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ARTICLE

Clinical and laboratorial characterization and post-surgical follow-up of 87 patients with non-functioning pituitary macroadenomas

Caracterização clínica e laboratorial e seguimento pós-cirúrgico de 87 portadores de macroadenomas hipofisários não funcionantes

Paulo Andrade de Mello[1], Luciana Ansaneli Naves[2], Aldo Pereira Neto[1], Eduardo Henrique Oliveira[3], Ivan Coelho Ferreira[3], Antônio Santos de Araújo Júnior[3], Franz Jooji Onishi[3], Luiz Augusto Casulari[4]

ABSTRACT

Objective: It was to assess the main characteristics of patients undergoing pituitary tumor surgery. **Method:** Eighty-seven patients (44 men; 44.8±13 years old) were included. **Results:** The main symptoms were visual alterations (87.3%), headache (70.1%), diminished libido (34.4%), galactorrhea (22.9%) and hair loss (19.5%). The axes affected were gonadotropic (72.6%), thyrotropic (48.4%) and corticotropic (38.7%), without significant changes after surgery. The average largest tumor diameter was 3.1 cm before surgery and 1.56 cm after surgery. The most frequent postoperative complications were hydro-electrolyte and acid-base disorders (12%), *diabetes insipidus* (9%), visual field alterations (9%), liquoric fistula (8%) and nasal obstruction (7%). The patients were affected by more than one complication. **Conclusion:** Although a decrease in tumor volume was achieved through surgery, hormonal deficiencies persisted in most of the patients and new surgical approaches were necessary for dealing with tumor recurrence or persistence.

Key words: pituitary neoplasms, neurosurgery, hormone, insufficient, pituitary adenomas, hypopituitarism.

RESUMO

Objetivo: Avaliar as principais características de pacientes operados de tumor de hipófise. **Método:** Foram incluídos 87 pacientes (44 homens; 44,8±13 anos). **Resultados:** Os principais sintomas foram alterações visuais (87,3%), cefaleia (70,1%), diminuição da libido (34,4%), galactorreia (22,9%) e queda de pelos (19,5%). Os eixos afetados foram gonadotrófico (72,6%), tireotrófico (48,4%) e corticotrófico (38,7%). Não houve mudanças significativas após a cirurgia. A média do maior diâmetro do tumor foi 3,1 cm antes da cirurgia e 1,56 cm após a cirurgia. As complicações pós-cirúrgicas mais frequentes foram distúrbios hidroeletrolíticos e ácido-básicos (12%), *diabetes insipidus* (9%), alterações do campo visual (9%), fístula liquórica (8%) e obstrução nasal (7%). Ocorreu mais de uma complicação no mesmo paciente. **Conclusão:** Embora tenha obtido diminuição da massa tumoral com a cirurgia, as deficiências hormonais persistiram na maioria dos pacientes e ocorreu necessidade de novas abordagens por recidiva ou persistência do tumor.

Palavras-Chave: neoplasia hipofisária, neurocirurgia, insuficiência, hormônio, adenomas hipofisarios, hipopituitarismo.

Pituitary tumors may be associated with significant morbidity, above all due to the compression effects on adjacent structures and endocrine effects from excessive production or hormone deficiency[1-3]. Pituitary tumors can be classified according to their ability to produce hormones (secreting or non-secreting adenomas), defined in terms of their clinical and hormonal elevation or from immunohistochemical analysis[1-3].

Clinically, non-functioning tumors lead to a silent clinical outcome, but can express functional capacity through immunohistochemistry, relating to frustrated production of peptides or their biochemical fractions, with no biological action[4-7]. Attempts to correlate certain markers with pathological potential have had no effect: expression of receptors for epidermal growth factor[5], Ki-67 antibodies with proliferative potential and C-erb-B2[7] did not correlate with

Study carried out at Hospital Universitário de Brasília, Brasília DF, Brazil.

[1]MD, PhD, Department of Neurosurgery, Hospital Universitário de Brasília, Universidade de Brasília (HUB-UnB), Brasília DF, Brazil;

[2]MD, PhD, Associate Professor of Endocrinology, Faculty of Medicine, UnB, Brasília DF, Brazil;

[3]MD, UnB, Brasília DF, Brazil;

[4]MD, PhD, Endocrinologist, HUB-UnB, Brasília DF, Brazil.

Correspondence: Paulo Andrade de Mello; SMDB / conjunto 7 / casa 1; 71680-070 Brasília DF - Brasil; E-mail: paulomello@terra.com.br

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the various biological aspects of non-functioning tumors. They also showed particular characteristics in relation to expression of receptors for somatostatin or for dopamine agonists because the response to pharmacological treatment is variable and dependent on the subtype of each receptor and its degree of expression in the tumor tissue[6].

Since these tumors have no specific clinical outcome resulting from hormonal hypersecretion, they are usually recognized late and present large lesions with complex surgical management[7,8]. Their main signs and symptoms result from compression of surrounding structures, such as optic chiasm, thus causing bitemporal hemianopsia and destruction of pituitary cells, which results in varying deficits of hormonal secretion[1,2,9].

The objective of this study was to present a sample of cases of non-functioning tumors that received surgical treatment at the University Hospital of Brasília. The main clinical and laboratory characteristics and surgical procedures, as well as the numbers of interventions and complications, were evaluated.

METHOD

This was an observational, descriptive and retrospective case study, in which patients operated at the Hospital Universitário de Brasília (HUB) between 1990 and 2006 were evaluated. Information was obtained from medical records, interviews and patient reviews at the neuroendocrinology outpatient clinics.

The inclusion criteria were that the patients should present a non-functioning pituitary adenoma defined by the absence of signs and symptoms of hormonal hypersecretion; the hormonal serum LH, FSH, TSH, cortisol, GH, IGF-1 and prolactin levels; or functional tests showing no excess hormones. The prolactin levels were the exception, which in some patients showed small increases due to compression of the pituitary stalk[10,11].

Patients with adenomas that through clinical and laboratory tests seemed to secrete pituitary hormones were excluded.

The hormone deficiency criterion was based on the presence of signs and symptoms of hormone deficiency and serum hormone measurements below normal values, according to the method used. Thyroid hormone deficiency was taken to be present when the level of free T4 was below 1 ng/mL. TSH was not considered for the diagnosis because production of this immunologically active hormone is common: it is recognized by the dosage test, but is biologically inactive[12]. Cortisol deficiency was taken to be present when the blood level was below 8 μg/dL at 8 o'clock in the morning, with or without signs and symptoms that might be associated with cortisol deficiency, i.e. weakness, asthenia, weight loss, postural hypotension, nausea and vomiting, diarrhea and myalgia[13]. In women, deficiency of gonadotropin secretion was defined by presence of amenorrhea before the age of menopause, decreased libido, and FSH, LH and estradiol levels different from those recommended for the age and menstrual cycle phase, according to the testing methods used at the time[13]. In men, gonadotropin deficiency was taken to be present when there was decreased libido and altered FSH, LH and total and free testosterone levels, in relation to those recommended for the age range[14,15]. No assessment was made of the routine GH axis, because this study was not directed towards hormone replacement given that the patients were adults. The tests for hormone levels were in the first cases measured by means of radioimmunoassay and, more recently, by immunoassay.

The sizes of the tumors in the first cases that were operated were measured on the image of the sella turcica obtained by means of computed tomography, with contrast in the anteroposterior plane. For more recent cases, images obtained by means of magnetic resonance on the sellar region with contrast were used.

The surgery on the first cases was performed by one of the neurosurgeon authors (Paulo Andrade de Mello) and, after 1996, another neurosurgeon (Aldo Pereira Neto) also participated.

The surgery consisted of a sublabial transseptal-transsphenoidal approach using a microscope described by Hardy, with some modifications[16,17]. In cases in which the tumor could not be removed, another new surgery procedure was carried out using either this approach or a transcranial one[18]. At the beginning of the series, a small number of patients were initially treated by means of a transcranial approach. In the immediate postoperative period, all patients were in the intensive care unit.

The statistical analysis was performed using Fisher's exact test or the χ^2 test for categorical variables and Student's *t*-test for continuous data with normal distribution. The $p \leq 0.05$ was taken to be statistically significant. The results were presented as means and standard deviations and percentages.

RESULTS

During the study period, 150 patients with pituitary macroadenomas were operated and had the following diagnoses: 91 (60.6%) with clinically non-functioning tumors, 40 (26.6%) with GH secretion, nine (6.0%) with prolactinomas, five (3.3%) with Cushing's disease and five (3.3%) with gonadotropin secretion.

Eighty-seven patients diagnosed with non-functioning pituitary adenoma were selected, since no detailed information was available on four patients, with no outpatient follow-up.

The patient distribution according to sex showed similar proportions: 44 men and 43 women. The average age at

the time of the first surgery was 44.8 years (SD=13), with extremes of 19 and 80 years of age. The vast majority of the patients were in the age range between 30 and 49 years (56.5%). The average ages of the males (45.3 years; SD=13.4) and females (44.1 years; SD=12.7) were similar.

The median follow-up period was 3.5 years, with a range from 6 months to 26 years.

The frequencies of initial manifestations are shown in Fig 1. It was observed that visual alterations were the most frequent (87.3%), followed by headache (70.1%), decreased libido (34.4%), galactorrhea (22.9%) and hair loss (19.5%). Galactorrhea, arthralgia and headache were more frequent only among women, while sweating and visual alterations were more frequent among men ($p<0.05$).

The distribution of patients' operations to surgical approach (either transsphenoidal or transcranial) and the number of surgeries is shown in Table 1. The transsphenoidal approach was initially adopted in 92% of the cases, and the transcranial approach in 8% of the cases. However, it was observed that, when new approaches were needed, the transsphenoidal approach was increasingly replaced by the transcranial technique. Among the 87 patients operated, 32 (36.7%) of them had to undergo a second procedure, and a percentage higher than in the first operation (n=13 [30.9%]) underwent the transcranial approach. Five patients (5.7%) underwent a third surgical procedure: one using the transsphenoidal technique and four using the transcranial technique (Table 1).

As shown in Table 2, the mean largest tumor diameter was 3.10 cm before surgery and 1.56 cm after surgery, with no significant difference between the men and women.

The surgical treatment was correlated with several complications, as shown in Table 3. The most frequent were hydroelectrolytic and acid-base disturbances, *diabetes insipidus*, visual field alterations, liquoric fistula and nasal obstruction. There were two deaths (3%) during the postoperative period of patients with tumors of large proportions. Some patients presented more than one complication.

Fig 2 shows the hormonal assessments before surgery and over the long-term follow-up of the patients. It was observed that, before surgery, the gonadotropic axis was the most affected (73%), followed by the thyrotropic axis (48%) and corticotropic axis (39%). Surgical treatment did not alter the deficits already present, with the exception of the corticotropic axis, in which more patients had deficits after surgery. Most patients remained indefinitely dependent on hormonal supplementation in relation to the affected axis.

Twenty-four patients (27%) received adjuvant radiotherapy: 13 of them were male and 11 female.

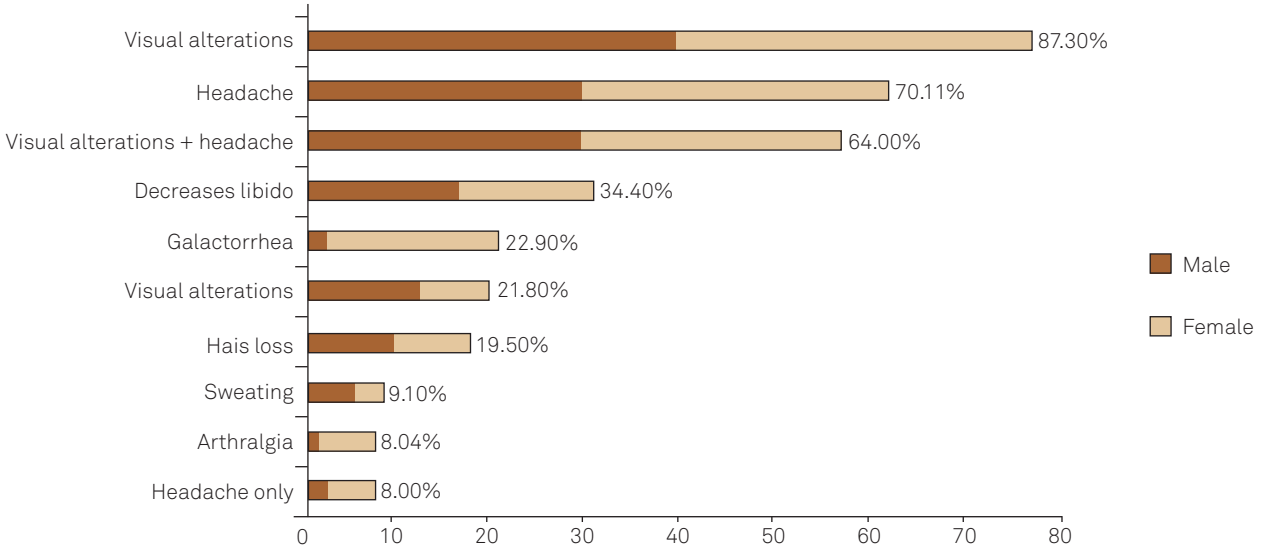

Fig 1. Frequencies of initial manifestations of the 87 patients with pituitary tumors.

Table 1. Distribution of patients undergoing to pituitary tumor surgery, according to the surgical technique.

	First surgery		Second surgery		Third surgery	
	TSE	TSC	TSE	TSC	TSE	TSC
Male	39	4	10	7	1	2
Female	41	3	9	6	0	2
Total	80 (91.9%)	7 (8.1%)	19 (69.1%)	13 (30.9%)	1 (20%)	4 (80%)

TSE: transsphenoidal surgery; TSC: transcranial surgery.

DISCUSSION

The present sample consisted only of non-functioning tumors, which represented 60.6% of pituitary tumors operated at UHB over the study period. The tumors most indicated for surgery are non-functioning, since they do not respond adequately to drug use[1-3]. However, it was recently reported that temozolomide may be useful for treating a few aggressive non-functioning tumors[19].

The frequency was similar between the sexes, which is in agreement with other samples[20], but higher prevalence among men has also been described[5]. As reviewed by Yamada[8], other immunohistochemistry-based studies showed predominance of men over women in silent gonadotropic cases and of women over men in silent adrenocorticotropic cases.

One of the clinical characteristics of non-functioning tumors is the higher frequency of diagnosis among the elderly[5]. It has been reported that 80% of pituitary tumors in the elderly over 65 years of age are non-secreting[21]. In this sample, most of the patients were over 40 years of age (61.7%). This can be explained, at least in part, by the delayed diagnosis caused by lower frequency of symptoms and signs relating to hormone secretion[1,2]. The slow progressive development of a lesion without functional indicators that would facilitate diagnosis seems to have led to two basic types of complaints among these patients: headache and visual disturbances. These symptoms have also been reported by other patients at the time of diagnosis[20,22]. Visual changes were present in 87.3% of the patients, given that the study population had only been referred to the hospital when they showed large lesions (average size of 3.1 cm). Regarding the high incident of headaches (70.1%), there may have been other explanations apart from the tumor size. As reviewed recently[23], the frequency has varied over a range from 33 to 72%, with several forms of presentation. Headaches relating to tumors of

Table 2. Tumor diameter before and after surgery.

	Before	After	p-value
Male	3.16±1.18*	1.65±1.4†	0.0004
Female	3.05±1.02	1.65±0.74	0.0009

*p=0.75 *versus* female; †p=0.99 *versus* female.

Table 3. Complications relating to surgical treatment on 87 patients with pituitary tumors.

Complication	n (%)*
Hydro-electrolyte and acid-base disorders	10 (12)
Diabetes insipidus	8 (9)
Visual field alteration	8 (9)
Liquoric fistula	7 (8)
Nasal obstruction	6 (7)
Ophthalmoplegia	4 (5)
Headache	4 (5)
Paresis or plegia	4 (5)
Meningitis	4 (5)
Sepsis and/or hospital infection	4 (5)
Deaths	2 (3)

*Several patients presented more than one complication.

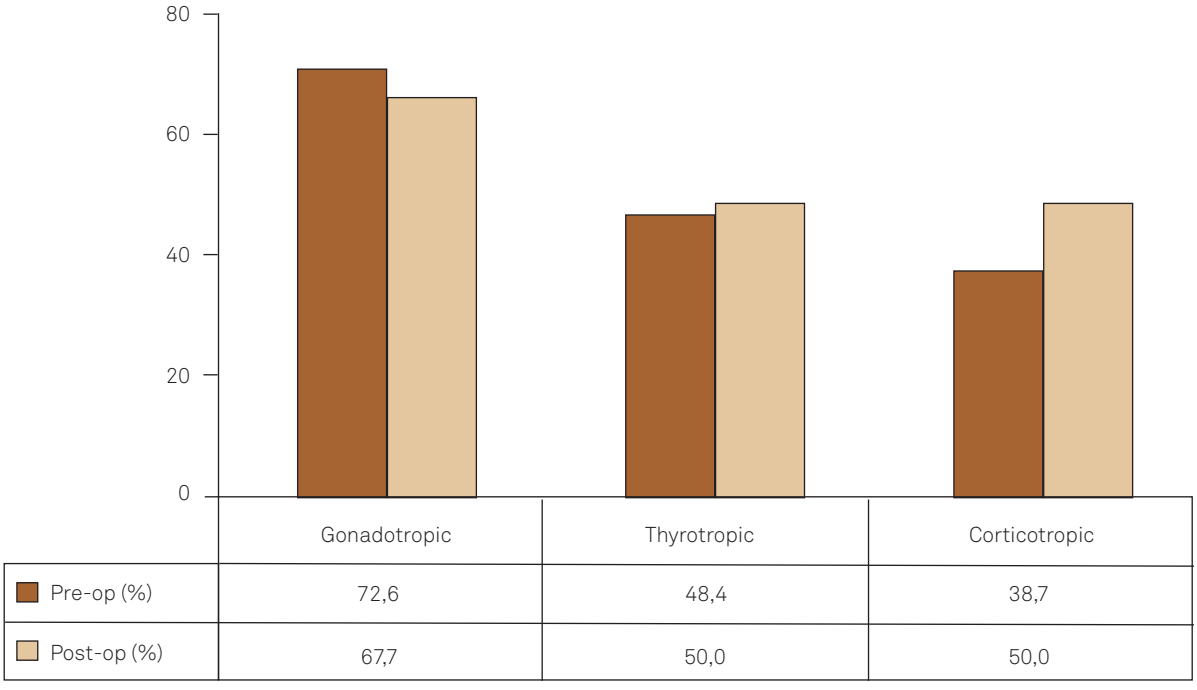

Fig 2. Hormonal assessments before surgery and over the long-term follow-up of the patients.

the hypophysis may involve pressure mechanisms on some structures, as well as a neuroendocrine origin. This has been discussed in detail by Freitas at al.[23].

Pituitary apoplexy[9,24] may be a form of presentation. Tumor presence is often discovered incidentally[20].

The basic principles of surgical management of tumors involving the pituitary gland include relieving the pressure on neighboring structures, particularly the visual structures, normalization of hypersecretion, preservation or restoration of pituitary function, prevention of tumor recurrence and collection of tissue for pathological and functional study[18].

These principles gain importance in the case of non-functioning adenomas, due to their complexity, which is primarily related to tumor size[7]. Monitoring the tumor volume before and after surgery showed that our patients' tumor size reduced on average from 3.1 to 1.56 cm, which suggests that for most of the patients treated only partial tumor removal was achieved. The fact that most of the patients were older, with large lesions and complex symptoms, guided the approach used and extent of surgical removal among these patients, in order not to produce new hormone deficiencies and injuries to important structures surrounding the tumor.

Most of the patients were operated by means of the transsphenoidal and transseptonasal techniques using a surgical microscope (Table 2). However, there has been a trend towards using transnasal endoscopy in healthcare services in Brazil[25-27] and abroad[28,29]. One of the advantages of using an endoscope would be the better viewing and resection of residual tumors due to the possibility of introducing the endoscope into the sella turcica and suprasellar region, which would facilitate the surgical cure[29]. Moreover, this might prevent bleeding in the cavernous sinus and lesions in the internal carotid artery[28]. These advantages would not be possible with the surgical microscope[26-29]. However, in operations on functioning tumors, Barbosa et al.[25] found no statistical differences in the results obtained with the two techniques. Total or near total removal of 83% of 93 non-functioning adenomas operated using solely the endonasal technique has recently been described[26]. Similar results were obtained with a small sample of 30 patients[27]. It is possible that the differences between what we obtained with our sample and the previous results were due to differences in the surgical techniques used.

The determining factor for signs and symptoms of compression is the pressure effect on neighboring structures. The immediate relief achieved through surgery seems to be directly related to the reduced intratumoral pressure[30-32]. In our sample, this was achieved through reduction of tumor volume and, more exceptionally, tumor exclusion. This difficulty in achieving tumor cure through surgery was also observed in 295 patients with non-functioning tumors, among whom this was achieved in only 35.5%[22]. Recurrence occurred in 19.2% of those who had no residual tumor after a mean of seven years after the surgery and in 58% of those with tumor residues after an average of five years. For the patients who received radiotherapy, the recurrence rate was 18.4% within eight years[22].

Hormone deficiency at the time of diagnosing a non-functional tumor is frequently observed[20]. The cases reported here had significant preoperative involvement in the gonadal, thyrotropic and corticotropic axes (Fig 2). The gonadal axis was also the one most frequently affected in other samples[22]. These axes remained affected and justified long-term replacement therapy. Although it could be inferred that relief of tumor compression after surgery could partially restore the affected pituitary axes, this expected result was not confirmed. This was also observed by other authors[20].

Surgery on large pituitary tumors was related to several complications, mostly of short duration (Table 1). Several patients presented more than one complication. Hydroelectrolyte and acid-base disorders occurred most frequently, and most were related to the presence of *diabetes insipidus*. The prevalence of *diabetes insipidus* after surgery using the endonasal endoscopic technique has been described as 3.5[26], 15[20] and 20%[25], but most cases were transient, as occurred with 9% of the cases operated in this study.

Liquoric fistula was present in 8% of the surgical patients and in many of them, fat grafting was used to prevent fistula, which in other studies would not have been the best choice[27]. All of these cases were treated with cerebrospinal fluid drainage only. Meningitis was present in 5% of the patients and required intensive antibiotic treatment. Meningitis was caused by liquoric fistula. Using only the endonasal technique, the presence of fistula has been described as 3.5[26] and 16%[27]. Of the cases, 77% were operated with this technique. The rest were operated with the aid of a microscope, and fistula occurred only in 10%, but no meningitis was observed as a complication.

Other complications observed after surgery (Table 3) were described in patients with large tumors, in which morbidity was very common[3].

There were two deaths (3%) during the postoperative period of patients with macroadenomas and large expansions, but it was not possible to obtain postmortem examinations to clarify the cause. However, the cause was suspected to be related to surgical management.

The long follow-up on the patients operated (4.5 years) suggested that most of them can live with residual tumors, provided that they are continually monitored, with replacement therapy administered to the major pituitary axes. Follow-up on patients with non-functioning pituitary tumors is necessary because it has been reported that 34.8% of such cases present increased tumor size after a mean time of 6.1 years after surgery. Using Kaplan-Meier analysis, the relapse rate was 23.1% after five years, 46.7% after 10 years and 67.9% after 15 years. Moreover, when a tumor regrowth rate was present

after surgery, it was significantly higher (p<0.001) than in patients with no tumor remains[33]. Similar results were observed by other authors[20]. However, this behavior is different from non-functioning tumors that are not selected for surgery, which in the majority (83%) of cases remain stable in size[9,20].

In conclusion, a significant reduction of tumor volume was achieved through surgery, but the hormonal deficiencies persisted in most of the patients. This led to the need for new approaches due to recurrence or persistence of tumor remains after the first surgery.

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