz AD. Pleural effusion and thickening due to cabergoline use in a patient with Parkinson's disease. *Eur J Intern Med.* 2005;16:129-31.
- [122] Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart.* 2004;90:e47.
- [123] Serratrice J, Disdier P, Habib G, Viallet F, Weiller PJ. Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev.* 2002;10:334-6.
- [124] Londahl M, Nilsson A, Lindgren H, Katzman P. A case of constrictive pericarditis during cabergoline treatment for hyperprolactinaemia. 10.1530/EJE-07-0584. *Eur J Endocrinol.* 2008;158:583-5.
- [125] Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med.* 2007;356:29-38.
- [126] Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med.* 2007;356:39-46.
- [127] Roth BL. Drugs and valvular heart disease. *N Engl J Med.* 2007;356:6-9.
- [128] Caputo C, Prior D, Inder WJ. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. *Lancet Diabetes Endocrinol.* 2015;3:906-13.
- [129] Caputo C, Prior D, Inder WJ. The Third Case of Cabergoline-Associated Valvulopathy: The Value of Routine Cardiovascular Examination for Screening. *J Endocr Soc.* 2018;2:965-9.
- [130] Drake WM, Stiles CE, Howlett TA, Toogood AA, Bevan JS, Steeds RP. A cross-sectional study of the prevalence of cardiac valvular abnormalities in hyperprolactinemic

patients treated with ergot-derived dopamine agonists. *J Clin Endocrinol Metab.* 2014;99:90-6.

[131]* 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.

[132] Steeds RP, Stiles CE, Sharma V, Chambers JB, Lloyd G, Drake W. Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: 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:G1-G8.

[133] Boyd A. Bromocriptine and psychosis: a literature review. *Psychiatr Q.* 1995;66:87-95.

[134] 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;80:863-8.

[135] Noronha S, Stokes V, Karavitaki N, Grossman A. Treating prolactinomas with dopamine agonists: always worth the gamble? *Endocrine.* 2016;51:205-10.

[136] Barake M, Evins AE, Stoeckel L, Pachas GN, Nachtigall LB, Miller KK, et al. Investigation of impulsivity in patients on dopamine agonist therapy for hyperprolactinemia: a pilot study. *Pituitary.* 2014;17:150-6.

[137] Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med.* 2014;174:1930-3.

[138] Dogansen SC, Cikrikcili U, Oruk G, Kutbay NO, Tanrikulu S, Hekimsoy Z, et al. Dopamine agonist-induced impulse control disorders in patients with prolactinoma: a cross-sectional multicenter study. *J Clin Endocrinol Metab.* 2019.

- [139] Barake M, Klibanski A, Tritos NA. MANAGEMENT OF ENDOCRINE DISEASE: Impulse control disorders in patients with hyperprolactinemia treated with dopamine agonists: how much should we worry? *Eur J Endocrinol.* 2018;179:R287-R96.
- [140] Athanasoulia-Kaspar AP, Popp KH, Stalla GK. Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist. *Endocr Connect.* 2018;7:R88-R94.
- [141] Andela CD, Scharloo M, Pereira AM, Kaptein AA, Biermasz NR. Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies. *Pituitary.* 2015;18:752-76.
- [142] Andela CD, Niemeijer ND, Scharloo M, Tiemensma J, Kanagasabapathy S, Pereira AM, et al. Towards a better quality of life (QoL) for patients with pituitary diseases: results from a focus group study exploring QoL. *Pituitary.* 2015;18:86-100.
- [143] Kars M, van der Klaauw AA, Onstein CS, Pereira AM, Romijn JA. Quality of life is decreased in female patients treated for microprolactinoma. *Eur J Endocrinol.* 2007;157:133-9.
- [144] Cesar de Oliveira Naliato E, Dutra Violante AH, Caldas D, Lamounier Filho A, Rezende Loureiro C, Fontes R, et al. Quality of life in women with microprolactinoma treated with dopamine agonists. *Pituitary.* 2008;11:247-54.
- [145]* Ioachimescu AG, Fleseriu M, Hoffman AR, Vaughan Iii TB, Katznelson L. Psychological effects of dopamine agonist treatment in patients with hyperprolactinemia and prolactin-secreting adenomas. *Eur J Endocrinol.* 2019;180:31-40.
- [146] Raappana A, Pirila T, Ebeling T, Salmela P, Sintonen H, Koivukangas J. Long-term health-related quality of life of surgically treated pituitary adenoma patients: a descriptive study. *ISRN Endocrinol.* 2012;2012:675310.

- [147]* Buchfelder M, Zhao Y, Schlaffer SM. Surgery for Prolactinomas to date. *Neuroendocrinology*. 2019.
- [148] Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, et al. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. *Eur J Endocrinol*. 2008;158:11-8.
- [149] Primeau V, Raftopoulos C, Maiter D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. *Eur J Endocrinol*. 2012;166:779-86.
- [150] Vroonen L, Jaffrain-Rea ML, Petrossians P, Tamagno G, Chanson P, Vilar L, et al. Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients. *Eur J Endocrinol*. 2012;167:651-62.
- [151] Buchfelder M, Schlaffer S. Surgical treatment of pituitary tumours. *Best Pract Res Clin Endocrinol Metab*. 2009;23:677-92.
- [152] Cappabianca P, Cavallo LM, Colao A, de Divitiis E. Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. *J Neurosurg*. 2002;97:293-8.
- [153] Halvorsen H, Ramm-Petersen J, Josefsen R, Ronning P, Reinlie S, Meling T, et al. Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures. *Acta Neurochir (Wien)*. 2014;156:441-9.
- [154] Laws ER, Wong JM, Smith TR, de Los Reyes K, Aglio LS, Thorne AJ, et al. A checklist for endonasal transsphenoidal anterior skull base surgery. *J Neurosurg*. 2015:1-6.
- [155] Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. *Pituitary*. 2017;20:489-98.

- [156] Amar AP, Couldwell WT, Chen JC, Weiss MH. Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. *J Neurosurg.* 2002;97:307-14.
- [157] Micko A, Vila G, Hoftberger R, Knosp E, Wolfsberger S. Endoscopic Transsphenoidal Surgery of Microprolactinomas: A Reappraisal of Cure Rate Based on Radiological Criteria. *Neurosurgery.* 2018.
- [158] Liu W, Zahr RS, McCartney S, Cetas JS, Dogan A, Fleseriu M. Clinical outcomes in male patients with lactotroph adenomas who required pituitary surgery: a retrospective single center study. *Pituitary.* 2018;21:454-62.
- [159] Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. *Pituitary.* 2012;15:71-83.
- [160] Gondim JA, Schops M, de Almeida JP, de Albuquerque LA, Gomes E, Ferraz T, et al. Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. *Pituitary.* 2010;13:68-77.
- [161] Jane JA, Jr., Laws ER, Jr. Surgical Treatment of Pituitary Adenomas. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. *Endotext.* South Dartmouth (MA)2000.
- [162] Barker FG, 2nd, Klibanski A, Swearingen B. Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab.* 2003;88:4709-19.
- [163] Soule SG, Farhi J, Conway GS, Jacobs HS, Powell M. The outcome of hypophysectomy for prolactinomas in the era of dopamine agonist therapy. *Clin Endocrinol (Oxf).* 1996;44:711-6.

- [164] Tamasauskas A, Sinkunas K, Bunevicius A, Radziunas A, Skiriute D, Deltuva VP. Transsphenoidal surgery for microprolactinomas in women: results and prognosis. *Acta Neurochir (Wien)*. 2012;154:1889-93.
- [165] Bevan JS, Adams CB, Burke CW, Morton KE, Molyneux AJ, Moore RA, et al. Factors in the outcome of transsphenoidal surgery for prolactinoma and non-functioning pituitary tumour, including pre-operative bromocriptine therapy. *Clin Endocrinol (Oxf)*. 1987;26:541-56.
- [166] Giovanelli M, Losa M, Mortini P, Acerno S, Giugni E. Surgical results in microadenomas. *Acta Neurochir Suppl*. 1996;65:11-2.
- [167] Sughrue ME, Chang EF, Tyrell JB, Kunwar S, Wilson CB, Blevins LS, Jr. Pre-operative dopamine agonist therapy improves post-operative tumor control following prolactinoma resection. *Pituitary*. 2009;12:158-64.
- [168] Thomson JA, Davies DL, McLaren EH, Teasdale GM. Ten year follow up of microprolactinoma treated by transsphenoidal surgery. *Bmj*. 1994;309:1409-10.
- [169] Jethwa PR, Patel TD, Hajart AF, Eloy JA, Couldwell WT, Liu JK. Cost-Effectiveness Analysis of Microscopic and Endoscopic Transsphenoidal Surgery Versus Medical Therapy in the Management of Microprolactinoma in the United States. *World Neurosurg*. 2016;87:65-76.
- [170] Zygourakis CC, Imber BS, Chen R, Han SJ, Blevins L, Molinaro A, et al. Cost-Effectiveness Analysis of Surgical versus Medical Treatment of Prolactinomas. *J Neurol Surg B Skull Base*. 2017;78:125-31.
- [171] Minniti G, Clarke E, Scaringi C, Enrici RM. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. *Rep Pract Oncol Radiother*. 2016;21:370-8.

- [172] Wilson PJ, Williams JR, Smee RI. Single-centre experience of stereotactic radiosurgery and fractionated stereotactic radiotherapy for prolactinomas with the linear accelerator. *J Med Imaging Radiat Oncol.* 2015;59:371-8.
- [173] Castinetti F, Regis J, Dufour H, Brue T. Role of stereotactic radiosurgery in the management of pituitary adenomas. *Nat Rev Endocrinol.* 2010;6:214-23.
- [174] Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab.* 2011;96:1992-2003.
- [175] Sheplan Olsen LJ, Robles Irizarry L, Chao ST, Weil RJ, Hamrahian AH, Hatipoglu B, et al. Radiotherapy for prolactin-secreting pituitary tumors. *Pituitary.* 2012;15:135-45.
- [176] Brada M, Ajithkumar TV, Minniti G. Radiosurgery for pituitary adenomas. *Clin Endocrinol (Oxf).* 2004;61:531-43.
- [177] Hoybye C, Grenback E, Rahn T, Degerblad M, Thoren M, Hulting AL. Adrenocorticotrophic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. *Neurosurgery.* 2001;49:284-91; discussion 91-2.
- [178] Maiter D. Management of Dopamine Agonist-Resistant Prolactinoma. *Neuroendocrinology.* 2019:1-9.
- [179] Popadic A, Witzmann A, Buchfelder M, Eiter H, Komminoth P. Malignant prolactinoma: case report and review of the literature. *Surg Neurol.* 1999;51:47-54; discussion -5.
- [180] Bengtsson D, Schroder HD, Andersen M, Maiter D, Berinder K, Feldt Rasmussen U, et al. Long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. *J Clin Endocrinol Metab.* 2015;100:1689-98.
- [181] McCormack AI, Wass JA, Grossman AB. Aggressive pituitary tumours: the role of temozolomide and the assessment of MGMT status. *Eur J Clin Invest.* 2011;41:1133-48.

[182] Raverot G, Sturm N, de Fraipont F, Muller M, Salenave S, Caron P, et al.

Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. *J Clin Endocrinol Metab.* 2010;95:4592-9.

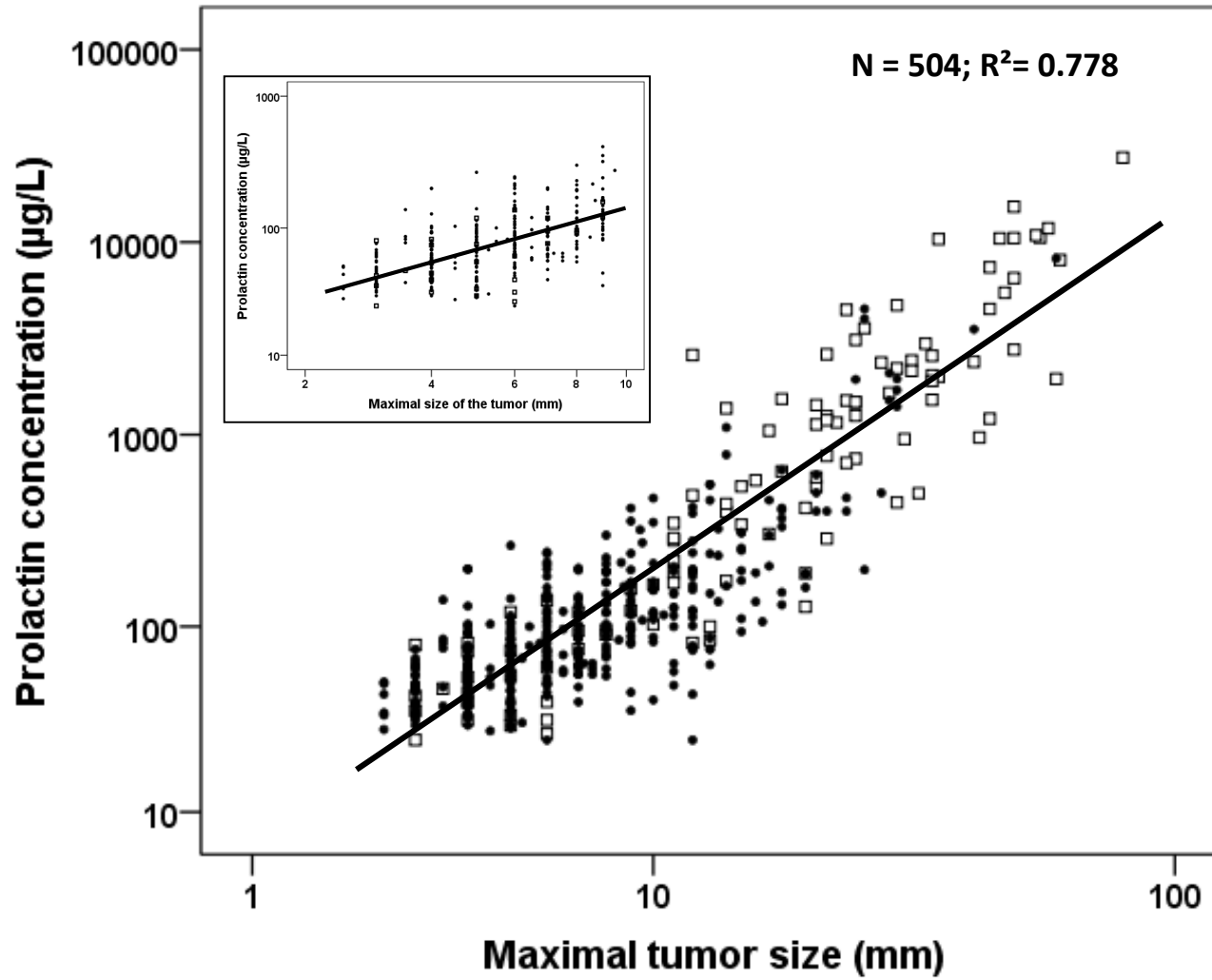


Figure 1

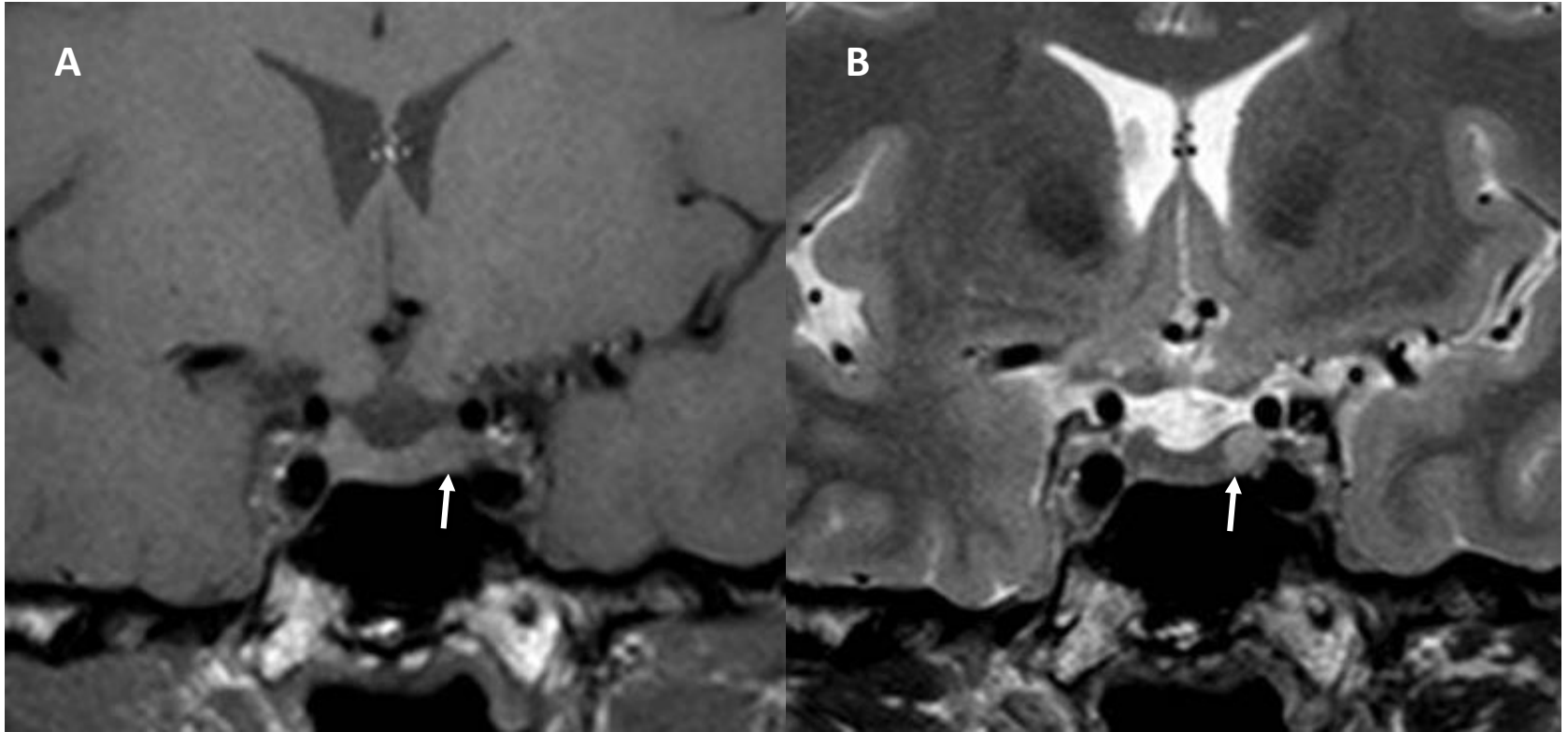


Figure 2

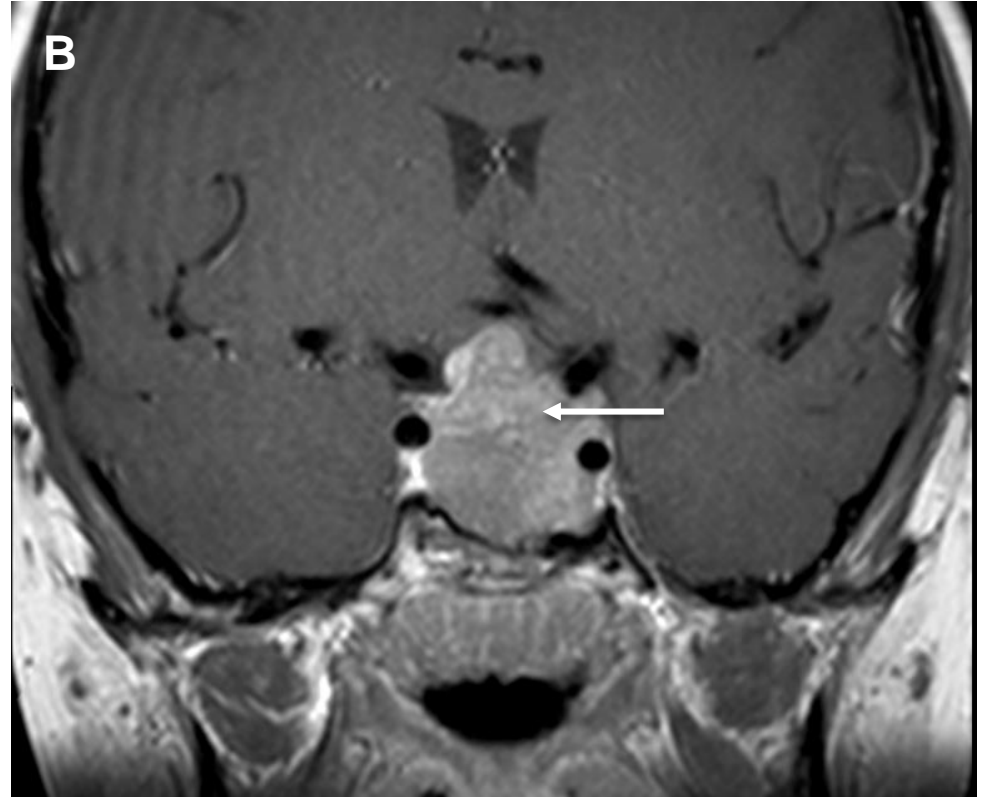
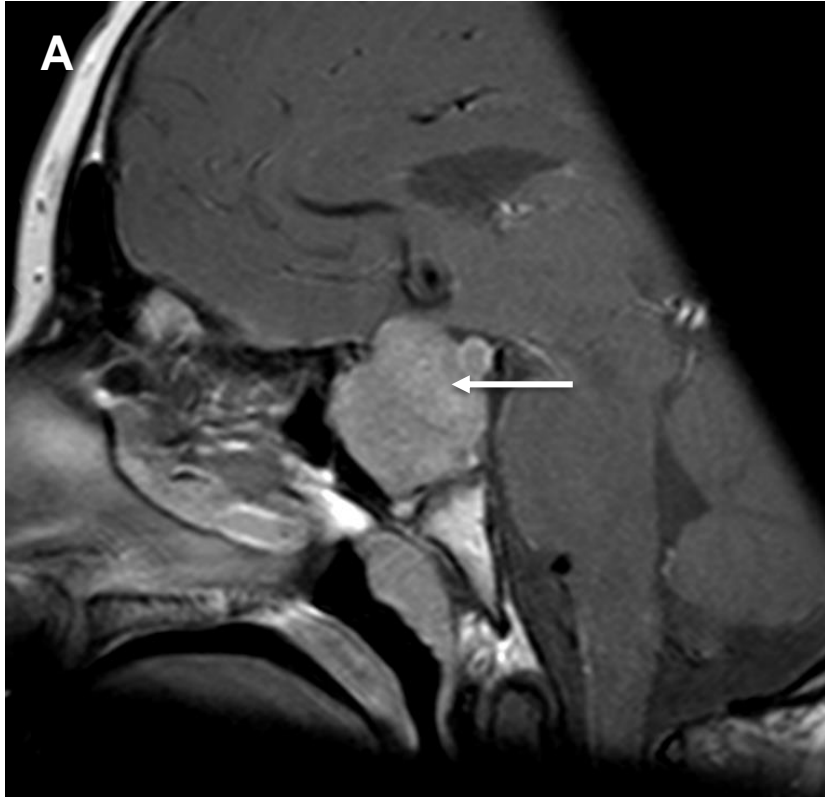
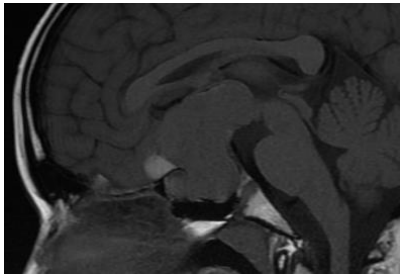
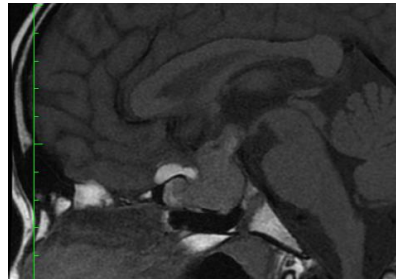


Figure 3



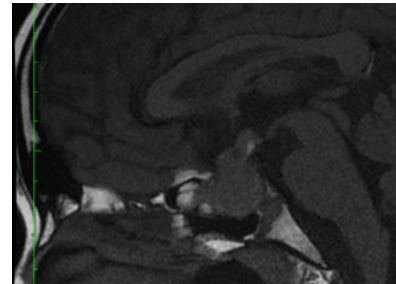
PRL : 4000 ng/ml

Basal



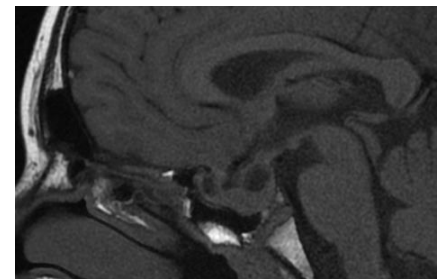
PRL : 890

Month 1



PRL : 580

Month 6



PRL : 350

Month 18

Figure 4

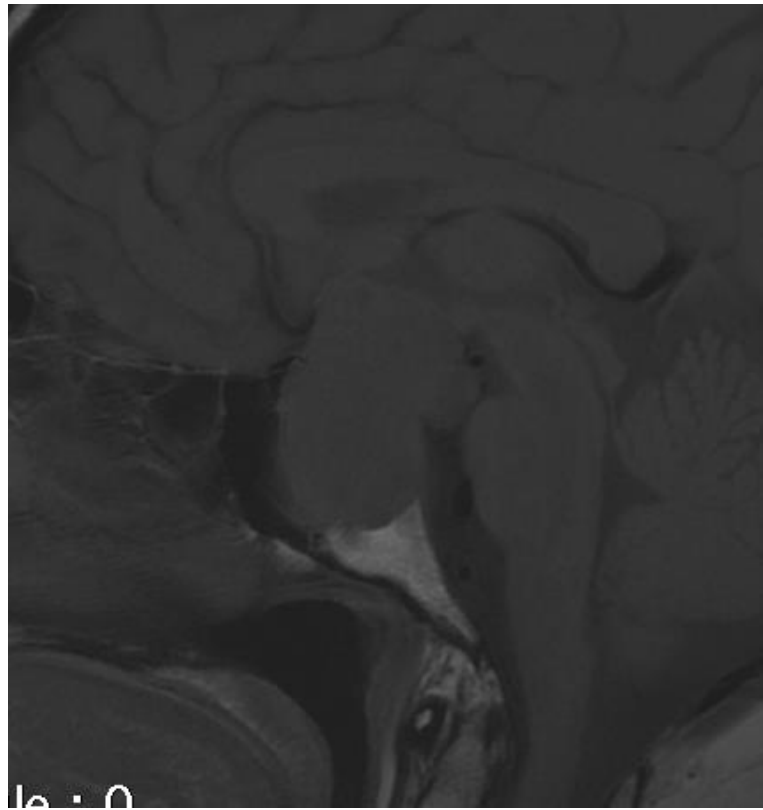
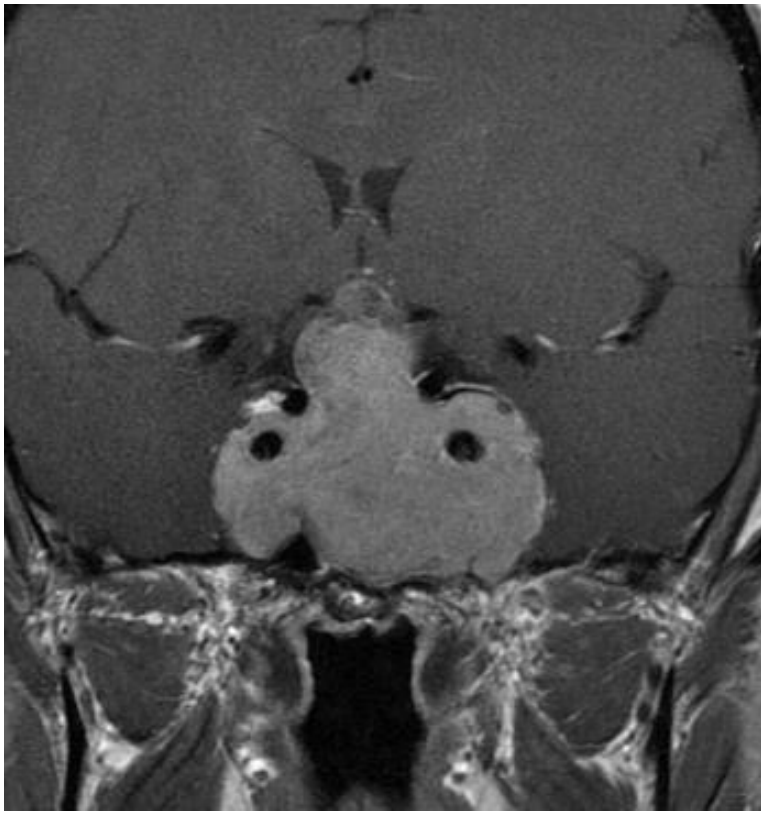


Figure 16.6

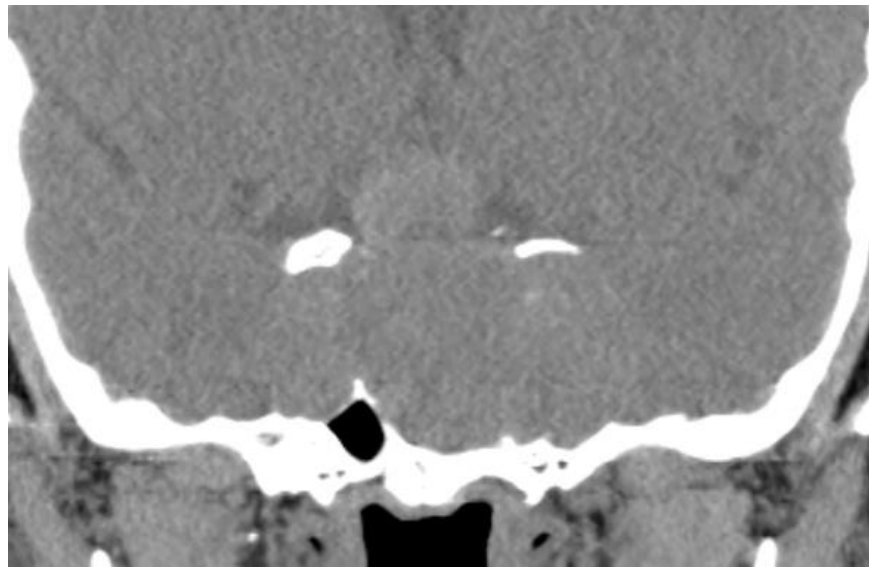


Table 1. Estimated prevalence of pituitary adenomas and of prolactinomas in several countries. Data from recent epidemiological studies (13-17,19,20)

	Belgium (Liege) n = 71 972	UK (Banbury) n = 81 149	Switzerland N = 54 607	Malta N = 417 600	Iceland N = 321 857	Finland N = 722 000	Argentina N = 150 000
Reference	13	15	16	17	19	14	20
Nb of pituitary adenomas (PA)	68	63	44	316	372	355	101
Prevalence of PA	0.94 ‰	0.78 ‰	0.81 ‰	0.76 ‰	1.15 ‰	0.49 ‰	0.67 ‰
% of PRLomas	66%	57%	56%	46%	47%	51%	58%
Estimated prevalence of PRLomas	63 / 10⁵	44 / 10⁵	45 / 10⁵	35 / 10⁵	54 / 10⁵	25 / 10⁵	39 / 10⁵

Table 2. The different etiologies of hyperprolactinemia (adapted from ref [2] with permission)

Pituitary Disease

Prolactinomas

Acromegaly

“Empty Sella syndrome”

Lymphocytic hypophysitis

Cushing’s disease

Hypothalamic Disease

Craniopharyngiomas

Meningiomas

Dysgerminomas

Nonsecreting pituitary adenomas

Other tumors

Sarcoidosis

Histiocytosis X

Neuraxis irradiation

Vascular

Pituitary stalk section

Intracranial hypotension

Neurogenic

Chest wall lesions

Spinal cord lesions

Breast stimulation

Medications

Phenothiazines

Haloperidol

Monoamine-oxidase inhibitors

Tricyclic antidepressants

Reserpine

Methyldopa

Metoclopramide

Amoxepin

Cocaine

Verapamil

Serotonin reuptake inhibitors

Ectopic secretion of PRL

Renal cell carcinoma

Gonadoblastoma

Ovarian teratoma

Perivascular epithelioid cell tumors

Resistance to PRL

Mutation of the PRL receptor gene

Other

Pregnancy

Hypothyroidism

Chronic renal failure

Cirrhosis

Adrenal insufficiency

Pseudocyesis

Idiopathic

Table 3. Remission rates of hyperprolactinemia following withdrawal of DAs in recent studies published between 2009 and 2018

First Author, year of publication	Reference	Size of the tumor	Type of DA	Nb of eligible patients	More than 50% reduction in tumor size as criterion	Follow-up duration (months)	% remission
Kharlip, 2009	(105)	micro	CAB	31/150	Y	5-48	15/31 (48%)
		macro	CAB	11/44	Y	2-23	5/11 (45%)
Huda, 2010	(106)	micro	BRC, CAB	40/72	N	58	9/40 (23%)
Barber, 2011	(108)	micro	BRC, CAB	45	Y	36	16/45 (36%)
		macro	CAB	15	Y	36	1/15 (7%)
Anagnostis, 2012	(107)	micro	BRC, CAB, QUIN	20/51	Y	49	12/20 (60%)
		macro	BRC, CAB, QUIN	6/28	Y	49	3/6 (50%)
Watanabe, 2017	(109)	macro	CAB	11/21	N	54	8/11 (73%)
Ji, 2017	(110)	micro	BRC, CAB	89/433*	N	24	13/30 (43%)
		macro	BRC, CAB	89/433*	N	24	25/59 (42%)
Texeira, 2017	(111)	micro	BRC, CAB	41/96	N	NA	32/41 (78%)
		macro	BRC, CAB	9/46	N	NA	4/9 (44%)
OVERALL		micro		207/560* (37%)			97/207 (47%)
		macro		111/441* (25%)			46/111 (41%)

DA : dopamine agonist ; CAB : cabergoline ; BRC : bromocriptine ; QUIN : quinagolide ; NA : information not available

* : details on tumor size not provided ; the overall number of eligible patients with micro- and macroprolactinomas was calculated based on the assumption of similar proportions of eligible and non-eligible patients in each tumor size subgroup in the study by Ji et al.