Acromegaly with Normal IGF-1 Levels Probably due to Poorly Controlled Diabetes Mellitus

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Acromegaly is characterized by the somatic disfigurement and excessive production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Here we report a patient with acromegaly and diabetes mellitus, who showed normal IGF-1 levels in spite of elevated GH levels. The patient was a 52-year-old woman with acromegalic manifestations. Serum GH level was elevated (32.4 ng/mL) with hyperglycemia (fasting plasma glucose, 277 mg/dL) and an extremely high level of glycosylated hemoglobin (HbA1c 17.7%), whereas serum IGF-1 level was within normal range (110 ng/mL, normal range 37-266). Brain magnetic resonance imaging detected a pituitary tumor, with involvement of the right cavernous sinus. Oral glucose tolerance test (OGTT) showed no suppression of serum GH. Thyrotropin-releasing hormone test showed paradoxical increases in serum GH. We therefore diagnosed acromegaly accompanied with diabetes mellitus. A large amount of insulin (34 units/day) was required to control the blood glucose level. The patient was treated with octreotide, a somatostatin analogue, followed by transsphenoidal surgery. After the surgery, serum GH levels were suppressed by OGTT, although basal serum GH levels remained to be high. Basal serum GH levels, however, were normalized 5 months later. Blood glucose became well controlled by the diet alone. In contrast, serum IGF-1 increased to the range of 219-233 ng/mL. Pre-operative serum IGF-1 levels were low probably due to poorly controlled diabetes mellitus. In conclusion, the presence of normal serum IGF-1 levels cannot exclude the diagnosis of acromegaly especially when the patient is accompanied by diabetes mellitus.

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satile fashion (Hamilton 1995), the measurement of serum GH levels is not always helpful for the diagnosis (Dimaraki et al. 2002). In contrast, the serum IGF-1 level is very useful for the diagnosis of acromegaly, because it correlates well to the symptoms of acromegaly (Clemmons et al. 1979). Furthermore, collecting the blood sample for the IGF-1 measurement is easier, because it does not require resting, and serum IGF-1 level shows no diurnal variation. Serum IGF-1 levels, however, have variations for age and gender, and are suppressed in some diseases and conditions including diabetes mellitus with poorly controlled glycemia (Ross et al. 1991; Bentham et al. 1993; Lim et al. 2007).

Here we report a patient with acromegaly and diabetes mellitus, who showed normal IGF-1 levels before the surgery. Furthermore, serum IGF-1 levels were increased after the surgery, in spite of the decreased serum GH levels.

**Clinical Findings**

A 52-year-old woman was admitted to our hospital because of body weight loss, thirst and polyuria. Her height and body weight were 153.7 cm and 56.6 Kg two years before the admission, and 154.2 cm and 51.5 Kg on admission, respectively. She had a normal stature, but showed manifestations characteristic for acromegaly: face characteristic for acromegaly such as thickened lips, widened and thickened fingers, thickened skin and enlarged shoe size. Informed consent to the case report was obtained from the patient.

Her blood pressure was 126/80 mmHg. Goiter was found. No abnormal findings were observed in her chest and abdomen. Neurological examination showed no abnormality. Ophthalmological examination showed no diabetic retinopathy and no visual field disturbances. She was in menopausal state and was not treated with any drugs such as estrogen, which may influence IGF-1 secretion.

High levels of fasting plasma glucose (277 mg/dL, normal range 70-109) and HbA1c (17.7%, normal range 4.3-5.8) were observed on admission, whereas fasting plasma glucose (102 mg/dL) and HbA1c (5.5%) were normal two years before the admission. Results of other examinations were as follows: aspartate aminotransferase, 29 IU/L (normal range 10-40); alanine aminotransferase, 45 IU/L (5-40); gamma glutamyl transpeptidase, 78 IU/L (< 30); total protein, 6.4 g/dL (6.7-8.3); blood urea nitrogen, 18 mg/dL (6-20); creatinine, 0.36 mg/dL (0.47-0.79); serum Na, 136 mmol/L (136-147); K, 4.4 mmol/L (3.6-5.0); Cl, 96 mmol/L (98-109); Ca, 9.2 mg/dL (8.7-10.1); CRP, 0.0 mg/dL (< 0.3); WBC, 3290/μL (3500-9100); RBC, 449 × 10^4/μL (376-500); hemoglobin, 15.3 g/dL (11.3-15.2); hematocrit, 44.9% (33.4-44.9); platelets, 27.7 × 10^4/μL (13.0-36.9); urinary glucose, > 1000 mg/dL; proteinuria, −; urinary ketone body, 3+.

Serum GH level was elevated (32.4 ng/mL, normal range 0.28-1.64), whereas serum IGF-1 level was within normal range (110 ng/mL, normal range 37-266). Serum GH was measured several times and ranged from 30 to 50 ng/mL. The other hormonal data were as follows: thyrotropin (TSH), 0.55 μU/mL (0.43-3.94); free-triodothyronine (fT3), 1.37 pg/mL (2.97-4.51); free-thyroxine (fT4), 0.68 ng/dL (0.82-1.59); thyroglobulin, 86 ng/mL (< 30); thyroglobulin antibody, < 0.3 U/mL (< 0.3); thyroid peroxidase antibody, < 0.3 U/mL (< 0.3); thyroid stimulating antibody, 102% (< 180); prolactin (PRL), 7.00 ng/mL (6.12-30.54); luteinizing hormone (LH), < 0.10 mIU/mL (< 87.36); follicle stimulating hormone (FSH), 1.38 mIU/mL (< 157.79); adrenocorticotropic (ACTH), 33.3 pg/mL (7.4-55.7); cortisol, 18.9 μg/dL (4.0-18.3). The thyroid function was normal two years before the admission (TSH, 0.87 μU/mL; fT3, 4.02 pg/mL; fT4, 1.25 ng/dL).

Head X-ray showed double contour of sellar floor and ballooning of the sella turcica, but forehead and mandibular intrusion were not obvious. Feet X-ray showed heel pad thickness (right 25 mm, left 24 mm). Hand X-ray did not show cauliflower like finger appearance. Brain magnetic resonance imaging (MRI) revealed a pituitary tumor which was suspected to invade right cavernous sinus (Fig. 1A). Abdominal ultrasonography, computed tomography and MRI did not detect a pancreatic tumor or other abnormalities.
Oral glucose tolerance test (OGTT) showed no suppression of GH (Fig. 2A), and TRH test showed a paradoxical elevating reaction of GH (Fig. 3). Bromocriptine, a dopamine agonist, and octreotide, a somatostatin analogue, suppressed serum GH levels (data not shown). GH releasing hormone (GRH) test showed slight serum GH elevation (data not shown). LH releasing hormone (LHRH) test and corticotropin releasing hormone (CRH) test showed almost normal reactions of serum LH, FSH and plasma ACTH (data not shown).

Hyperglycemia was treated with intensive insulin therapy. Total daily dose of insulin was 34 units. Octreotide treatment was undergone before the surgery in order to reduce tumor mass. Three-
week treatment with octreotide (100 μg three times a day) suppressed the serum GH level to 24.3 ng/mL. Serum IGF-1 level, however, elevated to 177 ng/mL disproportionately (Fig. 4). Total daily dose of insulin was decreased to 12 units during the treatment with octreotide.

She underwent transsphenoidal surgery. After the surgery, glycemic control was very good by only diet alone, and no insulin nor oral hypoglycemic agent was needed. OGTT after 10 days from the surgery showed suppression of GH, but the basal GH remained to be high (Fig. 2B). IGF-1 levels after the surgery were increased to the range of 219-233 ng/mL. Serum GH levels were normalized 5 months after the surgery. OGTT after one year from the surgery showed normal suppression of serum GH levels (Fig. 2C), indicating that the pituitary tumor was successfully removed.

**DISCUSSION**

GH stimulates IGF-1 synthesis. On the other hand, serum IGF-1 levels are suppressed not only by abnormality of GH receptors but also by some physical conditions such as nutritional deprivation, poorly controlled diabetes mellitus, liver dysfunction, renal failure, inflammatory diseases and malignant tumors (Grottoli et al. 2003). In emaciated patients such as anorexia nervosa, lower circulating levels of GH binding-proteins (GHBP) were reported to mediate GH resistance (Herington et al. 1986; Counts et al. 1992; Argente et al. 1997). There has been one report on a patient with acromegaly and diabetes mellitus with poorly controlled glycemia (Lim et al. 2007). In this case (Lim et al. 2007), serum GH levels were elevated but serum IGF-1 levels were normal. However, glycemic control with insulin

![Fig. 3. Serum GH, PRL and TSH levels after an intravenous TRH administration (500 μg).](image)

![Fig. 4. Serum GH and IGF-1 levels before and after the surgery. Octreotide (100 μg three times a day) was administered s.c. for three weeks (from 12 August to 1 September), followed by transsphenoidal surgery (2 September). Serum GH level (0.51 ng/mL) was normalized on 1 February.](image)
therapy was reported to decrease serum GH levels and increase serum IGF-1 levels.

Our current case had only mild liver dysfunction, and did not have renal failure, inflammatory diseases or malignant tumors. Accompanying diabetes mellitus was, however, poorly controlled, as indicated by strongly positive urinary ketone body and body weight loss. Furthermore, low T3 and T4 levels were observed together with increased serum cortisol and decreased serum LH levels, indicating that the nutritional state of this patient was very poor like patients with anorexia nervosa. It is known that low serum T3 level, elevated cortisol level, decreased LH level were observed in patients with anorexia nervosa (Stoving et al. 1999). After the treatment with insulin and octreotide, urinary ketone body disappeared, blood glucose was well controlled, but serum IGF-1 levels were elevated disproportionately to the serum GH levels. Serum IGF-1 levels were further elevated after transsphenoidal surgery.

It took 5 months after the surgery until serum GH levels were normalized as shown in Fig. 4. Serum GH levels did not increase in OGTT test 12 months after the surgery, indicating that a remaining pituitary tumor is not likely to explain the serum GH levels which remained to be higher during the post-operative period for a few months. The poor nutritional state which remained in this period may therefore explain these higher serum GH levels.

This patient was suspected acromegaly because of her typical stigmata of acromegaly. The onset of disease was supposed to occur several years ago because the changes of shoe size took several years. Two years before the admission, HbA1c level was 5.5%, indicating good glycemic control, and serum T3 level was normal. However, it was possible that both serum GH and IGF-1 levels might be elevated at that time, because continuously elevated serum IGF-1 promotes the symptoms of acromegaly (Clemmons et al. 1979). Greatly elevated serum GH and IGF-1 might then cause insulin resistance and diabetes mellitus, which result in imbalanced homeostasis, emaciation and suppressed serum IGF-1 levels. In conclusion, the present study has suggested that the presence of normal serum IGF-1 levels cannot exclude the diagnosis of acromegaly especially when the patient is accompanied by poorly controlled diabetes mellitus.

References


