Usefulness of the Thyrotropin-Releasing Hormone Test in Pre-Clinical Acromegaly

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KAGEYAMA, K., MORIYAMA, T., SAKIHARA, S., TAKAYASU, S., NIGAWARA, T. and SUDA, T. Usefulness of the Thyrotropin-Releasing Hormone Test in Pre-Clinical Acromegaly. Tohoku J. Exp. Med., 2005, 206 (4), 291-297 — Acromegaly is caused primarily by pituitary growth hormone (GH)-secreting tumors. It is usually recognized because of characteristic manifestations, and diagnosed clinically. However, there exists a mild stage of acromegaly, which poses a diagnostic problem due to the absence of typical clinical manifestations. Here we present four patients with pre-clinical acromegaly, who showed minimal acromegaloid features with elevated levels of insulin-like growth factor-I. Basal GH levels were within normal levels in 3 of 4 cases, while insulin-like growth factor-I levels were elevated above normal in all cases. Plasma GH levels were elevated in response to thyrotropin-releasing hormone (TRH) in all cases, indicating a diagnostic value of the TRH stimulation test. In contrast, an oral glucose tolerance test was not useful for the diagnosis, because of the low GH levels (less than 1 ng/ml) and/or secondary to diabetes mellitus. In response to a dopamine agonist, GH levels were increased in the two cases, whereas GH levels were decreased or remained unchanged in the other two cases. We therefore suggest that the TRH stimulation test would be helpful to examine the presence of pre-clinical acromegaly. Diagnosis of the early stages of acromegaly is important to prevent progression to overt acromegaly. growth hormone; acromegaly; insulin-like growth factor-I; pituitary tumor

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Acromegaly is caused primarily by pituitary growth hormone (GH)-secreting tumors. It is usually recognized because of characteristic manifestations with enlargement of the facial features, hands, and feet. The diagnostic criteria for acromegaly are still being discussed. While the clinical criteria are clear, the debate over the biochemical diagnosis is present in the literature (Dimaraki et al. 2002; Giustina and Melmed 2003). Moreover, a mild stage of acromegaly, which is not diagnosed by the present criteria, is known (Dimaraki et al. 2002; Trainer 2002). Plasma GH levels are generally elevated above normal, but not in all cases of acromegaly (Mims and Bethune 1974; Brockmeier et al. 1992). Thyrotropin-releasing hormone (TRH) stimulation test, oral glucose tolerance test (OGTT) and insulin-like growth factor (IGF)-I levels are helpful for the diagnosis of acromegaly. TRH-induced GH release would be caused by the abnormal induction or
sensitization of TRH receptors on pituitary somatotroph adenoma cells (Harvey 1990), and plasma GH levels are elevated in response to TRH in 70-80% of acromegaly (Irie and Tsushima 1972; Hanew et al. 1980). The plasma GH levels are examined by an OGTT, and acromegaly is diagnosed as a failure of decrease in plasma GH level to the normal level after an OGTT (Stewart et al. 1989). A single random measurement of the GH level would not be useful for the diagnosis or for excluding acromegaly, because a normal value may be a nadir level in an acromegalic patient; conversely, a high value may be a peak value in a normal individual (Thornor et al. 1998; Dimaraki et al. 2002). Measurement of GH levels every 10 min over 24 h, therefore, is more accurate, but is prohibitive except for research purposes. The serum IGF-I level would be a better reliable indicator for screening of acromegaly, because it reflects overall GH secretion during the previous 24 h (Thornor et al. 1998). However, the normal range for serum IGF-I levels varies with age and gender, and should be corrected for them (Turgut et al. 2003). Furthermore, IGF-I level also reflects the liver function and the nutrition status. Therefore, the diagnosis could be wrong if only the GH- and IGF-I-based criteria are used.

We report here four patients with minimal acromegaloid features and elevated IGF-I levels. We define these patients as pre-clinical acromegaly by their features and by their response to the TRH test, which may be a useful tool in diagnosing pre-clinical acromegaly.

### Table 1. Clinical and Laboratory Features

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>M/F</th>
<th>GH (ng/ml)</th>
<th>IGF-I (ng/ml)</th>
<th>Pituitary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>1.2</td>
<td>289</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>F</td>
<td>5.4</td>
<td>395</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>0.6</td>
<td>340</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>0.6</td>
<td>310</td>
<td>+</td>
</tr>
</tbody>
</table>

Normal IGF-I ranges: cases 1 and 2, 37-150 ng/ml; case 3, 38-207 ng/ml; case 3, 59-215 ng/ml.
cases, basal plasma GH levels were less than 1 ng/ml, while serum IGF-I levels were elevated above the normal range for each patient, compared with age- and gender-adjusted normal ranges (Table 1). Pituitary tumors were demonstrated by magnetic resonance imaging in the two cases. Hypertension and diabetes mellitus were not detected except in case 1.

**GH response to TRH**

The administration of TRH stimulates GH levels in acromegalic patients (Irie and Tsushima 1972; Hanew et al. 1980). The effects of TRH on GH levels were, therefore, examined in these patients. A significant response of GH level was set at a more than two-fold increase, compared with the basal level. As shown in Fig. 2, in all cases, plasma GH levels were increased in response to the intravenous administration of 200 μg, a dose for this loading study in Japan, of TRH (Fig. 2a), although pathophysiological conditions such as depression and liver cirrhosis were ruled out in the patients.

**GH response to oral glucose tolerance test**

The criterion for a normal GH response to OGTT is less than 1 mg/l by using an IRMA method. In case 1, OGTT was not performed because this patient already had a diagnosis of diabetes mellitus. In case 2, plasma GH levels were gradually suppressed to less than 1 ng/ml following OGTT (Fig. 2b). In cases 3 and 4, plasma GH levels remained less than 1 ng/ml following OGTT (Fig. 2b).

**GH response to bromocriptine**

Dopamine agonists stimulate GH secretion in normal subjects, but inhibit it in most cases of acromegalic patients. The effects of bromocriptine on GH levels were, therefore, examined in the patients. Changes in plasma GH levels were variable following bromocriptine, a dopamine agonist (Fig. 2c). In case 1, plasma GH levels remained unchanged. In cases 2 and 3, the plasma GH levels were elevated following administration of bromocriptine, whereas the plasma GH levels decreased after its administration in case 4.
Fig. 2. Hormone loading test results. (a) TRH test (TRH 200 μg, intravenous bolus). (b) OGTT (75 g glucose, per os). (c) Bromocriptine (bromocriptine 2.5 mg, per os).

<table>
<thead>
<tr>
<th>Case</th>
<th>BMI (kg/m²)</th>
<th>Signs/Symptoms</th>
<th>Roentgenograms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Perspiration</td>
<td>Hand deformity</td>
</tr>
<tr>
<td>1</td>
<td>33.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>21.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>24.6</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>23.5</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

BMI, body mass index; heel pad, heel pad thickness; hand deformity, cauliflower-like deformity in hand roentgenogram; submandibular angle, opening of submandibular angle in skull roentgenogram.
DISCUSSION

We present four patients with pre-clinical acromegaly. Pituitary tumors were demonstrated by magnetic resonance imaging in half the cases. In the cases where no pituitary tumor was evident, it is possible that the GH-producing tumor was too small to be detected by magnetic resonance imaging. Otherwise, although very rare, it is also possible that an ectopic GH-releasing hormone-producing tumor, stimulating GH and IGF-I secretion, could exist elsewhere. Basal GH levels were within normal levels (< 5 ng/ml) in 3 of 4 cases, while IGF-I levels were elevated in all cases. Plasma GH levels were elevated in response to TRH in all cases, while an OGTT was not useful for the diagnosis, because of the low basal GH levels (less than 1 ng/ml) in two cases or diabetes mellitus in one case. In response to a dopamine agonist, GH levels were increased in the two cases, while they remained unchanged or were decreased in the other two cases. In the four cases presented here, elevated plasma IGF-I levels and GH levels that responded to TRH infusion, suggested unregulated abnormal secretion of GH from the pituitary tumor (Diez et al. 2001). The patients, however, had minimal acromegaloid features, suggesting that the tumor secretes GH that is insufficient to cause typical clinical symptoms in acromegaly, so-called pre-clinical acromegaly. In cases of pre-clinical acromegaly, the TRH stimulation test might be a useful tool.

Pre-clinical Cushing’s syndrome has been well recognized (Suda 2002). We present here four patients with pre-clinical acromegaly. Patients with acromegaly may develop the clinical symptoms gradually (Thorner et al. 1998). Most cases of pre-clinical acromegaly, therefore, might be in the very early stages of acromegaly development. Considering the complications of acromegaly such as hypertension, diabetes mellitus, and colon polyps, or the observation of a pituitary adenoma, appropriate testing is an important part of the decision process as to whether pre-clinical acromegaly should receive treatment, in order to possibly prevent the irreversible changes and complications of acromegaly.

The biochemical diagnostic criteria for acromegaly are still under debate. Recently, the following criteria were proposed by Trainer (2002): during an initial random GH and IGF-I test, if the GH is less than 0.3 \( \mu g/l \) and the IGF-I is normal, then acromegaly is excluded; but if either the GH is 0.3 \( \mu g/l \) or greater or serum IGF-I is above the age- and gender-related reference range, then the patient should proceed to have a 75-g OGTT and repeat IGF-I measurement. Failure of GH to suppress less than 0.3 \( \mu g/l \) during the OGTT and an elevated IGF-I is diagnostic of acromegaly; suppression of GH below this limit and a normal IGF-I excludes acromegaly, while the rare patient with GH suppression and an elevated IGF-I requires following. The revised GH criteria in combination with IGF-I would be useful for the diagnosis and follow-up of acromegaly, but may require additional diagnostic testing in order to diagnose pre-clinical acromegaly.

After glucose ingestion, the plasma GH level is suppressed in normal individuals. In acromegaly, the oral glucose ingestion may decrease partially, remain unchanged, or paradoxically increase the GH level (Thorner et al. 1998). The criterion for a normal GH response to OGTT is less than 1 mg/l using an RIA method (Beck et al. 1966; Cryer and Daughaday 1969). In case 1 in our study, an OGTT was not performed because the patient had diabetes mellitus. In case 2, plasma GH levels were gradually suppressed to less than 1 ng/ml following an OGTT. In cases 3 and 4, plasma GH levels remained suppressed below the normal limits. In most cases of pre-clinical acromegaly, basal GH levels are already lower than the criterion suggests. Therefore, with pre-clinical acromegaly, an OGTT is inadequate for the diagnosis.

Other provocative or inhibitory tests have been proposed for the diagnosis of acromegaly, including administration of TRH, LHRH, and dopamine agonists. These tests have paradoxical effects in acromegallic patients. GH levels are elevated by TRH and LHRH, in 70-80% and 30%, respectively, of acromegalic patients (Irie and Tsushima 1972; Hanew et al. 1980; Utsumi et al. 1992). Dopamine agonists stimulate GH secre-
We suggest that the TRH stimulation test would be useful to examine the presence of pre-clinical acromegaly. If the TRH stimulation test is negative or equivocal, we recommend that the elevated IGF-I levels should be followed, along with periodic TRH testing, especially with the advancement of pre-clinical features. It is important to diagnose the early stages of acromegaly, in order to prevent progression to overt acromegaly including the irreversible changes and complications that accompany this debilitating disease.

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References


