Clinical Study

Ketoacidosis as the initial clinical condition in nine patients with acromegaly: a review of 860 cases at a single institute

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Abstract

Objective: Excess GH causes insulin resistance and impaired glucose metabolism. The objective of this study was to clarify the prevalence of ketoacidosis as the initial presenting symptom of acromegaly.

Design and methods: Data were collected from 860 patients with acromegaly who underwent pituitary surgery at Toranomon Hospital over the last 32 years, between 1980 and 2011.

Results: Nine cases had ketoacidosis before being diagnosed with acromegaly, including seven males and two females with a mean ± S.D. age of 38.8 ± 14.2 years. Serum GH and IGF1 levels were 155 ± 203 ng/ml and 9.86 ± 0.68 SDS before pituitary surgery and 3.6 ± 1.7 ng/ml and 3.72 ± 3.40 SDS after surgery respectively. The maximum tumor diameter was 28.2 ± 11.6 mm (ranging from 15 to 47 mm, n=8). None of the patients were diagnosed with diabetes mellitus (DM) nor were they positive for antibodies related to type 1 DM. A possible precipitating factor for ketoacidosis in six cases was excessive ingestion of sugar-containing soft drinks. All the cases had invasive pituitary adenomas. After pituitary surgery, plasma glucose levels were under control without requiring insulin in all cases. Furthermore, six patients did not need oral hypoglycemic agents.

Conclusions: Approximately 1% of patients with acromegaly presented with diabetic ketoacidosis as their first clinical condition.

Introduction

Acromegaly is characterized by autonomous secretion of GH, which is usually due to a pituitary somatotrophic adenoma. GH stimulates synthesis and secretion of IGF1, especially in the liver (1). Diagnosis of acromegaly is usually delayed for years and leads to increased morbidity and mortality. Excess GH impairs metabolic regulation. Indeed, it is associated with hepatic and peripheral insulin resistance (2). Thus, patients with acromegaly are predisposed to developing diabetes mellitus (DM) in addition to skeletal complications and cardiovascular and respiratory diseases (3). Risk factors for impaired glucose metabolism include high serum levels of GH, older age, longer duration of the disease, family history of DM, and concomitant hypertension (4, 5, 6). The prevalence of diabetes among patients with acromegaly has been reported to range from 19 to 56% (3). Ketoacidosis is common among patients with type 1 DM. However, it is unusual for ketoacidosis to occur in patients with acromegaly in the absence of type 1 DM. Indeed, there are 18 cases of ketoacidosis complicated with acromegaly in the literature (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). Only eight cases with ketoacidosis as the first clinical condition of acromegaly have been anecdotally reported (13, 14, 15, 16, 17, 19, 20, 21). The epidemiology and mechanism of ketoacidosis in acromegaly have not been elucidated. To address these issues, we reviewed 860 cases of acromegaly that were seen at Toranomon Hospital over the last 32 years. Here, we present nine cases that had ketoacidosis as a clinical condition before being diagnosed with acromegaly.

Subjects and methods

Subjects

We reviewed clinical data from 860 acromegaly patients who underwent pituitary surgeries at a single institute, Toranomon Hospital (Tokyo, Japan), consecutively from 1980 to 2011. Charts were reviewed according to the diagnosis and institutional registry data available at the time of pituitary surgery.
We found nine cases whose first clinical condition was ketoacidosis before being diagnosed with acromegaly and evaluated their clinical characteristics. All data had been obtained from routine medical procedures and were collected retrospectively. This study was approved by the institutional review board at Toranomon Hospital.

The diagnosis of acromegaly was based on clinical findings, elevated serum levels of GH and IGF1 after adjusting for age and sex, and the presence of pituitary adenoma based on imaging studies. Although a 75 g oral glucose tolerance test (OGTT) is the standard diagnostic procedure for acromegaly, this test was not performed before surgery in any of the present cases because sufficient hyperglycemia was present in the absence of glucose challenge. A transsphenoidal pituitary adenomectomy was performed on each patient by expert neurosurgeons. The presence of a GH-secreting pituitary adenoma was confirmed by immunohistochemistry in each case. Patients underwent the 75 g OGTT within 1 month of surgery.

**Laboratory tests and their analyses**

Immunoreactive insulin (IRI) was measured by a chemiluminescent enzyme immunoassay (LUMIPULSE Presto insulin. Fujirebio, Inc., Tokyo, Japan). Plasma glucose was measured by the hexokinase method (Liquitech Glucose HK Test, Roche Diagnostics Japan). Serum and urinary C-peptide concentrations were measured with commercially available kits as follows. We used the C-peptide kit ‘Daichi’ (FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan) until January 2003. The Chemilumi C-peptide kit (Siemens Healthcare Diagnostics K. K., Tokyo, Japan) was used until February 2007. The LUMIPULSE Presto C-peptide kit (Fujirebio, Inc.) was used thereafter. The CV values of the intra- and interassays of each kit were < 10 and 20% respectively. Serum GH was measured with commercially available kits as follows. The GH RIA kit (Abbot Japan Co. Ltd.) was used until August 1989. The HGH kit ‘EIKEN’ (EIKEN CHEMICAL Co. Ltd., Tokyo, Japan) was used until May 2001. The ST AIA-PACK HGH kit (Tosoh Co., Tokyo, Japan) was used thereafter. Coefficients of correlation for C-peptide and GH were 0.990–0.994 and 0.740–0.910 respectively. IGF1 was measured with an IRMA (IGF1 IRMA Daiichi, TFB Co., Tokyo, Japan).

After surgery, all patients underwent a 75 g OGTT after an overnight fast. Blood samples were collected at baseline and 30, 60, 90, and 120 min after glucose ingestion. IRI, glucose, and GH were measured in blood samples. We used homeostatic model assessment (HOMA) computer software to estimate basal pancreatic β-cell function (HOMA-%β) and insulin resistance (HOMA-IR) from fasting blood glucose and serum IRI levels (24, 25). Insulinogenic index is an OGTT-based

### Table 1

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Plasma glucose at admission (mmol/l)</th>
<th>HbA1c (%)</th>
<th>Arterial blood pH</th>
<th>Urine ketone</th>
<th>Antibodies related to type 1 DM</th>
<th>Antigens related to DM</th>
<th>Soft drink more than 2 l/day</th>
<th>Family history of DM</th>
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<tbody>
<tr>
<td>1</td>
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<td>8.9±1.7</td>
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<tr>
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</table>

**Note:** DM, diabetes mellitus; GAD, anti-glutamic acid decarboxylase antibody; IA2, anti-insulinoma-associated protein 2 antibody; ICA, anti-insulinoma cell antibody.
estimate of early-phase insulin secretion, which is calculated as \( \frac{\text{IRI at 30 min} - \text{IRI at 0 min (\mu U/ml)}}{\text{glucose at 30 min} - \text{glucose at 0 min (mg/dl)}} \) (26).

### Statistical analysis

Results are expressed as the mean ± s.d. Student’s t-tests or paired t-tests were applied to determine whether the differences between two groups were statistically significant \( (P < 0.05) \). Statistical analyses were done with SPSS version 16.0.2.

### Results

Ketoacidosis was the first clinical condition in ~1.0% of 860 consecutive cases of acromegaly. Table 1 shows the baseline characteristics of patients with ketoacidosis. Nine cases (seven males and two females) were diagnosed with ketoacidosis because they had low arterial blood pH values of 7.27 ± 0.08 and urinary ketones before being diagnosed with acromegaly. All patients with ketoacidosis had hyperglycemia (41.4 ± 21.0 mmol/l) and high HbA1c (12.1 ± 1.8%), suggesting the presence of diabetic ketoacidosis. However, none of the patients had histories of DM nor were they positive for antibodies related to type 1 DM. Overconsumption of alcohol was not reported for any of the subjects. The average age was 38.8 ± 14.2 years. This age was significantly younger than 48.2 ± 13.4 years, which was the average age for the other acromegaly patients \( (P < 0.05) \). Six patients had recent histories of excessive ingestion of sugar-containing soft drinks in quantities exceeding 2 l/day (Table 1).

Medical care was provided for ketoacidosis and hyperglycemia, and all patients were suspected of having acromegaly because of their appearance. Parameters of intrinsic insulin secretion were evaluated after recovery from ketoacidosis but before pituitary surgery. The insulin secretion capacities were not depleted. The average urine C-peptide was 97 ± 46 mg/day (ranging from 53 to 195 mg/day, \( n = 7 \)). The increase in serum C-peptide 10 min after an i.v. injection of 1 mg glucagon was 3.0 ± 0.6 ng/ml (ranging from 2.3 to 3.3 ng/ml, \( n = 3 \)). At least one of the two parameters was examined in all nine cases.

Table 2 shows clinical data related to acromegaly before and after surgery. At the time of diagnosis, serum GH was 155 ± 203 ng/ml and IGF1 was 982 ± 98 ng/ml or 9.86 ± 0.68 SDS. The maximum tumor diameter was 28.2 ± 11.6 mm (ranging from 15 to 47 mm, \( n = 8 \)). Magnetic resonance imaging (MRI) was performed in all but one case of ketoacidosis. Images were not available for one of the earlier patients due to the absence of appropriate equipment. All the pituitary tumors that were visualized with MRI were macroadenomas with cavernous sinus invasion. Pituitary adenomas were totally resected in five cases.
Insulin resistance  

Blood glucose ↑  

Glucose toxicity  

Insulin secretion ↓  

Lipolysis ↑  

Free fatty acid ↑  

Adipotoxicity  

Ketosis or ketoacidosis  

Figure 1 Schematic of the possible mechanisms by which metabolic derangement in acromegaly promotes development of ketoacidosis.
As we reported, acromegaly exacerbates insulin resistance. However, some patients could not secrete sufficient insulin to overcome resistance (33). High plasma levels of glucose may reduce insulin secretion from b-cells, producing glucose toxicity. Excessive ingestion of soft drinks may further exacerbate glucose toxicity by impairing appropriate insulin secretion. Coexistence of acromegaly-associated insulin resistance and glucose toxicity due to overconsumption of soft drinks might be critical for the development of ketoacidosis due to deficient insulin action (Fig. 1). Enhancement of lipolysis by GH (36) is caused by loss of insulin activity, leading to increased ketone production by the Randle cycle. An increased level of ketones reduces insulin secretion, eventually leading to ketoacidosis. Thus, GH-mediated lipolysis may also be involved in the development of ketoacidosis in patients with acromegaly (Fig. 1).

In conclusion, our data indicate that ~1% of patients with acromegaly present with ketoacidosis as their first clinical condition. Each of the nine cases discussed here had specific manifestations of acromegaly during initial treatment for ketoacidosis. These findings are clinically significant, as they call attention to the importance of diagnosing acromegaly early.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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