

Giant Non-Functioning Pituitary Adenoma: Clinical Characteristics and Therapeutic Outcomes

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Abstract

Background. Giant pituitary adenoma (≥ 4 cm) is a rare tumor whose clinical features and prognosis are not well known.

Aim. To evaluate the clinical characteristics and therapeutic outcomes of giant non-functioning PA (gNFPA).

Patients and Methods. A retrospective multicenter study of gNFPA patients diagnosed in a 12-year period was performed. In each patient, clinical data and therapeutic outcomes were registered.

Results. Forty patients (24 men, age 54.2 ± 16.2 years) were studied. The maximum tumor diameter [median (interquartile range)] was 4.6 cm (4.1–5.1). Women had larger tumors [4.8 cm (4.2–5.4) vs. 4.5 cm (4.0–4.9); $p = 0.048$]. Hypopituitarism [partial ($n = 22$, 55%) or complete ($n = 9$, 22.5%)] at diagnosis was present in 77.5% of the patients. Visual field defects were found in 90.9%. The most used surgical technique was endoscopic endonasal transsphenoidal (EET) surgery ($n = 31$, 77.5%). Radiotherapy was used in 11 (27.5%) patients (median dose 50.4 Gy, range 50–54). Thirty-seven patients were followed for 36 months (10–67 months). Although more than half of these patients showed tumor persistence ($n = 25$, 67.6%), tumor size was significantly reduced [0.8 cm (0–2.5); $p < 0.001$]. At last visit, 12 patients (32.4%) showed absence of tumor on MRI. Hypopituitarism rate was similar (75.0%), although with significant changes ($p < 0.001$) in the distribution of the type of hypopituitarism. The absence of tumor at the last visit was positively associated with positive immunohistochemical staining for FSH ($p = 0.01$) and LH ($p = 0.006$) and negatively with female sex ($p = 0.011$), cavernous sinus invasion ($p = 0.005$) and the presence of Knosp grade 4 ($p = 0.013$).

Conclusion. gNFPA are more frequent in men but tumors are larger in women. Surgical treatment is followed by a complete tumor resection rate of approximately 30%. Positive immunostaining for gonadotropins is associated with tumor absence at last revision, while female sex and invasion of the cavernous sinuses with tumor persistence.

Key-words

Giant non-functioning pituitary adenoma, hypopituitarism, visual field defects, neurosurgery, and therapeutic outcome

Introduction

Pituitary adenoma (PA) is a common tumor. At present, PA is considered the third type of intracranial tumor, following to meningioma and glioma. With imaging techniques, its prevalence has increased to 22% in some series, with a wide range that varies from 1–40% [1–4].

PA can be functioning and non-functioning and its frequency depends on different factors, such as age at diagnosis and sex [5]. In young patients (second or third decade of life) and, mainly in women, the most frequent pituitary tumor is lactotrope adenoma (prolactinoma), usually less than 1cm (microprolactinoma), whereas non-functioning PA (NFPA), usually ≥ 1 cm (macroadenoma), is more common in adults (around six decade of life), without sex predilection [6].

Giant pituitary adenoma (gPA) (≥ 4 cm) constitutes approximately 6–10% of all PA [7–9]. Among them, the most frequent is NFPA, being more than double than functioning PA (68.8 vs. 31.2%) [7]. Symptoms of gPA mainly arise from the effect of the tumor mass, anterior pituitary hormonal deficiency and, in functioning gPA, clinical manifestations derived from hormonal hypersecretion. To date, little information is available on the clinical behavior and therapeutic results in the giant non-functioning pituitary adenoma (gNFPA) [10]. Therefore, we aimed to analyze the clinical features and therapeutic outcomes in a large series of gNFPA patients in our population.

Patients and Methods

A multicenter retrospective study of patients with gNFPA surgically treated over 12 years (2006 and 2018) was performed. Clinical data, hormonal study, imaging tests, and therapeutic outcomes were registered in each patient. Patient data were obtained under the standard medical care conditions. Patient confidential information was protected according to national normative.

Diagnosis of gNFPA was established when the maximal tumor diameter on MRI at diagnosis was ≥ 4 cm associated with the histological demonstration of the tumor and the absence of clinical symptoms or analytical hormonal data compatible with pituitary hyperfunction.

In every patient the following parameters were analyzed: age at diagnosis, main complaint at presentation, tumor size and extension by CT and MRI, visual field examination, hormonal study, type of surgery, pathological study and tumor size response to therapy. Type and number of pituitary deficiencies were also registered. Hypopituitarism was defined as deficient secretion of one or more pituitary hormones diagnosed by criteria of routine clinical practice.

To establish the diagnosis of hypopituitarism, baseline hormonal (thyrotropin, TSH; free thyroxine, FT4; follicle-stimulating hormone, FSH; luteinizing hormone, LH; testosterone (men), 17-betaestradiol (women); cortisol; and insulin-like growth factor type 1, IGF 1) and PRL measurements were performed in each laboratory using standard radioimmunoassay, immunoradiometric assay or enzymeimmunoassay methods, with their respective reference ranges. Hormonal status was evaluated at diagnosis, at 6 months after surgery, and again at their last clinical visit.

Statistical analysis

Results are expressed as mean \pm SD for normally distributed data or as median (interquartile range) for nonparametric data. The Kolmogorov test was used to check the normal distribution of the quantitative variables. The Student t-test was used for mean comparisons between two groups of subjects for normally distributed data, and the Mann-Whitney test was employed for nonparametric data. For ratio comparisons, the χ^2 test was used. Differences were considered significant when $p < 0.05$.

Results

Clinical data

We studied 40 patients (24 men, age 54.2 ± 16.2 years, male to female ratio of 1.5). Maximum tumor diameter [median (interquartile range)] was 4.6 cm (4.1–5.1). Age at diagnosis was similar in both sexes (male vs. female, 53.7 ± 16.3 vs. 54.9 ± 16.5 years, ns). Women had larger tumors than men [4.8 cm (4.2–5.4) vs. 4.5 cm (4.0–4.9); $p = 0.048$]. Moreover, tumors in women showed a significantly higher percentage of Knosp grade 4 than in men [$n = 8$ (50%) vs. $n = 3$ (12.5%), $p = 0.013$].

Hypopituitarism [partial (n = 22; 55 %) or complete (n = 9; 22.5%)] at diagnosis was present in approximately three quarters of patients (n =31; 77.5%) (Fig. 1). The most frequently affected hormonal axis was the gonadal axis (n=25; 62.5%), followed by the adrenal (n = 18; 45%), thyroid (n = 15; 37.5%) and somatotrophic (n=15; 37.5%) axes. Diabetes insipidus (DI) was uncommon (n =1, 2.5%). The only patient with DI was a 49-year-old male who had complete hypopituitarism with post-surgical DI who was referred to perform the fifth surgery after tumor persistence/recurrence.

The ocular fundus registered in 20 patients (50%) was pathological in 16 (80%), while visual field examination performed in 33 patients was pathological in 30 patients (90.9%). The most prevalent visual field defect was bilateral temporal hemianopsia (n = 18, 60%) followed by unilateral temporal hemianopsia (n = 8, 26.7%).

Surgical treatment and pathological results

The surgical technique most used was endoscopic endonasal transsphenoidal (EET) surgery (n = 31, 77.5 %) followed by the microscopic transsphenoidal (MT) (n=4, 10%), transfrontal (n=3, 7.5%) and pterional (n = 2, 5%) surgery. The percentage of postoperative complications was 32.5% (n = 13), mainly cerebrospinal fluid fistula (n=4, 10%) and permanent DI (n=3, 7.5%). There were no cases of perioperative mortality.

The immunohistochemical study was positive in 30 patients [FSH (n = 14; 46.7%), LH (n = 13; 43.3%), ACTH (n = 8; 26.7%), TSH (n = 3; 10%), GH (n = 3; 10%) and PRL (n = 1; 3.3%)]. Ki67 index was evaluated in 33 patients. Ki67 value most frequently observed were 2% (n=9; 27.3%), 3% (n=8; 24.8%) and 1% (n=4; 12.1%). Approximately one third of the patients showed Ki67 values > 3% (n = 11; 33.3%). No significant differences were found in the Ki67 index between males and females, and between those patients with tumor not showing regrowth and tumor persistence.

Clinical follow-up

Six months after surgery, complete resection of the tumor was achieved in 10 patients (25%) together with a significant reduction in maximum tumor diameter in patients with residual lesions [0.9 cm (0–2.5), p < 0.001]. At this point, the prevalence of

hypopituitarism was similar to that of the diagnosis (n = 31; 77.5%); although partial hypopituitarism (n = 18; 45%) decreased, completed hypopituitarism (n = 13; 32.5 %) increased (Fig. 1). The percentage of abnormal visual field decreased to 41.7% (n=14), being unilateral hemianopsia the most frequent (40%; n=13) campimetric alteration.

Radiotherapy was used in 11 (27.5 %) patients (median dose 50.4 Gy, range 50–54). Main used techniques were fractionated stereotactic radiotherapy (FSRT) (n=8; 72.7%), radiosurgery (n=2; 18.2 %) and conventional radiotherapy (n=1; 9.1%). During the study period, seven (17.5 %) patients required a second surgery [tumor regrowth (n = 4), tumor persistence (n = 2) and visual disturbances (n=1)] and 2 (5%) a third surgery [tumor regrowth (n=1) and headache and visual disturbances (n = 1)].

At last clinical visit, 37 patients (92.5%) could be evaluated after a follow-up period of >6 months. Median follow-up was 36 months (10–67 months). At this time, the maximum tumor diameter remained stable compared to the evaluation 6 months after surgery [0.8cm (0–2.5); p <0.001 vs. basal; ns vs. 6 months]. The maximum tumor diameter between 6 months and the last visit in irradiated tumors was similar [2.1 cm (1.2–2.9) vs. 2.4 cm (1.37–2.87); ns].

Twelve patients (32.4 %) showed absence of tumor on MRI (Fig. 2) and the number of patients with hypopituitarism was similar to the diagnosis (n = 30, 81.1%), with significant changes in the distribution of the type of hypopituitarism [partial hypopituitarism (n = 14; 37.8 %) and completed hypopituitarism (n = 16; 43.2%)] (Fig. 1). The visual field examination in the last revision carried out in 21 patients (52.5%) was pathological in 8 patients (38.1%), being the most common alteration unilateral temporal hemianopsia (n = 5, 62.5%).

The absence of tumor on last MRI was negatively associated with female sex (p=0.011), cavernous sinus invasion (p=0.005) and the presence of Knosp 4 grade (p = 0.013) (Fig. 2).

Discussion

The present study reports a large series of gNFPA patients surgically treated, with a median follow-up period of more than 6 months in 37 of them. Our survey shows that gNFPA is more frequent in men although its size is greater and more invasive in women. Hypopituitarism is present in approximately three quarters of patients and it is usually associated with bilateral temporal hemianopsia. Surgery is accompanied by a complete resection rate in ~30% of patients, visual field improvement and worsening of pituitary function. The positive immunostaining for gonadotropins is associated with a higher percentage of tumor absence, while the female sex and the invasion of the cavernous sinuses are associated with tumor persistence.

It is known that gNFPA is the most frequent histological type of gPA. They constitute approximately two thirds of the gPA tumors [7]. It has been suggested that this higher prevalence could be due to an absence of clinical syndrome associated with tumor hormone hypersecretion [10].

As it occurs with giant prolactinoma (gPRLoma), the prevalence of gNFPA is higher in males than in females [11,12]. Some series of gNFPA patients have reported a male to female ratio of 1.2 with a mean age at diagnosis of 48 and 54 years in men and in women, respectively [7]. In our cohort of patients the prevalence was also higher in males, with a slightly higher male to female ratio of about 1.5. However, in our study we did not find any significant difference in age in relation to the sex of the patients showing a mean age at diagnosis in the middle of the 6th decade of life.

We found a significantly larger tumor size in women compared to men. Moreover, gNFPA in women were more invasive. This finding has been also observed in nongNFPA patients. In fact, women with nongNFPA, the preoperative duration of symptoms is shorter, the tumors are larger and more invasive, and the clinical outcome is worse than in men [13, 14]. These findings are just the opposite of what have been described in gPRLoma [15, 16]. The explanation for these findings is not known. It is possible that gNFPA show a different clinical and biological behavior indicating specific gender differences as it has been reported in gPRLoma [10, 12, 17]. The confirmation of these findings could justify a more aggressive therapeutic behavior in women with gNFPA.

The incidence of pituitary dysfunction in NFPA patients in different studies varies widely. Recently, a positive correlation between the tumor size and maximum tumor diameter with the incidence and degree of hypopituitarism has been reported [18]. In this study, 43 patients with gNFPA (defined as tumor size > 3 cm) from Chinese population, the prevalence of hypopituitarism was close to 90% compared to 76.8% of patients with nongNFPA, being the central hypogonadism the most common pituitary deficiency [18]. The prevalence of hypopituitarism at diagnosis in our population was not as high as in Chinese population, but was present in most patients (77.5%) with hypogonadism as the main hormonal deficiency.

Recovery of the pituitary dysfunction after surgery in NFPA varies as a function of the extent of surgery resection and the degree of preoperative hypopituitarism. Although a recovery of anterior pituitary function has been reported in patients with gNFPA after surgery [18], in our series the percentage of hypopituitarism (complete or partial) remained stable, although the percentage of patients with complete hypopituitarism increased at the expense of a reduction in the percentage of patients with partial hypopituitarism. The differences found with the previous reports could be related to the larger size of the tumor, and therefore a more aggressive surgery, in our series of patients compared with those described in more recent series [18]. Another possible explanation would be the use of radiotherapy and several surgeries in a significant percentage of patients.

Visual acuity alteration and visual field loss is a well known clinical feature of pituitary adenoma at presentation [19, 20]. In fact, visual impairment and visual field defects are the most common (72%) preoperative symptoms followed by headache (13%) in NFPA patients [21]. Given the large size of the adenoma, suprasellar extension with compression of the chiasm and/or optic nerves is more frequent and severe in gNFPA patients. In our series, the ocular fundus was pathological in 80 % of the patients evaluated while the visual field was abnormal in 90%. However, unlike what happened with pituitary function, visual function improved significantly, indicating a beneficial effect of surgery despite a more aggressive surgical treatment in these patients.

Except for prolactinoma, surgical treatment is considered nowadays as the first choice in gPA [10]. At present, major advances in neurosurgical techniques have achieved more aggressive resections with a significant reduction in morbidity and mortality

associated with resection [22]. In a systematic review, Komotar et al in 2012 showed that EET surgery achieved higher rates of gross total resection (42.7%) compared with MT (30.9%) and open TC (9.6%) surgery in surgical series for pediatric and adult pituitary with gPA [23]. Despite the large size and tumor extension in gNFPA, EET surgery was the most used in our series, while other more aggressive techniques were used marginally. EET approach achieved a gross total resection rate in these tumors of 30% in our series.

Given the size and volume of gPA, the percentage of patients with tumor persistence after surgery is high. In this setting, radiotherapy has shown to be effective in the prevention and treatment of the tumor remnant progression and tumor recurrence [24]. In our series, radiotherapy had to be used in approximately one-third of patients. On the other hand, the use of several surgeries was also necessary for a not insignificant percentage (~20%) of patients.

Significant factors seem to limit the degree of resection in giant PA, such as a multilobular configuration of the adenoma and extension to the middle fossa. On the contrary, cavernous sinus invasion, tumor size, and intraventricular or posterior fossa extension did not influence the surgical outcome [25]. Other authors showed that invasiveness into the sphenoid sinus similarly was associated with a poorer outcome, even though the significance was of borderline importance. However, sex, age, type of adenoma, maximum tumor diameter, degree of suprasellar extension (craniocaudal diameter), retrosellar expansion, ethmoidal and nasal fosse involvement, history of previous pituitary surgery, and type of surgery did not affect surgical outcome [26]. Although some studies [27] have found a worse prognosis with a higher rate of recurrence in tumors with Ki67 values > 3% in patients with gNFPA, in our series, Ki67 value was not associated with tumor size at diagnosis, sex of the patients, invasiveness of cavernous sinus, and probability of tumor not showing regrowth. In this setting, tumor not showing regrowth was positively associated to positive immunohistochemical staining for FSH and for LH and negatively with female sex and cavernous sinus invasion.

Strengths of the study were the relatively large number of patients evaluated and the long follow-up time. Main limitations are those derived from the type study, retrospective and multicenter, which involved the lack of uniformity in both diagnostic

procedures (hormonal assays, optical equipments, and MRI sensitivity) and therapeutic offer (different neurosurgeons and diverse surgical techniques) among hospital centers. Another limitation is the measurement of only basal hormonal data to exclude hypopituitarism which could underestimate the true prevalence of hypopituitarism. Lastly, the absence of clinical information of the 3 patients who were lost in the follow-up should be considered as an additional limitation.

In conclusion, gNFPAs are more common in men but larger in women. The positive immunostaining for gonadotropins is associated with tumor absence at last revision, while the female sex and the invasion of the cavernous sinuses are associated with tumor persistence.

Conflict of Interest

Authors declare that they have no conflict of interest.

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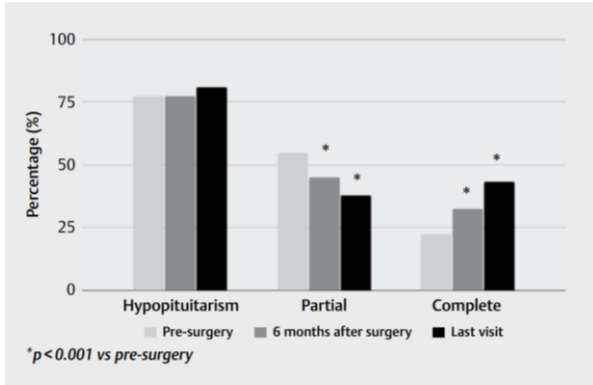


Fig. 1 Prevalence of hypopituitarism (partial and complete) at diagnosis, at 6 months after surgery and at the last clinical visit.

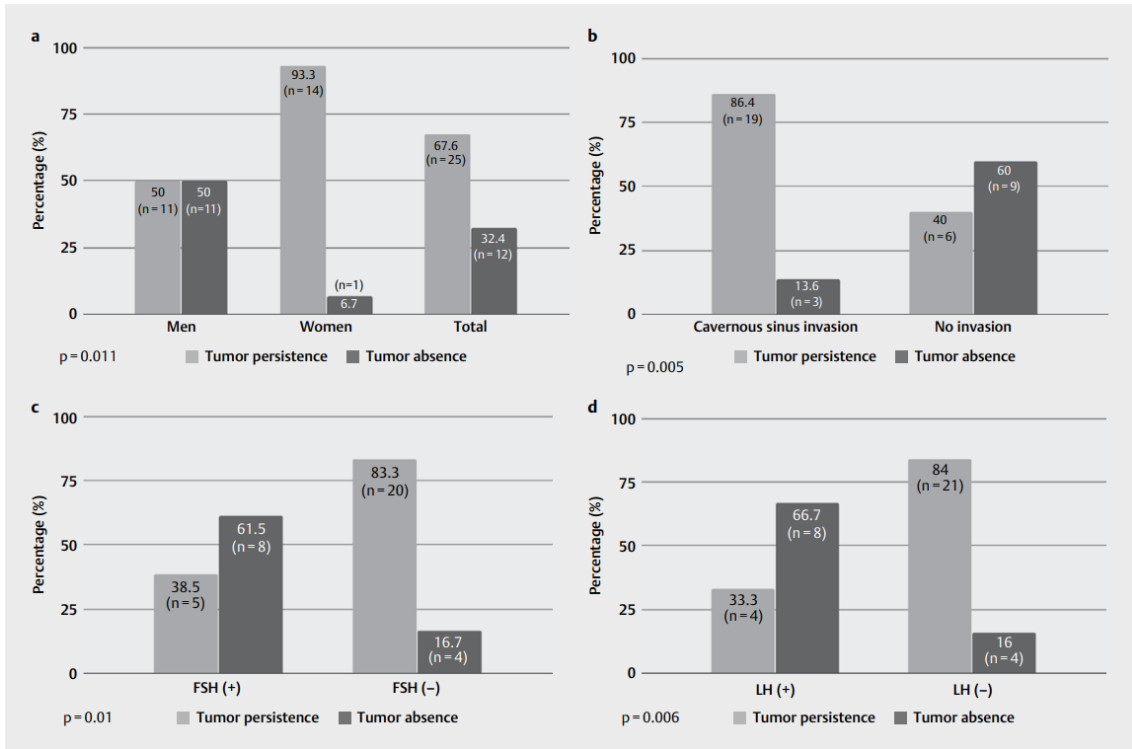


Fig. 2 Percentage of the absence of tumor on last MRI and tumor persistence in the last visit according to sex a, cavernous sinus invasion at diagnosis b and positive immunohistochemical staining for gonadotropins c and d.