

Early Diagnosis of Acromegaly

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A cromegaly is a rare condition with an annual incidence of 3 to 4 cases per million people. The age at diagnosis is generally 40 to 50 years. Recognition can be difficult because clinical features may be subtle early in the disease. It is associated with an almost 3-fold increase in mortality rate, primarily from cancer and cardiovascular disease. Approximately 75% of cases are caused by pituitary macroadenomas (> 10 mm in diameter).¹

The most specific means of diagnosing acromegaly is to measure serum growth hormone (GH) levels during an oral glucose tolerance test (OGTT). In patients with acromegaly, GH secretion is not suppressed during an OGTT, whereas in persons without acromegaly, GH secretion is suppressed during the OGTT. It has been debated how far GH levels should decline during the OGTT. In 1983, Schuster and coworkers² noted that GH levels fell to 2 ng/mL or lower in healthy subjects after ingestion of a 100 g glucose load. When basal GH levels are between 1 and 3 ng/mL, however, these proposed criteria for diagnosing acromegaly may not be helpful.³ In 1990, Hattori⁴ proposed that healthy subjects should suppress GH secretion to levels below 1 ng/mL after ingestion of glucose.

The circulating level of insulin-like growth factor I (IGF-I) is the best test to document chronic GH hypersecretion because of its long half-life. Even mildly raised GH levels are sufficient to elevate the serum IGF-I level. It has been suggested that a single IGF-I measurement could replace the OGTT because it is highly sensitive and specific for acromegaly. However, hypoproteinemia can result in a low IGF-I level in patients with acromegaly.⁵

This article presents the case of a man with subtle manifestations of acromegaly and an elevated IGF-I level. A sensitive chemiluminescent assay was used to determine his GH levels, which were below 3 ng/mL. GH levels did not decrease during an OGTT but were reduced by octreotide administration. The sensitive GH assay contributed to early diagnosis in this patient.

This case suggests that a revision of criteria for the interpretation of tests involving suppression of GH secretion in acromegaly is warranted to accommodate the increased sensitivity of modern GH assays.

CASE REPORT

Presentation to Neurology Clinic

A 38-year-old man with a history of chronic low back pain, nephrolithiasis, and papillary cancer of the thyroid initially presented to neurology clinic because of shooting pains in his legs. He also complained of leg weakness. His thyroid cancer had been treated 7 years previously with resection and radioiodine ablation followed by thyroxine replacement therapy.

Physical examination was notable for mild lower extremity proximal muscle weakness and partial sensory loss in the left leg. Reflexes and visual fields were normal. Results of magnetic resonance imaging (MRI) of the spine and nerve conduction studies were normal. After an unsuccessful empiric trial of glucocorticoids, the patient was referred to an endocrinology clinic.

Evaluation in Endocrinology Clinic

Physical examination in the endocrinology clinic revealed a man 185 cm tall and weighing 262 pounds. His blood pressure was 150/88 mm Hg. Coarse facies, irregular dentition, large hands and feet, and axillary skin tags were noted. MRI of the pituitary region

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Table 1. Blood Laboratory Results for the Case Patient

Variable	Result	Normal Range
Prolactin	6 ng/mL	< 18 ng/mL
Hemoglobin A1c	5.6%	4.3%–6.1%
Calcium	9.7 mg/dL	8.5–10.5 mg/dL
Phosphorus	4.6 mg/dL	2.5–4.5 mg/dL
IGF-I	806 ng/mL	114–492 ng/mL
FSH	1.5 mIU/mL	1.4–14 mIU/mL
LH	1.6 mIU/mL	1.4–7.7 mIU/mL
Testosterone	341 ng/dL	240–830 ng/dL

FSH = follicle-stimulating hormone; IGF-I = insulin-like growth factor I; LH = luteinizing hormone.

revealed a small focus of reduced enhancement in the inferior portion of the pituitary gland, thought to represent a microadenoma. He was currently taking 20 mg daily of prednisone.

The initial laboratory evaluation was notable only for an elevated IGF-I level of 806 ng/mL (Table 1). The patient's GH levels were measured using a sensitive chemiluminescent immunoassay during two 100-g OGTT tests performed before and after weaning from prednisone (Table 2). At the end of the second test (6 weeks after corticosteroid discontinuation), 100 U of octreotide were given subcutaneously and GH was measured 1 hour later to check the sensitivity of the assay for detection of low GH levels. The assay used for determination of GH levels was a solid-phase, 2-site chemiluminescent immunoassay (Immulate GH assay, Diagnostics Products, Los Angeles, CA). The capture antibody was a monoclonal IgG specific for GH, and the detection antibody was a polyclonal alkaline phosphatase-conjugated rabbit anti-GH IgG. The assay dynamic range was 0.1 to 40 ng/mL, with a coefficient of variation of 7.0% at 4.0 ng/mL.

After the patient was weaned from corticosteroids, his cortisol level rose from 17 to 26 mg/dL 60 minutes after injection of 250 µg synthetic adrenocorticotrophic hormone, indicating that his adrenal axis was intact.

Treatment and Outcome

Based on the clinical and laboratory data, the diagnosis of acromegaly was made and a transsphenoidal pituitary adenectomy was performed. On the right side of the gland, a microadenoma was identified and removed. The tumor cells stained as acidophils. Within 2 weeks of surgery the patient reported that his neurologic symptoms had resolved. Two months later his

Table 2. Oral Glucose Tolerance Test Results for the Case Patient

Time After Glucose Administration (min)	Blood Glucose (mg/dL)	Growth Hormone (ng/mL)
<i>OGTT performed while patient was on prednisone</i>		
0	92	1.8
30	116	1.6
60	215	1.4
90	266	1.6
120	240	1.8
<i>OGTT performed after weaning the patient from prednisone</i>		
0	85	2.5
30	116	1.7
60	162	1.3
90	168	1.5
120	139	1.5
Post-octreotide*		0.5
<i>OGTT performed postoperatively</i>		
0	88	< 0.1
30	135	< 0.1
60	160	< 0.1
90	158	< 0.1
120	179	< 0.1

OGTT = oral glucose tolerance test (100 g glucose).

*Growth hormone level measured 60 min after administration of 100 U octreotide.

IGF-I level was normal at 219 ng/mL, and his GH hormone levels during a repeated OGTT were all less than 0.1 ng/mL (Table 2).

DISCUSSION

The clinical features of acromegaly occur secondary to local effects of an expanding sellar mass and the direct as well as indirect effects of excess GH and its principle mediator, IGF-I, on peripheral tissues.⁶ Characteristic findings include macrognathia, macroglossia, and enlargement of the hands and feet.¹ Neurologic manifestations of acromegaly include headache, carpal tunnel syndrome, proximal muscle weakness, and a mixed sensorimotor neuropathy.⁷

The clinical presentation of this case was consistent with acromegaly, and the MRI showed a pituitary lesion near the size limit of detectability. However, the

biochemical data were unusual in that GH levels were invariably lower than 3.0 ng/mL, and after an OGTT the GH levels were less than 2.0 ng/mL.

Healthy individuals may have GH levels below the detection limit of some assays between secretory peaks. In contrast, patients with acromegaly have increased GH secretion on a continual basis, and hence, serum GH may remain detectable at all times in these patients. The majority of patients with acromegaly have GH levels greater than 5 ng/mL on fasting basal samples; however, in healthy subjects, minimal exercise may elevate the GH level significantly,⁸ confounding interpretation of the test results. For these reasons, dynamic GH testing using the OGTT is the most specific test for establishing the diagnosis.⁹ In a series of 216 patients with acromegaly, 8 had basal GH levels lower than 5 ng/mL.⁸ In all 8 of these patients, however, suppression to a level lower than 2 ng/mL failed to occur after glucose ingestion. In contrast, in the present case, the patient did suppress GH secretion to levels less than 2 ng/mL during OGTT testing.

The GH assays used in clinical practice have become progressively more sensitive in recent years,⁶ and criteria for a normal response to an OGTT have therefore changed. Recently published papers, however, still quote failure of an oral glucose load to suppress GH secretion to levels less than 2 ng/mL as the diagnostic criterion.³ Thorner and coworkers⁹ have suggested that a normal response to the 100 g OGTT is suppression of GH secretion to a level below 0.5 ng/mL on any measurement within 90 minutes of glucose ingestion using the chemiluminescent assay.

High glucocorticoid levels and hyperglycemia in normal individuals may inhibit growth hormone secretion.¹⁰ In the case patient, either or both of these factors may have been responsible for the low GH levels observed during the first OGTT. For this reason, the OGTT was performed a second time after the patient was weaned off of the prednisone. There have been mixed reports about the effect of diabetes on GH testing. Some have suggested that suppression of GH secretion may be impaired in the presence of diabetes mellitus, while others have refuted this observation.^{10,11} In the present case, the 2-hour glucose level during the first test was in the range at 240 mg/dL, indicative of diabetes mellitus. The GH level dropped to 1.4 ng/mL during this test. The second OGTT showed a 2-hour glucose level of 139 mg/dL, which is just below the criterion for impaired glucose tolerance (140–199 mg/dL). The patient's GH level fell to a nadir of 1.3 ng/mL during this test; hence, his mild hyperglycemia during this test did not affect GH levels. Sixty minutes after administra-

tion of 100 U of octreotide, the GH level dropped to 0.5 ng/mL, confirming that the chemiluminescent assay could detect levels lower than 1 ng/mL.

After surgery, his circulating glucose level 2 hours after glucose administration was in the impaired glucose tolerance range (179 mg/dL) and growth hormone levels throughout this OGTT were less than 0.1 ng/mL. The IGF-I level had also declined into the normal range.

CONCLUSION

This case demonstrates that patients with acromegaly may have basal and depressed GH levels lower than 2 ng/mL after glucose ingestion, as well as only subtle changes visible on MRI of the pituitary. The presence of impaired glucose tolerance or the concurrent administration of corticosteroids may contribute to the low GH levels in these patients, but did not in the case presented. In diagnosing acromegaly, it is important to use a highly sensitive GH assay that can detect levels below 1.0 ng/mL, and to use diagnostic criteria that reflect the capabilities of the new sensitive assays. The use of less sensitive assays for GH testing and relying on the previously accepted normal upper limits of GH during an OGTT could lead to confusion in the diagnosis of the disease and in the assessment of recurrence. In the case presented, the sensitive chemiluminescent assay was instrumental in the early diagnosis of acromegaly in the patient, and high IGF-I levels corroborated the diagnosis. **HP**

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