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CONSENSUS

Criteria for Cure of Acromegaly: A Consensus Statement*†

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ABSTRACT

In February 1999, a workshop was held in Cortina, Italy to develop a consensus defining the criteria for cure of acromegaly. The workshop was sponsored by the University of Brescia and hosted by the Italian Society of Endocrinology. Invited international participants included endocrinologists, neurosurgeons, and radiotherapists skilled in the management of acromegaly. This statement summarizes the consensus achieved in these discussions. (*J Clin Endocrinol Metab* **85:** 526–529, 2000)

Therapeutic Goals

The therapeutic goals in acromegaly are to eliminate morbidity and to reduce mortality to the expected age- and sex-adjusted rates by using safe treatments that remove the tumor mass or control its growth and restore GH secretion and action to normal. The biochemical goals of therapy are to reduce circulating insulin-like growth factor I (IGF-I) levels to normal for age and sex and to reduce serum GH concentrations to less than 1 μg/L after an oral glucose load.

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Baseline Biochemical Parameters

Baseline biochemical parameters for the diagnosis of acromegaly include a fasting or random GH and IGF measurement. If a random GH level is less than 0.4 μg/L and IGF is in the age- and gender-matched normal range (1, 2), the diagnosis of acromegaly is excluded in a patient who has no other intercurrent illness (Table 1). If either of these levels is not achieved, a glucose tolerance test should be performed with 75 g oral glucose and subsequent measurements of glucose and GH every 30 min over 2 h. During this time, the GH level should fall to 1 μg/L or less for acromegaly to be excluded (3). Although mean integrated 24-h GH levels of less than 2.5 μg/L also exclude acromegaly, these values correlate tightly with results of the glucose suppression test, which is most cost-effective (4). Tests that do not offer additional information for the diagnosis of acromegaly include TRH, GHRH, or GnRH stimulation, measurement of IGF binding protein 3, and studies of spontaneous GH secretion by frequent sampling (5).

Dynamic Testing

Oral glucose tolerance test (OGTT)

Failure of GH suppression after glucose loading in the appropriate clinical context suggests the diagnosis of acromegaly, but the results should always be considered in conjunction with an IGF-I measurement because other conditions can cause discordantly elevated GH levels. Using all

TABLE 1. Acromegaly biochemical diagnosis

Random GH <0.4 μg/L and normal IGF-I
Excludes acromegaly
GH nadir during OGTT <1 μg/L and normal IGF-I
Excludes acromegaly

current commercial assays, the cut-off GH value separating normal subjects from those with acromegaly is less than 1 μg/L. However, with the introduction of newer more sensitive assays it is anticipated that a lower cut-off value can be defined in the future (6).

A paradoxical rise in serum GH provides no additional value beyond that attained by failure to suppress GH. Care needs to be taken in interpretation of the test in the immediate postoperative period due to effects of concomitant glucocorticoid administration and other perioperative medications, including glucose, dopamine, opiates, and anesthetics. Although no data exist regarding the superiority of 75 or 100 g glucose, it is recommended that 75 g be used to achieve a level of standardization. The attained blood glucose levels are of importance with respect to the diagnosis of diabetes mellitus, but do not affect interpretation of the GH result. Although GH responses may differ between male and female subjects and show some influence of age, these factors are not considered important for diagnostic interpretation of the GH response to glucose.

False-positive responses (*i.e.* failure of normal suppression) may occur in patients with diabetes mellitus, liver disease, renal disease, adolescence, and anorexia nervosa. False negative responses (*i.e.* normal suppression) may be encountered in acromegaly itself. However, in both situations interpretation should be tempered by the simultaneous availability of IGF-I levels and consideration of the associated clinical findings.

Stimulatory tests

TRH and GnRH stimulation tests of GH secretion have been used as a second tier evaluation of abnormal GH dynamics in the diagnosis of acromegaly and in assessing responses to therapeutic intervention (7). These tests offer no advantage over the OGTT and, as serious side effects may occasionally occur in response to TRH, their use is not recommended for diagnosis. Nearly all patients with acromegaly respond to GH secretagogues, and all have paradoxical inhibitory responses to galanin. However, none of these agents is of proven value in the evaluation of patients with acromegaly at the present time.

Although nearly all patients respond to GHRH stimulation (8), this agent is not of value in the diagnosis of GH-secreting tumors nor in distinguishing them from those with ectopic GHRH secretion. In suspected cases of the rarely encountered latter condition, a serum GHRH level is the preferred test.

Assays

The assays used for the diagnosis, management, and follow-up of acromegaly are GH and (total) IGF-I measurements. Both assays should have adequate sensitivity (for GH, at least 0.5 μg/L), established validity, specificity, reliability, and uniform reproducibility (9, 10). IGF-I concentrations must be compared with age-dependent normative data generated across all age groups and both sexes. Systemic diseases, including catabolic states and hepatic or renal failure and malnutrition, may result in lowered IGF-I levels (10). Repeat assay and follow-up may be helpful when IGF-I values are borderline, or clinical and biochemical data are not congruent. Assays for antilymphocyte serum, free IGF-I, IGF binding protein-3, and urinary GH are of no additional independent diagnostic value, but some methods serve currently as research tools (11). Refinements of GH assay performance will likely lead to revised normative criteria of GH suppression after glucose loading, but the clinical relevance of such enhanced sensitivity is not currently apparent. In the rare case of suspected ectopic GHRH syndrome, circulating GHRH concentrations should be measured.

Using Cure Criteria for Evaluating Treatment

Definition of cure

Control is achieved when all attributes of disordered GH secretion are restored to normal. Biochemically, this is evident when circulating IGF-I is reduced to an age-adjusted normal range and nadir GH after an oral glucose load is less than 1 μg/L.

Surgery

Ideally, the GH-secreting adenoma should be completely resected, with preservation or subsequent restoration of pituitary function (12). Surgical effectiveness varies greatly depending on expertise in pituitary surgery, both the size and extension of the anatomic mass, and the preoperative level of GH (13–16). Tumor resection generally results in a rapid and substantial reduction of serum GH levels immediately postoperatively and corresponding lowering of IGF-I levels in the weeks following surgery.

Historically, patients have been classified as "cured" or "noncured." This concept was based on outcomes of surgical interventions with imprecise biochemical evaluation and is misleading for patients and clinicians. If rigorous criteria are used for the interpretation of surgical results (GH nadir after OGTT <1 μg/L), approximately 80% of patients with microadenomas and substantially less than 50% of patients with macroadenomas can be defined as controlled. Patients in whom disease has been controlled, as defined by older criteria, may, in fact, demonstrate increased GH secretion when retested 1 or more years after surgery (17).

Medical treatment

After long-term somatostatin receptor ligand administration, GH levels are suppressed to less than 2.5 μg/L in 65% of patients and IGF-I levels are normalized in ~70% of patients (18, 19). New slow-release formulations of long-acting somatostatin receptor ligands result in persistent GH and IGF-I suppression after im depot injection (20, 21). Drug levels peak at 28 days and are sustained for over 4 weeks. Persistently controlled mean GH levels (<2 μg/L) are achieved in over 70% of octreotide-sensitive patients (20). Lanreotide injected every 14 days provides similar GH and

IGF-I control (21). High doses of long-acting dopamine receptor agonists rarely normalize IGF-I levels (22, 23), but data on long-term control of GH and IGF-I with these agents is not yet available. Future treatment options may include receptor-subtype selective somatostatin ligands and GH receptor antagonists (24).

Radiotherapy

Beneficial effects of radiotherapy on GH levels are delayed, and about 90% of patients achieve random GH levels of less than 5 μg/L after 18 yr (25). Ineffectiveness of radiotherapy in lowering IGF-I despite attenuation of GH levels has been reported (26). However, shrinkage or at least prevention of continued pituitary tumor mass growth is usually achieved with radiotherapy. Stereotactic radiosurgery is currently under investigation, and early results show that after 1.4 yr, 8 of 16 patients achieve GH levels less than 5 μg/L (27).

Interpretation of Treatment Outcomes

Results of the different treatment modalities should be interpreted using the criteria enunciated above and applied for evaluating disease control in assessing disease therapy. Additionally, the efficacy of surgical and radiotherapeutic procedures should be evaluated in the long term by the use of anatomic tools, including magnetic resonance imaging (MRI) and visual field evaluation. Moreover, after these procedures, residual pituitary function should be preserved and hypopituitarism avoided. After surgery and after initiating medical treatment, biochemical assessment should be performed at 6–12 weeks. IGF-I normalization may only occur several months later. After radiotherapy, long-term biochemical assessment is required to assess efficacy and the development of pituitary failure. All patients with acromegaly require periodic lifelong evaluation.

Clinical outcomes

The morbidity and mortality associated with active acromegaly comprise a continuum associated with disease activity, requiring effective and sustained long-term treatment. Morbidity and mortality rates are significantly increased due either to a direct deleterious impact of raised GH and IGF-I levels and/or to acromegaly-related co-morbidity, including cardiovascular disease, diabetes, respiratory dysfunction, and sleep apnea. GH levels seem to be the single most important determinant of mortality in acromegaly (28, 29). Importantly, imprecise biochemical assessment (*i.e.* insufficiently sensitive GH assays and lack of information regarding IGF-I normal ranges) contribute to the uncertainty in the literature regarding dose-response relations between biochemical activity and improvement in morbidity and mortality rates. Nevertheless, the existing epidemiologic information strongly suggests that a decrease in GH level in acromegaly is beneficial and may lead to improved or even normalized mortality rates. Failure to control GH is associated with a 3.5-fold enhanced mortality, as compared to patients in whom GH is controlled whose mortality is not different from controls (14, 15, 30). It is, therefore, recommended that patients with acromegaly, especially those under 40 yr of age, should be treated aggressively to lower the GH/IGF-I indices as close to "normal" as clinically possible. Decrease or even normalization of GH/IGF-I may not always result in consistent reversal of the indices of cardiovascular morbidity, especially hypertension and sleep apnea. Thus, aggressive cotreatment of hypertension, diabetes, heart disease, and hyperlipidemia should be instituted. Sleep apnea should be actively assessed and, if necessary, treated independently. The question of whether increased cerebrovascular morbidity and mortality may be iatrogenic secondary to cranial irradiation, is not resolved.

The association between acromegaly and malignant diseases is not resolved fully. There is increased general mucosal hypertrophy in active acromegaly, which is reflected in the appearance of colonic polyps in a high proportion of acromegalic patients, even at an unusually young age. Colonic polyps are often of a premalignant nature (31). Thus, even though conflicting data exist regarding incidence and mortality from colon cancer in acromegaly, aggressive diagnostic vigilance is justified. All patients should have pan-colonoscopy at diagnosis, and this procedure should be repeated periodically as determined by individual risk factors, including presence of polyps, family history, and presence of skin tags. Screening for breast and prostate cancer should be conducted according to standards used in the general population. Additional basic research assessing GH/IGF-I effects on neoplastic transformation and reevaluation of the clinical use of IGF-I as a marker of disease activity are needed.

The aim of treatment is to control the disease by suppressing GH hyperactivity, reducing the size or impeding the

TABLE 2. Acromegaly treatment outcomes

Outcome	Criteria	Management
Controlled	Nadir GH <1 μg/L	Asses GH/IGF-I axis
	Age-sex-normalized IGF-I	Evaluate pituitary function
	No clinical activity	Periodic MRI
		No treatment or no change in current treatment
Inadequately controlled	Nadir GH >1 μg/L	Assess GH/IGF-I axis
	Elevated IGF-I	Evaluate pituitary function
	Clinically inactive	Periodic MRI
		Assess cardiovascular, metabolic, and tumoral comorbidity
		Weigh treatment benefit or consider new treatment *vs.* low risk of elevated GH
Poor control	Nadir GH >1 μg/L	Assess GH/IGF-I axis
	Elevated IGF-I	Evaluate pituitary function
	Clinically active	Periodic MRI
		Actively treat or change treatment

growth of the pituitary mass, and eliminating secondary comorbid complications. Such control of acromegaly may be achieved through either single or combined surgery, radiotherapy, and/or medical treatment. Patients can, thus, be classified depending on the degree of disease control. Good control implies that the patient does not exhibit GH hyperactivity, as measured by available assays, and should enjoy a mortality risk similar to the general population. Inadequate control implies the presence of GH hypersecretion, but minimally enhanced morbidity. Nevertheless, morbidity is inexorable in these patients and ultimately becomes life-threatening. Poor control implies that parameters of GH hyperactivity are present with a high risk of morbidity and mortality. Thus, control of acromegaly depends on evolution of the disease and on therapeutic outcomes (Table 2).

Cost-effective analysis of treatment should be undertaken to determine the benefit of improvement in quality of life and additional quality-adjusted life years, and the cost of disease-associated disabilities. In well-controlled patients, the cost of follow-up includes periodically assessing GH and IGF-I secretion, evaluation of anterior pituitary function, and ophthalmologic and MRI evaluation. Inadequately controlled patients require the same evaluation, and the rationale for additional nonsurgical treatment must be weighed against their relatively low risk and their cost. Long-term exposure to unacceptable levels of GH and IGF-I will lead to deleterious cardiac, respiratory, and rheumatoid dysfunction. These and other comorbidities are directly caused by GH and IGF-I, and, as they account for enhanced mortality, there is a compelling rationale for aggressively controlling GH and IGF-I levels as tightly as possible (32). In poorly controlled patients, the same evaluation should be performed and the cost of additional nonsurgical treatment, including somatostatin analogs and radiotherapy, should be weighed against clinical benefits. Followup of acromegalic patients and their treatment is a considerable burden to the health-care system, but is compensated by the small number of afflicted patients.

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