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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

ACROMEGALY, which is caused by a GH-secreting pituitary adenoma in an overwhelming majority (99%) of cases,[26] is a clinical syndrome associated with significant risks of morbidity and mortality. Left untreated, the mortality rate is greater than that for age-matched controls and deaths occur from complications including hypertension, cardiac disease, diabetes, pulmonary disorders, and associated malignancies.[13,41,42,44,45,49,56] Microsurgical adenomectomy, performed by a transsphenoidal approach, has evolved to be the most common first-line treatment modality for acromegaly.[1,2,4,10,14,18,20,25,32,35,39,46,48,49,51,52] Radiation therapy and pharmacotherapy with the somatostatin analog octreotide are useful nonsurgical options or adjuncts.[41,42] The determination of a cure in the postoperative period is used to direct subsequent management and follow-up regimens that are costly and may require additional biochemical testing, imaging, and initiation of pharmacotherapy.

Abbreviations used in this paper: GH = growth hormone; IGF-I = insulin-like growth factor–I; OGTT = oral glucose tolerance test; TRH = thyrotropin-releasing hormone.

The generally accepted criteria for predictive assessment of long-term remission of acromegaly are in evolution.[3,6,11,22,23,41,42] Several biochemical tests have been proposed in the postoperative period, including measurements of basal GH, mean GH, and IGF-I, as well as the GH responses to an oral glucose load and TRH. Each of these tests has limited value in predicting long-term remission, especially with the advent of novel ultrasensitive GH assays. We therefore evaluated the utility of predicting long-term biochemical remission by reference to a single fasting GH level on the 1st postoperative day.

Clinical Material and Methods

From October 1973 until August 1990, 205 patients with acromegaly were surgically treated at the Department of Neurosurgery of the University of Southern California School of Medicine. Patient records were retrospectively reviewed for data from a detailed history and physical examination, neuroophthalmological evaluation where appropriate, neuroradiological reports, operative notes, histo-

TABLE 1

Normal values of IGF-I detected by radioimmunoassay, as stratified by age and sex

Patient Age Group (yrs)	Normal IGF-I Levels (ng/ml)	
	Males	Females
0–2	22–87	22–93
3–5	20–126	29–150
6–9	45–167	53–212
10–12	158–282	161–580
13–15	152–484	298–536
16–18	211–454	204–475
>18	90–318	116–270

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.

TABLE 2

Relationship between intermediate postoperative GH levels (2.2–8 ng/ml) and final IGF-I level

Tumor Size	Initial Postop GH Level (ng/ml)	Last IGF-I Level (≥5 yrs postop)
microadenoma	2.2	elevated
microadenoma	3.3	elevated
microadenoma	3.6	normal
microadenoma	3.8	elevated
microadenoma	4.8	elevated
microadenoma	5.5	elevated
microadenoma	5.8	elevated
microadenoma	6.2	elevated
macroadenoma	4.2	elevated
macroadenoma	4.8	elevated
macroadenoma	5.2	elevated
macroadenoma	6.0	elevated
macroadenoma	6.6	elevated
macroadenoma	7.2	elevated
macroadenoma	7.8	elevated

Short-Term Endocrine Outcome

The major variable examined was the postoperative Day 1 fasting morning serum GH level. In our laboratory, human GH is analyzed using a diagnostic immunochemiluminescence kit (Nichols Institute Diagnostics, San Clemente, CA) that utilizes a primary monoclonal antibody. Normal values are reported to be 0 to 8 ng/ml. Of the 181 patients studied, in 131 (72%) the GH levels were lower than 8 ng/ml on the 1st postoperative day. These included 107 (84%) of the 127 patients with microadenomas and 24 (44%) of the 54 with macroadenomas. Stratification of these results revealed that intermediate values of GH, ranging from 2.2 to 8 ng/ml, were measured in 15 of these patients (8% of the total, eight microadenomas and seven macroadenomas); in the remaining 116 patients GH values lay within the range of less than 0.5 to 2 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

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.

TABLE 3

*Relationship between immediate postoperative level of GH and outcome in patients with acromegaly stratified by size of lesion**

Type of Lesion & GH Level	Total No. of Patients	Patients W/ Normal Level of IGF-I	Patients W/ Elevated Level of IGF-I
patients w/ microadenomas (127 patients)			
<2 ng/ml GH	99	99	0
2–8 ng/ml GH	8	1	7
>8 ng/ml GH	20	0	20
patients w/ macroadenomas (54 patients)			
<2 ng/ml GH	17	16	1
2–8 ng/ml GH	7	0	7
>8 ng/ml GH	30	0	30

* Final outcome determined by level of IGF-I measured 5 years postoperatively.

Discussion

Transsphenoidal Surgery in Acromegaly

Transsphenoidal microsurgical adenomectomy is currently the accepted first-line therapy for GH-secreting tumors encountered in patients with acromegaly.[1,2,4,10,14,18,20,24,25,32,35,39,41,42,46,48,49,51,52] A large combined analysis of 1360 patients with acromegaly conducted by Ross and Wilson[46] 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 series[39]) 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.[6,24,52]

Radiation therapy significantly lowers postoperative GH levels in a large number of patients with refractory disease (a 50–79% response is commonly cited[8,15,28–31,34,36,43,53]), 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.[9,33,55] Adjuvant 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

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.[11,23,40–42] 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 IGF-I during the early postoperative period does not accurately reflect GH status because IGF-I levels take several weeks to return to baseline level after successful tumor resection.[27] Furthermore, the systemic insult of surgery and calorie deprivation may also lower IGF-I levels. Thus, measuring this peptide is not helpful in determining a postoperative management course. Additionally, the IGF-I immunoassay is relatively costly, more than $80 at our institution as compared with $14 to determine a serum GH level. Thus, although we have observed that an IGF-I level at 5 years correlates closely with disease activity and accurately assesses the patient's ultimate acromegalic status, it is an imprecise test when used during the early postoperative period.

Historically, determination of the serum GH level has been the most commonly used test of acromegalic activity. Two major problems exist when using GH levels to determine postoperative acromegalic activity, however. First, GH secretion is pulsatile, varying greatly among individuals and achieving transient levels as high as 30 ng/ml in healthy people.[41] Second, GH has a relatively short serum halflife (~ 20 minutes), thus allowing the possibility that an isolated measurement may not be indicative of the true physiological status of the patient.[41,50] Twenty-four hour integrated mean GH measurements are therefore more accurate, but require considerable effort and expense. Other tests, such as the OGTT and the TRH stimulation test have been performed and usually suppress GH in patients who have been cured.[3,5,6,19,22,38,41,51,54] Recent consensus has suggested that an OGTT in which the nadir GH level is less than 1 ng/ml following oral glucose loading, together with a normal sex- and age-matched IGF-I level should be used to define chemical control following either medical or surgical treatment.[23]

Unfortunately, administration of an OGTT during the early postoperative period may be impractical and, for reasons previously stated, IGF-I measurement may be unreliable. In the present study we evaluated the predictive value of an early postoperative serum GH level. If GH measurements are to be used, a specific reproducible value should be determined that distinguishes patients at risk for persistent or recurrent disease activity from those who are truly cured. The trend in the literature has been toward a progressive lowering of the value accepted as indicative of disease control. In the last 15 years, various reports have increased this stringency from 10 to 8 to 5 ng/ml.[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.[21]

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,[6,23] 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).[38] 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[12] 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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