Assessment of long-term remission of acromegaly following surgery

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Object. The criteria for remission of acromegaly following transsphenoidal adenoma resection are in evolution. In the present study the authors evaluate the utility of predicting long-term remission by reference to a single fasting growth hormone (GH) level on the 1st postoperative day.

Methods. A retrospective analysis was conducted on 181 patients with acromegaly who underwent transsphenoidal resection between 1973 and 1990 and completed a 5-year follow-up period. Fasting serum GH levels were obtained in all patients on the 1st postoperative day in the absence of exogenous glucocorticoids. All patients participated in a follow-up evaluation lasting at least 5 years, which included measurements of serum insulin-like growth factor–I (IGF-I) levels as an index of acromegalic activity.

Among the 181 patients, GH levels ranged from 0 to 8 ng/ml in 131 (72%) on the 1st postoperative day, suggesting biochemical remission. This group included 107 (84%) of the 127 patients with microadenomas, but only 24 (44%) of the 54 with macroadenomas. Nevertheless, 15 (11%) of the 131 patients who initially had attenuated GH levels displayed recurrent acromegaly within the first 2 years (with elevated levels of IGF-I in all cases, and abnormalities appearing on magnetic resonance images in nine cases). Only one of 116 patients in whom the initial postoperative GH level was lower than 2 ng/ml experienced a recurrence, whereas 14 (93%) of the 15 patients with postoperative GH levels between 2.2 and 8 ng/ml subsequently displayed biochemical evidence of acromegaly.

Conclusions. The findings indicate that a fasting morning serum GH level lower than 2 ng/ml on the 1st postoperative day portends long-term biochemical remission of acromegaly, whereas higher levels are a significant marker for recurrent disease.

Key Words • acromegaly • pituitary adenoma • transsphenoidal surgery • growth hormone • insulin-like growth factor–I
pathological reports, pre- and postoperative endocrinological studies, and follow-up clinic reports.

Of a total of 205 patients, 181 (88%) were identified who had completed a 5-year follow-up period and this group formed the basis for this study. Seventeen patients (8%) did not complete 5 years of follow up and seven patients (3%) died of complications of their acromegaly before the end of the 5-year period. These 24 patients were excluded from the study. All patients underwent a preoperative history and physical examination, an imaging study (sellar polytomography plus pneumoencephalography and/or angiography between 1973 and 1976; computerized tomography scanning between 1976 and 1982, or magnetic resonance imaging between 1982 and 1990), an assessment of pituitary function including a fasting GH level and documentation of the GH nadir following a 75-mg glucose load and/or the response of GH to TRH stimulation, and a neuroophthalmological examination whenever indicated.

All patients underwent transnasal transsphenoidal resection of their tumors, which was performed using standard techniques.17 Glucocorticoids were not administered during the immediate postoperative period. A fasting serum GH level was obtained in all patients at 7 a.m. on the morning after surgery.

Patients were again evaluated at 6 and 12 weeks postoperatively, and every 6 months thereafter. At each of these visits, an assessment of the patient’s acromegalic status was obtained, including the fasting GH level between 1973 and 1984, or the serum IGF-I during subsequent years once the appropriate assay became available. Because of the length of the follow-up period, IGF-I measurement was obtained in all patients one or more times during the follow-up period.

### Results

#### Demographic Data

The age range of the patients was 8 to 63 years. The study included 94 male (52%) and 87 (48%) female patients. One hundred twenty-seven patients (70%) had microadenomas (< 10 mm) and 54 (30%) harbored macroadenomas (≥ 10 mm).

#### Preoperative Endocrine Status

The 181 patients included in this study all presented with the classic signs and symptoms of acromegaly. Preoperative endocrinological testing among the 127 patients with microadenomas revealed elevated GH levels or failure of GH suppression in response to glucose loading; in no case was the fasting GH elevated above 40 ng/ml. Similarly, 24 patients harboring macroadenomas were found to have GH levels less than 40 ng/ml, whereas in 30 patients with macroadenomas (56% of all macroadenomas) the fasting GH levels were greater than 40 ng/ml.

#### Long-Term Clinical and Endocrine Outcome

To assess long-term outcome, we measured the patient’s serum IGF-I level at the end of a follow-up period that lasted at least 5 years. Our laboratory performs a radioimmunoassay procedure, in which the IGF-I in the unknown specimen competes with a known quantity of radioactively labeled IGF-I for binding sites on a specific antibody. The normal IGF-I values used were age and sex stratified (Table 1). In all cases, a normal IGF-I level at this 5-year interval correlated with complete remission of most reversible symptoms of acromegaly. Using the results of this test as our outcome marker, we found that 115 (99%) of the 116 patients with a Day 1 postoperative GH less than 2 ng/ml exhibited a sustained normal IGF-I level. Only one patient...
remission of acromegaly

with a macroadenoma was found to have biochemical evidence of persistent disease, despite the low postoperative GH value. Of the 15 patients with intermediate values of GH (2.2–8 ng/ml), only one patient who harbored a microadenoma and had a Day 1 postoperative fasting GH of 3.6 ng/ml appears to have attained a long-term biochemical remission of his disease (Table 2). If the standard for remission is considered to be a value of less than 2 ng/ml, this patient would be considered to be in remission (by IGF-I criteria) despite the fact that the early GH level was high.

Ninety-nine percent of patients in whom the Day 1 fasting serum GH was lower than 2 ng/ml experienced sustained long-term normalization of their IGF-I level, whereas 93% (14 of 15) of patients with GH levels less than 8 ng/ml but greater than 2 ng/ml did not experience remission of their disease (Table 3). In nine of the latter patients, computerized tomography or magnetic resonance images demonstrated a residual sellar mass. Twelve of these patients received radiation therapy; in two cases, this therapy resulted in normalization of the patient’s IGF-I level within 2 years. One patient underwent a second surgery at another institution, which did not result in an alteration in either the GH or IGF-I levels.

Of the seven patients who died of acromegaly before completion of a 5-year follow-up evaluation, all harbored macroadenomas preoperatively and none had postoperative GH values less than 8 ng/ml. All these patients were treated with external beam radiation (5000 cGy) for residual tumor without normalization of GH or IGF-I levels (when available) levels during follow up.

Discussion

Transsphenoidal Surgery in Acromegaly

Transsphenoidal microsurgical adenomectomy is currently the accepted first-line therapy for GH-secreting tumors encountered in patients with acromegaly.1,2,4,10,14,18,20,24,25,32,33,39,41,42,46,48,49,51,52 A large combined analysis of 1360 patients with acromegaly conducted by Ross and Wilson46 documented an overall postoperative cure rate of 60.4%. An even higher rate of cure can be found for microadenomas, exceeding 76 to 84% in a recent large surgical series.2,14,18,20,37,39,41,51,52

In the current series, we deemed 78% of the microadenomas and 31% of the macroadenomas to be in long-term biochemical remission, with an overall remission rate of 64%. These rates were determined using very stringent criteria for remission: a postoperative GH level less than or equal to 2 ng/ml, a normal age- and sex-matched 5-year IGF-I level, and clinical evidence of disease remission at 5 years. This long-term follow up and use of three stringent criteria, including a clinical correlation, is unique in the literature concerning acromegaly.

It should be noted that 205 patients were initially treated, but 24 were excluded from the study due to the lack of a 5-year follow up. This number includes seven patients harboring macroadenomas who died before they could participate in the 5-year follow up. All these patients had postoperative GH levels greater than 8 ng/ml, and all had elevated IGF-I levels before their deaths. If these patients were to be included, the overall cure rate would decrease to 62% and the cure rate for macroadenomas would drop to 28%. There would be no effect on the GH study results, however, because in all patients the postoperative GH levels were elevated.

Seventeen patients were lost to follow up before the 5-year follow up was completed. Twelve patients had microadenomas; in 10 of these, the GH levels were lower than 2 ng/ml and the IGF-I levels were either normal or unknown at follow up. In two patients the GH levels were higher than 2 ng/ml and the IGF-I levels were unknown. Five patients had macroadenomas; in two of these the GH levels were less than 2 ng/ml and IGF-I levels were normal at a limited follow up; in the other three patients the GH levels were elevated and the early IGF-I levels were elevated or unknown. It is unlikely that addition of these patients would substantially change the overall results of this study.

Treatment for Patients in Whom Transsphenoidal Surgery has Failed

The initial treatment of choice for the typical patient harboring a GH-secreting pituitary adenoma is resection. The management dilemma arises for the patient with persistent disease activity despite surgery. A repeated operation has a low rate of success (19% in one series39) and a higher rate of complication (19% suffered serious local complications and 63% had surgically induced hypopituitarism in the large series of Long, et al.,39 significantly higher than that seen in primary transsphenoidal surgery). Thus, whereas some authors advocate additional exploratory surgery under certain conditions,20,46 others do not.2,45,52

Radiation therapy significantly lowers postoperative GH levels in a large number of patients with refractory disease (a 50–79% response is commonly cited15,28–31,34,36,45,55), but it can take as long as 10 years to have a significant effect, during which time the patient continually experiences the deleterious effects of GH excess. Medical therapy with the dopamine agonist bromocriptine or the somatostatin analog octreotide lowers GH levels in many patients, but these medications are often poorly tolerated and rarely result in a cure of the disease process.53,55 Adjunctive therapies for persistent or recurrent disease thus have significant limitations due to morbidity and the low rate of disease control. This fact, coupled with the serious long-term rates of morbidity and mortality associated with unrecognized persistent disease, makes it crucial for the treating physician to determine

<table>
<thead>
<tr>
<th>Type of Lesion &amp; GH Level</th>
<th>Total No. of Patients</th>
<th>Patients W/ Normal Level of IGF-I</th>
<th>Patients W/ Elevated Level of IGF-I</th>
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<tbody>
<tr>
<td>patients w/ microadenomas</td>
<td></td>
<td></td>
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<tr>
<td>&lt;2 ng/ml GH</td>
<td>99</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>2–8 ng/ml GH</td>
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<tr>
<td>&gt;8 ng/ml GH</td>
<td>20</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>patients w/ macroadenomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 ng/ml GH</td>
<td>17</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>2–8 ng/ml GH</td>
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<tr>
<td>&gt;8 ng/ml GH</td>
<td>30</td>
<td>0</td>
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* Final outcome determined by level of IGF-I measured 5 years postoperatively.
whether the patient who has undergone the initial surgery is likely to experience a sustained remission.

Defining Chemical Control

The accepted standards of what constitutes chemical control of acromegaly are evolving.\(^{3,12,23,40-42}\) The most advantageous laboratory test would correlate closely with disease activity. Recent studies have led to the consideration of IGF-I as the best marker for biochemical control. The production of IGF-I, a peptide whose plasma concentration is largely attributable to hepatic release, but which is found in many tissues, is the major determinant of acromegalic activity.\(^{3,6,7,16,19,22,27,41}\) Although GH stimulates the production and release of IGF-I, controversy exists as to the log-linear correlation of GH and IGF-I levels. Nevertheless, it seems that the major end-tissue effects of cellular proliferation are directly mediated by IGF-I.\(^{41,47}\) Unfortunately, measuring the association between IGF-I concentrations and mortality.\(^{38}\) Unfortunately, no article in the literature has documented the integration mean GH measurements are therefore more accurate than GH levels as the single most important determinants of disease control, an immediate postoperative GH level provides a simple, inexpensive, and reliable assay for determining the rational postoperative management of these patients.\(^{3,32,35,38,41,42,51,52}\) In a recent study the authors examined a postoperative GH level of 3 ng/ml as prognostic for control, but found an 11% recurrence rate using this criterion.\(^{31}\)

A further lowering of the level constituting remission is supported by the observation that half of all patients in whom the postoperative GH level is below 5 ng/ml still have elevated IGF-I levels,\(^{5,23}\) whereas five of six patients with GH levels between 2 and 5 ng/ml were found to have elevated IGF-I in another series (although only two of these patients had evidence of persistent disease activity). Thus, these more recent studies support a GH level of less than 2 ng/ml as predictive of disease control.

The observation of an elevated IGF-I level with no clinical evidence of persistent disease in the series reported by Levitt and associates\(^{38}\) indicates the key issue underlying this stringency from 10 to 8 to 5 ng/ml.\(^{3,32,35,38,41,42,51,52}\) A further lowering of the level constituting remission is supported by the observation that half of all patients in whom the postoperative GH level is below 5 ng/ml still have elevated IGF-I levels,\(^{5,23}\) whereas five of six patients with GH levels between 2 and 5 ng/ml were found to have elevated IGF-I in another series (although only two of these patients had evidence of persistent disease activity). Thus, these more recent studies support a GH level of less than 2 ng/ml as predictive of disease control.

The observation of an elevated IGF-I level with no clinical evidence of persistent disease in the series reported by Levitt and associates\(^{38}\) indicates the key issue underlying this point in question; that is, correlation of measurable indicators of acromegalic activity with the risks of morbidity and mortality associated with the disease process itself. Unfortunately, no article in the literature has documented the association between IGF-I concentrations and mortality.\(^{38}\) Nevertheless, compelling evidence now confirms that serum GH levels are the single most important determinants of death rates.\(^{45}\) Bates and colleagues\(^{22}\) found that 48 patients with acromegaly in whom mean GH levels were between 2.5 and 5 ng/ml had mortality rates double those for age-matched controls, whereas 31 patients with acromegaly in whom mean GH levels were less than 2.5 ng/ml were not at increased risk. Although patients with GH levels between 2 and 2.5 ng/ml may not be at increased risk for death, they are at risk for recurrence, given the data of the current study.

The present study shows that an immediate GH level of less than or equal to 2 ng/ml is indicative of long-term surgical success (as verified by 5-year IGF-I levels) and can be used to make an accurate prediction in 99% of cases. Despite the acknowledged limitations of postoperative GH testing, this result is borne out over this large series of 181 patients with prolonged follow up of at least 5 years.

Conclusions

The findings of this study indicate that a fasting serum GH level lower than 2 ng/ml on the 1st postoperative day predicts biochemical remission of acromegaly. Although an IGF-I measurement is a bioactive indicator of long-term disease control, an immediate postoperative GH level provides a simple, inexpensive, and reliable assay for determining the rational postoperative management of these patients.

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References

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Endocrinol Metab 50: 578–585, 1980
growth hormone dynamics and somatomedin C (insulin-like 
growth factor I) levels in predicting the long-term benefit after 
transsphenoidal surgery for acromegaly. J Lab Clin Med 109: 
340–354, 1987
cepts in diagnosis and management. West J Med 162: 340–352, 
1995
5. Arosio M, Giovanelli MA, Riva E, et al: Clinical use of pre-
and post-surgical evaluation of abnormal GH responses in acro-
1992 (Reference unverified)
7. Barkan AL, Beitzins IZ, Kelch RP: Plasma insulin-like growth fac-
tor-I/somatmedin-C in acromegaly: correlation with the degree 
of growth hormone hypersecretion. J Clin Endocrinol Metab 67: 
67–73, 1988
is ineffective in normalizing plasma insulin-like growth factor-
I in patients with acromegaly. J Clin Endocrinol Metab 82: 
3187–3191, 1997
ment of acromegaly with long-acting somatostatin analogue SMS 201-
995: shrinkage of invasive pituitary macroadenomas and improved 
surgical remission rate. J Clin Endocrinol Metab 67: 
1040–1048, 1988
10. Baskin DS, Bogen JE, Wilson CB: Transsphenoidal microsurgi-
cal removal of growth hormone-secreting pituitary adenomas. A 
tuitarism on life expectancy. J Clin Endocrinol Metab 81: 
1169–1172, 1996
term survival in acromegaly. A study of 166 cases diagnosed be-
lowing transsphenoidal surgery for acromegaly. Horm Res 35: 
113–118, 1991
15. Chun M, Masko GB, Hetelekidis S: Radiotherapy in the treat-
ment of pituitary adenomas. Int J Radiat Oncol Biol Phys 15: 
305–309, 1988
egaly by measurement of somatomedin-C. N Engl J Med 
301: 1138–1142, 1979
17. Coulwell WT, Weiss MH: The transsphenoidal approach, in 
Baltimore: Williams & Wilkins, 1998, pp 553–574
18. Davis DH, Laws ER Jr, Istrup DM, et al: Results of surgical treat-
ment for growth hormone-secreting pituitary adenomas. J Neuro-
surg 79: 70–75, 1993
tween insulin-like growth factor-I levels and growth hormone 
concentrations during diurnal profiles and following oral glucose 
20. Fahlbusch R, Honegger J, Buchfelder M: Surgical management of 
1992
follow-up evaluation in 115 patients who underwent transsphenoi-
for the cure of acromegaly: comparison between basal growth 
hormone and somatomedin C plasma concentrations in active and 
non-active acromegalic patients. J Endocrinol Invest 11: 57–60, 
1988
23. Giustina A, Barkan A, Casanueva FF, et al: Criteria for cure of ac-
romegaly: a consensus statement. J Clin Endocrinol Metab 85: 
526–529, 2000
acromegaly—long-term results in 100 patients. Surg Neurol 23: 
513–519, 1985
25. Hardy J, Somma M: Acromegaly: surgical treatment by transphe-
noidal microsurgical removal of the pituitary adenoma, in Tindall 
GT, Collins WF (eds): Clinical Management of Pituitary Disor-
ders. New York: Raven Press, 1979, pp 209–217 (Reference un-
verified)
Therapy in Endocrinology and Metabolism, ed 4. Phila-
growth factor I levels after treatment of acromegaly. Ann Clin 
28. Kim MS, Lee SI, Sim JH: Gamma knife radiosurgery for func-
tioning pituitary microadenoma. Stereotact Funct Neurosurg 72 
functioning pituitary adenomas. Stereotact Funct Neurosurg 72 
(Suppl 1): 101–110, 1999
adenoma with bragg peak proton beam, in Denome PJ, Jedy-
nak CP, Peillon F (eds): Pituitary Adenomas, Biology, Physiol-
opathology and Treatment: Second European Workshop La 
209–217 (Reference unverified)
31. Kramer S: The value of radiation therapy for pituitary and parapi-
GH-secreting pituitary adenomas: an outcome study using mod-
ern remission criteria. J Clin Endocrinol Metab 86: 4072–4077, 
2001
33. Lamberts SW, Uitterlinden P, del Pozo E: SMS 201-995 induces 
a continuous decline in circulating growth hormone and somato-
medin-C levels during therapy of acromegalic patients for over 
for recurrent surgically treated acromegaly: comparison with frac-
35. Laws ER Jr, Fode NC, Redmond MJ: Transsphenoidal surgery 
following unsuccessful prior therapy. An assessment of benefits 
36. Laws ER Jr, Vance ML: Radiosurgery for pituitary tumors and cranio- 
37. Leavens ME, Samaan NA, Jesse RH Jr, et al: Clinical and endo-
crinological evaluation of 16 acromegalic patients treated by 
38. Levitt NS, Ratanjee BD, Abrahamson MJ: Do “so-called” normal 
growth hormone concentrations (2-5 μg/l) indicate cure in acro-
repeated transsphenoidal surgery in acromegaly. J Neurosurg 85: 
239–247, 1996
sphenoidal adenomectomy by endocrinological testing and so-
matomedin-C measurement in acromegaly. J Neurosurg 70: 
561–567, 1989
42. Melmed S: Tight control of growth hormone: an attainable out-
come for acromegaly treatment. J Clin Endocrinol Metab 83: 
3409–3410, 1998
43. Morange-Ramos I, Regis J, Dufour H, et al: Short-term endocri-
nological results after gamma knife surgery of pituitary adenomas. 


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