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ARTICLE

Long term follow-up of growth hormone-secreting pituitary adenomas submitted to endoscopic endonasal surgery

Seguimento de longo prazo de adenomas hipofisários secretores do hormônio do crescimento submetidos à cirurgia endoscópica endonasal

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ABSTRACT.

Objective: The aim of this study was to evaluate the results of the endoscopic transsphenoidal technique for growth hormone (GH)-secreting adenomas. **Methods:** A retrospective analysis based on medical records of 23 acromegalic patients submitted to endoscopic transsphenoidal surgery. Biochemical control was defined as basal GH < 1ng/ml, nadir GH < 0.4ng/ml after glucose load and age-adjusted IGF-1 normal at the last follow-up. **Results:** The overall endocrinological remission rate was 39.1%. While all microademonas achieved a cure, just one third of macroadenomas went into remission. Suprasellar extension, cavernous sinus invasion and high GH levels were associated with lower rates of disease control. The most common complication was diabetes insipidus and the most severe was an ischemic stroke. **Conclusion:** The endoscopic transsphenoidal approach is a safe and effective technique to control GH-secreting adenomas. The transcavernous approach may increase the risk of complications. Suprasellar and cavernous sinus extensions may preclude gross total resection of these tumors.

Keywords: acromegaly; growth hormone-secreting pituitary adenoma; endoscopy

RESUMO

Objetivo: O objetivo do estudo é analisar os resultados da cirurgia de ressecção endoscópica transesfenoidal para adenomas secretores do hormônio do crescimento (GH). **Métodos:** Revisão retrospectiva baseada em análise de prontuários de 23 pacientes acromegálicos submetidos à cirurgia endoscópica. Remissão foi definida por GH < 1ng/ml, nadir de GH ≤ 0,4ng/ml no teste oral de tolerância a glicose e IGF-1 normal para idade. **Resultados:** A taxa de remissão endocrinológica foi 39,1%. Enquanto todos microadenomas alcançaram controle hormonal, apenas um terço dos macroadenomas obtiveram remissão. Extensão suprasselar, invasão do seio cavernoso e altos níveis de GH foram associados a menores taxas de controle da doença. A complicação mais comum foi diabetes insipidus e a mais grave foi acidente vascular encefálico isquêmico. **Conclusão:** A abordagem endoscópica transesfenoidal é segura e efetiva para controle de adenomas hipofisários secretores de GH. A abordagem ao seio cavernoso pode aumentar a morbidade da cirurgia. Extensões suprasselares e no seio cavernoso podem dificultar a ressecção completa e o controle da doença.

Palavras-chave: acromegalia; adenoma hipofisário secretor de hormônio do crescimento; endoscopia

Supraphysiological levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are related to acromegaly[1,2]. This chronic disease is most commonly caused by pituitary tumors[3,4]. The increase in GH levels can cause cardiovascular and cerebrovascular diseases, which commonly result in death. Acromegaly carries a mortality rate at least twice as high as in the general population[4].

The main goal of treatment is the normalization of GH, IGF-1 levels and nadir GH < 0.4ng/ml after an oral glucose load, to reduce symptoms and mortality[5,6,7,8]. The options for acromegaly treatment include medical therapy, surgery, and radiotherapy. The surgical treatment provides rapid control of GH and IGF-1 levels and it is the first line of treatment for GH-secreting adenomas[1,9,10]. In 1893, in England, the first

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pituitary surgery for acromegaly was performed by Caton and Paul, under the supervision of Sir Victor Horsley[11,12,13], while the first transnasal resection of a pituitary tumor was performed by Schloffer in 1907[14]. Cushing[15] systematically used a transsphenoidal approach in sellar lesions and this technique was subsequently refined and popularized by Guiot[16] and Hardy[17,18]. The objectives of the surgical approach are gross tumor resection, relief of mass effect, normalization of hormone levels, reduction of recurrences and avoidance of postoperative complications, resulting in reduced morbidity and mortality[3,19,20].

The microsurgical transsphenoidal route has been the main approach for this disease. The endoscopic technique is a recent innovation[3,21,22] that allows a panoramic wide angle view to effectively reach supra- and parasellar lesions. Therefore has been suggested that the endoscopic technique may be preferred over the conventional technique, especially in patients with invasive macroadenomas[23,24,25].

The aim of this study was to evaluate the results of the endoscopic transsphenoidal technique for the control of GH-secreting adenomas.

METHODS

Patient population

A retrospective analysis based on medical records of acromegalic patients who underwent endoscopic transsphenoidal surgery, between February 2005 and April 2015.

The records of 104 patients that had pituitary surgery were reviewed, 26 had GH-secreting adenomas, and three were excluded because of missing data.

This study was approved by the Research Ethics Committee of Santa Casa de Misericórdia de São Paulo (project number 36634114.9.0000.5479).

Endocrinological evaluation

Growth hormone, IGF-1, oral glucose tolerance, and the remaining pituitary hormones were measured preoperatively, three months postoperatively, and at the last follow-up.

Hormonal control was defined as GH < 1.0 ng/ml and not higher than 0.4 ng/ml after glucose load, and IGF-1 levels normal for age[7].

Neuroimaging examination

Tumors were classified according to their size (macroadenomas > 1cm, microadenomas ≤ 1cm) and extension (sellar, suprasellar, parasellar).

Invasion of the cavernous sinus was considered when the magnetic resonance imaging (MRI) demonstrated Grade 2 or higher in the Knosp classification[26].

Surgical procedure

All the patients were submitted to an endoscopic endonasal transsphenoidal approach with a technique described in our previous publication[18]. All operations were performed by the same neurosurgeon.

Statistical analysis

Data was analyzed with OpenEpi Software, a web-based epidemiologic and statistical calculator for public health[27]. Descriptive statistics, such as mean, standard deviation and range were used to describe continuous variables, and percentages were used to describe categorical variables. Statistical analysis, consisting of the Chi-square test or Fisher exact test, Chi-square for trend and Student's t test, were performed to predict the remission rate based on tumor extension, GH and IGF-1 levels. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patients characteristics

Of the 23 patients evaluated for GH-secreting adenomas, nine (39.1%) were male and 14 (60.9%) were female. The mean age was 41.7 ± 11.9 years (range 15-65 years). The clinical manifestations of these patients are presented in Table 1. All the patients presented with clinical signs of acromegaly. Diabetes mellitus was the most common associated disease (56.5%). Approximately half of these patients presented with decreased visual acuity or visual fields, headaches, and bone and joint pain. No severe cardiovascular disease was identified and one patient presented with a cardiac valve lesion during follow-up. The mean preoperative GH values were 28.2 ± 35.6 ng/ml (range 2.4–151 ng/ml) and IGF-1 values were 730.7 ± 212.5 ng/ml (range 268–1178 ng/ml). Mean follow-up time was 46.9± 28.2 months (range 8–125 months).

Tumor characteristics

The majority of the tumors were classified as macroadenomas corresponding to 91.3% of the cases (21 patients). From all macroadenomas, 10 (47.6%) showed cavernous sinus invasion and 11 (52.4%) showed suprasellar extension (Table 2).

All the patients were submitted to endoscopic endonasal transsphenoidal resection of adenoma as the first-line treatment. In 15 patients (65%), this procedure was preceded by medical therapy. None was submitted to pituitary gland removal on the first approach. The material used to close the sella was absorbable hemostatic (Gelfoam – Upjohn, Kalamazoo), fibrin glue, a mucoperiosteal flap and fat graft with fascia lata, which are described in Table 3. Immunohistochemistry investigation of the removed tissue identified it as adenoma with expression for GH in all cases but one, which was identified as normal gland tissue (Table 4). In nine cases (39.1%), the pituitary adenoma showed expression only for GH and in eight cases (34.8%), it was mixed GH and prolactin.

Table 1. Clinical manifestations in 23 patients with acromegaly.

Variable	n (%)
Effects of GH / IGF-1 excess	
Acral enlargement	23 (100)
Facial changes	17 (73.9)
Increased genitalia	1 (4.3)
Direct effects of tumor	
Visual disturbance	12 (52.2)
Headache	11 (47.8)
Diplopia	1 (4.3)
Osteoarticular manifestations	
Bone and joint pain / carpal tunnel syndrome	11 (47.8)
Respiratory manifestations	
Obstructive sleep apnea	3 (13)
Deepening of the voice	6 (26.1)
Cutaneous manifestations	
Hyperhidrosis	9 (39.1)
Diabetes mellitus	13 (56.5)
Hypertension	9 (39.1)
Dyslipidemia	5 (21.7)
Others endocrine manifestations	
Amenorrhea	8 (34.8)
Sexual dysfunction / decreased libido	6 (26.1)
Galactorrhea	4 (17.4)
Colonic disease	
Hyperplastic polyps / diverticula	5 (21.7)
Hormonal disorders	
Hyperprolactinemia	10 (43.5)
Hypogonadism	7 (30.4)
Hypothyroidism	5 (21.7)
Hypocortisolism	4 (17.4)
Panhypopituitarism	4 (17.4)
Hyperparathyroidism (NEM1)	1 (4.3)

GH: growth hormone; IGF-1: insulin-line growth factor 1.

Table 2. Magnetic resonance imaging characteristics on 23 preoperative patients.

Variable	n (%)
Microadenoma (< 1 cm)	2 (8.7)
Macroadenoma (> 1 cm)	
S	6 (26.1)
S + CS	4 (17.4)
S + SS	5 (21.7)
S + SS + CS	6 (26.1)

S: sellar; SS: suprasellar; CS: cavernous sinus.

Table 3. Material used to close the sella in the first approach of 23 patients.

Variable	n (%)
Absorbable hemostatic	4 (17.4)
Absorbable hemostatic + fibrin glue	2 (8.7)
Fat graft / fascia lata + fibrin glue	3 (13)
Mucoperiosteal flap + fibrin glue	13 (56.5)
Mucoperiosteal flap + fibrin glue + fat graft / fascia lata	1 (4.3)

Table 4. Immunohistochemistry investigation of the lesion in 23 patients.

Variable	n (%)
Normal gland tissue	1 (4.3)
Adenoma with immunohistochemistry expression for GH	9 (39.1)
Adenoma with immunohistochemistry expression for GH and PRL	8 (34.8)
Adenoma with immunohistochemistry expression for GH and ACTH	2 (8.7)
Adenoma with immunohistochemistry expression for GH, PRL and ACTH	1 (4.3)
Adenoma with immunohistochemistry expression for GH, PRL and TSH	1 (4.3)
Adenoma with immunohistochemistry expression for GH, ACTH, TSH, FSH and LH	1 (4.3)

GH: growth hormone; PRL: Prolactin, ACTH: Adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

After the first approach, nine patients (39.1%) achieved hormonal remission, evaluated by serum GH levels < 1 ng/ml, IGF-1 levels normal for age and GH levels suppressed to < 0.4 ng/ml after glucose load. However, one of these patients could not be evaluated with the oral glucose test, because of diabetes. Postoperative MRI showed total tumor resection in eight cases (43.5%) and the presence of a residual lesion in 15 cases (56.5%), one of which had no clinical correlation. All 14 patients (60.9%) with persistent disease after the first surgery received medical treatment (Octreotide). Three of them were submitted to a second approach. After the second surgery, one patient achieved hormonal remission and medical treatment was suspended, the other patient was controlled with permanent medication. Both patients had an MRI demonstrating apparent total tumor resection. The third patient had a subtotal tumor resection and still lives with active disease. Another two patients received stereotactic radiotherapy. One of them was controlled with medication and presented with progressive hormonal level reduction over the eight years of follow-up. The other patient lives with persistent disease. Of the nine patients who received only medical treatment, only two achieved biochemical remission.

No recurrence of the GH-secreting adenoma occurred in the follow-up. Seven patients (33.3%) reported significant body soft tissue reduction. Of the 12 patients with visual disturbance, five (41.7%) showed improvement postoperatively. Of the 13 patients with diabetes mellitus, half had glycated hemoglobin reduction and a quarter could reduce their medication. Of the 10 patients with hypertension, two (20%) showed improvement.

Complications

In our study, surgical complications occurred in 13 patients (56.5%). Diabetes insipidus was the most common complication (39.1%). Seven (30.4%) were transient, six patients required treatment for a maximum of three days, and one for one year prior to resolution. Two patients (8.7%) had permanent diabetes

insipidus. Five patients (21.7%) developed cerebrospinal fluid (CSF) leaks; three were treated successfully with external lumbar drainage and two required a new approach to close the sella with a mucoperiostal flap, fat graft, fascia lata and fibrin glue. The correlation of the development of CSF leaks and the material used to close the sella is shown in Table 5. Four patients (17.4%) had otorhinolaryngologic complications; three of them had epistaxis, two were controlled with only nasal tampons, and one with a nasal catheter and nitroprusside. One patient had transient cacosmia. Two patients (8.7%) developed new panhypopituitarism. Postoperative meningitis was seen in one patient (4.3%), who had also suffered a CSF leak. The most severe complication was an ischemic stroke of the basal ganglia that occurred in one (4.3%) patient who was submitted to a transcavernous sinus approach with extensive manipulation of the carotid artery. This was associated with postoperative pneumonia, hemiparesis and dysphagia. There were no mortalities during the follow-up.

The postoperative complications of three patients submitted to a second transsphenoidal surgery was one case (33.3%) of meningitis and one (33.3%) of permanent diabetes insipidus. Panhypopituitarism persist in two of these patients.

Remission rate based on tumor extension and preoperative hormonal levels

The endocrinological remission rate was 39.1% for all tumors. The best results were achieved for microadenomas, with 100% of disease control. For macroadenomas, remission was obtained in seven patients (33.3%). The postoperative MRI showed total tumor resection in eight patients (34.8%) and residual tumor was identified in 15 patients (65.2%), one of which had no correlation with biochemical levels. Remission and non-remission groups are compared according to adenoma characteristics in Table 6. For statistical analysis, tumors were grouped into non-invasive (microadenomas and sellar macroadenoma), invasive in only one compartment (sellar macroadenoma with suprasellar extension or invasion of the cavernous sinus), and invasive in more than one compartment (sellar macroadenoma with suprasellar extension and cavernous sinus invasion). A meaningful statistical correlation was found between the tumor extension and persistent disease. The highest degrees of invasion tend to be associated with a lower biochemical remission rate ($p = 0.015$). It was also observed that the noninvasive tumors were associated with an increased probability of disease control when compared to invasive tumors ($p = 0.017$).

While preoperative IGF-1 serum levels did not show a statistically significant difference between patients who demonstrated remission and those who did not (respectively 622.3 ± 252.7 ng/ml [range 268–1178ng/ml] and 800.3 ± 154.2 ng/ml [range 607–1047 ng/ml]; $p = 0.08$), preoperative serum GH levels revealed a meaningful statistical difference between biochemical remission and non-remission groups (respectively 8.6 ± 7.9 ng/ml [range 2.4–25.6 ng/ml] and 40.7 ± 41 ng/ml [range 2.7–151 ng/ml]; $p = 0.01$).

Table 5. Correlation between the complication of CSF and material used to close the sella.

Material	Without CSF (n = 18)	With CSF (n = 5)
Absorbable hemostatic	3 (75%)	1 (25%)
Absorbable hemostatic + fibrin glue	2 (100%)	0 (0%)
Fat graft / fascia lata + fibrin glue	2 (33.3%)	1 (66.7%)
Mucoperiosteal flap + fibrin glue	10 (76.9%)	3 (23.1%)
Mucoperiosteal flap + fibrin glue + fat graft / fascia lata	1 (100%)	0 (0%)

CSF: cerebrospinal fluid.

Table 6. Tumor characteristics on MRI in remission and non-remission groups.

Variable	Remission (n = 9)	Non-remission (n =14)
Microadenoma	2 (100%)	0 (0%)
Macroadenoma		
S	4 (66.7%)	2 (33.3%)
S + CS	2 (50%)	2 (50%)
S + SS	1 (20%)	4 (80%)
S + SS + CS	0 (0%)	6 (100%)

MRI: Magnetic Ressonance Imaging; S: sellar; SS: suprasellar; CS: cavernous sinus.

DISCUSSION

Serum GH excess is associated with high morbidity and mortality rates[3,4,19,20]. The current first-line therapy for acromegaly is gross total resection of the adenoma. It aims to reduce symptoms, relieve compressive effects, improve acromegalic features, reverse cardiovascular risk and restore life expectancy[5,28].

The advantages offered by the endoscopic technique[3,21,22,28], which enables the use of different angles to operate, may facilitate resection of invasive lesions and, consequently, increase remission rate. However, the resection of adenomas in the cavernous sinus should be carefully considered due to the risk of neurovascular complications.

Long-term results of acromegalic patients submitted to endoscopic endonasal surgery are rarely reported in the literature. In this study, the patients were followed on average for 46.9 months, much longer than published in recent studies[1,3,4,5,27]. Only Wagenmakers et al.[23] presented long term follow-ups with a mean time of 56 months.

Remission rates after endoscopic endonasal transsphenoidal surgery for GH-secreting pituitary adenomas vary broadly, from 28.8% to 74.6%[1,3,5,11,18,23,28]. The highest

values were achieved using old criteria to define a cure[1,3,23]. As shown in recent papers, the best results were achieved in microadenomas (56–100%) compared to macroadenomas (27–71.7%)[1,4,18,28]. The worst outcomes were related to suprasellar and parasellar lesions. Therefore, the overall remission rate of 39.1% found in this study and the better remission rate for the microadenomas (100%) rather than macroadenomas (33.3%) were expected.

Recent literature has suggested some helpful predictors for tumor gross resection and endocrine remission are tumor size[3,4,5,11,28], extension of the lesion[1,3,4,5,11,28] and hormonal levels[4,23,28].

Concerning tumor extension, Campbell et al.[3] and Buliman et al.[4] evidenced that Knosp grades 3 or 4 were less likely to achieve remission. Univariate analysis of Sarkar et al.[28] demonstrated that absence of cavernous sinus invasion and suprasellar extension were prognostic factors. While Gondim et al.[1] associated higher levels of suprasellar/parasellar extension and sella floor erosion with lower disease control (p = 0.01 and p = 0.02, respectively), Bunderen et al[11]. analysis reached borderline significance levels, suggesting that parasellar and infrasellar extension tend to be independent predictors of persistent disease. On the other hand, in the study by Wagenmakers et al.[23], an invasive tumor did not have significant influence on the remission rate. It was observed in this study that the absence of suprasellar or cavernous sinus invasion were signs of a good prognosis, and there was a tendency for a lower rate of remission, the higher the degree of tumor invasion.

Additionally, a significant correlation was observed between preoperative GH serum levels and the endocrinological outcome. Univariate analysis of Sarkar et al.[28] established that preoperative GH levels below 40 ng/ml are independent prognostic factors. Buliman et al.[4] also noticed lower GH levels among patients with complete hormonal remission rates. However, there are other studies that indicate no significant difference in preoperative GH levels between patients who achieved remission and those who did not[3,5]. Our results are comparable to Sarkar et al.[28] and Buliman et al.[4], revealing a statistically meaningful influence in this hormone level and the remission rate (p = 0.01). In our study, preoperative IGF-1 serum levels did not differ significantly between remission and non-remission groups (p = 0.08), which is in concordance with Buliman et al.[4], Wangenmakers et al. [23] and Sarkar et al.[28].

In this study, the postoperative complication rate was 56.5%, including one major complication (ischemic stroke). This result is significantly higher than observed in recent papers[1,3,4,5,11,18,23,28], probably due to the greater prevalence of macroadenomas with extrasellar extension (65.2%) in our cohort (Figure 1). Large suprasellar and parasellar extensions with invasion of cavernous sinus may add a significant risk of complications to the procedure.

Transient diabetes insipidus occurred in seven patients (30.4%), which is just comparable with the 37.5% rate of Wangenmakers et al.[23]; in others studies this percentage varied from 3.3% to 9.1%[1,3,4,18,28]. Permanent diabetes insipidus occurred in two patients (8.7%), which is a little higher than the 6.7% found by Bunderen et al.[11] and our own previous experience[18]. Five patients (21.7%) developed CSF leak and two (8.7%) developed panhypopituitarism, which is in concordance with a variation of 0% to 34.8%[1,3,4,5,11,18,23,28] and 8.3% to 18.2%[5,28], respectively, shown in recent literature. Wangenmakers et al.[23] described similar epistaxis rates to our study (13% and 10%, respectively). No patient experienced decreased visual fields or acuity after surgery, while five (41.7%) patients presented with improvement.

In conclusion, the endoscopic transsphenoidal approach is a safe and effective technique to control GH-secreting pituitary adenomas as seen after a long-term follow-up. The transcavernous approach may add a higher risk of complications to the procedure. Tumors with suprasellar extension associated with cavernous sinus invasion may impair the total resection of these tumors and disease control.

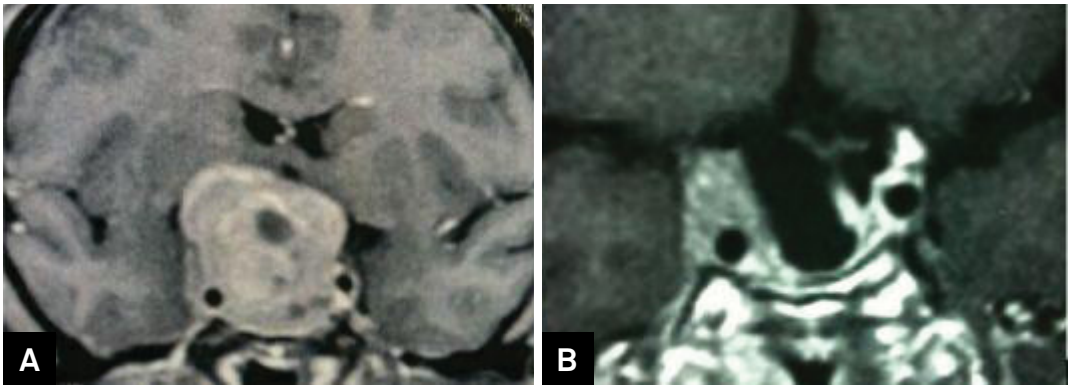

Figure. A) MRI T1 with gadolinium showing a pituitary adenoma with large suprasselar extension and invasion of the right cavernous sinus. B) Postoperative MRI demonstrating tumor remnant within the right cavernous sinus.

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