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Endocrinological outcomes following endoscopic and microscopic transsphenoidal surgery in 113 patients with acromegaly

Sauradeep Sarkar[a], Simon Rajaratnam[b], Geeta Chacko[a], Ari George Chacko[a,*]

[a] Section of Neurosurgery, Department of Neurological Sciences, Christian Medical College, Vellore, India
[b] Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, India

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ABSTRACT

Background: To describe outcomes and complications in patients undergoing transsphenoidal surgery for acromegaly using the 2010 consensus criteria for biochemical remission.
Methods: Retrospective review of 113 treatment naïve patients who underwent transsphenoidal surgery with the endoscopic ($n=66$) and the endonasal microscopic technique ($n=47$). Cure was defined if the age and sex-adjusted IGF-1 level was normal and either the basal GH was <1 ng/ml or the nadir GH was <0.4 ng/ml following oral glucose suppression at last follow-up.
Results: The mean age at presentation was 38.1 ± 7.1 years and 86% of tumors were macroadenomas. Adenoma sizes averaged 21.1 ± 9.7 mm, but 56% of all tumors were ≥2 cm in size and 43.4% were invasive. Remission rates between endoscopic and microscopic transsphenoidal surgery did not differ significantly overall (28.8% versus 36.2%). On univariate analysis, a preoperative GH level <40 ng/ml, adenoma size <20 mm and non-invasiveness were predictors of remission at follow-up. Although there were no statistically significant differences in remission rates between the endoscopic and microsurgical groups, surgically induced hypopituitarism was less frequent with the former.
Conclusions: We report our surgical experience with predominantly large, invasive GH adenomas using the 2010 criteria for cure. Patients with smaller, non-invasive tumors with lower preoperative GH levels are most likely to achieve remission. Outcomes with either the microscopic or endoscopic approach do not differ significantly, although the rate of surgically induced hypopituitarism may be higher with the former. Transsphenoidal surgery remains the first line of treatment for patients with acromegaly, but invasive adenomas will frequently require adjuvant therapy.

1. Introduction

The management of growth-hormone secreting pituitary adenomas is primarily surgical, although failure is common with macroadenomas invading the cavernous sinuses. The advent of endoscopes in skull base surgery has complemented and, in some centers, replaced the traditional microscopic transsphenoidal approach to adenomectomy in these patients. Despite these innovations, acromegaly remains a difficult disease to cure, with a large proportion of patients requiring adjuvant radiation (RT) or medical therapy for residual tumor. The previous definition of remission was based on criteria formulated in 2000, and this required a nadir GH < 1 ng/ml in addition to normal IGF-1 values when adjusted for age and sex [1]. Following an updated consensus arrived at in 2010, these requirements have been modified, and now interpret a postoperative random GH < 1 ng/ml or a nadir post-suppression GH < 0.4 ng/ml in addition to normalized IGF-1 levels as representative of biochemical remission [2].

Most outcome estimates following transsphenoidal surgery are based on older guidelines, and only a limited number of studies describe remission rates with the new criteria for cure [3–8]. We retrospectively analyzed the records of patients who had undergone transsphenoidal surgery for acromegaly at our institution, and present our experience with the latest definitions of cure.

Abbreviations: CSF, cerebrospinal fluid; DI, diabetes insipidus; ETSS, endoscopic transsphenoidal surgery; GH, growth hormone; IGF-1, insulin-like growth factor 1; ICA, internal carotid artery; MR, magnetic resonance; MTSS, microscopic transnasal transsphenoidal surgery; RT, radiation therapy; SRS, stereotactic radiosurgery.

* Corresponding author at: Department of Neurological Sciences, Christian Medical College, Vellore, India. Tel.: +91 416 228 3031; fax: +91 416 223 2103; mobile: +91 9487519464.
E-mail address: agchacko@cmcvellore.ac.in (A.G. Chacko).

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2. Materials and methods

2.1. Patient profile

Between January 2005 and April 2013, 144 patients were evaluated for growth-hormone secreting pituitary adenomas at the Christian Medical College, Vellore, a tertiary care referral center catering to patients from all over India and Bangladesh.

The surgical procedures performed were either endoscopic transsphenoidal (ETSS) or microsurgical transnasal transsphenoidal (MTSS). Transcranial approaches were used in two patients with giant invasive adenomas, who were excluded from this analysis. In one patient the procedure was abandoned prematurely without tumor removal due to difficulties in negotiating the dural sinus that extended across the entire sella floor during a microscopic approach. Following radiotherapy, this patient remained disease-free at 6 years' follow-up. Ten patients with previous surgery and 18 patients (8 ETSS, 10 MTSS procedures) without adequate follow-up at the time of writing were excluded from analysis. Our results are therefore based on data assimilated from 113 patients, with a mean follow-up period of 33.5 ± 26.8 months (range 4–106 months).

All patients underwent a thorough neurological and endocrinological work-up prior to surgery that included formal visual acuity and field testing, and assessment of serum GH, IGF-1, prolactin, random and 8AM cortisol, T3, free T4, thyrotropin (TSH), follicle-stimulating (FSH) and luteinizing (LH) hormones. Cortisol reserve was evaluated by dynamic stimulation with 250 μg of synthetic cosyntropin; a peak cortisol of >18 μg/dl with an increase of >7 μg/dl or an absolute peak >20 μg/dl was considered a satisfactory response. A basal cortisol of <5 μg/dl was also considered as evidence of central hypoadrenalism. Central hypothyroidism was defined as a free T4 <0.8 ng/dl with a subnormal TSH response. Serum testosterone was measured in male patients before surgery and at follow-up. Central hypogonadism was defined as a testosterone level <200 ng/dl in males and amenorrhea in females with inappropriately low FSH and LH levels.

Radiological evaluation comprised contrast magnetic resonance (MR) imaging in all patients, and direct coronal computed tomography imaging with bone windows for the endoscopic surgeries. Tumor sizes were calculated based on the maximum anteroposterior, craniocaudal or transverse diameters, and were classified as microadenomas (≤10 mm) or macroadenomas (>10 mm). Hardy's system was used to grade the suprasellar extension of all macroadenomas. Knosp grades of 3 and 4 defined cavernous sinus invasion. Early postoperative hypopituitarism was defined as new onset central hypothyroidism or hypocortisolism diagnosed in-hospital, and which required substitution therapy at discharge. However, only endocrine deficits detected or diagnosed at remote follow-up were considered as definitive evidence of hypopituitarism, and were stratified according to the appropriate hormonal axis. Patients were declared to be in remission if their age and sex-adjusted IGF-1 level was normal with either a random GH < 1 ng/ml or a nadir GH < 0.4 ng/ml following suppression with oral glucose on follow-up dated at least 3 months after surgery.

2.2. Surgical approach and techniques

All procedures were performed by the senior author (AGC). Microsurgical techniques were employed for 47 patients, with endoscopic assistance in 11 of these cases. Since 2009, we have favored the pure endoscopic approach and these accounted for the remaining 66 patients.

For the microsurgical cases, an endonasal transseptal transsphenoidal dissection was performed with placement of a Hardy speculum in the nose. No lumbar subarachnoid catheters were used but the end tidal CO_2 was kept at around 40 mmHg during tumor removal to help force the tumor into the sella. For the pure endoscopic surgeries, a binostril approach enabled placement of the endoscope in the right nostril, held by the first assistant, while the surgeon had both hands free to introduce instruments through both nostrils. Over the last year, lumbar subarachnoid catheters for cerebrospinal fluid (CSF) drainage were often inserted to facilitate tumor extirpation from within the folds of the arachnoid. On recognizing that the capsule of pituitary adenomas is formed by compressed normal adenohypophysis, our surgical strategy has involved intracapsular excision to preserve pituitary function. In the endoscopic group, aggressive removal was attempted with 30 or 45 degree endoscopes in cases with cavernous sinus invasion, although residual tumor was often left behind lateral to the intracavernous segment of the internal carotid artery (ICA).

2.3. Postoperative management

After discharge, patients were asked to review with fasting and post-suppression GH assays and IGF-1 levels at 3 months following surgery, and annually thereafter, unless florid clinical or biochemical evidence of residual disease demanded more intensive follow-up. Postoperative MR imaging was performed only if residual disease was suspected on the basis of elevated GH or IGF-1 values. Patients with residual disease were offered choices of conventional/stereotactic radiation therapy or stereotactic radiosurgery (SRS). Medical therapy was limited to cabergoline, as other alternatives were not economically feasible in our setting.

2.4. Statistical analysis

Data was entered into an electronic database and analyzed with SPSS software (version 11.0, Chicago, IL). Categorical variables were analyzed with the chi square or Fisher's exact test, and means of continuous variables were analyzed with the Student's *t*-test. A univariate analysis was used to estimate the odds ratio and 95% confidence interval for factors predicting remission at last follow-up. We also performed a multivariate analysis to estimate predictors of remission after controlling for other variables. Statistical significance was defined by a p value of <0.05.

3. Results

Preoperative and postoperative characteristics of the entire surgical cohort are summarized in Table 1. This table also compares the endoscopic and microscopic transsphenoidal procedures.

3.1. Clinical and operative details

The mean age at presentation was 38.1 ± 7.1 years (range 16–75 years), and patients were evenly distributed across both genders. Median time to diagnosis from onset of symptoms was 24 months (range 3–408 months). Acromegalic features were present in all patients but one patient was diagnosed during evaluation for lumbar canal stenosis. Vision was affected in almost one-third of patients, with bitemporal field deficits demonstrable in the majority of these cases. Approximately a third of patients were diagnosed with diabetes mellitus (29.2%) and/or hypertension (37.1%) preoperatively. TSH deficiency was the commonest preoperative endocrine deficit. However, only 3 patients required more than one hormonal replacement prior to surgery.

An adenoma was visualized on preoperative MR imaging in all cases. Overall, the mean adenoma size was 21.7 ± 9.7 mm (range 4–50 mm), but 63 tumors (55.8%) were ≥2 cm in size. Almost half had invasive tumors. Patients in the ETSS group had significantly