

INVESTIGACIÓN ORIGINAL

REMISIÓN BIOQUÍMICA DE PACIENTES ACROMEGÁLICOS SOMETIDOS A CIRUGÍA ENDOSCÓPICA

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Resumen: Objetivo. La cirugía transnasal transesfenoidal endoscópica es la base del tratamiento para la acromegalia en nuestro centro. Realizamos un estudio retrospectivo de 2008 – 2011 para determinar si este abordaje induce remisión bioquímica, y comparamos nuestras observaciones con series publicadas.

Métodos. Analizamos retrospectivamente nuestra base de datos, e identificamos los pacientes sometidos a cirugía transnasal transesfenoidal endoscópica como tratamiento primario de acromegalia. Valoramos las imágenes y perfiles endocrinológicos pre-operatorios, y utilizamos los criterios del Consenso de Acromegalia de 2009 para determinar la remisión bioquímica.

Resultados. Ocho pacientes recibieron adenomectomía endoscópica primaria. Uno tenía un microadenoma, otro un macroadenoma no invasivo, y seis presentaban macroadenomas invasivos. La media de los niveles del factor de crecimiento similar a la insulina tipo I tres meses post-cirugía fueron 633 ng/mL (199 ng/mL-1600 ng/mL), mientras que los de la hormona de crecimiento fueron 10,20 ng/mL (0,96 ng/mL – 16,60 ng/mL). Dos pacientes cumplieron criterios de remisión; un macroadenoma no invasivo y un microadenoma. Cuatro de los pacientes restantes tuvieron remisión con análogos de somatostatina.

Conclusiones. Este es el primer reporte de cirugía transnasal transesfenoidal endoscópica como terapia primaria de acromegalia en Costa Rica. La cura en pacientes con macroadenomas grandes e invasivos puede ser difícil y requiere de terapia multimodal.

Palabras clave: Acromegalia, Procedimiento quirúrgico endoscópico, Adenoma pituitario, Somatostatina

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BIOCHEMICAL REMISSION OF ACROMEGALIC PATIENTS WHO UNDERWENT ENDOSCOPIC SURGERY

Abstract: Objective. Endoscopic transnasal transsphenoidal surgery is the cornerstone of therapy for acromegaly at our Center. We conducted a retrospective study to determine whether this approach induced biochemical remission, and compared our observations to published series.

Methods. We performed a retrospective analysis of our Pituitary Surgery database, and identified all patients that underwent endoscopic transnasal transsphenoidal surgery as primary treatment for acromegaly. Pre-operative imaging and endocrinological panels were assessed, and the 2009 Acromegaly Consensus Group criteria were used to determine whether biochemical remission was achieved.

Results. Eight patients underwent primary endoscopic adenectomy. One had a microadenoma, one had a non-invasive macroadenoma, and the remaining six patients presented invasive macroadenomas. Median insulin-like growth factor I levels at three months of surgery were 633 ng/mL (199 ng/mL - 1600 ng/mL), while growth hormone levels were 10,20 ng/mL (0,96 ng/mL-16,60 ng/mL). Two patients met criteria for remission, with a non-invasive macroadenoma and a microadenoma. Four of the remaining patients achieved remission after administration of somatostatin analogues.

Conclusions. This is the first report of endoscopic transnasal transsphenoidal surgery as primary treatment for acromegaly in Costa Rica. Attaining cure in patients with large, invasive macroadenomas can be elusive, and a multi-modal approach is necessary.

Key words: Acromegaly; Endoscopic surgical procedure; Pituitary adenoma; Somatostatin

INTRODUCCIÓN

Hormone-secreting pituitary adenomas are responsible for approximately 99% of the cases of acromegaly. Therefore, over the past forty years, the treatment of choice for this condition has been transsphenoidal surgery (TSS) for tumor resection. The effectiveness of TSS has been shown by numerous authors, but the remission rates appear

to significantly drop for invasive adenomas [1]. In Latin America, and at our institution, Hospital Mexico, many patients with acromegaly present large tumors that are not confined to the sella turcica [2]. However, access to somatostatin analogues is not always subsidized by government agencies, which renders the management of large, invasive lesions challenging from both medical and socioeconomic standpoints. Because surgical

treatment is the cornerstone of therapy for acromegaly at our center regardless of tumor size and extrasellar expansion, we conducted a retrospective study of the Pituitary Surgery Database of the recently founded Skull Base Surgery Unit of our Center. Our interest was to present the initial results of endoscopic transnasal transsphenoidal surgery (ETSS) at our Unit, and compare them, in terms biochemical remission in patients with growth hormone (GH)-secreting adenomas, to other published series.

PATIENTS AND METHODS

We performed a retrospective analysis of our Pituitary Surgery database, where we identified eleven patients with GH-secreting adenomas. These patients had been referred to our Center for neuroendocrinological management, and they underwent ETSS for tumor resection between January 2008 and September 2011. The evaluation was performed with the authorization of the Ethics Committee of our Center, (CLOBI protocol number: CLOBI-HM-027-2011) and informed consent was obtained from all subjects regarding the proposed operation.

The inclusion criteria were the following: diagnosis of acromegaly based on GH levels > 1 ng/mL, insulin-like growth factor (IGF) I levels greater than the normal range for age and sex, and imaging evidence for a pituitary adenoma. Patients must have undergone ETSS at our Center between January 2008 and September 2011 as their primary treatment, and they must have been followed for at least six months by our multidisciplinary team of endocrinologists, neurosurgeons, and ear, nose and throat (ENT) surgeons with laboratory analyses and imaging.

Preoperative endocrinological assessment was performed at our Center by means of radioimmunoassay. A full endocrinological panel was obtained, in order to determine serum GH and IGF-I levels, as well as further hormone deficiencies. If other hormone disorders were identified, the corresponding treatment was

started. In the post-operative period, serum GH and IGF-I were assessed at three and six months. The 2009 Acromegaly Consensus Group criteria [3] for cure were used to determine biochemical remission in all of our patients. Accordingly, patients with normal IGF-I levels for age and sex, and random GH levels lower than 1,0 ng/mL, three months after surgery, were considered in biochemical remission. Alternatively, patients with elevated IGF-I levels at three months, were considered in biochemical remission only if their GH nadir during an oral glucose tolerance test (OGTT), was less than 0,4 ng/mL.

In case that biochemical remission was not achieved, the individual cases were raised to the Board of Directors of the Pharmacotherapy Committee of our institution. Each case was analyzed by this Committee in order to determine whether the patient would warrant a somatostatin analogue agent. If the decision was positive, somatostatin analogues were administered and IGF-I and GH levels were measured six months later to assess biochemical remission based on the aforementioned criteria.

All patients were evaluated by an ophthalmologist for visual acuity and visual fields. The latter were assessed through static perimetry. Visual field compromise, such as homonymous hemianopia, bitemporal hemianopia or quadrantanopia, was then correlated to imaging findings.

All patients were also classified according to their comorbidities. Hypertension, dyslipidemia, diabetes mellitus, obstructive sleep apnea, osteoarthritis and cardiovascular disease were sought in these patients in order to assess acromegaly manifestations.

All patients underwent pre-operative radiological evaluation by means of contrast-enhanced computed tomography (CECT) or gadolinium-enhanced magnetic resonance imaging (MRI). All pituitary adenomas were classified according to maximum tumor diameter as microadenomas (< 10 mm) or macroadenomas ($>$

10 mm). They were further classified according to the modified Hardy system considering their extension and invasion. Imaging studies were obtained post-operatively to assess tumor persistence or recurrence. Because of the resources of our institution, it is possible to perform both pre-operative CECT and MRI, but the post-operative follow-up imaging is mainly performed by means of CECT. Only select cases undergo post-operative MRI because of the availability of these studies in our socioeconomic context.

All patients underwent endoscopic transnasal transsphenoidal surgery at our Center. An ENT surgeon was responsible for the nasal and sphenoidal phases of the operation, during which the middle turbinate was identified and resected in order to create an adequate surgical pathway. Ethmoidectomies were not routinely performed. An ample sphenoidotomy was completed in all cases, and all the anatomic landmarks inside the sphenoid sinus were explored before proceeding with the adenomectomy.

The sellar phase of the surgery was then performed by a neurosurgeon, who was responsible for the tumor removal. Once the neoplasm was resected, the endoscope was moved forward into the cavity, in order to identify tumor remnants in the recesses created by the descent of the suprasellar cistern. Sellar repair was performed in cases of extended approaches or intraoperative cerebrospinal fluid (CSF) leakage by means of dural substitutes, surgicel®, gelfoam® or fibrin glue. Nasal packing was not routinely performed after the surgery.

Patients were then monitored closely for post-operative complications, such as meningitis, epistaxis, pneumocephalus, CSF leakage, pneumonia and death. Strict measurement of urine output and urinary density were also carried out in order to identify diabetes insipidus.

RESULTS

We identified eleven patients who underwent ETSS for GH-secreting adenomas between January 2008 and September 2011. From this initial group, two patients had already undergone craniotomies before resecting the GH-secreting pituitary adenoma, and were therefore excluded. Another patient was excluded because she had received pre-surgical medical treatment with somatostatin analogues. The remaining eight patients were composed by seven males and one female, with a median age of 41,5 years (min:31, max: 57).

Among our cohort, pre-operative median IGF-I levels were 615,5 ng/mL (min: 555 ng/mL, max: 1281 ng/mL), while the median values for GH were 20,70 ng/mL (min: 3,13, max: > 40,00). No thyroid hormone or testosterone deficiencies were identified. One patient suffered from hypocortisolism, which was treated with hydrocortisone, 25 mg per day. Hyperprolactinemia was evinced in two of our patients.

Only one patient exhibited visual field disturbances, which consisted of superior bitemporal hemianopia. On imaging, this patient was found to have a tumor with suprasellar extension. Further comorbidities included hypertension (4/8), dyslipidemia (2/8), diabetes mellitus (2/8), and cardiovascular disease (1/8). No cases of obstructive sleep apnea or osteoarthritis were identified.

The eight patients underwent radiologic assessment of their lesion with CECT scan, and six had gadolinium-enhanced MRI in addition. Seven patients presented macroadenomas, while only one patient had a microadenoma of 4 x 5 mm.

From the seven macroadenomas, five cases exhibited extrasellar extension or invasion. The majority of the cases (5/7) exhibited local spread into the sphenoid sinus with focal perforation of the sellar floor, and 3/7 evidenced extension into the cavernous sinus (Table 1).

The median duration of the surgical procedure was 217.50 minutes (min: 150 minutes, max: 335 minutes), and the median hospital stay for all patients was 7 days (min: 5, max: 11). Even though the surgical procedures were not followed by significant complications, median hospital stay of 7 days was due to endocrine control. Several patients live in remote areas where access to endocrine follow-up is limited, so it was in our best interest to discharge these patients with optimal endocrine control.

Among the cohort, the median IGF-I levels at three months after surgery were 633 ng/mL (min: 199 ng/mL, max: 1600 ng/mL), while the corresponding GH levels were 10,20 ng/mL (min: 0,96 ng/mL, max: 16,60 ng/mL). At six months post-operatory, the patients presented median IGF-I levels of 626 ng/mL (min: 98 ng/mL, max: 1497 ng/mL), and GH levels of 8,21 ng/mL (min: 0,24 ng/mL, max: 17,50 ng/mL). From these patients, one did not have IGF-I and GH values, three months after surgery; nevertheless, at six months, this patient met criteria for biochemical remission (Table 2).

Table 1. Modified Hardy classification for the extension of the GH-secreting adenomas treated at Hospital Mexico, San Jose, Costa Rica by means of primary ETSS between years 2008 - 2011

Suprasellar/Parasellar extension	Nº of cases	Percentage (%)
0: None	5	62,5
A: expansion intro suprasellar cistern	0	0
B: anterior recesses of 3rd ventricle obliterated	0	0
C: floor of 3rd ventricle grossly displaced	0	0
D: intracranial (intradural); anterior, middle or posterior fossa	0	0
E: Into or beneath the cavernous sinus (extradural)	3	37,5
Invasion/Spread		
I: sella normal or focally expanded, tumor ≤ 10 mm	1	12,5
II: sella enlarged; tumor ≥ 10 mm	2	25
III: Localized perforation of the sellar floor	5	62,5
IV: diffuse destruction of sellar floor	0	0
V: spread via CSF or blood-borne	0	0
TOTAL	8	100

Another patient also achieved biochemical remission based on his endocrinological panels at three and six months post-surgery. These patients had a non-invasive macroadenoma and a microadenoma, respectively.

From the six patients who did not achieve biochemical remission, five underwent additional CECT imaging assessment within one year after surgery, in addition to the immediate post-operative scans. None of the patients showed

persistence and/or recurrence of the adenoma in the imaging studies (Figure 1).

Five cases were raised to and approved by the Pharmacotherapy Committee of our Institution, and received somatostatin analogues (Sandostatin LAR® - Octreotide) 8 months after the surgery (min: 4 months, max: 18 months). The median random GH levels of these patients after receiving medical therapy were 0,82ng/mL (min: 0,34 max: 4,46 ng/mL) and the IGF-I ones were 370 ng/mL



(min: 246 ng/mL, max: 617 ng/mL). Four of these patients achieved biochemical remission after the addition of the drug, whereas one remained with elevated GH and IGF-levels.

Table 2. Initial, 3-month and 6-month post-operative GH and IGF-I levels of patients undergoing primary ETSS to treat their acromegaly between years 2008 - 2010 at Hospital Mexico, San Jose, Costa Rica.

Patient	Type of adenoma (modified Hardy scale)	Initial GH (ng/mL)	3-mo post-op GH (ng/mL)	6-mo post-op GH (ng/mL)	Initial IGF-I (ng/mL)	3-mo post-op IGF-I (ng/mL)	6-mo post-op IGF-I (ng/mL)
1	O II	24,50	16,60	15,60	1066	633	645
2	O III	>40,00	3,65	3,00	1111	663	681
3	E III	8,01	15,40	17,50	570	589	571
4	E III	>40,00	5,85	3,77	624	593	607
5	O III	14,80	10,20	12,65	570	908	832
6	E III	>40,00	13,60	13,10	1281	1600	1497
7	Microadenoma	3,13	,96	0,24	607	199	164
8	O 0	16,90	N/A	.53	555	N/A	98

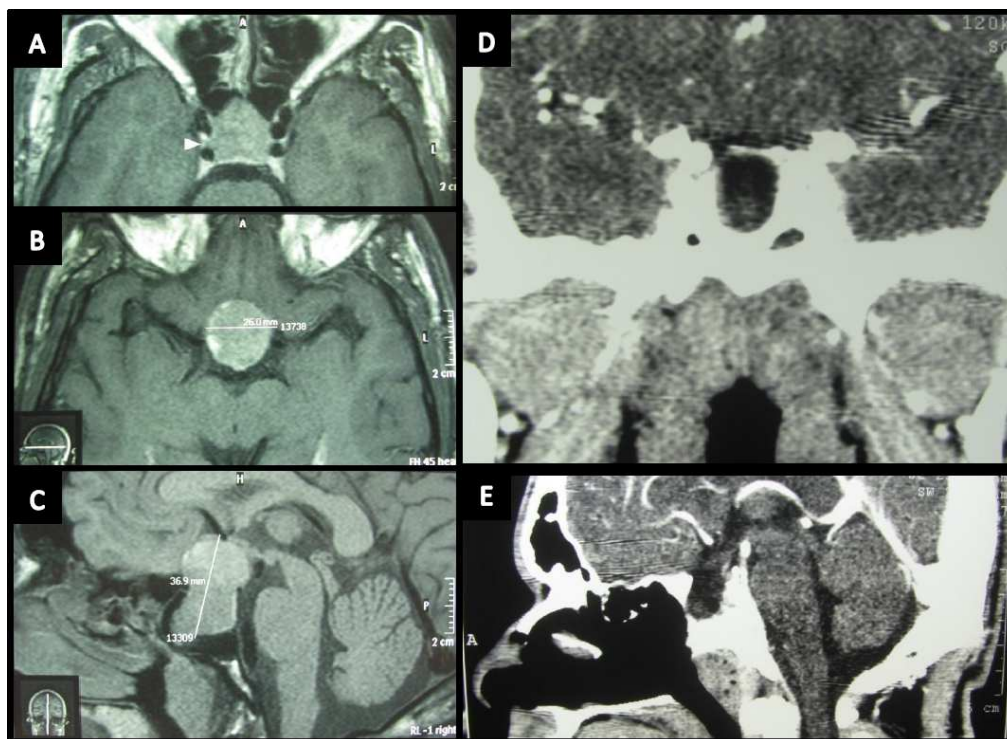


Figure 1: A - C) Preoperative T1-weighted axial and sagittal cuts showing cavernous sinus invasion and sphenoid sinus erosion of the macroadenoma. D - E) Post-operative CECT, axial and sagittal cuts, showing no tumor remaining.

DISCUSSION

Because acromegaly is associated with three-fold higher morbidity and mortality than the average person, the goal of its treatment is to achieve normal GH and IGF-I levels. ETSS has become the surgical treatment of choice at our institution because it offers improved visualization, preservation of sinonasal function, improvement in the resection of suprasellar and parasellar components of the adenoma, and reduction of hospital length of stay when compared to microscopic transsphenoidal and transcranial techniques [4-6]. Furthermore, the improved visualization and identification of extrasellar components through the advancement of the endoscope into the tumor cavity leads to a greater extent of resection and safety [7]. In our cohort, gross total resection was achieved in all cases, and no evidence of residual tumor in post-surgical imaging studies was found, which supports this notion.

On the other hand, the complications of ETSS are usually minor and include transient diabetes insipidus and CSF leak, with incidences comparable or inferior to those reported with the microsurgical technique [8-9]. Our data confirm the low morbidity and mortality of this surgical procedure, with only three cases of transient diabetes insipidus, and no other reported complications.

In spite of good surgical outcomes, disease control in acromegaly can be elusive. Several literature reports estimate that approximately 40 – 60% of macroadenomas, particularly those with extrasellar invasion, are not controlled by surgery alone [10]. One of the first studies performed in the United States for ETSS in GH-secreting adenomas reported 42% of post-surgical endocrinological remission in macroadenomas [11]. In this cohort, 41.7% of patients exhibited invasion of the cavernous sinus, and 29.2% had suprasellar tumor extension. These findings were reproduced by Gondim et al [12] in their retrospective analysis of 67 Brazilian patients, where they found that less than 45% of patients

with sphenoid sinus invasion had biochemical control of their acromegaly after primary ETSS. Additionally, van Bunderen et al [13] reported only 30% of remission after primary ETSS in their cohort of 30 Dutch patients, the majority of which exhibited extrasellar extension of their macroadenoma. Furthermore, in their retrospective study of 60 American patients, Jane et al [14] found that more invasive adenomas were significantly less likely to achieve biochemical remission after ETSS than those limited to the sella turcica, while Campbell et al [4] found that higher Hardy and Knosp grades were associated with significantly lower remission rates.

The data obtained from our cohort coincide with these international observations. The majority of our patients with macroadenomas (5/7) presented tumors with extrasellar extension and sphenoid sinus erosion, which has been demonstrated by numerous authors [4, 12-16] to significantly reduce the likelihood of biochemical remission after surgery. It is therefore not at all surprising that, in our cohort, those patients with smaller lesions (microadenoma and non-invasive macroadenoma) attained biochemical remission after primary surgical treatment, whereas those patients with invasive tumors failed to reach cure. Because of the size of our cohort and the recent foundation of the Endoscopic Skull Base Surgery Unit at our Center in 2008, our remission rates in invasive adenomas were to be expected.

The proximity of vital vascular and brain structures is what typically makes these lesions more surgically challenging, but remission can also be elusive due to dural tumor microfoci that persistently hypersecrete GH and are not readily visualized and resected during surgery [17-18]. These microfoci were likely the reason for persistently elevated GH levels seen in our patients in spite of gross total resection as seen in the post-operative imaging studies.

Because of the latter, the Acromegaly Consensus Group recommends multimodal treatment and involvement of a multidisciplinary

team to treat invasive macroadenomas [19]. One of the alternatives in the management of these patients is the use of pre-operative somatostatin analogues. Because these drugs can lead to normalized GH and IGF-I levels, as well as tumor shrinkage, it is thought that they could improve the likelihood of biochemical remission after a radical resection [20]. Several studies have confirmed these theoretical advantages [22-25], but they differ from one another in patient selection, class of somatostatin analogue used, duration of treatment, variables analyzed, and follow-up. Therefore, there are no international, validated guidelines for the use of pre-surgical somatostatin analogues. Nevertheless, the Latin American panel of experts advocates for the use of first-line medical therapy as a viable alternative to surgery, particularly in patients with invasive adenomas [2]. The main argument to support this recommendation is the prospective, multicenter study performed by Mercado et al [26] to assess the efficacy of primary octreotide in a Latin American population, which provides more epidemiologically-relevant data for our region, according to their observations.

The cost of medical treatment, however, is a major limiting factor in developing countries such as ours. Therefore, at our institution we primarily perform surgical excision by means of ETSS, and then assess the need for medical therapy in case of persistence or recurrence. This approach corresponds to the more traditional algorithms published [10, 17, 18], and is acceptable because of the low morbidity and mortality associated to the surgical procedure at our Center. Nevertheless, it is important to point out that the majority of our patients present large, invasive tumors, and that surgery is not likely to provide endocrine remission by itself.

CONCLUSIONS

Optimization of the acromegaly treatment protocols at our Institution is necessary. The

inclusion of somatostatin analogues in the post-operative period as part of the routine management of patients with invasive GH-secreting macroadenomas, should be pursued, so that our patients do not suffer from the deleterious effects of raised IGF-I and GH levels.

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