THERAPY OF ENDOCRINE DISEASE

The challenges in managing giant prolactinomas

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Abstract

Giant prolactinomas are rare tumours, representing only 2–3% of all prolactin (PRL)-secreting tumours and raising special diagnostic and therapeutic challenges. Based on several considerations developed in this review, their definition should be restricted to pituitary adenomas with a diameter of 40 mm or more, significant extrasellar extension, very high PRL concentrations (usually above 1000 µg/l) and no concomitant GH or ACTH secretion. Giant prolactinomas are much more frequent in young to middle-aged men than in women, with a male to female ratio of about 9:1. Endocrine symptoms are often present but overlooked for a long period of time, and diagnosis is eventually made when neurologic complications arise from massive extension into the surrounding structures, leading to cranial nerve palsies, hydrocephalus, temporal epilepsy or exophthalmos. PRL concentrations are usually in the range of 1000–100 000 µg/l, but may be underestimated by the so-called 'high-dose hook effect'. As in every prolactinoma, dopamine agonists are the first-line treatment allowing rapid alleviation of neurologic symptoms in the majority of the cases, a significant reduction in tumour size in three-fourths of the patients and PRL normalization in 60–70%. These extensive tumours are usually not completely resectable and neurosurgery has significant morbidity and mortality. It should therefore be restricted to acute complications such as apoplexy or leakage of cerebrospinal fluid (often induced by medical treatment) or to patients with insufficient tumoural response or progression. Irradiation and temozolomide are useful adjuvant therapies in a subset of patients with aggressive/invasive tumours, which are not controlled despite combined medical and surgical treatments. Because of these various challenges, we advocate a multidisciplinary management of these giant tumours in expert centres.

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Introduction

Prolactinomas represent the commonest pituitary tumours with a prevalence of 3.5–5/10 000 inhabitants in recent epidemiological studies (1, 2, 3). Most of these tumours are small, confined to the pituitary fossa, slow growing and found predominantly in women.

Larger prolactin (PRL)-secreting adenomas may, however, occur, especially in men and in younger patients, causing mass effect symptoms and often requiring a more intensive treatment (4, 5, 6). At the end of the spectrum, giant prolactinomas are very rare, representing only 2–3%

Invited Author's profile

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of all PRL-secreting tumours (7, 8) and may raise particular difficulties in their diagnosis and management.

About 150 papers have been published on this condition over the last three decades but most of them were single case reports with peculiar clinical presentation, diagnostic pitfalls or complicated course. Large series are limited and evidence-based recommendations are therefore lacking. Even a commonly accepted definition of what should be called a 'giant prolactinoma' is not available, and although the therapeutic goals for prolactinomas usually include normalization of hormone levels, restoration of eugonadism and reduction of tumour size with a rapid relief of mass effects, this is not always achievable in giant tumours.

In this review on giant prolactinomas, we will propose a simple and widely acceptable definition of the condition, discuss both diagnostic and therapeutic challenges in its management and describe special features related to the very rare occurrence of this type of tumour in women and children.

Definition and epidemiology

Although Jefferson in 1940 had already described a series of pituitary tumours with a very large extrasellar extension (9), a more specific definition of 'giant' pituitary adenomas was introduced in 1979 by Symon *et al.* (10) for adenomas extending by more than 40 mm in any direction from the midpoint of the jugum sphenoidale. Later, the term 'giant prolactinoma' was naturally used to designate very large invasive PRL-secreting tumours but various definition criteria have been proposed.

A tumour size criterion is universally recognized (6, 7, 8, 11, 12, 13, 14, 15) and is important as giant prolactinomas will cause specific complications related to invasion of the dura, the subarachnoid space, the clivus, the nasopharyngeal space, internal auditory canals and surrounding brain structures. Thus, such tumours are more aggressive and usually not completely resectable. The most commonly used criterion is by far a largest tumour diameter of 40 mm or more. This particular extension has been fixed arbitrarily by similarity with the dimensions of the so-called giant cerebral aneurysms (16). However, some authors have defined giant prolactinomas more precisely as tumours extending in excess of 40 mm from the midpoint of the jugum sphenoidale (8) or approaching within 6 mm of the foramen of Monro (17). Furthermore, others have restricted their definition to tumours with a superior margin of more than 20 mm above the jugum sphenoidale, regardless of the volume

of the intra-, para- or infrasellar portions of the adenoma (18, 19). Finally, invasiveness of surrounding structures is also considered by several authors as a necessary part of the definition (13, 20).

The minimal cut-off PRL concentration to be used in the definition is even more subject to debate. As serum hormone levels generally parallel tumour size, giant prolactinomas are typically associated with very high PRL concentrations, above 1000 µg/l (21 000 mU/l) (4, 15, 21). While most non-surgical series published in the literature indeed used this criterion of 1000 µg/l (7, 12, 15, 20, 22, 23, 24), higher cut-off levels of 2000 µg/l (25), 3000 µg/l (8) or even 4000 µg/l (11) have also been used. At the opposite, lower and more conservative PRL thresholds of 200 or 250 µg/l, similar to those used for non-giant macroprolactinomas, have also been proposed previously (6, 26), although assay problems were mentioned in the latter report and accurate PRL concentrations were not available in some cases. In a recent surgical series of ten men with a monohormonal giant prolactinoma (27), there were two cases with a serum PRL level below 1000 µg/l: the only non-invasive tumour (365 µg/l) and another one with a PRL value of 985 µg/l. Thus, although a diagnostic PRL level below 1000 µg/l may still be consistent with a giant prolactinoma, the vast majority of patients will exhibit much higher values. Finally, concomitant secretion of growth hormone (GH) or adrenocorticotrophic hormone (ACTH) should always be ruled out, as mixed tumours clearly represent a different type of pathology.

Based on the above-mentioned considerations, we therefore propose the following definition of a giant prolactinoma: i) a pituitary adenoma with a largest diameter of 40 mm or more in any direction and with massive extrasellar extension; ii) a very high baseline PRL concentration, usually above or equal to 1000 µg/l using a modern and well-standardized assay and iii) exclusion of concomitant GH or ACTH secretion.

As already mentioned, giant prolactinomas are rare tumours. In the series of Shrivastava *et al.* (7), they accounted for ten cases (0.5%) among 2000 pituitary tumours seen in a 20-year period, while in the study of Corsello *et al.* (8), ten giant tumours (4%) were observed among 228 patients with a prolactinoma admitted in their tertiary referral centre during a 6-year period. While prolactinomas occur most frequently in 20- to 50-year-old females (4), giant forms are much more prevalent in young to middle-aged men, with a male to female ratio of about 9:1 and a mean age around 40 years ((6, 7, 8, 15, 28) and data reviewed in Table 1).

Table 1 General characteristics and frequency of classical symptoms in patients with a giant prolactinoma. Data are presented as mean $\pm$ s.d. or as median and (P5–P95) intervals.

Author (year)	Reference	No. of patients	Sex ratio (M:F)	Age (years)	PRL at diagnosis (μ g/l)	Tumour diameter (mm)	Male hypogonadism	1 or 2 years amenorrhoea	Visual symptoms	Headaches
Davis (1990)	(11)	10	9/1	43 $\pm$ 17	7857 (4708–27 871)	58 $\pm$ 15	3/9	1/1	6/10	5/10
Van der Lely (1992)	(69)	4	3/1	58 $\pm$ 8	7950 (4350–65 355)	NA	NA	NA	NA	NA
Grebe (1992)	(13)	4	4/0	40 $\pm$ 7	10 020 (5046–59 840)	83 $\pm$ 17	3/4	NR	3/4	2/4
Petakov (1998)	(128)	4	3/1	39 $\pm$ 13	4150 (2288–11 164)	NA	2/3	1/1	4/4	4/4
Saeki (1998)	(22)	10	7/3	36 $\pm$ 14	6885 (1800–16 100)	51 $\pm$ 12	0/7	3/3	1/10	9/10
Shrivastava (2002)	(7)	10	10/0	46 $\pm$ 8	78 500 (7357–99 999)	68 $\pm$ 9	4/10	NR	10/10	6/10
Corsello (2003)	(8)	10	10/0	45 $\pm$ 13	3900 (1604–15 794)	41 $\pm$ 8 ^a	NA	NR	7/10	5/10
Wu (2006)	(26)	20	16/4	32 $\pm$ 12	5000 (1282–11 600)	58 $\pm$ 15	9/16	4/4	14/20	10/20
Shimon (2007)	(25)	12	12/0	39 $\pm$ 10	11 703 (2372–36 315)	47 $\pm$ 10	5/12	NR	9/12	NA
Cho (2009)	(20)	10	10/0	37 $\pm$ 11	6225 (1932–31 760)	51 $\pm$ 11	NA	NR	4/10	7/10
Acharya (2010)	(23)	10	5/5	36 $\pm$ 10	3313 (1307–36 817)	45 $\pm$ 9	NA	5/5	7/10	9/10
Madsen (2011)	(119)	5	5/0	45 $\pm$ 18	NA	48 $\pm$ 2	NA	NR	NA	NA
Yang (2011)	(78)	12	10/2	46 $\pm$ 11	1134 (260–11 882) ^b	44 $\pm$ 5	6/10	2/2	10/12	4/12
Yarman (2012)	(76)	4	4/0	31 $\pm$ 10	3540 (1826–9545)	45 $\pm$ 7	3/4	NR	4/4	4/4
Delgrange (2013)	(15)	15	0/15 ^c	49 $\pm$ 24	8400 (2607–24 125)	47 $\pm$ 7	NR	8/15	6/15	5/15
Total		140	108/17 ^c	41 $\pm$ 14	6420 (1262–71 800)	52 $\pm$ 14	43/70 (61%)	24/31 (77%)	93/131 (71%)	70/119 (59%)

NA, precise information was not available; NR, information is not relevant.

^aThis study included three patients with tumour measuring <40 mm (31, 32 and 33 m).

^bThis study included two patients with PRL concentration below 1000 μ g/l (201 and 400 μ g/l).

^cAs the study of Delgrange *et al.* was specifically focused on women, these numbers were not included in the estimation of the total sex ratio.

Diagnostic challenges

The diagnosis of a giant prolactinoma, although straightforward in most cases, may be surprisingly delayed in some cases, as the mode of presentation may be atypical for a pituitary tumour. Furthermore, at the time of diagnosis, the radiological signs of an aggressive skull base tumour and potential pitfalls in PRL measurements (*cfr. infra*) may be misleading and orientate the clinician to incorrect diagnoses and unnecessary surgery and/or irradiation (29, 30).

Presenting features

Typical symptoms and signs of hyperprolactinaemia or pituitary mass are observed in a significant subset of patients but they will not always draw medical attention. A review of available literature (Table 1) shows that primary or secondary amenorrhoea is reported in more than three-fourths of women with a giant prolactinoma, male hypogonadism in 61% of men and visual problems and recurrent headaches in 71 and 59% of patients respectively. Data regarding galactorrhoea are often missing and the observed rate of 10% might be underestimated. This feature is rare in men and was reported in a recent study to be present in eight of 24 women with a giant prolactinoma (33%), all younger than 50 years (15). The presence of hypopituitarism is observed in about one third of patients in whom information is available, but careful endocrine evaluation at diagnosis was not routinely performed or reported. Moreover, endocrine symptoms were often present for a long period of time, up to 40 years (15, 31), and giant prolactinomas have been diagnosed on several occasions in adult women with a history of unexplored primary amenorrhoea (15, 32, 33).

Atypical presentations are quite frequent and have been the subject of numerous case reports in the literature, usually reflecting a large tumour extension into the surrounding intracranial structures. Giant prolactinomas may extend in four different directions and frequently invade the sphenoid, ethmoid and/or cavernous sinus or the clivus. Suprasellar, infra- and anterosellar, parasellar and retrosellar extensions are observed each in about 60% of the reported cases. Depending on the direction and size of these extensions, several neurologic symptoms or complications, unusual for pituitary tumours, may be observed (Fig. 1A and B). These include impaired hearing (12, 13, 34, 35), unilateral hemiparesis (35), temporal epilepsy (36) – usually manifesting by complex partial seizures with oral automatism, olfactory hallucinations,

Figure 1

Schematic coronal view (A) and axial view (B) of the pituitary region and surrounding structures showing the possible extensions of a giant prolactinoma and resulting symptoms and complications.

loss of awareness and disorientation – or dementia due to frontal lobe extension (37).

Hydrocephalus is another rare complication arising from a giant tumour interfering with the flow of cerebrospinal fluid (CSF) within the ventricular system, most often at the level of the foramen of Monro (30, 38, 39). This condition can also be associated with papilloedema and uni- or bilateral proptosis and may rapidly resolve with medical treatment (31, 38, 40, 41, 42, 43, 44, 45, 46).

When very large prolactinomas extend laterally in the cavernous sinus, they will frequently cause cranial nerve palsies (30, 47, 48, 49). The VI (or abducens) nerve is usually involved first, typically resulting in a binocular horizontal diplopia that worsens with gaze. Other nerves frequently involved are the III, IV and V cranial nerves, with resulting eyelid ptosis, vertical or diagonal diplopia and/or trigeminal dysaesthesia or neuralgia. Exceptionally, the tumour may extend through the inferior petrosal sinus to emerge within the internal jugular vein, causing inferior cranial nerve palsies (IX, X and XII) (11).

Spontaneous CSF rhinorrhoea may occur but is rather uncommon in untreated giant prolactinomas, being most often induced by surgery or by a too effective medical treatment causing rapid tumour shrinkage (8, 47, 50). In a review of existing literature, Lam *et al.* (51) recently reported 52 patients with non-surgically induced CSF leaks in the setting of a pituitary adenoma. Among them, 42 patients (81%) had a PRL-secreting tumour. The exact

tumour size was reported only in a minority of cases, but PRL concentrations were above 1000 µg/l in 37 cases and above 10 000 µg/l in 13, thus suggesting the presence of a giant prolactinoma in a large subset of these patients. Interestingly, a majority of the prolactinoma-associated CSF leaks (86%) occurred following initiation of dopamine agonist (DA) therapy with bromocriptine (BRC) or cabergoline (CAB), and only six patients had spontaneous CSF leakage as the presenting symptom of their prolactinoma. Meningitis may occur in about 15–20% of these patients before the leak is repaired (52).

In very rare cases, a large anterior tumoural extension into the nasopharynx will produce nasal stuffiness, snoring, epistaxis and respiratory problems (20, 34, 53, 54), and the diagnosis of prolactinoma may sometimes be made through biopsy of a nasal polypoid mass (54, 55). Orbital invasion is another rare extrasellar extension of pituitary tumours and will cause exophthalmos and optic nerve compression at the orbital apex (31, 46, 56). Finally, in the opposite direction, posterior and inferior extension may cause ataxia by cerebellar compression (57, 58) or cranio-cervical junction instability (12, 13, 59).

Hormonal evaluation

Giant prolactinomas are usually associated with very high serum PRL concentrations, in the range of 1000–100 000 µg/l when measured with a two-site monoclonal

IRMA or chemiluminometric assay (ILMA) ((4, 5, 6, 7, 11, 12, 13, 14, 15), Table 1). When such very high PRL concentrations are observed, diagnosis is obvious (60, 61). There is a significant correlation between baseline PRL concentration and tumour size (Fig. 2), but this relationship is weaker than that observed in non-giant macroprolactinomas (4, 5). Lower PRL concentrations (between 250 and 1000 µg/l) may be rarely observed in giant prolactinomas. However, such a discordance between tumour size and hormonal levels should always prompt a new measurement of PRL concentrations after serial dilution and, if confirmed, will usually result from a large necrotic or hemorrhagic component or from a heterogeneous histopathological content.

Despite the accuracy and specificity of recent PRL IRMAs and ILMAs, very high antigen levels may impair the normal sandwich 'antibody 1–antigen–antibody 2' coupling (through saturation of all PRL binding sites), resulting in a marked underestimation of PRL concentrations, thus misleading the clinician to a wrong diagnosis of another pituitary or perisellar tumour with stalk compression. This phenomenon, known as the 'hook effect' (62, 63), is more likely to occur in giant prolactinomas with very high PRL levels (above 10 000 µg/l) and has indeed been reported on several occasions (19, 29, 42, 48, 64, 65, 66). Thus, in every new patient with a large skull base tumour, determination of the PRL level should be done with serial dilution (ten- and 100-fold) to avoid this pitfall (30, 67).

Figure 2

Correlation between baseline prolactin concentration (expressed on a log scale) and maximal tumour diameter recorded in 93 patients (data retrieved from references (7, 8, 15, 20, 22, 23, 25, 26, 76)). Closed triangle, men; closed circle, women.

Imaging studies

Cerebral CT or MRI scan often reveals a very large tumour of the skull base with suprasellar extension and involvement of adjacent structures, evoking in first instance the diagnosis of another invasive brain tumour such as a glioma, a meningioma, a metastatic carcinoma or a chordoma. A nasopharyngeal carcinoma may also be suspected when the tumour extensively invades the sphenoid sinus and the nasopharynx. If symptoms are atypical and endocrinological disturbances are not obvious, this may lead to inappropriate biopsy of the tumour and/or surgical treatment (34, 68, 69). A full pituitary hormonal evaluation is therefore mandatory in the assessment of every large skull base tumour.

Therapeutic challenges

Giant prolactinomas raise specific therapeutic issues and the first goal of treatment is usually to obtain a rapid relief of neurologic symptoms. This has led in the past to consideration of surgery as the primary treatment of giant prolactinomas. The mortality rate was, however, not negligible, being still between 5 and 10% in the early eighties (70). The surgical morbidity is also high (71), and some authors have therefore proposed a limited surgical biopsy for histological studies followed by either radiation therapy (10) or medical treatment with BRC (72). However, because of the lack of significant reduction of serum PRL levels and tumour size after irradiation, many of these patients also received BRC (12, 13). As medical treatment resulted in most cases in a marked and rapid reduction of tumour size, it has progressively become the first and main therapeutic option in patients with giant prolactinomas. This is well emphasized by the study from Yu *et al.* (73), in which 18 patients initially underwent surgery which resulted in one death, many complications (including seven visual deterioration, 11 diabetes insipidus and two hemiplegia) and post-operative PRL levels higher than 200 µg/l in all cases. In contrast, the group of patients treated initially with BRC ($n=12$) did better both in terms of reduction of tumour volume with visual improvement and in terms of lowering of serum PRL levels.

Medical treatment with DAs

Acute and severe neurologic complications of giant prolactinomas are often quickly relieved with DAs. This is well illustrated when considering two dramatic complications, hydrocephalus and exophthalmos. A significant

improvement of symptomatic hydrocephalus has been reported within a few days of treatment with BRC or CAB, avoiding in most cases the need for CSF diversion (40, 43, 56, 72). There are also several reports of rapid resolution under medical treatment alone of proptosis induced by giant prolactinomas (31, 46, 56). This highlights the primary role of medical therapy in the management of giant prolactinomas, even in the presence of severe and/or unusual neurologic symptoms.

To get a better overall picture of the effects of medical treatment in this setting, we have reviewed the individual responses of 97 patients with giant prolactinomas to a primary DA therapy (Table 2). Patients were selected using the following criteria: i) evidence of a giant prolactinoma using the above-mentioned definition criteria (serum PRL ≥ 1000 $\mu\text{g/l}$; largest diameter ≥ 4 cm and absence of acromegaly or Cushing's syndrome); ii) absence of previous surgery or radiotherapy; and iii) inclusion in a series reporting at least three patients with a giant prolactinoma treated with DAs as first-line treatment. Thus, in some publications, only a subset of patients was included. Isolated case reports describing exceptionally dramatic response (or non-response) as well as very small series reporting special complications were not considered. The hormonal and tumoural responses to treatment observed in the 97 selected patients and the type of DA used are summarized in Table 2.

Five series collecting a total of 40 patients (7, 8, 23, 25, 26) gave precise data regarding visual field evaluation before and following DA treatment. Visual field defect was

present in 29/40 cases (73%) and improved in all but one patient (96%). In 14 cases (48%), the normalization of the visual field was complete. Improvement occurred promptly, sometimes 1 or 2 days after the initial administration of the DA (22). The mean time before improvement recorded in one study was 5 days (range 2–15 days) (7). Of note, an improvement of visual field defect can be observed even in the absence of significant tumour response (22, 25).

The amount of tumour size reduction was often difficult to compare between published series because of the different parameters used (larger diameter, height, tumour volume derived by various calculations). There were also differences in the time period until final assessment, with long-term treatment (>12 months) resulting in greater reduction in tumour size (20). In line with the Response Evaluation Criteria in Solid Tumours (RECIST) recommendations, one-dimensional measurements were used when available and significant response was defined as a reduction $\geq 30\%$ in tumour diameter. When the three diameters before and after treatment were mentioned (20, 26, 74), they were summed to calculate the percentage decrease; otherwise, reduction in maximal tumour diameter was recorded (15, 23, 25, 75, 76). The individual tumour responses recorded in 58 patients are presented in Fig. 3, which shows a significant size reduction in 83% of the patients.

When only volumetric data were available (7, 8, 44), a $>65\%$ reduction in tumour volume was considered significant. In most cases, the assessment was performed

Table 2 Efficacy of primary treatment with dopamine agonists in giant prolactinomas.

Author (year)	Reference	Cases analysed	Gender	Drug	VFD improvement	Tumour response	Normal prolactin	Follow-up (months)
Davis (1990)	(11)	2, 3, 7, 9	3M/1F	BRC	NA	NA	2/4	54 (36–84)
Saeki (1998) ^a	(22)	1, 3–10	7M/2F	BRC	NA	5/8	4/9	108 (48–204)
Freda (2000)	(44)	1, 8, 10, 13, 20	4M/1F	PER	NA	2/5	3/5	15 (12–47)
Orrego (2000)	(74)	11, 14, 22	3M	PER	NA	3/3	3/3	6 (3–26)
Shrivastava (2002)	(7)	1–7, 9, 10	9M	BRC	8/8	6/9	2/9	NA (60–144)
Corsello (2003)	(8)	1, 5, 8–10	5M	CAB	3/4	2/5	4/5	19 (13–68)
Wu (2006)	(26)	3, 4, 14, 15, 18, 19	5M/1F	BRC	3/3	5/6	1/6	32 (7–71)
Shimon (2007)	(25)	2, 4–12	10M	CAB	7/7	6/9	9/10	NA
Delgrange (2009) ^b	(75)	$n=8$	8M	CAB	NA	8/8	6/8	NA (≥ 12)
Cho (2009)	(20)	1–10	10M	CAB	NA	9/10	7/10	19 (9–43)
Acharya (2010)	(23)	1–10	5M/5F	BRC/CAB	7/7	5/7	7/10	NA
Yarman (2012)	(76)	2, 3, 12, 19	4M	BRC/CAB	NA	3/4	4/4	66 (43–111)
Delgrange (2014)	(15)	1–13, 15	14F	BRC/CAB	NA	11/14	6/14	41 (3–198)
Total		$n=97$	73M/24F		28/29 (96%)	65/88 (74%)	58/97 (60%)	37 (3–204)

BRC, bromocriptine; PER, pergolide; CAB, cabergoline; VFD, visual field defect; tumour response, $>30\%$ decrease in tumour diameter, or $>65\%$ reduction in tumour volume; normal prolactin, ≤ 25 $\mu\text{g/l}$ (or ≤ 525 mU/l). NA, precise information not available. ^aTumour size reduction was not precisely given and considered as significant when tumours had disappeared or became 'remarkably shrunken'. ^bFrom our series of 122 macroprolactinomas published in 2009, only eight of the nine cases of giant prolactinoma are recorded, one female patient being also included in our more recent study (Delgrange 2014).

Table 3 Characteristics of patients with a giant prolactinoma according to their tumoural and hormonal response (responsive vs resistant) to dopamine agonist treatment. Data are shown as median (range) and prevalence is shown as number (%). *P* values were calculated using the non-parametric Mann–Whitney *U* and χ^2 tests. Tumoural response was considered when a >30% decrease in tumour diameter or a >65% reduction in tumour volume was observed. Hormonal response was considered when serum prolactin levels were ≤ 25 $\mu\text{g/l}$ (or ≤ 525 mU/l). Hormonal resistance was defined by the absence of normalization of serum prolactin levels despite a cabergoline dose ≥ 2.0 mg/week or a bromocriptine dose ≥ 15 mg/day.

	Tumour size			Prolactin level		
	Responsive	Resistant	<i>P</i> value	Responsive	Resistant	<i>P</i> value
No. of patients	65	23		58	18	
Age (years)	38 (16–70)	46 (15–87)	0.28	39 (16–70)	40 (17–72)	0.68
Age <30 years (<i>n</i>)	17 (26%)	5 (22%)	0.67	12 (21%)	5 (28%)	0.53
Female sex (<i>n</i>)	15 (23%)	5 (22%)	0.89	12 (21%)	7 (39%)	0.12
Basal prolactin ($\mu\text{g/l}$)	8000 (1076–100 000)	6021 (1256–100 000)	0.61	5063 (1076–43 163)	8162 (2540–42 009)	0.18
Tumour diameter (mm)	44 (40–80)	43 (40–72)	0.52	44 (40–72)	47 (40–80)	0.15
No. with cabergoline (<i>n</i>)	41 (63%)	11 (48%)	0.20	40 (69%)	13 (72%)	0.79
Normal PRL (<i>n</i>)	43 (66%)	11 (48%)	0.12			

was not influenced by age, gender, baseline PRL, tumour size or drug choice (Table 3). By comparison, hormone resistance rates previously reported in invasive macroprolactinomas were 33% with BRC (78) and 24% with CAB (75).

Tumour shrinkage and hormonal response being independent of tumour size or pretreatment PRL levels, the treatment protocol used for macroprolactinomas (79) can be applied to giant prolactinomas, and it is not advised to start with a higher dose and/or to increase it more rapidly as some patients may normalize PRL levels rapidly and show massive tumour size reduction, which may favour CSF leakage or apoplexia (47). Regarding the type of DA, even though there is no proof of a higher efficacy of CAB over BRC in the management of giant prolactinomas, CAB is certainly better tolerated and generally recommended as first-line treatment. There are almost no data regarding the use of quinagolide in this setting. In one case reported by Cackett *et al.* (56), quinagolide was associated with CAB because of insufficient response to the first drug.

Even in case of very favourable response, medical therapy needs to be maintained almost invariably lifelong in the setting of a giant prolactinoma. To our knowledge, only one case of successful withdrawal of DA treatment has been reported, but it concerned a mixed PRL–ACTH giant adenoma (22, case 2), which is not included in our analysis because of the associated Cushing's syndrome. Careful surveillance is warranted during medical treatment because of the risk of occurrence of CSF leakage and more frequent dissociation between hormonal and tumoural responses. The delay from initiation of medical

therapy to onset of CSF rhinorrhoea may range from a few days to a few months.

Surgery of giant prolactinomas

Surgical cure rates have been reported in a limited number of patients with giant prolactinomas operated via the transsphenoidal, transcranial or combined routes. Except for one study reporting a significant remission rate (18), all other surgical series on giant tumours reported the post-operative persistence of hyperprolactinaemia and significant tumour residue (11, 12, 80, 81). Furthermore, as already mentioned, the morbidity and mortality rates associated with surgical intervention are considerably higher for giant pituitary adenomas than for smaller, non-invasive adenomas (4), and indications must therefore be parsimonious.

Among the 97 selected patients with giant prolactinoma who received DAs as first-line treatment, only 14 had been submitted to surgery. The indications for surgery were a CSF leak in five cases (three under BRC and two under CAB), intolerance to BRC in one, insufficient tumour response in six and tumour progression despite medical treatment in three. One patient was operated twice, first for CSF rhinorrhoea and tumour resection and next for disease progression despite CAB treatment. Another complication that can occur following favourable response to medical therapy is chiasmal and even frontal lobe herniation (82), leading to secondary visual deterioration. This complication can resolve after dose reduction (83) but will also sometimes need pituitary surgery and chiasmopexy. Also, pituitary apoplexy was not recorded as

surgical indication in this selected series but may occur either in the natural course of the disease or as a complication of medical treatment (47, 58, 84, 85).

Debulking surgery was carried out because of insufficient tumour response in six patients, after 3–48 months of treatment. In every case, medical treatment needed to be continued afterwards and PRL levels were not normalized. The role of surgery in resistant giant prolactinomas is difficult to establish and the indication depends on the portion of the residual tumour potentially resectable and on the experience of the neurosurgeon. During DA treatment, the suprasellar and intrasellar parts of the tumour usually shrink first (26), and the residual tumour, which is located laterally in the cavernous sinus or posteriorly in the clivus, is often hardly resectable (11). In line with recently published data in patients with DA-resistant prolactinomas (86, 87), partial tumour resection might allow for better hormonal control with a lower dose of DA. However, such a benefit has not been specifically demonstrated in the case of giant tumours. A series from Hamilton *et al.* (88) reported surgical results in patients hyporesponsive to DAs, including 21 with giant prolactinomas, but this subgroup of patients was not considered separately so that the success rate is unknown. In another study on the surgical outcome of prolactinomas, only one out of ten patients with giant prolactinomas was considered in post-operative remission (27). Tumour progression or regrowth despite treatment with DAs is another clear indication for surgery, which was found in three out of our 97 selected cases. In the first case (22, case 9), PRL decreased from 9200 to 105 µg/l and maximal tumour diameter from 41 to 24 mm after 1 month of BRC treatment; 8 months later, visual field defect revealed regrowth of the tumour despite lowered PRL level (48 µg/l). The tumour was subtotally removed and immunostaining was negative for PRL and the other hormones, suggesting that the regrowing tumour was not PRL producing. In another case (7, case 4), transsphenoidal surgery was carried out 6 weeks after initiation of BRC treatment because PRL levels continued to rise. The third case (15, case 3) has already been mentioned as operated twice but immunocytochemistry revealed a mixed PRL–GH adenoma despite normal IGF1 levels. This illustrates that surgery should be followed by careful immunocytochemical studies to define the precise type of pituitary adenoma and evaluate proliferation markers such as the Ki-67 index, mitotic count and p53 immunoreactivity in order to establish the grade of the tumour (89). This is of particular interest in case of dissociation between hormonal and tumoural responses.

Other treatments

Radiotherapy may be used post-operatively in aggressive and proliferative giant tumours, which are not controlled by DA treatment (17), although there is no prospective study demonstrating its usefulness in this setting. As already mentioned, most of these irradiated patients will not normalize their PRL levels and medical therapy needs to be continued (12, 13).

Temozolomide (TMZ) is an oral alkylating agent inhibiting tumour cell growth, which has shown some efficacy in pituitary carcinomas and aggressive pituitary tumours (90, 91, 92, 93). TMZ may be a salvage therapeutic option for patients with clinically aggressive giant prolactinomas that remain uncontrolled despite multiple conventional treatment modalities. In a recent review of available literature, Whitelaw and colleagues reported a good response to TMZ in 15 of 20 aggressive or metastatic prolactinomas and a strong association between negative immunostaining for methylguanine methyltransferase (MGMT) and response to therapy (94). However, such relationship between clinical response and MGMT staining has not been confirmed in all studies (92, 93), and because of the very low number of patients with MGMT-positive prolactinoma reported to date ($n=2$), candidates for TMZ treatment trial can hardly be selected on this basis.

Special features

Giant prolactinoma in women

Giant prolactinomas are much less common in women than in men. In a recent review (15), we collected data from 34 patients and are now aware of four further cases (36, 95, 96, 97). The female:male ratio is around 1:9 (15 Table 1). The low occurrence of large prolactinomas in women has been mistakenly attributed to an earlier detection because of hormonal symptoms such as amenorrhoea and galactorrhoea. However, the median age at diagnosis of giant prolactinoma is almost 10 years lower in men than in women (15). Furthermore, in children before the age of 14 years, giant prolactinomas are detected on the basis of tumoural rather than hormonal symptoms and there is still a large male predominance at this age, all cases reported so far being in boys (except for one report of a giant cystic prolactinoma in a 9-year-old girl, which was in fact a mixed PRL–GH adenoma at pathological examination (98)). This confirms our previous data demonstrating that the sex-related difference

in prolactinoma size is not due to a longer delay before diagnosis in males but rather to greater growth potential in this gender (5).

We also observed a gender-related difference in the distribution of giant prolactinomas by decades of life (15). In men, the incidence peaks during the fourth decade of life and then decreases sharply, pointing towards a 'frailty' effect, whereas in women, the diagnosis period seems to have a bimodal distribution with an early-onset group of 11 patients with a median age at diagnosis of 25 years (range 15–27) (15, 95) and a later onset group of 27 patients diagnosed at a median age of 50 years (range 37–87) (15, 36, 96, 97). Early onset may reflect a stronger hereditary pathogenesis, and systematic search for *MEN1* or *AIP* mutations would be interesting in this setting. In the late-onset group of patients, the long delay frequently observed before diagnosis despite the presence of amenorrhoea is intriguing. At least three explanations have been proposed (15): the low prevalence of associated galactorrhoea probably due to long-standing hypo-oestrogenic state, the frequent use of oral contraception maintaining regular menstrual bleeding despite hyperprolactinaemia and in some cases misdiagnosis due to a 'hook effect'. The presence of a functioning reproductive axis seems to prevent tumour expansion in view of the very low occurrence of giant prolactinomas during the fourth decade. It has been shown that lactotroph cell proliferative activity was higher in men and older women (beyond 40 years of age) than in young women (99). Taken together, these data challenge the common assumption of a proliferative role of oestrogens in human prolactinomas.

Giant prolactinoma in children

Prolactinomas are rare during the paediatric period (accounting for <2% of intracranial tumours (100, 101, 102), but become more frequent during the adolescent years (103, 104). Furthermore, prolactinomas in children are often more aggressive and invasive and macroadenomas at presentation are proportionally more frequent than in adults (101, 104).

Giant prolactinomas also occur in children and adolescents and, as in adults, they are much more frequent in boys than in girls. Among 16 cases collected from the literature and fulfilling all definition criteria of a true giant prolactinoma (55, 56, 72, 95, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114), there were 15 boys with a mean age of 10.8 years (range: 6–14 years) and a mean tumour diameter of 65 mm (range: 40–99 mm) and only one 14.5-year-old girl (95). These giant tumours may also lead

to the same various neurologic complications as in adults, such as blindness and cranial nerve palsies (106), hydrocephalus (56, 72), proptosis (56, 105, 108) or nasopharyngeal symptoms (71, 114), and they should be considered in the differential diagnosis of every large and erosive paediatric skull base tumour.

Pre-pubertal children will generally present with a combination of headache, visual disturbances and growth failure (4). In the peri-pubertal period, the most common symptoms are again mass effects together with endocrine symptoms such as delayed puberty, primary amenorrhoea or menstrual irregularities in girls, or gynaecomastia in boys. Impairment of other pituitary hormone secretions is also common in patients with large adenomas and extrasellar extension (4).

Therapeutic strategy is the same in children as in adults. In the absence of complications requiring immediate surgery, such as apoplexy or CSF leak, DAs should be considered as first-line treatment, irrespective of the size of the tumour and the presence or not of severe visual defects. Both BRC and CAB have demonstrated a very good efficacy in children with giant prolactinomas, although experience remains so far limited (56, 95, 106, 108, 109).

A final aspect to consider is that a large prolactinoma in a child may represent the first manifestation of a *MEN1* syndrome, or be related to a genetic predisposition (i.e. an aryl hydrocarbon receptor interacting protein (*AIP*) mutation) to develop familial pituitary adenomas (111, 115). Appropriate genetic testing is therefore highly recommended in such cases, as detailed in several recent reviews (116, 117, 118).

Perspectives in the management of giant prolactinomas

Predicting pituitary tumour behaviour remains nowadays a challenge and the pathogeny of giant pituitary adenomas is largely unknown. Despite invasive features such as bone erosion and extension into surrounding CN structures, mitotic rates and immunohistochemistry for p53 and MIB-1 (Ki67) are often minimally increased (119). On the other hand, one single case study has demonstrated strong immunoreactivity for VEGF and FGF2 (two potent angiogenic factors) and for CD31 (an endothelial marker) in a giant invasive macroprolactinoma, thus suggesting high tumoural vascularization (57). Identification of new molecular markers highly expressed or down-regulated in these giant tumours should help to better understand their origin and progression (27, 120)

and to find new therapeutic modalities, such as drugs interfering with angiogenesis or cell proliferation. An example of such strategy is the recent observation of specific expression of ErbB receptors in prolactinomas, which was associated with tumour invasion and response to DAs (121). Thus, targeting ErbB receptors might be a future effective therapy in patients with large aggressive prolactinomas. Fukuoka *et al.* (122) have also demonstrated a suppressive effect of lapatinib, a tyrosine kinase inhibitor, on PRL-secreting tumours in rats and on PRL mRNA expression and secretion from human prolactinoma cell cultures *in vitro*.

Another interesting therapeutic track is to explore and use the selective expression of somatostatin receptor (SSTR) subtypes, which is found in prolactinomas, mostly the SSTR-1 and SSTR-5, less frequently the SSTR-2 (123, 124). The presence of a high SSTR-2/5 expression in resistant prolactinomas, evidenced by intense tracer uptake at ¹¹¹In-pentetreotide scintigraphy, may be correlated with a good response to combined therapy with CAB and octreotide (125). Very recently, the effectiveness of peptide receptor radionuclide therapy with 111-indium-DTPA octreotide has been reported in a patient bearing a giant CAB- and octreotide-resistant prolactinoma (49). The multi-ligand somatostatin analogue pasireotide could also be a potential therapeutic option for patients with DA-resistant prolactinomas, as a higher efficacy of this compound over octreotide has been demonstrated regarding inhibition of PRL secretion by prolactinoma cells *in vitro*, in relation to SSTR-5 expression (126). Unfortunately, SSTR-2 and SSTR-5 expression pattern seems to be rarely found in PRL-secreting adenomas (127).

Conclusions

Giant prolactinoma are rare tumours, often raising both diagnostic and therapeutic challenges. They are much more frequent in men than in women and the diagnosis is often delayed, resulting from the occurrence of neurologic complications due to massive extension into the surrounding structures, rather than from long-standing, unrecognized endocrine symptoms. Although there is no current consensus, we suggest to define giant prolactinomas as pituitary tumours with a diameter of 40 mm or more, significant extrasellar extension, high PRL concentration usually above or equal to 1000 µg/l and no concomitant GH or ACTH secretion. As in macroprolactinomas, DAs are the first-line treatment allowing in the majority of cases PRL normalization, a marked reduction of tumour size and alleviation of neurologic symptoms.

Extensive neurosurgery has significant morbidity and mortality and should therefore be restricted to some acute complications or to resistant patients in which a significant debulking is feasible. Irradiation and TMZ are useful adjuvant therapies in a subset of patients with aggressive/invasive tumours that are not controlled by surgery and DA. In every case, a specialized multidisciplinary approach of these giant tumours seems warranted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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