IDDM Accompanied by a Growth Hormone–Producing Pituitary Adenoma

A case report

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CASE HISTORY — A 30-year-old Japanese man who presented with recurrent ketoacidosis caused by IDDM was found to have increased secretion of growth hormone (GH). On initial cranial magnetic resonance imaging (MRI), no pituitary lesion was detected; however, a pituitary microadenoma was found 2 years later during a repeat MRI. In spite of the hypersecretion of GH, serum IGF-I was dramatically suppressed. Transsphenoidal surgery was performed to resect the pituitary tumor that was histologically an acidophilic pituitary adenoma. Although the GH excess rapidly improved postoperatively, the IGF-I level remained low. Subsequent insulin therapy initiated 1 year after the operation elevated the serum IGF-I level to within the normal range.

DISCUSSION — The first case of coexistent IDDM and a GH–producing pituitary adenoma suggests that patients with uncontrolled IDDM may develop GH hypersecretion. Furthermore, the low IGF-I levels may be closely associated with the GH excess and with the development or progression of GH–secreting pituitary adenomas.

There is a close association between glucose intolerance and the secretion of growth hormone (GH). Although secondary diabetes caused by GH is well known (1), there have been no reports of patients with diabetes who manifest signs of acromegaly. We present a rare case that suggests IDDM may stimulate the hypersecretion of GH by a developing pituitary microadenoma. This case is very illustrative because it demonstrates that the positive feedback mechanisms that decrease IGF-I levels induce GH secretion, which may subsequently be involved in the development of pituitary adenomas.

CASE HISTORY — A 30-year-old Japanese man was admitted to our hospital because of severe generalized fatigue in October 1995. On emergent examination, blood gas analysis showed severe acidosis (base excess, −18.3 mmol/l) and a blood glucose of 380 mg/dl. Urinary glucose was 93–150 g/day, and a test for urinary ketone bodies was highly positive. Liver and renal function tests were normal, and multiple electrolyte imbalances (serum sodium, 127 mmol/l; potassium, 4.1 mmol/l; chloride, 87 mmol/l) were found. The patient was diagnosed with diabetic ketoacidosis (DKA) and treated with continuous insulin injection and fluid replacement. The patient had had similar episodes of DKA since 1990, which began at age 25 years. Although the patient had received fluid replacement with intermittent insulin injections during hospitalizations in 1990 and 1991, continuous insulin therapy was not initiated. In 1991, the patient was also found to have an increased serum GH level of 20 ng/ml (normal, <0.46 ng/ml). The patient had no acromegalic features and cranial magnetic resonance imaging (MRI) showed no abnormalities of the pituitary region at that time. In 1992 and 1994, his serum basal GH levels were 30 and 57 ng/ml, respectively. Although the cranial MRI performed in 1992 did not detect pituitary lesion (Fig. 1*A*), a low-intensity pituitary mass was found in December 1993 on T1-weighted cranial MRI (Fig. 1*B*). Preoperative endocrinologic testing showed otherwise normal pituitary function except for the hypersecretion of GH. The patient underwent transsphenoidal surgery to remove the pituitary tumor in March 1994 after preoperative glucose control was obtained with intermittent insulin. The resected tumor was proved to be an acidophilic pituitary adenoma by pathology. After surgery, the patient has been followed as an outpatient and has not required insulin therapy. On admission to our hospital in October 1995, physical examination revealed the following: height, 179.2 cm; body weight, 40.2 kg (~30 kg loss over 5 years); blood pressure, 90/60 mmHg; pulse, 90 bpm (regular); auscultation of lungs and heart, normal; palpation of abdomen, normal; neurological findings, slightly decreased tendon reflexes of all extremities; ophthalmologic findings, bilateral cataracts due to uncontrolled diabetes; and dermatologic findings, candidiasis genitalia. Endocrinologic findings included a serum GH that was slightly elevated at 1.85 ng/ml. Nevertheless, serum IGF-I, IGF-II, and IGF binding protein-III (IGFBP-III) were depressed to 24.5 ng/ml (normal, 100–315 ng/ml), 240 ng/ml (normal, 515–807 ng/ml) and 2.09 μg/ml (normal, 2.69–4.26 μg/ml), respectively. In 1991, 1992, and 1994, serum IGF-I were decreased: 14.1, 9.63, and 11.1 ng/ml, respectively. Although the remaining pituitary hormone levels and tests of adrenal function were normal, hypothyroidism (free triiodothyronine, 2.66 pg/ml; free thyroxine, 0.62 ng/dl) was identified (normal, 4–5.8 pg/ml; 1.03–2.21 ng/dl, respectively). The HbA_{1c} was increased to 14.4% (normal, 4.3–6.2%). Urinary C-peptide excretion was suppressed below the detectable range. Immunologic examination revealed the presence of anti-GAD antibody (15.1 U/ml) (normal, <5 U/ml).

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Abbreviations: DKA, diabetic ketoacidosis; GH, growth hormone; MRI, magnetic resonance imaging.

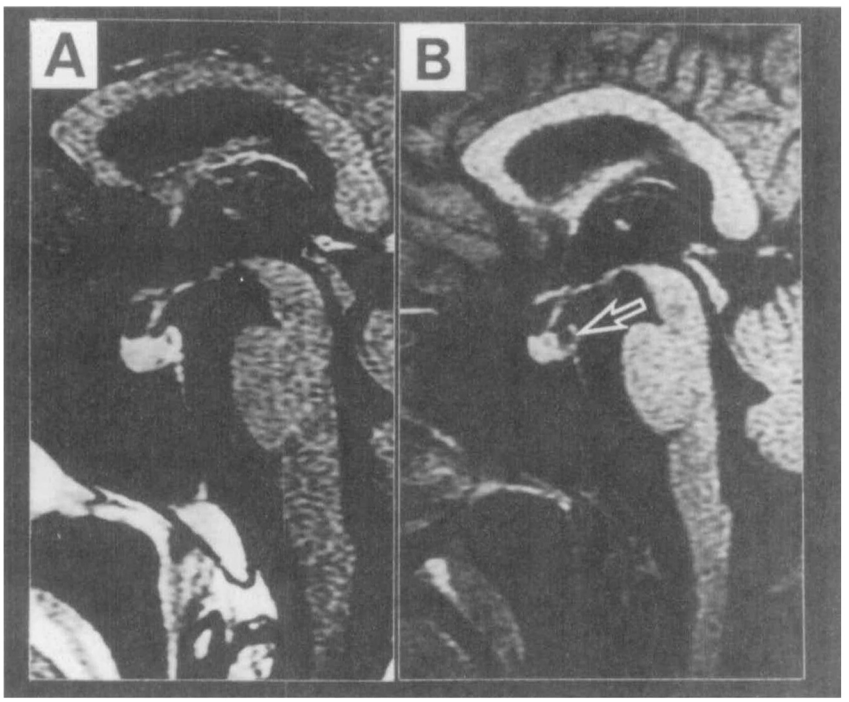

Figure 1—*Cranial MRI findings. In 1992, the patient had no detectable lesion in the pituitary region (A). In December 1993, MRI exhibited a low-intensity pituitary mass (B, see arrow).*

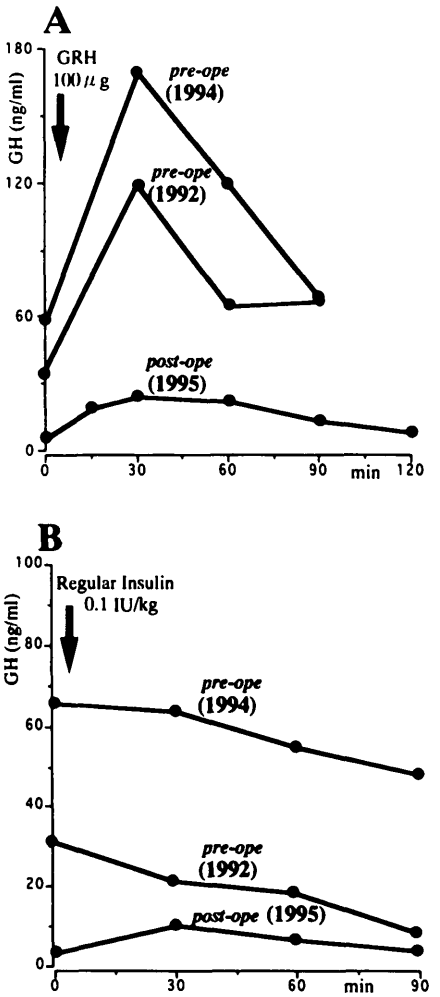

Figure 2—*Endocrinologic stimulation tests. The GRH loading test revealed a GH response that became excessive between 1992 and 1994, and postoperatively the GH hyper-response disappeared (A). The insulin loading test demonstrated a paradoxical decrease in GH that was exacerbated preoperatively. Postoperatively, this paradoxical response of GH disappeared (B).*

In terms of HLA, HLA-DR4 was positive. These findings confirmed the patient's diagnosis of IDDM.

The endocrinologic stimulation test revealed a GH response to GH–releasing hormone (GRH) that was exacerbated gradually until the transsphenoidal operation (Fig. 2*A*). The GH response to regular insulin showed a paradoxical decrease that persisted until the operation (Fig. 2*B*). After pituitary adenomectomy, GH responses to both GRH and insulin were apparently improved. Serum basal GH secretion for the 3 years before the operation had gradually increased. Nevertheless, serum IGF-I had remained low, and the discrepancy between basal serum GH and IGF-I levels was remarkable. Postoperatively, serum GH levels rapidly decreased with a mild increase in IGF-I. After insulin injection therapy, serum IGF-I concentration increased dramatically (128.6 ng/ml) (Fig. 3). The patient has continued self-injection insulin therapy and remains well without diabetic symptoms.

DISCUSSION — IDDM is characterized by a deficiency of intrinsic insulin due to the destruction of pancreatic β-cells. The pathogenesis of IDDM involves autoimmune mechanisms, and it has been reported that there is an association between HLA with the existence of autoantibodies to pancreatic antigens (2–4). In patients with diabetes, IGF-I and other growth factors have been studied to determine their roles in diabetic retinopathy and nephropathy. Although some investigators have described low serum IGF-I levels in uncontrolled IDDM patients, GH secretion was found to be elevated (5–9). These findings suggest a decreased sensitivity of hepatic cells to GH–related IGF-I synthesis in uncontrolled diabetes patients. In fact, it has been reported that dietary or protein restriction in rats causes a decrease in GH receptors or IGF-I messenger RNA in hepatic cells, respectively (10,11). Moreover, an IGF-I decrease in rats with poor nutrition did not resolve by GH administration (12). These findings suggest that a nitrogen imbalance or a catabolic state may be the dominant factor associated with diminishing IGF-I levels (13–15). Although damage caused by abnormal glucose metabolism in IDDM suppresses IGF-I synthesis, it has been reported that long-term therapy with insulin can elevate serum IGF-I levels (16). In the present case, insulin therapy for 6 months increased the IGF-I level to within the normal range, presumably related to improvements of glucose utilization and nitrogen imbalance.

There have been no previous reports describing IDDM associated with acromegaly or a GH–producing pituitary tumor, despite many descriptions of an association between GH and IGF-I. In acromegalic patients, elevated serum GH accompanied by increased serum IGF-I are characteristic findings (17). Nevertheless, the laboratory data in the present case show a discrepancy between serum GH and IGF-I levels. Considering the patient's clinical course, this discrepancy suggests that low serum IGF-I may secondarily stimulate pituitary GH secretion. It is also possible that a state of GH resistance (18), rather than a direct suppression of GH effects on hepatic cells, resulting from GH or GH–receptor abnormalities (i.e., Laron-type dwarfism or loss of GH bioactivity) could explain his course. In

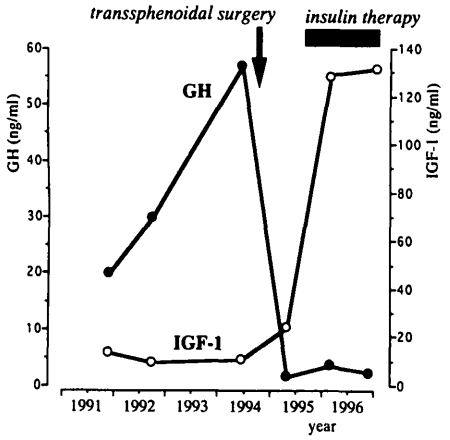

Figure 3—*Hormonal changes. Serum GH levels gradually increased preoperatively. Nevertheless, serum IGF-I levels remained extremely low. Postoperatively, serum GH levels rapidly decreased with a mild increase in IGF-I. Serum IGF-I levels recovered to within the normal range after the initiation of insulin therapy.*

addition, the increased GH level itself probably worsened the patient's glucose control by increasing glycogenolysis and/or gluconeogenesis. In fact, serum IGF-I levels, which parallel diabetic control, mildly increased in response to the postoperative GH decrease (Fig. 3).

In the present case, IGF-I levels were low during the pre- and postadenomectomy periods. IGF-II, which does not change during short-term fasting and refeeding (19), also was decreased. These findings suggest that the catabolic state induced by uncontrolled IDDM continues for a long time. Bermann et al. (20) have reported that IGF-I administration suppresses the pulsatile secretion of GH via hypothalamic somatostatin secretion. However, there have been no descriptions of positive feedback mechanisms for IGF-I deficiency induced GH hypersecretion. We suspect that the mechanism complicating this case of catabolic IDDM and GH–secreting pituitary adenoma was as follows: lowered IGF-I either directly stimulated pituitary GH secretion or decreased hypothalamic somatostatin, which resulted in GH hypersecretion via an increased GH response to GRH. The latter effect was also observed in our case (Fig. 2A). Bereket et al. (21) found that children with IDDM placed on insulin therapy increased their IGF-I, II, and IGFBP-III to near-normal levels, consistent with our patient's course. Increases in IGF-I were not accompanied by significant changes in GH in the Bereket et al. study, which may reflect subject age, duration of disease, or the technique used to determine GH concentrations (21). IGF-I has been used to treat catabolic patients (22) or insulin-resistant diabetes (23). It has also been reported that a patient's nitrogen balance improves because of the anabolic effects of IGF-I (22,24). Therapeutic trials with IGF-I may help to clarify the GH–IGF-I axis.

In conclusion, we encountered a patient with IDDM who manifested features of a GH–producing pituitary adenoma. The patient's serum IGF-I was markedly lowered, and this change may have induced GH hypersecretion. This complicated patient was observed for 6 years before he developed pituitary manifestations of dynamic hormonal change. This case report not only supplies insight into the development and progression of pituitary adenomas, but also clinically demonstrates a positive feedback mechanism in which GH hypersecretion is caused by lowered IGF-I.

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