Giant Prolactinoma in Men: Clinical Features and Therapeutic Outcomes

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ABSTRACT

The aim of the study was to evaluate the clinical features and long-term therapeutic outcome of giant prolactinoma (gPRLoma) in men and to compare them with those of a group of male patients with non-gPRL macroprolactinomas (non-gPRLomas). A retrospective and multicenter study of gPRLomas in men diagnosed in a 20-year period was performed. Clinical data and treatment outcome were registered. The diagnosis of gPRLoma was established when the maximal tumor diameter was ≥ 40 mm or the tumor had ≥ 20 mm of suprasellar extension associated to hyperprolactinemia (PRL > 1000 ng/ml). Non-gPRLoma was considered when tumor diameter was ≥ 10 mm and < 40 mm associated to hyperprolactinemia (PRL ≥ 200 ng/ml). Twenty-three patients with gPRLoma (age 38.3 ± 13.5 years) followed for at least 3 months (follow-up 87.1 ± 60.5 months, range 3–211 months) were evaluated. A group of 42 patients with non-gPRLoma (age 42 ± 16.6 years; NS; follow-up 89 ± 65.9 months, range 3–222 months; NS) served as a control group. More than half (56.5 %) of the gPRLoma patients were younger than 40 years at diagnosis. Visual disturbances were significantly more common in gPRLoma than in non-gPRLoma patients (65.2 vs. 25.6 %; p = 0.004). Prevalence of hypopituitarism was similar in both groups of patients (73.9 % vs. 80.9 %; gPRLoma vs non-gPRLoma; NS). Serum PRL concentrations were significantly higher in gPRLoma than in non-gPRLoma patients [median (IR), 3978 ng/ml (1179–9012) vs. 907 ng/ml (428–3119); p < 0.001]. Maximum tumor diameter in gPRLomas was 4.8 ± 0.8 cm and 2.4 ± 0.7 cm in non-gPRLoma (p < 0.001). All patients were treated with dopamine agonists (DA). Twelve (52.2 %) gPRLoma patients and 32 (73.8 %) non-gPRLoma patients were treated with DA as monotherapy (p = 0.045). Surgery was used in 12 (52.2 %) gPRLoma patients and in 12 (28.6 %) non-gPRLoma patients (p = 0.054). Lastly, radiotherapy was used in 5 (21.7 %) gPRLoma patients and in 6 (14.2 %) non-gPRLoma patients (NS). At last visit, PRL was similar in both groups of patients [16 ng/ml (4–30) vs. 11 ng/ml (4–25); gPRLomas vs. non-gPRLomas; ns] and tumor size decreased significantly (p < 0.001) in both groups of patients. Clinical cure (maintained normoprolactinemia without therapy for > 1 year and no radiological evidence of pituitary tumor) was achieved in 2 (8.7 %) gPRLoma patients and in 2 (4.8 %) non-gPRLoma patients (NS). gPRLomas in men are usually diagnosed at a mean age of 40 years, an age similar to that of non-gPRLomas. The only clinical difference with non-gPRLomas is their greater prevalence of visual disturbances. The therapeutic approaches and tumor outcomes were similar to those obtained in patients with non-gPRLomas. Complete cure in gPRLoma is rare, but similar to that achieved in non-gPRLomas, reached in less than 10 % of patients.
Introduction

Prolactinomas are the most frequent functioning pituitary adenomas, accounting for about 60% of primary pituitary tumors. These tumors are more frequently (>70%) diagnosed in women of childbearing age. They are usually small (<1.0 cm, microprolactinoma), intrasellar, and slow growing tumors. Macroprolactinomas (≥1 cm) are more commonly diagnosed in young males, are more symptomatic, requiring more intensive and long-term treatment [1–3].

Giant prolactinomas (≥4 cm [gPRLoma]) are rare tumors, predominantly diagnosed in males, with a male to female ratio of about 9:1 [4–8]. They are usually accompanied by endocrine symptoms, as a consequence of hormonal pituitary deficiencies, and frequent neuro-ophthalmological complications. Symptoms may also be related to hyperprolactinemia and/or to compression of other neighboring structures. Given their large size, these tumors often pose a therapeutic challenge [9]. As in any prolactinoma, regardless of size, the first-line treatment of gPRLomas is medical with dopamine agonists (DA).

Depending on the therapeutic response, adjuvant treatment with surgery, radiotherapy and/or bromocriptine, especially in those more aggressive and invasive cases, can be considered [9, 10].

To date, a small number of series have evaluated patients with gPRLoma [4–8, 11–15]. On the other hand, little is known about progressive and invasive cases, can be considered [9, 10].

Patients and Methods

We retrospectively investigated the clinical records of a group of male patients diagnosed of gPRLoma in a 20-year period and followed-up for at least 3 months in four Spanish medical centers: hospital Ramón y Cajal (Madrid), hospital Doce de Octubre (Madrid), hospital de Bellvitge (L’Hospitalet de Llobregat, Barcelona), and hospital General (Segovia). These gPRLoma patients were compared with a group of male patients with non-gPRLomas.

Diagnosis of gPRLoma was established when the maximal tumor diameter was >40 mm or the tumor had >20 mm of suprasellar extension associated to hyperprolactinemia (PRL >1000 ng/ml). Non-gPRLoma was considered when tumor diameter was ≥10 mm and <40 mm associated to hyperprolactinemia (PRL ≥200 ng/ml).

In every patient we assessed the following clinical parameters: age at diagnosis, main complaint at presentation, tumor size and extension by CT and MRI, and hormonal and tumor size responses to therapy (DA, surgery and/or radiotherapy). We also registered other tumor mass effects and hyperprolactinemia-related complaints at diagnosis. Results of the visual field examination were also evaluated. Type and number of pituitary deficiencies were also registered. Hypopituitarism was defined as deficient secretion of one or more pituitary hormones diagnosed following the criteria of routine clinical practice, that is, central hypothyroidism (normal/low TSH and low free T4), secondary adrenal insufficiency (normal/low ACTH and low cortisol), hypogonadism (normal/low gonadotropins with low total testosterone in men and low estradiol in women), and GH deficiency (normal/low GH with low IGF-1 for the patient’s age).

Results

Clinical data

Twenty three gPRLoma patients (age 38.3 ± 13.5 years; median 36 years; range 16–64 years) followed for at least 3 months (follow-up 87.1 ± 60.5 months, range 3–211 months) were evaluated. A group of 42 non-gPRLoma men (age 42 ± 16.6 years; median 38.5 years; range 15–79 years; ns; follow-up 89 ± 65.9 months, range 3–222 months; ns) served as a control group. Maximum tumor diameter in gPRLomas was 4.8 ± 0.8 cm and 2.4 ± 0.7 cm in non-gPRLoma (p < 0.001).

More than half (56.5%) of the gPRLoma patients were younger than 40 years at diagnosis. The percent distribution of gPRLoma patients according to age at diagnosis was similar to that found in non-gPRLoma patients (Fig. 1).

Visual disturbances were significantly more common in gPRLoma than in non-gPRLoma patients (65.2% vs. 25.6%; p = 0.004); without differences in other symptoms, such as headaches, impotence, decreased libido, and gynecomastia. Galactorrhea was rare, showing only one patient (4.3%) in gPRLoma group and none in non-gPRLoma group. Other compression symptoms seen in gPRLoma patients were cognitive impairment and memory loss in one patient and seizures in another patient.

Prevalence of some degree of hypopituitarism at diagnosis was similar in both groups of patients (73.9% vs. 80.9%; gPRLoma vs. non-gPRLoma), without significant differences in the type of hormonal axis affected or in the prevalence of complete hypopituitarism. The most commonly associated affected pituitary was gonadal axis.
Apart from PRL [median (IR), 3978 ng/ml (1179–9012) vs. 907 ng/ml (428–3119); p < 0.001], only cortisol and free thyroxine (FT4) were significantly different between gPRLoma and non-gPRLoma patients (▶ Table 2).

### Therapeutic approaches and outcomes

All patients of the series were treated with DA. Twelve (52.2 %) gPRLoma patients and 32 (73.8 %) non-gPRLoma patients were treated with DA as monotherapy (p = 0.045). In these patients, no significant differences in the follow-up time, type and number of drugs used, time on DA therapy, and cumulative dose between both groups of patients were observed. Throughout the follow-up period [70.5 (3–180) months vs. 48 (3–140) months, non-gPRLoma vs. gPRLoma, ns], treatment with DA monotherapy achieved a similar degree of control of hyperprolactinemia and tumor size in both groups of patients.

DA monotherapy was accompanied by an improvement in visual field examination in 88 % of the gPRLoma patients and in 70 % of the non-gPRLoma patients (ns). This therapy decreased the incidence of any type of hypopituitarism (at least 1 hormone deficiency) in both groups of patients, although, this reduction was more pronounced in the non-gPRLoma group (from 78.1 % to 21.8 % vs. from 66.6 % to 50 %; p = 0.03) at the expense of the gonadal axis. DA monotherapy was associated with a significant reduction of hypogonadism in the non-gPRLoma group (▶ Table 1). Only 2 (6.2 %)

### Table 1 Prevalence of complete hypopituitarism and hormonal involvement by axes at diagnosis and at last visit in 12 g-PRLoma and 32 non-gPRLoma patients treated with DA monotherapy (A) and in 23 g-PRLoma and 42 non-gPRLoma patients treated with multimodal therapy (B).

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<tr>
<td>Secondary adrenal insufficiency</td>
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§§ p < 0.01 at diagnosis vs. at last visit.; Hipp p < 0.01 gPRL vs. non-gPRLoma.; Hipp p < 0.01 at diagnosis vs. at last visit.; Hipp p < 0.05 gPRL vs. non-gPRLoma.
non-gPRLoma patients achieved cure criteria while complete cure was not achieved in any patient with gPRLoma (Table 3).

Surgery was used in 12 (52.2%) gPRLoma patients and in 12 (28.6%) non-gPRLoma patients (p = 0.054). Six patients (9.2%; 3 (13%) gPRLomas and 3 (7.1%) non-gPRLomas) underwent surgery on 2 occasions. The main causes of reoperation were resistance to medical treatment (n = 4; 2 gPRLomas) and tumor growth (n = 2; one gPRLoma).

Lastly, radiotherapy was used in 5 (21.7%) gPRLoma patients and in 6 (14.2%) non-gPRLoma patients (ns). Mean dose of radiotherapy was similar in both groups (47.4 ± 2.4 Gy vs. 52.5 ± 6.1 Gy; gPRLomas vs. non-gPRLomas, ns).

After a similar follow-up period, PRL at last visit was similar in both groups of patients. The tumor size decreased significantly in both groups of patients (Fig. 2). Visual field examination in those patients with altered initial study showed an improvement in 77.7% of the gPRLoma patients and in 60% of the non-gPRLoma patients (ns). Lastly, the percentage of some degree of hypopituitarism at the last clinical visit decreased in both groups, although it was more pronounced in the non-gPRLoma group (69.6% vs. 35.7%; gPRLoma vs non-gPRLoma; p = 0.009). Multimodal therapy was associated with a significant reduction of central hypogonadism, GH deficiency, and complete hypopituitarism in the non-gPRLoma group, while in gPRLoma patients an increase in the prevalence of central hypothryoidism and GH deficiency was observed.

At last visit, tumor size decreased significantly (p < 0.001) in both groups of patients. Maximum tumor size decreased by 66.6% in gPRLomas and 58.3% in non-gPRLomas. Final tumor size was significantly lower in non-gPRLoma than in gPRLoma patients (p < 0.05). Tumor was present at the last MRI in 14 (60.7%) gPRLoma patients and in 26 (61.9%) non-gPRLoma patients (ns). Clinical cure was achieved in 2 (8.7%) gPRLoma patients and in 2 (4.8%) non-gPRLoma patients (ns) (Table 4).

Discussion

The present study describes a large series of men (n = 65) with PRLomas with a follow-up period of more than 3 months, in which clinical characteristics and therapeutic results of 23 gPRLoma patients are analyzed and compared with 42 non-gPRLoma patients. Our survey shows that gPRLomas in men are usually diagnosed at a mean age of 40 years, an age similar to that of non-gPRLomas. At diagnosis, the only clinical difference with non-gPRLomas is their greater prevalence of visual disturbances; while the prevalence of pituitary involvement is comparable. Treatment with DA in monotherapy in gPRLoma patients achieves significant reductions in serum PRL levels similar to those obtained in non-gPRLoma patients. When multimodal treatment is considered, the results in relation to serum PRL levels are similar to those obtained in patients with non-gPRLomas, although the final maximum tumor size remains significantly higher in gPRLomas than in non-gPRLomas.
Lastly, complete cure in gPRLoma is rare, reached in less than 10% of patients without significant differences with non-gPRLomas. gPRLomas are rare tumors accounting for 0.5–1% of all pituitary tumors and 2–3% of prolactinomas [5, 6, 13]. As occurs with non-gPRLomas, gPRLomas have a predilection for male sex (male/female, ratio 8–9/1) [7, 9, 13, 16] and they have been reported in approximately one-quarter of men with prolactinomas [17].

In a large series of 199 macroadenomas, Espinosa et al. in 2016 [13] reported a prevalence of gPRLoma in 3.1% of patients with a clear male predominance in gender distribution (89%) and a mean age at diagnosis of 44 years, without significant differences with non-gPRLomas (40 years). To the best of our knowledge, our study is the first one that has compared gPRLomas and non-gPRLomas in men. In our study, the age at diagnosis of gPRLoma was slightly lower (38 years) than that reported by Espinosa, and, similarly, without significant differences with non-gPRLomas. The different mean age at diagnosis could be explained by the presence of women in the latter study; since it has been reported that the median age at diagnosis of gPRLoma is significantly lower (~10 years) in males compared to females (35 vs. 44 years, respectively, p < 0.05) [16].

Clinical symptoms associated with gPRLoma can be secondary to the compression of surrounding brain structures, hypopituitarism, and hyperprolactinemia [9]. Regarding presenting symptoms at diagnosis, comparing with non-gPRLomas, our study only found significant differences in visual alterations, which were more frequently reported in gPRLoma patients, given their positive association with tumor size. Similar data have been reported in series of gPRLoma patients composed of men and women [13]. As previously reported by these authors, other symptoms such as headache and erectile dysfunction were similar in gPRLoma and non-gPRLoma patients.

Galactorrhea associated with prolactinoma is more frequent in women than in men. This also occurs in gPRLomas, in which galactorrhea is rare in men while in women it appear in a third of the patients [9, 16]. Although a higher prevalence of galactorrhea has been reported in patients with non-gPRLomas compared with gPRLomas [13], it is possible that this finding is related to a higher number of women analyzed in the first group. Our study confirmed the low prevalence of galactorrhea in males with macroadenomas, regardless of size.

The presence of at least one pituitary hormone deficiency (partial hypopituitarism) is present in virtually all (98%) patients with gPRLomas [13]. However, panhypopituitarism is less common, having been reported in around 17–33%; and diabetes insipidus is usually absent [9, 13]. In our series, the prevalence of hypopituitarism was also elevated without differences between gPRLomas and non-gPRLomas. As previously reported in gPRLoma patients with mixed population (men and women) [13], in our male gPRLoma patients the most common hormone derangement was hypogonadotropic hypogonadism. In addition, the incidence and severity (testosterone levels) were comparable in both groups of patients, despite the different serum PRL concentrations. Although we did not find significant differences in the incidence of pituitary dysfunction between the two study groups, we observed a greater degree of hormonal involvement of the thyrotropic and corticotropin axes in gPRLoma patients, expressed as a significant reduction in serum FT4 and cortisol concentrations, respectively, indicating a greater degree of pituitary dysfunction likely related to a larger tumor size.

DA therapy is an effective and well-tolerated first line of therapy in gPRLomas. It is accompanied by a reduction or normalization in serum PRL levels and a significant tumor shrinkage in the majority of the gPRLomas, regardless of their size [9, 13, 14, 16–18]. In fact, DA therapy is considered today superior even to surgical and radiotherapy treatment [6, 7, 9, 13, 19, 20]. Our study suggests that DA monotherapy would achieve a similar degree of control of hyperprolactinemia and tumor size in both gPRLoma and non-gPRLoma male patients. Moreover, it is followed by an improvement in visual field defects and hypopituitarism in both groups of patients.

Surgical treatment (transsphenoidal, transcranial surgery, or combined surgical approaches) is currently considered a second-line treatment, after DA therapy, in the management of gPRLoma. Surgery as first-line therapy would be indicated in gPRLoma patients with spontaneous pituitary tumor apoplexy, acute and progressive visual deterioration, spontaneous CSF leak, and cranial hypertension [9]. However, even in these cases, post-surgical treatment with DA drugs is usually necessary [11, 14, 15]. In our series, surgery was used in a large number of patients with gPRLoma (52%), virtually four times more common than that reported by other series [13]. Of note is the high number of patients (29%) with non-gPRLomas in whom surgery was used, without significant differences with gPRLoma patients. These findings are probably related to the fact that all the patients in our series were male, a clinical condition that has been shown to be associated with a worse biological behavior in these tumors and, therefore, they would be more susceptible to surgical treatment in both first and second therapeutic lines [9].

Radiation therapy is not commonly used in gPRLomas. It is usually used in those tumors not controlled with DA drugs after surgery. It has been used in a very variable way between 0–25% of gPRLomas [13, 15]. In our series, radiotherapy was used as the third line of treatment in all patients. Due to the small number of the

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<th>Table 4</th>
<th>Response of hyperprolactinemia, tumor size, and cure rate in the entire group of study patients.</th>
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<tbody>
<tr>
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<td>gPRLoma (n = 23)</td>
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<tr>
<td>Basal PRL (ng/ml)</td>
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<tr>
<td>PRL (ng/ml) at last visit</td>
<td>16 (4–30)</td>
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<tr>
<td>Normoprolactinemia at last visit, n (%)</td>
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<tr>
<td>Initial maximum tumor size (cm)</td>
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<td>Final maximum tumor size (cm)</td>
<td>1.6±1.5</td>
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<td>Cure rate, n (%)</td>
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Data are mean SD, median (interquartile range), or number of patients (percentage) as appropriate. ns: Not significant.
sample size we could not draw conclusions about the effect of radiotherapy in this type of patients.

Although gPRLomas usually respond quite well to DA, they often require multimodal therapy to achieve a reduction in tumor size and control of hyperprolactinemia [14, 15]. When we consider the entire group of patients we observed an adequate response in terms of tumor size reduction and hyperprolactinemia control. When we compared these responses with those obtained in patients with non-gPRLomas, we observed a similar response in terms of hyperprolactinemia control. However, the final tumor size was significantly higher in giant prolactinomas. This may be due to a larger initial tumor size, although a worse therapeutic response to multimodal treatment in these patients cannot be ruled out. It is noteworthy that in our series a high percentage (~60%) of patients with visible tumor in the last MRI and a relatively small cure percentage (~10%) in both groups of patients and without significant differences between both groups, suggesting a very long-term follow-up in the majority of patients with macroprolactinomas. Lastly, multimodal therapy achieved an improvement in visual acuity and a slightly reduction in the prevalence of hypopituitarism in both study groups.

In conclusion, gPRLomas in men are usually diagnosed at the age of 40 years, an age similar to that of non-gPRLomas. At diagnosis, the only clinical difference with non-gPRLomas is their greater prevalence of visual disturbances; being the prevalence of hormonal involvement comparable. The therapeutic approaches and tumor outcomes (control of hyperprolactinemia and tumor size reduction) were similar to those obtained in non-gPRLoma men. However, a larger final tumor size and a higher prevalence of hypopituitarism were found in gPRLoma patients. DA monotherapy achieves similar tumor outcomes in both groups of patients. Complete cure in gPRLoma is rare, reached in less than 10% of patients, being similar to that obtained in non-gPRLomas, indicating the need for long-term follow-up in both groups of patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

References