Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 101290

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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

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ARTICLE INFO

Article history:
Available online 10 July 2019

Keywords:
prolactin
pituitary adenoma
dopamine agonist

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.

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https://doi.org/10.1016/j.beem.2019.101290
1521-690X/

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].

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.

Diagnosis

Clinical consequences of hyperprolactinemia

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

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	$63/10^5$	$44/10^5$	$45/10^5$	$35/10^5$	$54/10^5$	$25/10^5$	$39/10^5$

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].

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].

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].

Biochemical diagnosis

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 μg/l, virtually all patients with macroprolactinomas have levels greater than 100 μg/l and most patients with microprolactinomas present levels ranging from 50 to 150 μg/L [56,57] (Fig. 1).

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 μg/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 subfractionate 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.

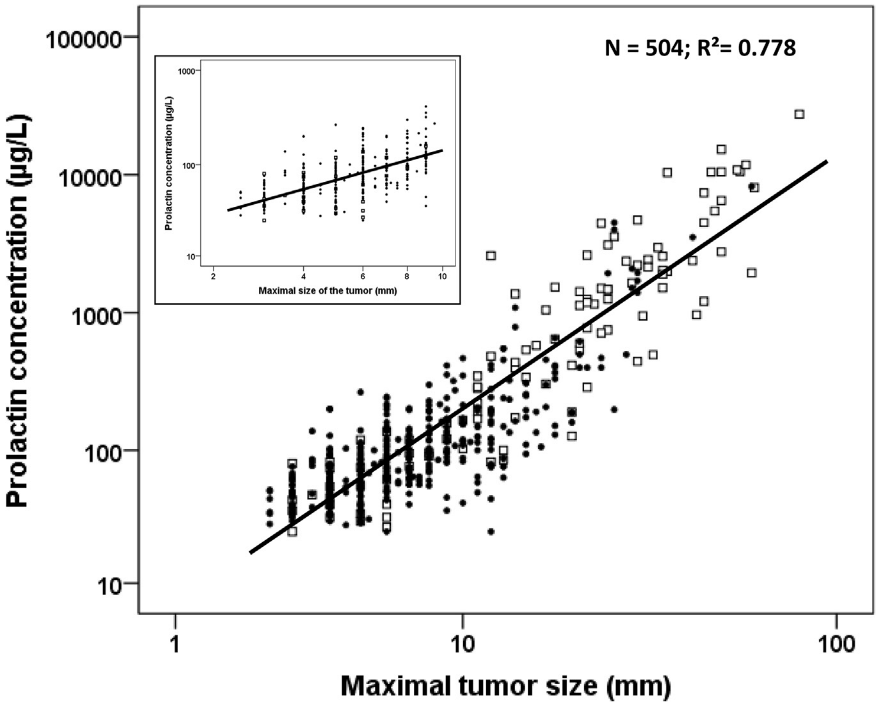

Fig. 1. Correlation between pretreatment serum PRL concentration and maximal tumor size at diagnosis in 504 patients with a prolactinoma (□: 108 men with a micro (n = 29) or a macroadenoma (n = 79) and ●: 396 women with a micro (n = 293) or a macroadenoma (n = 103). Note the Log10 scale for both axes. 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).

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 (11–16% 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%–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).

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 [81–83]. 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

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

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] (Figs. 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.

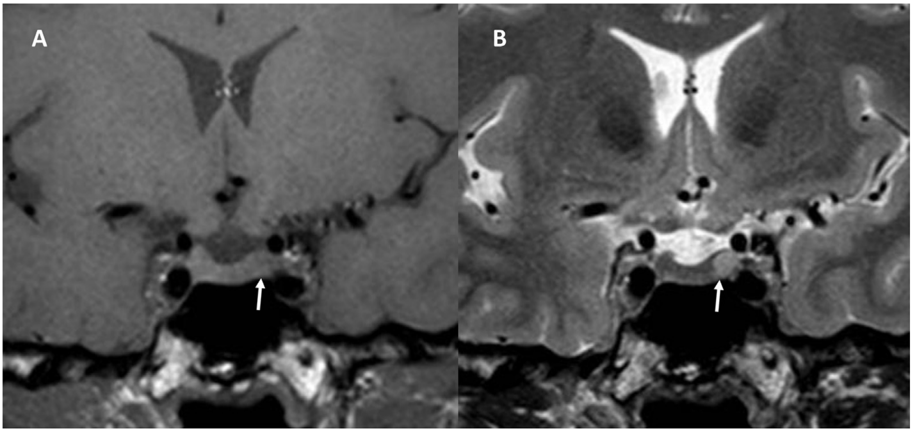

Fig. 2. Microprolactinoma. The microprolactinoma is not visible (isointense) (white arrow) on MRI T1W coronal section (A) and becomes visible as an hyperintense lesion (white arrow) in the left part of the pituitary on T2W coronal section (B).

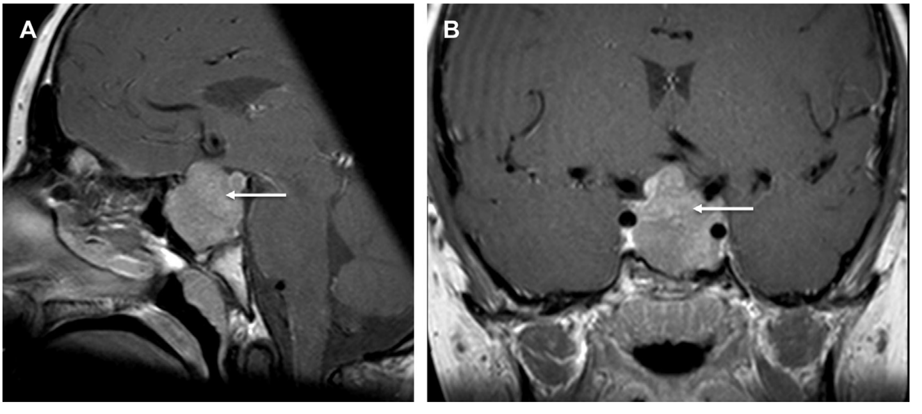

Fig. 3. Macroprolactinoma. MRI sagital (A) and coronal (B) T1W sections after injection of gadolinium showing a macroprolactinoma with suprasellar extension (white arrow).

Pituitary macroadenomas generally exhibit extrasellar extension that usually extends upwards towards the optochiasmatic cistern (Fig. 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 hyper-intensity. In the subacute stage, the sedimentation of blood and hemoglobin derivatives (deoxy-hemoglobin 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 (Fig. 4), particularly in men, which, in combination with subsequent tumor shrinkage following treatment with DAs, may result in spontaneous CSF rhinorrhea [49].

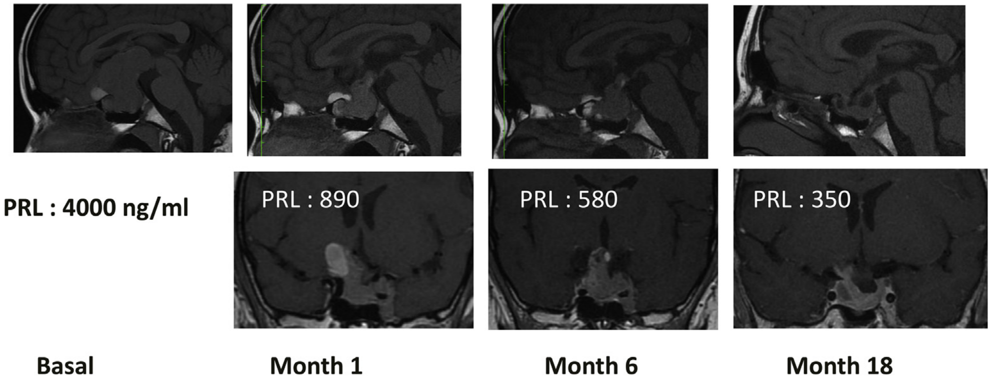

Fig. 4. Sagital (upper pannels) and coronal (lower pannels) T1W MRI sections illustrating the shrinkage of a giant macroprolactinoma under treatment with dopamine.

Treatment

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).

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.

Efficacy of the different DAs

The "old" agent bromocriptine. Bromocriptine is an ergot derivative that functions as both a D_1R and D_2R 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.

The "new" agent cabergoline. Cabergoline is an ergot derivative that is more (but not strictly) selective for D_2R 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 $\geq$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 50–100% [56] (Fig. 5). Approximately 80–90% of patients present a rapid response (within

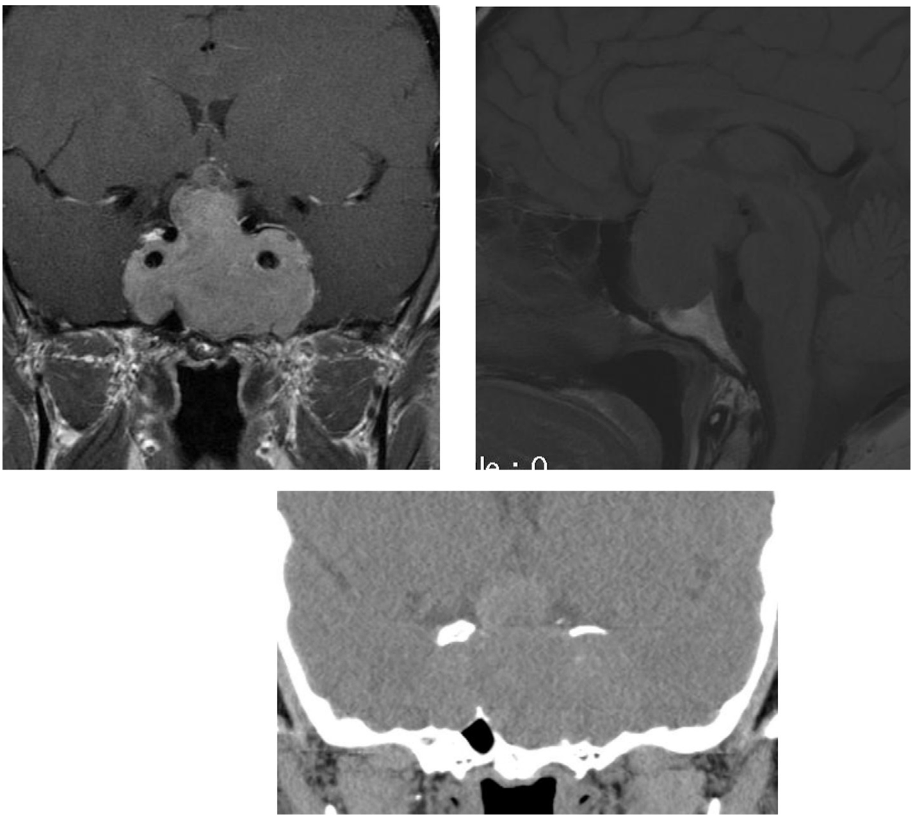

Fig. 5. Giant macroprolactinoma in a 35 y-old male patient. T1-weighted MRI coronal section after gadolinium injection and sagittal section (upper pannels); CT scan, coronal section showing erosion of the skull base by the macroprolactinoma (lower pannel) (reproduced by permission from ref [2]).

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.

Quinagolide. Quinagolide is a non-ergot dopamine agonist with selective D_2R 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.

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 ($\geq$2 mg/week) to normalize PRL levels. Cabergoline de-escalation had no negative long-term effects on the tumor size [101].

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

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[a]	N	24	13/30 (43%)
		macro	BRC, CAB	89/433[a]	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**[a] **(37%)**			**97/207 (47%)**
		macro		**111/441**[a] **(25%)**			**46/111 (41%)**

DA: dopamine agonist; CAB: cabergoline; BRC: bromocriptine; QUIN: quinagolide; NA: information not available.
[a] 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.

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].

Side effects of DAs

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-HT_1R and D_1R 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 D_2R 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.

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 serotoninergic 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 1811 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 $\leq$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 preexisting 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 wand subsequent drug cessation. Risk factors include the dosage of DA, male gender, younger age and being unmarried [140].

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 is 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 [183].

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.

Surgical treatment

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 dues 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).

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].

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 4363 patients (2137 with a microprolactinoma and 2226 with a macroprolactinoma) [56] and the second focused on 12 more recent series published between 2005 and 2015, including a total of 1583 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 3152 patients, a median recurrence rate of 18% was observed after a median follow-up period of 4.9 $\pm$ 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 1–3% 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.

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.

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 44–120 months after fractionated external beam RT (EBRT) and in 16–46% of patients after a median follow-up of 30–96 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].

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/m^2 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 D_2R 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 D_2R and modulating downstream pathways involved in either PRL secretion or cell proliferation.

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