Objective: To characterise distinctive clinical features of giant prolactinomas in women.

Design: A multicentre, retrospective case series and literature review.

Methods: We collected data from 15 female patients with a pituitary tumour larger than 4 cm and prolactin levels above 1000 µg/l and identified 19 similar cases from the literature; a gender-based comparison of the frequency and age distribution was obtained from a literature review.

Results: The initial PubMed search using the term ‘giant prolactinomas’ identified 125 patients (13 women) responding to the inclusion criteria. The female:male ratio was 1:9. Another six female patients were found by extending the literature search, while our own series added 15 patients. The median age at diagnosis was 44 years in women compared with 35 years in men ($P < 0.05$). All cases diagnosed before the age of 15 years were boys. In women ($n = 34$), we observed a minor peak incidence during the third decade of life and a major peak during the fifth decade. Amenorrhoea was a constant feature with seven cases of primary amenorrhoea. In eight women with onset of secondary amenorrhoea before the age of 40 years, the diagnosis was made 2–31 years later (median 9 years) and in all but one because of tumour pressure symptoms. The prolactin levels were above 10 000 µg/l in 15/34 and misdiagnosis due to ‘hook effect’ occurred in two of them. Eighteen patients were treated with cabergoline; standard doses ($< 2.0$ mg/week) were able to normalise prolactin in only 4/18 patients, and 7/18 patients were resistant to weekly doses ranging from 3.0 to 7.0 mg.

Conclusion: Giant prolactinomas are rare in women, often resistant to dopamine agonists and seem to be distributed in two age groups, with a larger late-onset peak.
extension but also serum prolactin levels, which generally parallel tumour size. As large invasive prolactinomas are characterised by serum prolactin levels $>1000 \mu g/l$ (5), and a similar figure is used in most recent series to define giant prolactinomas (1, 3, 4).

We have collected original data from 15 female patients with tumours larger than 4 cm and prolactin levels above 1000 $\mu g/l$, and 19 similar cases were identified in the literature. In this report, the frequency distribution of giant prolactinomas by age and gender will be presented and the distinctive clinical characteristics of these rare tumours in females will be discussed.

Subjects and methods

Case finding

This was a collaborative, retrospective study involving several academic centres from Belgium, Denmark, France and Sweden. All centres were asked to include data from all women with a giant prolactinoma seen between 1992 and 2012. All patients met the diagnostic criteria generally accepted for giant prolactinoma (1, 3, 4), i.e. a tumour diameter $\geq 40$ mm and serum prolactin levels above 1000 $\mu g/l$ without features of acromegaly or Cushing’s syndrome.

Literature review

The PubMed database was searched at the end of December 2012 using the term ‘giant prolactinomas’. Only articles written in English were selected ($n=99$). Review articles were excluded as well as reports with insufficient detail to allow a correct compilation of individual data concerning gender, age at presentation, tumour diameter and PRL levels. From the remaining articles ($n=68$), subjects with a giant prolactinoma, defined using the above-mentioned criteria, were included to compare the age distribution of these tumours between genders.

The literature review was extended from the references of these reports and by searching PubMed, in females, using additional terms such as ‘prolactin hook effect, invasive prolactinomas, prolactinomas and hydrocephalus, prolactinomas and epilepsy, prolactinomas and cerebrospinal fluid leakage’. Data from our 15 patients and from the literature review were analysed to determine age at presentation, initial PRL level, maximum tumour diameter, clinical presentation, duration of symptoms prior to diagnosis, treatment, maximal dopamine agonist (DA) treatment dose, nadir PRL level and final tumour size. Prolactin values expressed as mU/l were converted to $\mu g/l$ using a conversion factor of 21. Medians were compared using the non-parametric Mann–Whitney $U$ test and the level of significance was set at $P<0.05$.

Results

The initial PubMed search identified 125 patients with a pituitary tumour larger than 40 mm and serum prolactin levels $>1000 \mu g/l$. There were 112 men and 13 women (10%) (6, 7, 8, 9, 10, 11, 12) (Table 1, case nos 1–13).

The extended literature search identified another six female patients (13, 14, 15, 16, 17, 18) (Table 1, case nos 14–19) while our own series added 15 patients (Table 2), bringing the total female population to 34 patients. Their median age at diagnosis was 44 years (range 16–87 years) compared with 35 years in the reported 112 men (range 7–80 years) ($P<0.05$). The distribution of giant prolactinomas by gender and decades of life is presented in Fig. 1. Men showed a unimodal and relatively symmetric distribution with a peak during the fourth decade of life. In women, the distribution seemed bimodal with a minor peak incidence during the third decade and a major peak during the fifth decade. The median age of the ten women with an early onset of the disease was 25 years (range 16–27) compared with 49 years (range 37–87) in the later-onset group of 24 women. All subjects aged $<15$ were diagnosed because of mass effects and were boys ($n=10$).

When considering women alone, ($n=34$; Tables 1 and 2), the pre-treatment symptoms included amenorrhoea, galactorrhoea, visual disturbances and headache and also various symptoms related to the mass effects such as new onset of seizures, nasal congestion and exophthalmos. The tumour caused hydrocephalus in three cases (Table 1, case nos 15–17). One case was diagnosed as a pituitary incidentaloma after a head trauma (Table 2, case no. 6). Data regarding galactorrhoea and menstrual disturbances were available in 24 and 31 of the 34 women respectively. Galactorrhoea was present in eight of 24 patients and was never recorded after the age of 50. Amenorrhoea was present in all 31 documented cases and was primary in seven cases. It was the presenting symptom in three cases diagnosed before the age of 20, but in another three women the diagnosis was delayed until after the age of 40, despite the presence of a primary amenorrhoea, so that the age at diagnosis in this group of patients ranged from 16 to 55. The age of onset of secondary amenorrhoea ($n=24$) was not always mentioned and difficult to interpret when occurring after
the age of 40, as the lack of menses could have resulted at that time from hyperprolactinaemia or from menopause. In eight women with onset of secondary amenorrhea before the age of 40 years, the diagnosis of prolactinoma was made 2–31 years later (median 9 years) and in all but one because of tumour symptoms.

Tumour size ranged from 40 to 75 mm (median 44) and prolactin level from 1100 to 43 163 μg/l (median 8723). The prolactin levels were ≥10 000 μg/l in 15/34 cases and misdiagnosis due to ‘hook effect’ occurred in two of them (Table 1, case nos 4 and 7). Cavernous sinus invasion was present in all except one patient (Table 2, case no. 1) from our own series.

All female patients (n=34; Tables 1 and 2) were treated by DAs. Pergolide normalised the prolactin level in one case. Bromocriptine was used in 15 patients: prolactin levels did not normalise in eight, but the dose administered was unknown in four of them and %7.5 mg/day in the other four patients, due to drug intolerance in two. In the seven patients with normalisation of prolactin levels, the daily bromocriptine dose ranged from 5 to 30 mg. The remaining 18 patients were treated with cabergoline, which was able to restore normoprolactinaemia in 10 (55%). Four patients responded to standard doses (≤2.0 mg/week) (19) and six to doses ranging from 2.0 to 7.0 mg. Seven cases were resistant to the prolactin-lowering effect of cabergoline despite weekly doses of 3.0–7.0 mg, while one patient

| Table 1 Giant prolactinomas in women: data from the literature review. |
|---|---|---|---|---|---|---|
| Case no. | References | Age (years) | Presentation | Prolactin level (μg/l) | Tumour size (mm) | Dopamine agonist (maximum dose) | Surgery and/or radiotherapy |
| 1 | (6) | 48 | Headaches | 11 381 | 9 | > 40 | BRC (30 mg/day) | S on BRC (personal choice) |
| 2 | (7), case 4 | 43 | Weight gain Visual defect (amenor) | 15 000 | 21 | 72 | BRC (10 mg/day) |
| 3 | (7), case 10 | 41 | Visual defect (amenor) | 13 538 | 1700 | 70 | BRC (2.5 mg/day) | S on BRC (intolerance to BRC) |
| 4 | (8) | 25 | Headaches (amenor) | > 16 000 (hook) | 4950 (after 4 weeks) | > 40 | BRC (dose?) | RT on BRC (intolerance to BRC) |
| 5 | (9), case 9 | 37 | Facial pain | > 8000 | 226 | 75 | BRC (7.5 mg/day) | |
| 6 | (9), case 14 | 25 | Headaches | 1100 | 312 | 42 | BRC (dose?) | S and RT before CAB (misdiagnosis) |
| 7 | (10) | 45 | Visual defect | 14 640 (hook) | 1 | 50 | CAB (3 mg/week) | |
| 8 | (11), case 1 | 50 | Visual defect Cranial nerve palsy | 1256 | 13 | 40 | CAB (2 mg/week) |
| 9 | (11), case 2 | 17 | Visual defect | 43 163 | 14 | 45 | CAB (2 mg/week) |
| 10 | (11), case 3 | 40 | Visual defect | 13 700 | 3983 | 43 | CAB (3.5 mg/week) |
| 11 | (11), case 6 | 47 | Visual defect | 2540 | 1278 | 40 | CAB (3 mg/week) |
| 12 | (11), case 10 | 25 | Visual defect | 1961 | 7 | 42 | BRC (7.5 mg/day) |
| 13 | (12), case 32 | 44 | Visual defect | 1134 | 3 | > 40 | BRC (10 mg/day) |
| 14 | (13) | 55 | Visual defect | 33 143 | 21 | > 40 | BRC (30 mg/day) |
| 15 | (14) | 27 | Hydrocephalus | 8238 | 272 | > 40 | BRC (dose?) |
| 16 | (15) | 44 | Hydrocephalus (primary amenor) | 9780 | 19 | > 40 | BRC (5 mg/day) |
| 17 | (16) | 81 | Hydrocephalus | 6800 | 5 | > 40 | BRC (30 mg/day) |
| 18 | (17), case 20 | 54 | Hydrocephalus | 4100 | 2 | 40 | Pergolide |
| 19 | (18) | 54 | Proptosis | 8723 | ND | 55 | BRC (dose?) |

Amenorrhea, amenorrhoea; CAB, cabergoline; BRC, bromocriptine; S, surgery; RT, radiotherapy; hook, hook effect.
with persistent hyperprolactinaemia was still on a dose <1.5 mg/week. Medical treatment was complicated in four of the 34 patients by the occurrence of cerebrospinal fluid rhinorrhoea (Table 1, case nos 14 and 16 as well as one case in the series from Acharya et al. (11); Table 2, case no. 3).

From our population of 15 patients (Table 2), 14 received DAs as primary therapy and a significant reduction in tumour diameter (≥30%) was observed in all but three patients: case no. 6, who exhibited a cystic transformation of the tumour; case no. 13, who also demonstrated hormonal resistance to cabergoline; and case no. 14, who at the time of evaluation had only received a short course of low-dose bromocriptine treatment. MEN1 syndrome was recognised in one case (Table 2, case no. 1). Familial history was negative in all other cases and a search for MEN1 (Table 2, case nos 6 and 8) or AIP (Table 2, case nos 4 and 8) mutation was negative.

**Discussion**

Giant pituitary adenomas are defined as tumours with the largest diameter of 4 cm or more. This particular extension has been fixed arbitrarily (20), the same 4 cm diameter being used to classify aneurysms as giant. However, the tumour size at diagnosis may point to specific aspects in the pathogenesis of pituitary adenomas. Very large tumours have a different clinical presentation, most of them are invasive, and the arbitrary division of pituitary tumours into microadenomas, macroadenomas and giant adenomas is helpful to compare the results of treatment, as tumour size is a relevant prognostic marker for the success of treatment. As far as prolactinomas are concerned, most giant tumours are treated medically with cabergoline, without histological diagnosis. Serum prolactin levels generally parallel tumour size and giant invasive prolactinomas are typically associated with prolactin levels >1000 μg/l (5). Most non-surgical series of giant prolactinomas published in the literature used as diagnostic criteria a serum prolactin level higher than 1000 μg/l (1, 3, 7, 11), 2000 μg/l (21), 3000 μg/l (2) or even 5000 μg/l (22). In one series (9), prolactin level was reported as >200 μg/l, but difficulties at the laboratory were mentioned and accurate prolactin levels were not available in some cases. In a recent surgical series including ten patients (all men) with monohormonal giant prolactinoma (23), the serum prolactin level ranges from 365 to 7556 μg/l. All but one tumour were invasive. There were two cases with a serum prolactin below 1000 μg/l: the only
non-invasive tumour (365 μg/l) and another one whose serum prolactin level was 985 μg/l (personal data from G Raverot & J Trouillas). Thus, although a lower prolactin level may be consistent with the presence of a giant prolactinoma, in the setting of this retrospective non-surgical series and in order to compare with the existing literature, we decided to use as diagnostic criteria a tumour diameter > 40 mm and a serum prolactin concentration higher than 1000 μg/l.

Giant prolactinomas, as defined above, are relatively rare and published series generally include about ten patients with either no (1–3, 21, 23), 1 (22) or 2 (7) women respectively. The series from Acharya et al. (11) was an exception including five men and five women. The largest series published to date (9) consisted of four women and 16 men but used a less stringent criterion for inclusion (serum prolactin > 200 μg/l), as already mentioned. From the present review, it can be established that women represent about 10% (13/125) of patients with a giant prolactinoma.

It appears that men with giant prolactinomas are younger at diagnosis than women and that all cases aged < 15 years described until now (n = 10) are boys. This is in keeping with our previous study (24) demonstrating that the gender-related difference in tumour size is not only due to a longer delay before diagnosis in male compared with female patients but rather to an overall greater growth potential of prolactinomas among males. Data collected here, however, illustrate that, at variance with a common idea, the clinical symptoms of hyperprolactinaemia in women (amenorrhoea and/or galactorrhoea) do not always lead to a prompt diagnosis of the disease and that only a small subset of female prolactinomas will show an important growth over time. In the present review, the delay before diagnosis ranged from 2 to more than 30 years. This is not a unique feature of giant prolactinomas. In the historical study by Nabarro (25), although most tumours were intrasellar at diagnosis (84%), 15 of the 83 patients with secondary amenorrhoea had had the condition for more than 10 years. In another series (24), although eight of 51 women were amenorrhoeic for more than 10 years, six had microadenomas.

Nowadays, in Europe, 35% of women of childbearing age receive either an oral contraception, which can maintain regular menstrual bleeding despite hyperprolactinaemia, or an intrauterine device, which, if releasing levonorgestrel, can lead to amenorrhoea irrespective of the prolactin level. Thus, in many situations, the clinician can no more rely on the hallmark of hyperprolactinaemia, namely the menstrual disturbance. On the other hand, the prevalence of galactorrhoea is roughly 50% (25) but decreases in long-standing hypo-oestrogenic states with a proportion of one of three in our series. Thus, as in men, in case of a giant skull base tumour, prolactinoma should always be excluded, irrespective of age and/or duration of amenorrhoea and/or presence of galactorrhoea, in order to avoid errors in the management of these women. In this setting, prolactin assay should be done after serum sample dilution to overcome a potential ‘hook effect’ due to very high antigen levels (10), which can constitute another cause of diagnostic delay.

Cabergoline should be the first-line therapy for these tumours, although only a minority will be controlled with standard doses (21). Most giant prolactinomas are invasive towards the cavernous sinus (14 of 15 in the present series) and invasive macroprolactinomas have been shown to be less responsive to DA therapy (19). An overview of the response to treatment with cabergoline observed in series of at least three patients with previously untreated giant prolactinoma is shown in Table 3. Among the 16 female patients, only three normalised their prolactin level with weekly doses < 2.0 mg and five other women did so on higher doses. The response rate observed in men, although slightly higher, is not significantly different. The therapeutic approach proposed when the response to cabergoline is insufficient has recently been reviewed elsewhere (26). It should be noticed that there are no data regarding the use of temozolomide in women with giant prolactinomas and that radiotherapy was performed in only two cases (see Table 1) but resulted in visual loss in one (9).

The fact that only a subset of female prolactinomas will show an important growth potential with time is
likely dependant on factors limiting angiogenesis (27). Histological data (28) indicating that prolactinomas are often highly vascularised in men, whereas the tumours frequently are haemorrhagic in women, were recently confirmed by magnetic resonance imaging studies (29). However, the mechanism explaining this gender-related difference in blood supply remains unknown. Five cases of giant prolactinomas in women come from the same Indian series of ten patients (11). The authors postulated that the overrepresentation of women may be due to a late presentation related to economic and social factors in their country. However, the relatively young age of their patients (ranging from 17 to 50 years) compared with the whole series (median age at diagnosis 44 years) does not support this hypothesis and an impact of environmental factors (30) or genetic factors (31, 32) cannot be ruled out. In our series, only one patient was found to have MEN1 while other cases seem to be distributed in two age groups: a small group with early onset that may reflect a stronger hereditary pathogenesis and a larger late-onset group where a number of genetic or epigenetic events are probably required to reach a giant size. The woman with MEN1 syndrome was diagnosed at the age of 16 years. Intriguingly, the four patients responding to standard doses of cabergoline belonged to the late-onset group. Patients with MEN1 or AIP mutation have been reported to be younger at diagnosis with tumours that are larger and less responsive to treatment (31, 32).

A similar bimodal frequency distribution among age groups of females was recently observed for meningiomas (35). Like prolactinomas, meningiomas are more frequent among women while male gender is associated with higher grade tumours. In meningiomas, clinical and histopathological studies have shown an inverse relationship between the progesterone receptor expression level and tumour grade and recurrence. Available data regarding expression of sex steroid receptors in pituitary adenomas are scarce, but in one study (36), microadenomas were characterised by a higher progesterone receptor expression than macroadenomas, while haemorrhagic macroadenomas had a high oestrogen receptor expression. Thus, the expression of sex steroid receptors and their relationship with angiogenesis should be further studied in prolactinomas and may help to elucidate part of the gender differences observed in the behaviour of these tumours. In addition, the fact that some giant prolactinomas might already occur in very young boys before the onset of puberty should keep open the possible contribution of neonatal sex steroid imprinting.

In conclusion, only 10% of giant prolactinomas occur in women and they seem to be equally responsive to DAs similar to tumours found in men. In contrast to the unimodal distribution observed in the male gender, female giant prolactinomas seem to be distributed according to two age groups, with a larger late-onset peak. If confirmed in further studies, the observed age-incidence curves may help to establish a multistage model of tumorigenesis including a frailty effect.

### References

(2) Men (n=5) 3/5 2/5
(21) Men (n=10) 9/10 6/10
(3) Men (n=10) 6/10 10/10
(37) Men (n=3) 3/3 ND
(11) Men (n=4) 3/4 2/3
Women (n=4) 2/4 1/2

**Table 3** Overview of the response to treatment with cabergoline in previously untreated giant prolactinomas in men and women. Tumour shrinkage was considered significant when obtaining a > 30% reduction in tumour diameter and/or a > 65% reduction in tumour volume.

- **Gender**
  - Men (n=32)
  - Women (n=16)
- **PRL normalisation (n)**
  - Men (24/32, 75%)
  - Women (2/16, 50%)
- **Significant tumour shrinkage (n)**
  - Men (20/28, 71%)
  - Women (11/14, 79%)

In conclusion, only 10% of giant prolactinomas occur in women and they seem to be equally responsive to DAs similar to tumours found in men. In contrast to the unimodal distribution observed in the male gender, female giant prolactinomas seem to be distributed according to two age groups, with a larger late-onset peak. If confirmed in further studies, the observed age-incidence curves may help to establish a multistage model of tumorigenesis including a frailty effect.
Declaration of interest

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

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