

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 Mello¹, Luciana Ansaneli Naves², Aldo Pereira Neto¹, Eduardo Henrique Oliveira³, Ivan Coelho Ferreira³, Antônio Santos de Araújo Júnior³, Franz Jooji Onishi³, Luiz Augusto Casulari⁴

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 hidroeletrólíticos e ácido-básicos (12%), *diabetes insipidus* (9%), alterações do campo visual (9%), fistula líquórica (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 hipofisários, 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 deficiency¹⁻³. 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 analysis¹⁻³.

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 action⁴⁻⁷. Attempts to correlate certain markers with pathological potential have had no effect: expression of receptors for epidermal growth factor⁵, Ki-67 antibodies with proliferative potential and C-erb-B2⁷ did not correlate with

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

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

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

³MD, UnB, Brasília DF, Brazil;

⁴MD, 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

Conflicts of interest: There is no conflict of interest to declare.

Received 01 February 2012; Received in final form 28 November 2012; Accepted 05 December 2012.

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 tissue⁶.

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^{12,9}.

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 inactive¹². 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 myalgia¹³. 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 time¹³. 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-transphenoidal 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 one¹⁸. 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 hydro-electrolytic 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.

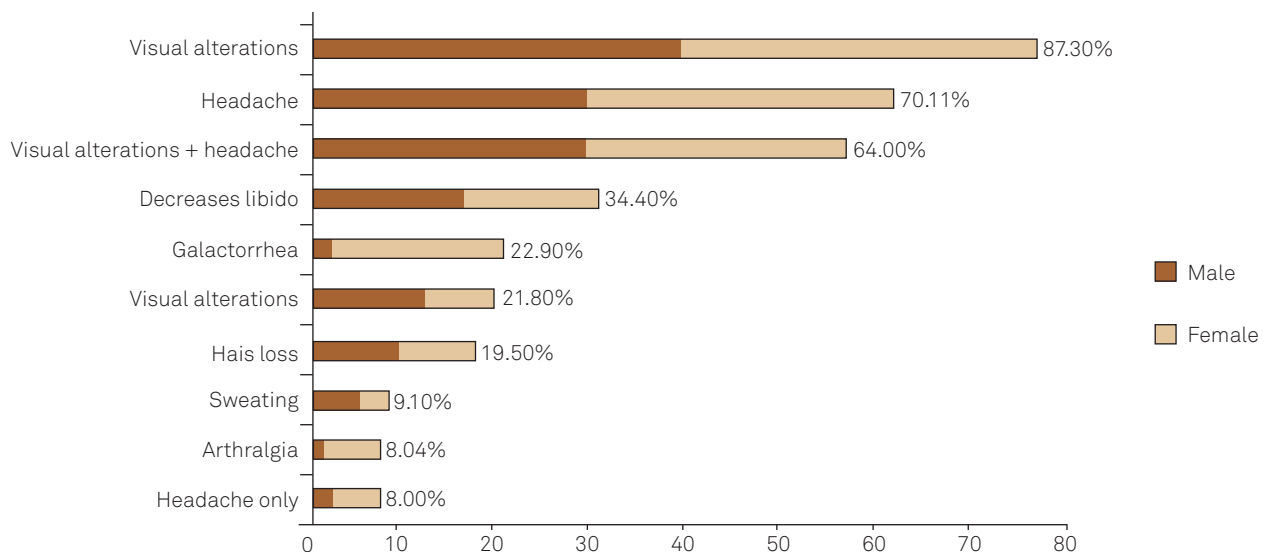


Fig 1. Frequencies of initial manifestations of the 87 patients with pituitary tumors.

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

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)
<i>Diabetes insipidus</i>	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.

adequately to drug use¹⁻³. However, it was recently reported that temozolomide may be useful for treating a few aggressive non-functioning tumors¹⁹.

The frequency was similar between the sexes, which is in agreement with other samples²⁰, but higher prevalence among men has also been described⁵. As reviewed by Yamada⁸, other immunohistochemistry-based studies showed predominance of men over women in silent gonadotropic cases and of women over men in silent adrenocorticotrophic cases.

One of the clinical characteristics of non-functioning tumors is the higher frequency of diagnosis among the elderly⁵. It has been reported that 80% of pituitary tumors in the elderly over 65 years of age are non-secreting²¹. 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 secretion¹². 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 recently²³, the frequency has varied over a range from 33 to 72%, with several forms of presentation. Headaches relating to tumors of

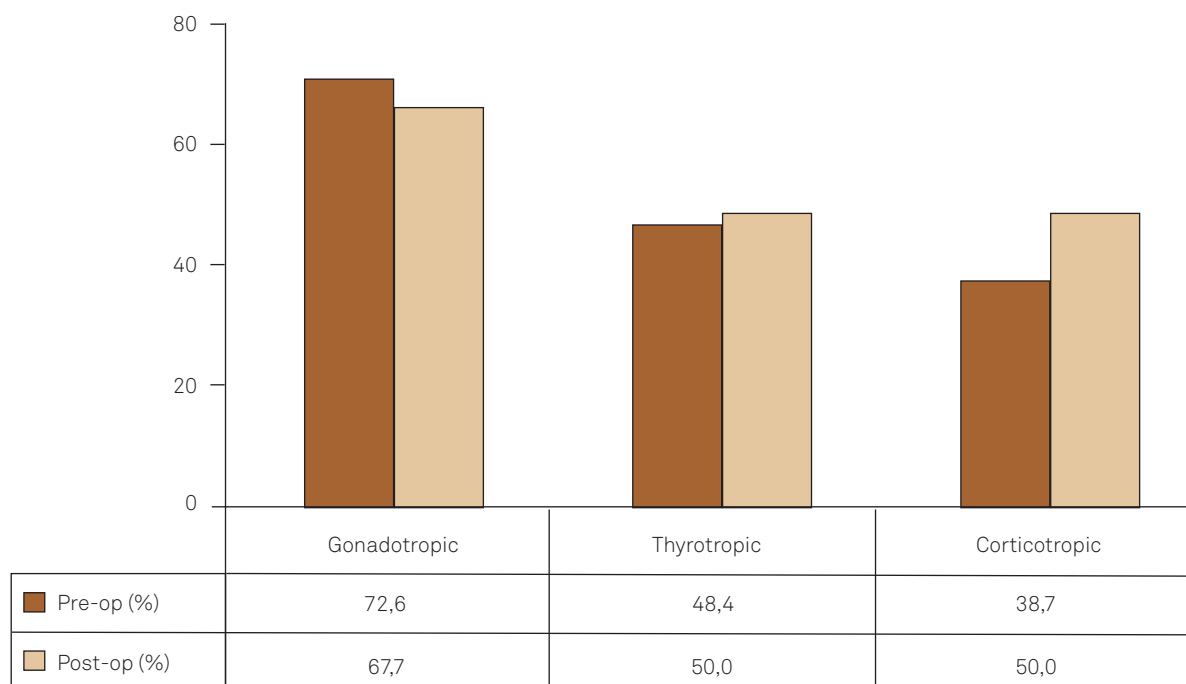


Fig 2. Hormonal assessments before surgery and over the long-term follow-up of the patients.

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

Pituitary apoplexy^{9,24} may be a form of presentation. Tumor presence is often discovered incidentally²⁰.

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 study¹⁸.

These principles gain importance in the case of non-functioning adenomas, due to their complexity, which is primarily related to tumor size⁷. 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 Brazil²⁵⁻²⁷ 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 cure²⁹. Moreover, this might prevent bleeding in the cavernous sinus and lesions in the internal carotid artery²⁸. These advantages would not be possible with the surgical microscope²⁶⁻²⁹. 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 described²⁶. Similar results were obtained with a small sample of 30 patients²⁷. 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 pressure³⁰⁻³². 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 years²².

Hormone deficiency at the time of diagnosing a non-functional tumor is frequently observed²⁰. 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 samples²². 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 authors²⁰.

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 3.5²⁶, 15²⁰ 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 choice²⁷. 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 3.5²⁶ 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 common³.

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 remains³³. Similar results were observed by other authors²⁰. 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.

References

- Naves LA, Vilar L, Monalisa A, Casulari LA, Mello PA. Adenomas hipofisários clinicamente não-funcionantes. In: Vilar L, Kater CE, Naves LA, Freitas MC, Bruno OD (Eds). *Endocrinologia Clínica*. 4. ed. Rio de Janeiro: Guanabara Koogan; 2009. p. 101-112.
- Vilar L, Naves LA, Freitas MC, Oliveira Jr S, Leite V, Canadas V. Tratamento medicamentoso dos tumores hipofisários. Parte II: Adenomas secretores de ACTH, TSH, clinicamente não funcionantes. *Arq Brasil Endocrinol Metabol* 2000;44:455-470.
- Chanson P, Salenave S. Diagnosis and treatment of pituitary adenomas. *Minerva Endocrinol* 2004;29:241-275.
- Oliveira Machado AL, Adams EF, Schott W, Nomikos P, Fhalbusch R, Buchfelder M. Analysis of secretory, immunostaining and clinical characteristics of human "functionless" pituitary adenomas: transdifferentiation or gonadotropinomas. *Exp Clin Endocrinol Diabetes* 2005;113:344-349.
- Rishi A, Sharma MC, Sarkar C, et al. A clinicopathological and imunohistochemical study of clinically non-functioning pituitary adenomas: a single institutional experience. *Neurol India* 2010;58:418-423.
- Karbonits M, Carlsen E. Recent clinical and pathophysiological advances in non-functioning pituitary adenomas. *Horm Res* 2009;71:S123-S130.
- Ferreira JEAF, Mello PA, Magalhães AV, et al. Caracterização clínica e imunoistoquímica dos adenomas clinicamente não-funcionantes. *Arq Neuropsiquiatr* 2005;63:1070-1078.
- Yamada S. Epidemiology of pituitary tumors. In: Thapar K, Kovacs K, Scheithauer BW (Eds). *Diagnosis and management of pituitary tumors*. New Jersey: Human Press; 2001. p. 57-70.
- Dekkers OM, Hammer S, de Keizer RJW, et al. The natural course of non-functioning pituitary macroadenomas. *Eur J Endocrinol* 2007;156:217-224.
- Vilar L, Naves LA, Casulari LA. Hiperprolactinemia - Problemas no diagnóstico. *Brasília Med* 2005;42:41-47.
- Vilar L, Casulari LA. Agonistas dopaminérgicos para prolactinomas: quando, quanto e por quanto tempo? *Brasília Med* 2009;46:267-275.
- Faglia G, Bitensky L, Pinchera A, et al. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. *J Clin Endocrinol Metab* 1979;48:989-998.
- Naves LA, Oliveira Jr AR, Vilar L. Hipopituitarismo - diagnóstico e tratamento. In: Vilar L, Kater CE, Naves LA, Freitas MC, Bruno OD (Eds). *Endocrinologia Clínica*. 4. ed. Rio de Janeiro: Guanabara Koogan; 2009, p. 23-36.
- Casulari LA, da Motta LD. Diagnostic of andropause: a problem not yet solved. *Arq Brasil Endocrinol Metabol* 2008;52:1401-1402.
- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91:1995-2010.
- Hardy J. Surgery of pituitary gland using the trans-sphenoidal approach. Comparative study of 2 technical methods. *Union Med Can* 1967;96:702-712.
- Dumont AS, Kanter AS, Jane JA, Laws Jr ER. Extended transsphenoidal approach. In: Laws Jr ER, Sheehan JP (Eds). *Pituitary surgery - a modern approach*. Frontier of Hormone Research. v. 34. Basel: Karger; 2006. p. 29-45.
- Maartens NE, Kaye AH. Role of transcranial approaches in the treatment of sellar and suprasellar lesions. In: Laws Jr. ER, Sheehan JP (Eds). *Pituitary surgery - a modern approach*. Frontier of Hormone Research. v. 24. Basel: Karger 2006. p. 1-28.
- Syro LV, Ortiz LD, Scheithauer BW, et al. Treatment of pituitary neoplasms with temozolomide: a review. *Cancer* 2011;117:454-462.
- Anagnostis P, Adamidou F, Polyzos SA, Efstathiadou Z, Panagiotou A, Kita M. Non-functioning pituitary adenomas: a single center experience. *Exp Clin Endocrinol Diabetes* 2011;119:314-319.
- Minniti G, Esposito V, Piccirilli M, Amato Fratticci A, Santoro A, Jaffrain-Rea ML. Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. *Eur J Endocrinol* 2005;153:723-735.
- Ferrante E, Ferraroni M, Castrignanò T, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumours. *Eur J Endocrinol* 2006;155:823-829.
- Freitas TS, Ferreira IC, Pereira Neto A, et al. Treatment of severe trigeminal headache in patients with pituitary adenomas. *Neurosurgery* 2011;68:1300-1308.
- Motta LACR, Mello PA, Lacerda CM, Pereira Neto A, Motta LDC, Farage Filho M. Pituitary apoplexy: clinical course, endocrine evaluations and treatment analysis. *J Neurosurg Sci* 1999;43:25-36.
- Barbosa ER, Zymberg ST, Santos RP, Machado HR, Abucham J. Controle hormonal dos adenomas hipofisários pela cirurgia transesfenoidal: evolução dos resultados nos primeiros cinco anos. *Arq Bras Endocrinol Metab* 2011;55:16-28.
- Gondim JÁ, Schops M, de Almeida JP, et al. Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. *Pituitary* 2010;13:68-77.
- Santos ARL, Fonseca Neto RM, Veiga JCE, et al. Endoscopic endonasal transsphenoidal approach for pituitary adenomas. Technical aspects and report of casuistic. *Arq Neuropsiquiatr* 2010;68:608-612.
- Tao Y, Jian-Wen G, Yong-Qin K, et al. Transesphenoidal surgery assisted by a new guidance device: results of a series of 747 cases. *Clin Neurol Neurosurg* 2011;113:626-630.
- Yang I, Wang MB, Bergsneider M. Making the transition from neurosurgery to endoscopic trans-sphenoidal pituitary neurosurgery. *Neurosurg Clin N Am* 2010;21:643-651.
- Arafat MB, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. *J Clin Endocrinol Metab* 2007;85:1789-1793.
- Gondim JA, Tella Jr OI, Schops M. Intrasellar pressure and tumor volume in pituitary tumor. *Arq Neuropsiquiatr* 2006;64:971-975.
- Pereira-Neto A, Borba AM, Mello PA, Naves LA, Araujo Jr. AS, Casulari LA. Mean intrasellar pressure, visual field, headache intensity and quality of life of patients with pituitary adenoma. *Arq Neuropsiquiatr* 2010;68:350-354.
- Reddy RG, Cudlip S, Byrne JV, Karavitaki N, Wass JA. Can we ever stop imaging in surgically treated and radiotherapy naive patients with non-functioning pituitary adenoma? *Eur J Endocrinol* 2011;165:739-744.