The influence of age on the GH–IGF1 axis in patients with acromegaly

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Abstract

Objective: The purpose of this study was to investigate the influence of age on GH and IGF1 axis, and complications in patients with acromegaly.

Subjects and methods: From the medical records, we retrospectively analyzed clinical features and complications in 87 newly diagnosed patients with active acromegaly (34 males, 53 females; aged 18–82 years) who were admitted to Tokyo Women’s Medical University between 1999 and 2006. We divided the patients into three groups according to age: ≤ 30 years old (young group), 31–60 years old (middle-aged group), and ≥ 61 years old (elderly group).

Results: The median GH levels in young, middle-aged, and elderly groups were 18.5, 8.8, and 6.7 μg/l respectively, and the IGF1 levels were 810, 717, and 740 μg/l respectively. The values were not significantly different among the groups. However, the serum IGF1 SDS were significantly higher in the elderly group (10.2) than those in young and middle-aged groups (6.6 and 6.2 respectively, \(P<0.001\)). The age difference in the higher IGF1 SDS was remarkable in female patients. In the elderly group, glucose intolerance and hypertension were found in 94 and 53% of the patients respectively and the incidences were higher than those in the other groups.

Conclusion: This study suggests that the relatively high IGF1 secretions in elderly patients might be involved in the progression of clinical complications in acromegalic patients. Therefore, awareness of the early symptoms and examination of serum GH and IGF1 are important for patients with acromegaly.

Introduction

Acromegaly is a slow-developing disease resulting from the overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF1). It is usually caused by pituitary somatotroph adenomas, and the main causes of death are cardiovascular disease, cerebrovascular disease, respiratory disease, or malignancy (1–4). Excessive secretion of GH induces various complications, including diabetes mellitus, hypertension, and hyperlipidemia. Furthermore, the prevalence of colonic polyps increases in patients with acromegaly (5, 6).

Secretion of GH and IGF1 increases at puberty and then decreases with age in healthy men. The decrease in GH and IGF1 could be involved in age-related changes in body composition, structure function, and metabolism. However, it is not clear whether there is a relationship between GH and IGF1 secretion and complications due to changes with age in acromegalic patients. In the present study, we investigated the influence of age on the GH and IGF1 axis, and complications in patients with acromegaly.

Subjects and methods

Subjects

We examined 87 newly diagnosed patients with active acromegaly (34 males, 53 females; aged 18–82 years) who were admitted to the Department of Medicine, Institute of Clinical Endocrinology, at Tokyo Women’s Medical University between 1999 and 2006. The diagnosis of acromegaly was based on clinical signs, lack of serum GH suppression to <1 μg/l during a 75 g oral glucose tolerance test (OGTT), and elevated serum IGF1 levels. An OGTT was not performed in patients with overt diabetes mellitus. All patients underwent transphenoidal surgery and GH-secreting tumors were diagnosed pathologically.

Methods

Patients were divided into the following three groups based on age: ≤ 30 years old (young group, \(n=9\)), 31–60 years old (middle-aged group, \(n=62\)), and ≥ 61
years old (elderly group, n = 16). Using medical records, we investigated the endocrinological data, complications, and properties of the pituitary tumors for each patient.

Patients were considered to be glucose intolerant if their plasma fasting glucose (PG) was higher than 110 mg/dl and/or PG level 2 h after an OGTT was >140 mg/dl. Diabetes mellitus is defined as having fasting PG level above 126 mg/dl, PG level 2 h after OGTT above 200 mg/dl, or arbitrary PG levels above 200 mg/dl. Impaired glucose tolerance is defined as having the fasting PG levels 110–125 mg/dl and/or PG level 2 h after OGTT 140–199 mg/dl. Hypertension was diagnosed when patients had systolic blood pressure ≥135 mm/Hg or diastolic blood pressure ≥85 mm/Hg or were currently using antihypertensive drugs. Hyperlipidemia was considered if serum cholesterol levels were higher than 220 mg/dl and/or serum triglyceride levels were >150 mg/dl. Pituitary tumor size was measured by magnetic resonance imaging (MRI) for all the patients. We performed immunohistochemical analyses of the pituitary tumors.

**Assay**

The serum GH concentrations were measured using an IRMA kit (Daiichi Radioisotope Laboratories, Tokyo, Japan) up until March 2005, and then were measured using an immunoenzymometric assay kit (Tosoh Co. Ltd, Tokyo, Japan). In Japan, from April 2005, serum GH concentrations were measured using recombinant human GH (rhGH) standard (7). As a result, the GH values measured using the rhGH standard were on average 60% lower than those values measured using the standards for pituitary-derived GH. Therefore, when using the IRMA kit, we adjusted the serum GH concentration to the rhGH standard. Serum fasting GH levels were an average of two or three different days.

Serum IGF1 concentrations were measured using the IRMA kit (Daiichi Radioisotope Laboratories). As serum IGF1 levels are dependent on gender and age, we used the normal reference values for gender- and age-matched controls by the kit (8). The reference values were determined using 728 healthy subjects (M/F: 471/257, 17–19y: 12/8, 20–29y: 141/101, 30–39y: 104/40, 40–49y: 75/31, 50–59y: 95/36, 60–69y: 29/15, 70y+: 13/24). Using this reference, the serum IGF1 SDS was calculated.

**Tumor volume**

The sagittal, axial, and coronal diameters were measured by MRI, and then we considered the maximal tumor diameter and calculated tumor volume by the formula \((\text{volume} = \text{sagittal} \times \text{coronal} \times \text{axial diameters}) \times \pi/6\).

**Statistical analysis**

All statistical analyses were performed using StatView 5.0 (Abacus Concepts Inc., Berkeley, CA, USA). All data are expressed as median values. Differences between and among the groups were analyzed using the Mann–Whitney and Kruskal–Wallis tests respectively. Spearman’s rank test was used to assess the correlation between serum GH and IGF1 levels, and tumor volumes and age. Significance was established at \(P<0.05\).

**Results**

The age and gender distribution of all 87 patients with acromegaly are shown in Fig. 1. Characteristics of GH, IGF1, tumor types, and tumor sizes for the three groups are shown in Table 1. The median serum GH levels in the young, middle-aged, and elderly groups were 18.5 μg/l (range 2.7–33.8), 8.8 μg/l (range 0.9–83.6), and 6.7 μg/l (range 0.5–22.5) respectively (Fig. 2). There were no significant differences in serum GH levels among the three groups. The median serum IGF1 levels in the young, middle-aged, and elderly groups were 810 μg/l (range 470–1270), 717 μg/l (range 306–1400), and 740 μg/l (range 457–1200) respectively (Fig. 2). There were no differences in IGF1 levels among the three groups. However, the serum IGF1 SDS ranged from 5.3 to 16.2 (10.2) in the elderly patients (Fig. 2), and the values were significantly higher than the values for the young (6.5, range 2.8–8.5) and middle-aged patients (6.2, range 2.0–12.2), \(P<0.001\).

The serum IGF1 levels and IGF1 SDS in male patients were higher than those in female patients (875 vs 686 μg/l, \(P<0.03\); 8.0 vs 5.8 SDS, \(P<0.05\)). The sex differences were not found in the elderly group (754 vs 733 μg/l; 8.5 vs 11.2 SDS).

Co-secreted GH and prolactin tumors were found in 17% of the young group, 34% of the middle-aged.
and 30% of the elderly groups, and there were no significant differences in the incidences among the groups. With respect to tumor size, macroadenomas with a diameter $\geq 1$ cm were found in 78% of the young patients, 79% of the middle-aged patients, and 63% of the elderly patients, and the percentage of macroadenoma was not different among the groups. However, the tumor volumes decreased with age ($R_s = -0.3$, $P < 0.001$), and the volumes in the elderly patients were significantly lower than those in other groups (Table 1). The tumor volumes correlated with serum GH ($R_s = 0.3$, $P < 0.01$), but not serum IGF1 ($R_s = 0.02$).

Clinical complications in the acromegaly patients are shown in Table 2. In the elderly group, 15 of 16 patients (94%) were diagnosed with glucose intolerance, and 8 of 15 patients (53%) were diagnosed with hypertension. The incidences of glucose intolerance and hypertension increased with age. There were no differences in the prevalence of hyperlipidemia among the three groups. Of 87 patients, 66 underwent colonoscopy for screening examination, and colonic polyps were found in 2 (25%), 24 (56%), and 10 (67%) patients in the young, middle-aged, and elderly groups respectively.

Discussion

We analyzed the clinical characteristics of 87 newly diagnosed patients with active acromegaly who were admitted to Tokyo Women’s Medical University Hospital between 1999 and 2006.

Secretions of GH and IGF1 increase at puberty and then decrease with age in healthy men. In the present study, the number of patients in the young-aged group was small; however, no differences in the serum GH and IGF1 levels were found in any of the young, middle-aged, or elderly acromegalic patients. These findings suggested that serum GH and IGF1 did not decrease with age in the acromegalic patients.

Furthermore, we found that the serum IGF1 S.D. scores in the elderly group were higher than those in young and middle-aged groups. As it has been previously reported that the GH responsiveness does not increase with age in healthy subjects and patients

### Table 1 Characteristics of growth hormone (GH), insulin-like growth factor I (IGF1), and tumors in young, middle-aged, and elderly patients with acromegaly.

<table>
<thead>
<tr>
<th></th>
<th>Young (≤30 years)</th>
<th>Middle-aged (31–60 years)</th>
<th>Elderly (≥61 years)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9</td>
<td>62</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>4/5</td>
<td>39/23</td>
<td>10/6</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8</td>
<td>23.9</td>
<td>23.4</td>
<td>$P = 0.47$</td>
</tr>
<tr>
<td>Median GH (µg/l)</td>
<td>18.5</td>
<td>8.8</td>
<td>6.7</td>
<td>$P = 0.39$</td>
</tr>
<tr>
<td>IGF1 (µg/l)</td>
<td>810</td>
<td>717</td>
<td>740</td>
<td>$P = 0.44$</td>
</tr>
<tr>
<td>IGF1 SDS</td>
<td>6.5</td>
<td>6.2</td>
<td>10.2</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>83%</td>
<td>66%</td>
<td>70%</td>
<td>$P = 0.66$</td>
</tr>
<tr>
<td>GH/PRL</td>
<td>17%</td>
<td>34%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>78%</td>
<td>79%</td>
<td>63%</td>
<td>$P = 0.38$</td>
</tr>
<tr>
<td>Microadenoma</td>
<td>22%</td>
<td>21%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Tumor volume (mm³)</td>
<td>4712</td>
<td>1357</td>
<td>615</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td></td>
<td>(128–60 790)</td>
<td>(39–52 360)</td>
<td>(33–17 593)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Serum GH (upper), IGF1 (middle), and IGF1 SDS (lower) in young, middle-aged, and elderly patients with acromegaly. Closed circles, males; open circles, females.
with GH deficiency (9–11), it is difficult to explain the finding of higher IGF1 SDS in the elderly acromegalic patients. In the present study, the age differences in the higher IGF1 SDS were remarkable in female patients and the sex differences in IGF1 and IGF1 SDS were found in young and middle-aged patients but not in elderly patients. In addition, the higher tendency of IGF1/GH ratios in the elderly group than others was found in female but not male patients. In patients with GH deficiency, it has been reported that the gender difference remains in elderly patients, i.e., women above 60 years have lower IGF1 than men, in spite of similar GH secretion (12). Therefore, it is interesting to note the relatively higher IGF1 levels in elderly female patients with acromegaly. As estrogen decreases the IGF1 production in the liver (13), the higher IGF1 SDS in the female elderly acromegalic patients could be due to the decrease in estrogen. However, lower estrogen levels are also true in elderly healthy women. Furthermore, one of the possible explanations for higher IGF1 SDS in the elderly female patients might be low IGF1 reference material of elderly female subjects. Further study will be required using larger numbers of patients with elderly acromegaly.

In this study, tumors were classified based on size and immunohistochemistry, and there were no significant differences in immunohistological tumor type or the percentage of macroadenoma in the three groups. The tumor volumes decreased with age and correlated with GH as previously reported (14, 15). The data might indicate that serum GH levels are low in elderly patients. However, as described above, serum GH did not decrease with age. It is difficult to explain these discordant results. The significant correlation between tumor size and serum GH was found only in the elderly group; a further study would be required. In the World Health Organization 2004 report on histological typing of endocrine tumors, GH-secreting pituitary adenomas were classified into seven pathological types based on the tumor features, such as densely granulated somatotroph adenomas, sparsely granulated somatotroph adenomas, mammosomatotroph adenomas, etc. (16). Densely granulated somatotroph adenomas grow slowly and are usually present in patients older than 50 years of age. Whereas more rapidly growing, sparsely granulated somatotroph adenomas are usually present in younger patients (17). Therefore, a more precise classification of pituitary adenomas using electron microscopy might be required to analyze whether there are age effects on the character of the tumor or not.

Glucose metabolism was analyzed based on blood glucose levels during an OGTT. Glucose intolerance develops in 71% of patients with acromegaly. In this study, 33% of the young group, 72% of the middle-aged group, and 94% of the elderly group had glucose intolerance. In a national survey in Japan, glucose intolerance (HbA1c above 5.6%) was seen in 19.6% of the population (18), with 1.5, 13.1, and 30% in young, middle-aged, and elderly persons respectively. These data suggest that the relatively high GH and IGF1 secretion in patients with acromegaly might involve progression of glucose intolerance. Moreover, the lack of decrease with age in GH and IGF1 secretion might be the cause of the high incidence of glucose intolerance seen in elderly patients.

The incidence of hypertension increased with age, and hypertension was found in 53% of the elderly group. In a national survey in Japan (19), the incidence of hypertension in persons above 60 years was 19.2%. As glucose intolerance, the relatively high GH and IGF1 secretion might involve progression of hypertension.

It is known that the prevalence of colonic polyps increases in patients with acromegaly. We performed a screening examination using colonoscopy in our acromegalic patients. Of 87 patients, 66 (76%) underwent colonoscopy screening and 34 (54%) of 66 patients had colon polyps. In our study, the prevalence of colon polyps was not different among the young, middle-aged, and elderly patients. In a previous prospective study, there were also no statistically significant differences between the mean age of the patients with and without adenomatous colon polyps (6). However, the prevalence of colonic polyps in acromegalic patients under 55 years of age was higher than in controls under 55 years of age. These findings suggested that the prevalence of colonic polyps was influenced by high GH and IGF1 rather than age.

In conclusion, the relatively high IGF1 secretions in elderly patients might involve progression of clinical complications in those with acromegaly. Long-term excessive GH secretion causes many complications.
Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Funding

This work was supported in part by Grants-in-Aid for Scientific Research (C) (No. 16590913, 17590968) from The Ministry of Education, Science and Culture, Japan, a research grant from the Foundation for Growth Science, Japan, and a research grant from the Ministry of Health, Labour and Welfare, Japan.

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Received 17 July 2008
Accepted 17 July 2008