Clinical and Medical Diagnosis of Acromegaly

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The biochemical diagnosis of acromegaly and assessment of the clinical activity of the disease can be made by measurement of the insulin-like growth factor-I (IGF-I) concentration in the serum. False-positive increases seldom occur. This determination has largely replaced measurement of the growth hormone (GH) response to the oral administration of glucose, which in normal individuals suppresses to less than 2 μg/L. In normally fed individuals with normal liver and renal function, circulating IGF-I levels reflect the integrated effect of GH at the tissue level and also correlate with mean 24-hour GH levels. Measurement of the IGF-I concentration differentiates subjects with active untreated acromegaly from normal individuals, but the serum IGF-I level also reflects the clinical activity of the disease. However, it remains debatable whether this particular parameter represents most faithfully the course of the disease. Computed tomography and magnetic resonance imaging have greatly facilitated the diagnosis of pituitary abnormalities in acromegalic patients. Evidence of a pituitary tumor is found in almost all patients. Most adenomas are larger than 10 mm in diameter at the time of diagnosis, and extrasellar extension is present in approximately one third of cases.

ACROMEGALY is a chronic, slowly developing disease characterized by progressive disfigurement and disability. Apart from the cosmetic changes, a multitude of complaints interfere with normal daily working life in most patients, and secondary complications related to the cardiovascular and respiratory systems, as well as to tumor formation, often cause premature death if no effective therapy is administered.[1,2]

In virtually all patients, the clinical syndrome of acromegaly is caused by a growth hormone (GH)-secreting pituitary adenoma. Excessive production of this hormone also results in an increased production of tissue growth factors such as insulin-like growth factor-I (IGF-I). An early diagnosis of acromegaly is difficult, and in the majority of patients the long delay in diagnosis results in the development of irreversible complications in several organ systems.

Acromegaly occurs with equal frequency in both sexes. Most patients are diagnosed between the ages of 40 and 60 years.[3] Based on epidemiological studies, the age prevalence of the disease is between 55 and 70 years, and the annual incidence may be three to four cases per million inhabitants.[4]

Most signs and symptoms of acromegaly are the result of the long-standing overproduction of GH and/or IGF-I, but they may also be related to pressure effects of the pituitary adenoma, causing loss of anterior pituitary function and headache, and in the case of suprasellar extension of the tumor, the development of visual-field defects and loss of visual acuity.

The disfigurement of the face is insidious in most patients and occurs slowly. Therefore, the most frequent mode of diagnosis is by a new physician who replaces the regular doctor and sees the patient for the first time.[5]

In Table 1, the main clinical features of 600 acromegalic patients, from seven series in the literature, are presented. The high incidence of menstrual disorders and decreased libido and/or potency are related not only to anterior pituitary insufficiency but also to the fact that 30% to 40% of GH-secreting pituitary adenomas co-secrete prolactin.[1,2]

As stated above, the signs and symptoms in patients with acromegaly often progress only slowly. For this reason, the diagnosis is often missed for many years. The mean delay between the onset of symptoms and the time of diagnosis in a group of 44 acromegalic patients was 6.5 years (4.1 years in female and 8.6 years in male patients).[6]

Table 1. Main Clinical Features of Acromegaly

	% Present in 600 Patients From Seven Series in the Literature
Acral enlargement and soft-tissue overgrowth	100
Increased perspiration	85
Headache	70
Paresthesias	65
Glucose intolerance and/or diabetes mellitus	45
Cardiovascular abnormalities	20
Hypertension	20
Goiter	25
Menstrual disorders	60
Decreased libido/impotence	45
Visual-field defects	20

The laboratory diagnosis of acromegaly and assessment of the clinical activity of the disease may be best achieved by measuring the IGF-I concentration in the serum.[7,8] In normally fed individuals with normal liver and renal function, circulating IGF-I levels reflect the integrated effect of GH at the tissue level and also correlate with the mean 24-hour GH levels.[9]

Although in some untreated acromegalic patients random serum GH concentrations are so high that they can be considered virtually diagnostic, multiple sampling is often necessary to exclude spontaneous fluctuations in normal values. To standardize this procedure, a test can be used that measures GH levels in response to an oral glucose load. Normally, GH levels are suppressed to less than 2

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μg/L after 2 hours. However, in acromegaly the suppression does not occur to this extent. In many cases, even a paradoxical increase of GH levels is observed in response to glucose. The oral glucose test has been recently replaced by measurement of the IGF-I concentration in a single serum sample. In a prospective study, we compared the diagnostic value of measurement of a single IGF-I value with the GH level 2 hours after a 75-g oral glucose load in 33 previously untreated patients[10] (Fig 1). Increased IGF-I levels were found in 32 of 33 patients. The only exception was a patient with clinically nonactive acromegaly, in whom alcoholic liver disease evidently precluded an increased peripheral formation of IGF-I in response to excess pituitary GH secretion. No false-positive elevated IGF-I levels were observed in normal adult patients. This study supports the concept that the measurement of one single IGF-I concentration is in general sufficient for the biochemical diagnosis of acromegaly, and that the oral glucose test with GH measurements can be omitted in most instances.

During follow-up evaluation of acromegalic patients during and/or after therapy, the measurement of IGF-I concentrations in the serum also is helpful and informative. Previous studies have shown that in acromegalic patients the serum IGF-I level correlates well and in general better with the clinical activity of the disease than serum GH levels.[7,8] The long half-life of IGF-I, which is mainly due to its two specific carrier proteins, excludes the necessity for standardized or repeated sampling.

In untreated acromegalics, there exists a correlation between fasting, postprandial, and mean 24-hour serum GH levels and IGF-I concentrations.[8,11,12] However, circulating GH levels of 10 to 20 μg/L seem to activate maximally the peripheral IGF-I generation in man, and a further increase in GH secretion by pituitary adenomas generally will not result in a further increase in IGF-I production.[11,12,13] The relation between random serum GH and IGF-I levels in 66 untreated acromegalic patients is shown in Fig 2.

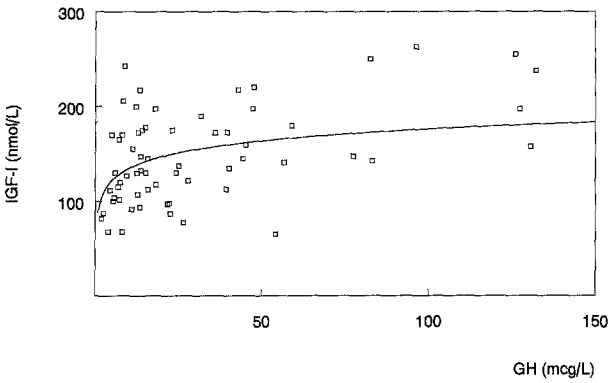

Fig 2. Relationship between random circulating GH and IGF-I levels in 66 untreated acromegalic patients.

In the assessment of the activity of GH-secreting pituitary adenomas during and after octreotide treatment, a single IGF-I determination is of similar value as the measurement of a 24-hour profile of GH secretion.[14] In Fig 3, the close relation between IGF-I and mean 24-hour GH levels is shown in 20 acromegalic patients after 2 years of treatment with 200 to 300 μg octreotide per day. Also, the measurement of 24-hour urinary GH excretion seems to be an accurate indicator of disease activity in acromegaly, but the need for concentration of the urine by centrifugal ultrafiltration is a disadvantage.[15]

Another question is whether the measurement of one single IGF-I value is in all cases sufficient during the long-term follow-up evaluation of acromegalic patients, or whether the additional measurement of one (standardized) GH level provides additional information.[11-19] In Fig 4, the relationship is shown between circulating GH and IGF-I values, both determined 2 hours after breakfast in 49 acromegalic patients during the long-term follow-up period between 6 months and 18 years after surgery and/or radiotherapy. The clinical activity of these patients had also

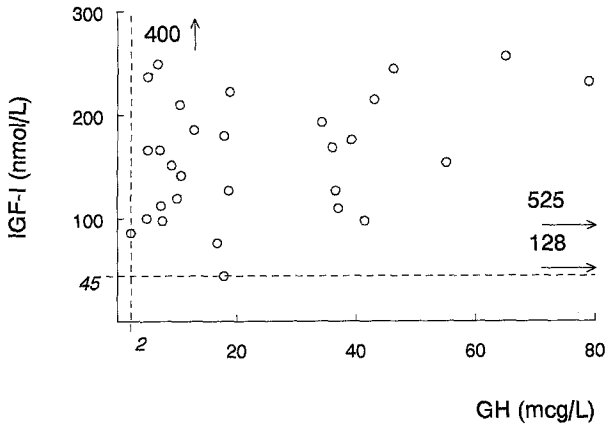

Fig 1. Relationship between serum IGF-I and GH levels 2 hours after a 75-g oral glucose tolerance test in 33 untreated acromegalic patients. Normal levels are less than 2 μg/L for GH and less than 45 nmol/L for IGF-I (----). Two patients had GH levels that, at 525 and 128 μg/L respectively, were off-scale of the graph, and one patient had an IGF-I level (400 nmol/L) that was off-scale.[10]

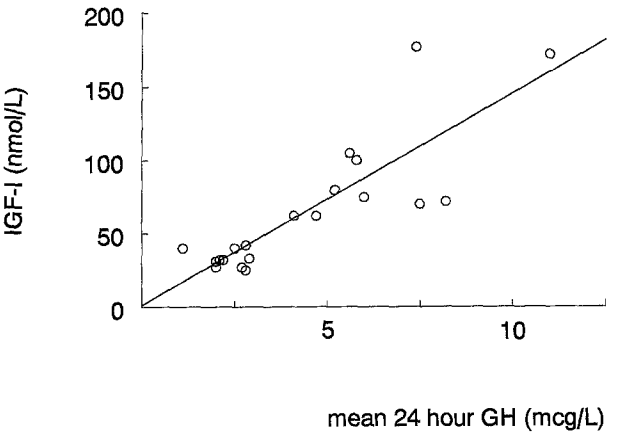

Fig 3. Relationship between serum IGF-I concentration and mean 24-hour GH level (mean of 19 samples) in 20 acromegalic patients after a mean octreotide therapy period of 100 weeks (200 to 300 μg/d); $r = .85$, $P < .0001$.

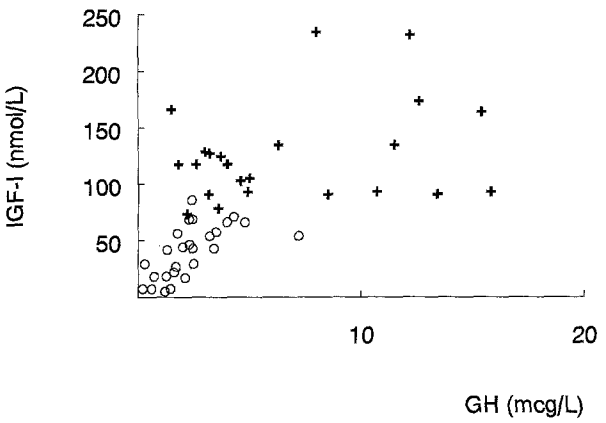

Fig 4. Relationship between serum IGF-I and GH levels both measured 2 hours after breakfast in 49 acromegalic patients during follow-up evaluation after surgery and radiotherapy. (0) Patients without clinical activity; (+) those with clinical activity of the disease.

been evaluated independently: every patient who had two or more of five complaints (soft-tissue swelling, excessive perspiration, paresthesias, headache, or arthropathy) was arbitrarily considered to have clinically active disease.

There was a statistically significant correlation between circulating GH and IGF-I levels (Fig 4; n = 49, $P < .001$). IGF-I values were normal in 16 patients and elevated in 33 patients. All 23 patients demonstrating clinical activity of the disease had increased IGF-I levels. In addition, there were 10 patients with slightly elevated IGF-I values who were clinically considered "cured." In all these 10 patients, the post-breakfast GH levels were higher than 2 μg/L. The combination of IGF-I and GH measurements demonstrated that both values were "normal" in 10 of the 26 clinically cured patients, that both values were abnormal in 10 other patients, and that either IGF-I or GH levels had normalized in the remaining six cases. These data suggest that a single determination of both IGF-I and GH correlates rather weakly with the clinical severity of the disease.[20] However, the combination of an IGF-I and a GH determination also leaves a grey zone in which some patients do not demonstrate further clinical activity, while one or both biochemical parameters are still elevated.

CONCLUSIONS

Computed tomography and magnetic resonance imaging techniques have greatly facilitated the diagnosis of pituitary abnormalities in acromegalic patients. Evidence of a pituitary tumor is found in almost all patients. Most adenomas are larger than 10 mm in diameter at the time of diagnosis. Extrasellar extension of the tumor is present in approximately one third of cases. Tumors infiltrating the bone and other surrounding structures are frequent and can be recognized at neuroradiological examination in as many as 40% of cases.

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