Transsphenoidal Surgery for Growth Hormone–Secreting Pituitary Adenomas in 130 Patients

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Key words
- Acromegaly
- Growth hormone
- Pituitary adenoma
- Remission
- Transsphenoidal surgery

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
FSH: Follicular-stimulating hormone
GH: Growth hormone
IGF-I: Insulin-like growth factor I
LH: Luteinizing hormone
MRI: Magnetic resonance imaging
OGTT: Oral glucose tolerance test
TSH: Thyroid-stimulating hormone
TSS: Transsphenoid surgery


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OBJECTIVE: **Transsphenoid surgery is the treatment of choice for growth hormone (GH)-producing pituitary adenomas. The measures that may predict postoperative remission need to be elucidated.**

METHODS: **Transsphenoid surgery was performed in 163 patients by a single neurosurgeon from 1992 until 2010. Thirty-three patients were lost to follow-up, and the results of the remaining 130 are presented here.**

RESULTS: **A total of 81.5% of patients obtained a first postoperative day GH level less than 5 μg/L, whereas 60.5% achieved a value less than 2.5 μg/L. A total of 56.9% had achieved both a GH less than 2.5 μg/L and normal insulin-like growth factor I (IGF-I) on delayed follow-up and could be regarded as in remission. Duration of symptoms before surgery, age, preoperative GH, and IGF-I levels did not significantly influence a patient's remission. Analysis showed that cavernous sinus extension and larger tumor size were associated with decreased remission rate, whereas sellar floor invasion or suprasellar extension did not significantly influence remission.**

CONCLUSION: **The results of our study show that transsphenoid surgery is an optimal treatment modality for GH-secreting pituitary adenoma. Suprasellar or sellar floor invasion, and preoperative GH or IGF-I do not necessarily predict poor outcomes. Large tumor size and cavernous sinus extension contribute to greater recurrence rates.**

INTRODUCTION

Acromegaly is caused by a state of excess growth hormone (GH) secretion, in most cases by a benign pituitary adenoma (5, 27, 33). Clinical features of acromegaly is attributed to elevated levels of GH and insulin-like growth factor I (IGF-I). Transsphenoidal surgery is considered to be the first-choice treatment for GH-producing pituitary adenomas (7, 14, 22, 25, 28, 35).

An important factor to predict outcome after surgery is postoperative remission. Some factors have been advocated as predictors of remission, among them are tumor size (macro- vs. microadenomas) (30, 32, 33), extrasellar and cavernous sinus extension (6, 7, 21), preoperative mean basal GH concentration (7, 18), preoperative mean IGF-I level (7), mixed tumor types (21), and the experience of the surgeon (2, 26). Moreover, many studies have shown that mortality and morbidity after surgery returns to normal levels only by normalization of postoperative GH and IGF-I. However, standard measures that can predict long-term remission is still lacking, and a wide range of values have been described. Among the most acceptable are postoperative serum GH less than 5 μg/L (1), normal IGF-I (34), or GH after oral glucose tolerance test (OGTT) <1 μg/L when a sensitive assay or <0.4 μg/L when an ultrasensitive GH assay is used (8, 23). Some investigators also suggest that the OGTT is more reliable at 3 months postoperatively (24). Taking all these together, we find that most studies accept that more stringent criteria, that is that serum GH concentrations less than 2.5 μg/L are associated with better clinical outcomes (3, 4, 21, 29).

Here, we present the outcome of 130 acromegalic patients who underwent transsphenoidal surgery in our institution from 1992 to 2010. Then, we try to retrospectively review the factors that predict postsurgery remission in these patients.

MATERIALS AND METHODS

Subjects

One hundred sixty-three consecutive patients who underwent transsphenoid surgery (TSS) for a GH-secreting pituitary adenoma from December 1992 to March 2010 took part in this study. Thirty-three patients (20.2%) were lost from follow-up and thus, the results of the remaining 130 are presented here. The study design was approved by the Ethical Committee of Shahid Beheshti Medical University, and the study was performed in compliance with the statements of the Declaration of Helsinki.

Acromegaly was diagnosed on the basis of relevant clinical features, a mean GH level >5 μg/L, plasma IGF-I level greater than normal age- and sex-matched levels, or nadir GH after OGTT >1 μg/L. Then, the presence of a pituitary adenoma was confirmed by magnetic resonance imaging (MRI) in all (which included axial, coronal, and sagittal views in both T1 and

T2 weighted-images, and T1-weighted images after the addition of gadolinium), and dynamic sella region MRI in cases with microadenomas. Tumors were classified as microadenomas (largest tumor diameter <10 mm) and macroadenomas (largest tumor diameter >10 mm). Before surgery, all patients underwent a complete biochemical analysis (including a complete pituitary hormone profile consisting serum GH, IGF-I, T3, T4, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, adrenocorticotropic hormone, and 8-AM cortisol levels). Computed perimetry was obtained in patients with macroadenomas, those with evidence of chiasmal compression by tumor in MRI, or those with subjective or objective visual complaints. Computed tomography scans were performed in both axial and coronal sellar views.

Patients were considered to have achieved remission if a resolution in clinical features of acromegaly was observed, their GH level was less than 2.5 mg/L the first postoperative day, and they achieved a normal age- and sex-matched IGF-I on delayed follow-up. Acromegalic signs and symptoms were recorded on the basis of patient self-report, medical records, and previous photographs. Follow-up information was obtained from periodic visits to our clinic or through contacts by telephone with the patient's referring physician or with the patient and his family. Last-known data of the patients were used for final assessment.

The database included clinical symptoms and signs, the preoperative and postoperative laboratory and imaging results, operative findings, results of surgery, complications, clinical outcome, and postoperative management. Patients with previous surgery, radiation therapy, or medical therapy were excluded from the analysis. All surgical procedures were performed by one neurosurgeon (M.S., the senior author of this report).

Transsphenoidal surgery was performed via a transseptal transsphenoidal approach under surgical microscopic magnification. After tumor removal, sella floor was reconstructed by use of the patient's own bone. In those who experienced opening of the arachnoid during surgery, packing of CSF leakage site with fat and muscle pad was performed. Thereafter, routine

Table 1. Preoperative Demographic and Biochemical Data

Age, years	39.6 ± 12.6 (14–78)
M/F ratio	92/71 = 1.3
Symptom duration, months	46.7 ± 50.6 (2–300)
GH, μg/L	48.5 ± 53.9 (2.1–403.0)
GH after OGTT, μg/L	47.0 ± 54.6 (2.8–370.0)
IGF1, μg/L	1066.0 ± 417.5 (211–2023)

Data show mean, SD, and range (in parentheses), except for M/F ratio.
M/F, male/female; GH, growth hormone; OGTT, oral glucose tolerance test; IGF-I, insulin-like growth factor I.

histopathologic analysis was performed to establish the diagnosis. Immunohistochemistry studies were only performed after 2009; therefore, their results are not presented in the results of the current study.

GH was assayed by immunoradiometric assay (IRMA Kit; Cisbio International, Bedford, Massachusetts, USA). This assay used antihuman-GH mouse monoclonal antibodies with a sensitivity of 0.02 μg/L. Plasma IGF-I concentration was determined by radioimmunoassay (Nichols Institute Diagnostics Kit; Nichols Institute, San Juan Capistrano, California, USA). Recombinant human IGF-I was used for the standards and labeled with ^{125}I for the tracer. The antiserum for IGF-I showed no cross-reactivity with IGF-II, proinsulin, or insulin. A serum GH level was obtained in all patients on the first postoperative day. IGF-I levels were not checked on the first postoperative day because it is shown that they decrease very gradually in weeks, even in a successful surgery. GH after OGTT was not consistently performed on the first postoperative day or during follow-up; therefore, its results was not used in the analysis. The patients were scheduled to refer to follow-up clinics every 6 months during the first year and annually thereafter, or upon experience of clinical signs and symptoms related to the disease. These visits included physical examination, a thorough pituitary hormone profile, and a brain MRI with pituitary adenoma protocol. Moreover, another visit was planned 1 month after surgery to evaluate the pituitary hormones. Postoperative hormone deficits were acknowledged during this session. The results of MRI and GH and IGF-I levels of the last session of follow-up were recorded and used for analysis. All analyses were performed with PASW Statistics version 18 (Predictive Analytics Software; SPSS Inc, Cary, North Carolina, USA).

RESULTS

One hundred thirty-patients were reviewed in this study. The demographic data of patients are presented in Table 1. Preoperative GH, IGF-I, and GH after OGTT are presented in Tables 1 and 2. Preoperative imaging showed that 71% of tumors were macroadenmoas and 29% were microadenomas. A total of 8% had sellar floor invasion, 45.1% had suprasellar extension (beyond diaphragma sella), and 3.7% had cavernous sinus invasion. Cavernous sinus invasion was based on the Knosp classification (20). In our series, the tumor was considered to invade the cavernous sinus when the lateral tangent of the supra- and the intracavernous Internal carotid artery was crossed by the tumor, which is consistent with Knosp grade 3 (7, 20).

On surgery, normal gland was saved in 86.2% of patients. Evaluation of pituitary hormone profile (T3, T4, TSH, FSH, LH, prolactin, adrenocorticotropic hormone, and 8-AM cortisol plus estradiol and testosterone levels) 1 month after surgery

Table 2. Pre- and Postoperative Biochemical Data

Value	Preoperative	First Postoperative Day	Last Follow-Up
GH, μg/L	48.5 ± 53.9 (2.1–403.0)	6.8 ± 11.4 (0.1–62.0)	3.3 ± 3.8 (0.1–19.0)
IGF-I, μg/L	1066.0 ± 417.5 (211–2023)		442.8 ± 330.9 (39.0–1575.0)

Data show mean, SD, and range (in parentheses).
GH, growth hormone; IGF, insulin-like growth factor I.