Plasma GH Response to the Sequential 3 Day Administrations of GHRH Followed by Arginine Infusion in Patients with Idiopathic GH Deficiency and Normal Short Children

KUNIHIKO HANEW, ATSUSHI UTSUMI, AKIRA SUGAWARA, YASUYUKI SHIMIZU, SATORU TAZAWA* and KEISHI ABE

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980, and
*Department of Radiology, Shakaihoken Hospital, Sendai 980

HANEW, K., UTSUMI, A., SUGAWARA, A., SHIMIZU, Y., TAZAWA, S. and ABE, K. Plasma GH Response to the Sequential 3 Day Administrations of GHRH Followed by Arginine Infusion in Patients with Idiopathic GH Deficiency and Normal Short Children. Tohoku J. Exp. Med., 1993, 169 (2), 91-101 — To study the site of lesions in idiopathic growth hormone (GH) deficiency (IGHD), growth hormone releasing hormone (GHRH) was administered sequentially for 3 days to 19 patients with IGHD, 3 patients with GH deficiency (GHD) secondary to hypothalamic tumors, and 7 normal short children (NSC). GHRH (100 μg) was injected as a bolus on days 1 and 3, and was infused over 60 min on day 2. Of 19 patients with IGHD, 6 showed an improved GH response (group A), 5 a decreased response (group B) and the remaining 8 an unchanged response (group C) to sequential administration of GHRH. The response was unchanged in patients with secondary GHD or NSC. There was no significant correlation between the patterns of GH response and the findings on pituitary MR images or the delivery state at birth in IGHD patients. Ten patients with IGHD (4 of group A; 3 each of groups B & C) and 2 NSC showed much greater GH responses to arginine (0.5 g/kg i.v. for 30 min) injected with preceding GHRH than to arginine injected without preceding GHRH. These results indicate that hypothalamic lesions were primarily responsible for GH deficiency in about 60% of the patients with IGHD (groups A and B), and group C might have more severe hypothalamo-pituitary damages than the other groups. Hypothalamic somatostatin neurons seems to be functioning to a degree even in severe IGHD patients. ——— idiopathic GH deficiency; normal short children; GH; GHRH; arginine

In patients with idiopathic growth hormone (GH) deficiency (IGHD), plasma GH responses to bolus injection of growth hormone releasing hormone (GHRH) are variable and there are no correlations among the responses and the MRI...
findings of pituitary glands and pituitary stalks (Takano et al. 1984; Rogol et al. 1984; Schriock et al. 1984; Gelato et al. 1986; Kikuchi et al. 1988; Hanew et al. 1991). Therefore, the main sites of lesions in GH deficiency are not yet clear.

To clarify this, we have examined plasma GH response to 3 day sequential administrations of GHRH in IGHD patients using highly sensitive immunoradiometric GH assay (IRMA) kits. For the comparison, the same study was conducted in patients with secondary GHD and normal short children (NSC). Further, the activity of hypothalamic somatostatin neurons was indirectly evaluated by intravenous infusion of arginine, which is considered to release GH via inhibition of hypothalamic somatostatin secretion (Alba-Roth et al. 1988; Sato et al. 1990), with and without GHRH pretreatment. The relation between the GH responses and MRI findings of pituitary area or delivery state at birth were also studied.

These results indicate that 60% or more patients with IGHD have some degree of hypothalamic lesions. Exogenous GHRH appears to activate hypothalamic somatostatin neuron even in those patients.

**MATERIALS AND METHODS**

Nineteen patients with idiopathic GH deficiency (IGHD: 11 males and 8 females, aged 7.7 to 37.2 years), 3 patients with secondary GHD due to the sellar and suprasellar tumor (2 postoperative craniopharyngiomas, 1 postirradiated ectopic germinoma, all male, aged 6.8 to 22.9 years) (Table 1), and 7 short but endocrinologically normal children (normal short children: NSC; 5 males and 2 females, aged 5.8 to 13.4 years) were studied. Informed consent was obtained from every subject or their parents. All IGHD and secondary GHD patients had severe GH deficiency with peak GH values below 5 μg/liter after the administration of arginine and L-dopa. The diagnostic criteria of IGHD have been reported previously (Hanew et al. 1988). In patients with secondary GHD, all pituitary hormones were deficient (panhypopituitarism) and all patients had diabetes insipidus. These patients received replacement doses of glucocorticoid and thyroid hormone. Plasma IGF-I levels were low in all IGHD and secondary GHD patients (Table 1).

After an overnight fast, 100 μg of synthetic GHRH(1-44)NH₂ (GHRH; Sumitomo-Seiyaku, Osaka) was injected as a bolus on the first and third days for the comparison of two responses, and another 100 μg dose of GHRH dissolved in 100 ml saline was infused intravenously for 1 hr on the second day for the further priming of somatotrophs. Ten patients with IGHD and 2 NSC received arginine (0.5 g/kg i.v. over 30 min) without GHRH pretreatment and 120 min after the third dose of GHRH. When GHD patients are receiving HGH therapy, these studies were performed 2 weeks after discontinuation of the therapy.

Plasma GH was assayed in duplicate using highly sensitive commercial immunoradiometric assay (IRMA) kit (Daiichi, Tokyo). Briefly, 100 μl of standard GH or plasma sample, one polystyrene ball coated with monoclonal GH antibody and 100 μl of 125I labeled monoclonal GH antibody were added to microtiter wells and shaked for 1 hr at 37°C. The solutions were incubated at 4°C for 3 days and were aspirated and washed twice with distilled water. Thereafter the beads were transferred to plastic tubes and the radioactivities were counted. The sensitivity of the GH assay, calculated by the method of Rodbard et al. (1978), was 0.006 μg/liter and the intra- and interassay coefficients of variations were 2.2% and 3.5%, respectively. All samples from individual subjects were analyzed in the same assay. Plasma IGF-I was measured using a commercial RIA kit (Eiken, Tokyo) in
diluted, unextracted EDTA plasma. The intra- and interassay coefficients of variations were both 8%, and the minimum detectable level was 0.05 U/ml. The normal range of plasma GH and IGF-I are 0.1-5.0 μg/liter and 0.7-2.0 U/ml, respectively.

Magnetic resonance studies were performed on a 1.5 Tesla superconducting unit (Magnetom, Siemens, Erlangen). Three-mm thick contiguous T1-weighted images (SE pulse sequence, 500/20) were obtained in both coronal and sagittal planes with a 256 × 256 matrix and a 15-20 cm FOV. A pituitary stalk less than 1 mm thick was considered narrow (normal range, 1.0 to 1.9 mm), and an anterior pituitary gland less than 2.5 mm high was considered atrophic (normal range, 3.1 to 5.8 mm) (Hanew et al. 1991).

Statistical analysis was carried out using Student/Newman-Keuls test or Wilcoxon’s non-parametric test. All results are expressed as the mean ± s.e.

RESULTS

Plasma GH response to 3 day sequential administration of GHRH in patients with IGHD, secondary GHD and NSC

An increased or a decreased response was defined by the AUC over the baseline (calculated by trapezoidal integration) of a plasma GH response after the 3rd administration of GHRH being 50% larger or smaller, respectively, than that after the first GHRH. In 19 IGHD patients, 6 showed an increased (group A), 5 decreased (group B), and the remaining 8 unchanged response (group C) (Fig. 1).

In group A, the mean peak and AUC after GHRH were significantly greater on the 3rd day than the 1st day (mean of each peak: 6.026±0.851 vs. 1.961±0.390; AUC: 332.5±60.0 vs. 123.8±20.1 μg/liter × min, both p<0.01). In contrast, the GH response in group B was significantly reduced on the 3rd day than the 1st day (mean peak: 4.151±1.168 vs. 8.323±0.861 μg/liter; AUC: 224.7±69.5 vs. 567.0±90.4 μg/liter × min, both p<0.05). Group C did not show any significant changes of the GH responsiveness during the study (1st vs. 3rd day, mean peak: 3.308±0.709 vs. 4.292±0.868 μg/liter; AUC: 207.8±63.8 vs. 217.3±69.5 μg/liter × min). Plasma GH response on the 1st GHRH in group B was significantly greater than those in group A and C (mean GH & AUC, all p<0.01).

The basal GH values in these 3 groups in the 1st and 3rd day were not statistically significant (1st vs. 3rd day, group A: 0.254±0.072 vs. 0.415±0.137; group B: 0.347±0.056 vs. 0.792±0.163; group C: 0.522±0.274 vs. 0.763±0.373 μg/liter). In the majority of IGHD, basal plasma GH was below 1 μg/liter (range: 0.010 to 1.610 μg/liter).

Like group C, patients with secondary GHD (n=3) did not show any changes in the basal GH or responsiveness throughout the study (1st vs. 3rd day, basal GH: 0.225±0.063 vs. 0.117±0.017 μg/liter; mean peak: 3.750±1.165 vs. 3.925±1.07 μg/liter; AUC: 270.6±90.5 vs. 254.8±87.5 μg/liter × min).

Plasma GH response in 7 NSC on the 3rd day and the 1st day was not statistically significant (mean peak: 36.157±9.249 vs. 25.471±3.606 μg/liter; AUC: 2655.6±978.2 vs. 1452.9±434.8 μg/liter × min). The basal GH was also
not different on the 3rd day compared to the 1st day (1.814±0.704 vs. 1.329±0.421 μg/liter, P = NS). The basal GH in these subjects (range: 0.225 to 2.834 μg/liter) was higher than that of IGHD although some overlap between them was observed (mean basal GH: vs. group A & B, p < 0.05; group C, P = NS).

Plasma IGF-I in each group did not change throughout the study (1st vs. 3rd GHRH in all IGHD patients: 0.22±0.04 vs. 0.25±0.05 U/ml, P = NS).

**Plasma GH response to arginine with and without pretreatment of GHRH**

Four in group A, 3 each in groups B and C underwent arginine infusion singly or 120 min after the 3rd GHRH injection. Each group showed an enhanced GH response 120 min after the 3rd GHRH administration compared to single administration of arginine (Fig. 2; upper three). Therefore, these data were summarized together. As a whole, the GH response after GHRH was markedly enhanced as compared to that without GHRH administration [mean of maximal increment from 120 min (arginine after GHRH) or from 0 min value (single arginine):
Sequential GHRH in Idiopathic GH Deficiency

Fig. 2. Plasma GH response and the AUC to arginine following the 3rd GHRH injection (●●●) or to the single administration of arginine (○○○) in patients with idiopathic GH deficiency (number of patients: group A = 4, B = 3, C = 3). For the comparison, GH response to the single administration of arginine was shifted to 120 min on the graph (i.e., 0 min value corresponds to 120 min value). The arrow and the shaded area indicate the administration of GHRH or arginine, respectively. As baseline for the AUC, 0 min value (single arginine) or 120 min value (arginine after GHRH) were used. *p < 0.05; **p < 0.01.

Fig. 3. Plasma GH response to arginine with (●●●) or without (○○○) GHRH pretreatment in 2 normal short children. For the detail, see the legend for Fig. 2.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>CA (year)</th>
<th>BA (year)</th>
<th>Ht (cm)</th>
<th>BW (kg)</th>
<th>Pubertal state (BG/PH)</th>
<th>IGF-I (U/ml)</th>
<th>Pituitary MRI</th>
<th>Stalk</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>8.4</td>
<td>5.5</td>
<td>105.7</td>
<td>17.0</td>
<td>1/1</td>
<td>0.44</td>
<td>Transected</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>11.9</td>
<td>11.5</td>
<td>137.5</td>
<td>44.6</td>
<td>2/1</td>
<td>0.72</td>
<td>Transected</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>13.5</td>
<td>11.0</td>
<td>136.4</td>
<td>37.0</td>
<td>3/2</td>
<td>0.11</td>
<td>Narrowed</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>15.4</td>
<td>12.0</td>
<td>143.8</td>
<td>33.0</td>
<td>1/1</td>
<td>0.27</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>16.0</td>
<td>13.0</td>
<td>145.6</td>
<td>50.1</td>
<td>1/2</td>
<td>0.09</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>37.2</td>
<td>&gt;18.0</td>
<td>127.8</td>
<td>29.2</td>
<td>5/5</td>
<td>0.11</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>7.7</td>
<td>4.5</td>
<td>105.7</td>
<td>15.0</td>
<td>1/1</td>
<td>0.42</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>7.9</td>
<td>5.0</td>
<td>105.6</td>
<td>16.0</td>
<td>1/1</td>
<td>0.15</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>9.1</td>
<td>7.0</td>
<td>104.0</td>
<td>22.5</td>
<td>1/1</td>
<td>0.61</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>15.4</td>
<td>12.5</td>
<td>146.6</td>
<td>36.5</td>
<td>2/1</td>
<td>0.15</td>
<td>Narrowed</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>24.7</td>
<td>&gt;18.0</td>
<td>162.5</td>
<td>50.0</td>
<td>4/4</td>
<td>0.09</td>
<td>Transected</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>7.7</td>
<td>6.0</td>
<td>119.5</td>
<td>25.2</td>
<td>1/1</td>
<td>0.11</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>12.4</td>
<td>9.5</td>
<td>139.6</td>
<td>44.0</td>
<td>1/1</td>
<td>0.20</td>
<td>Narrowed</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>13.2</td>
<td>6.5</td>
<td>132.0</td>
<td>30.0</td>
<td>1/1</td>
<td>0.11</td>
<td>Transected</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>13.3</td>
<td>6.0</td>
<td>133.1</td>
<td>36.3</td>
<td>1/1</td>
<td>0.09</td>
<td>Transected</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>14.5</td>
<td>12.0</td>
<td>132.8</td>
<td>35.0</td>
<td>1/1</td>
<td>0.05</td>
<td>Narrowed</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>15.4</td>
<td>13.0</td>
<td>145.8</td>
<td>46.5</td>
<td>1/1</td>
<td>0.27</td>
<td>Transected</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>17.8</td>
<td>13.5</td>
<td>147.3</td>
<td>64.0</td>
<td>4/3</td>
<td>0.18</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>18.8</td>
<td>13.5</td>
<td>163.2</td>
<td>60.5</td>
<td>3/3</td>
<td>0.07</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

2ry GHD

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>CA (year)</th>
<th>BA (year)</th>
<th>Ht (cm)</th>
<th>BW (kg)</th>
<th>Pubertal state (BG/PH)</th>
<th>IGF-I (U/ml)</th>
<th>Pituitary MRI</th>
<th>Stalk</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>M</td>
<td>6.8</td>
<td>5.5</td>
<td>118.3</td>
<td>31.0</td>
<td>1/1</td>
<td>0.66</td>
<td>Sellar and suprasellar mass (φ 33 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>11.8</td>
<td>9.5</td>
<td>135.5</td>
<td>50.0</td>
<td>1/1</td>
<td>0.32</td>
<td>Sellar and suprasellar mass (φ 40 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>22.9</td>
<td>&gt;18.0</td>
<td>178.0</td>
<td>75.0</td>
<td>4/4</td>
<td>0.20</td>
<td>Stalk mass (φ 15 mm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CA, chronologica age; BA, bone age; BG/PH, Tanner breast and genital stage or pubic hair stage.
Sequential GHRH in Idiopathic GH Deficiency

The correlation between GH response patterns to the sequential GHRH administration and MRI findings of the pituitary area or delivery state at birth in IGHD patients

As shown in Table 1, there is no recognizable tendency between GH response patterns to the sequential GHRH administration and MRI findings of pituitary gland and pituitary stalk in patients with IGHD. The abnormal delivery in these 19 patients was observed in 12, i.e. 3/6 in group A, 3/5 in group B and 6/8 in group C, and no specific relations were observed between the GH response patterns and the delivery status.

The correlation between GH response patterns to the 1st and 3rd GHRH administration, and between 3 GH response patterns and HGH therapy

There was no significant correlation between GH response (max. ΔGH & AUC) to the 1st and the 3rd GHRH injections (r=0.100 & 0.352, P=NS). Also, there were no differences in total doses or duration of HGH therapy among the 3 groups of IGHD (data not shown).

DISCUSSION

While patients with classical IGHD uniformly show impaired GH responses to provocative stimuli such as arginine, insulin-induced hypoglycemia, glucagon-propranolol, clonidine and L-dopa which act on pituitary gland through hypothalamus, they sometimes show adequate GH responses to GHRH (Rogol et al. 1984; Schriock et al. 1984; Takano et al. 1984; Gelato et al. 1986; Kikuchi et al. 1988; Hanew et al. 1991; Romer et al. 1991). Therefore, hypothalamic lesions were considered to be primarily responsible for GH deficiency in some cases of IGHD.

Accordingly, it was expected in some patients that sequential administrations of GHRH would activate hypofunctional somatotrophs and result in gradual improvement of GH responsiveness. In fact, several authors have reported such improved GH responses in some but not all IGHD patients after 3 to 7 day sequential administration of GHRH (Borges et al. 1984; Chihara et al. 1985; Gelato et al. 1985; Takano et al. 1985). In our study, however, patients with IGHD showed 3 types of GH response patterns, i.e, increased (group A), decreased (group B) and unchanged responses (group C), while NSC showed a slight but insignificant decrease in GH.

After the repetitive administration of GHRH it is also expected that hypothalamic somatostatin secretion is increased by GHRH itself or by GH or tissue
IGF-I generated by GHRH (Berelowitz et al. 1981a, b; D'Ercole et al. 1984; Zeytin et al. 1988), resulting in reduced GH responsiveness. Based on such an assumption, arginine was administered 120 min after the 3rd GHRH administrations, since arginine is thought to stimulate GH release through the inhibition of hypothalamic somatostatin secretion (Alba-Roth et al. 1988; Sato et al. 1990). IGHD patients actually showed clearly enhanced responses to arginine 120 min after GHRH administration compared to arginine administration without preceding GHRH administration. It seems that hypothalamic somatostatin neuron is functioning in greater or less degree in these patients. These results, together with the unchanged plasma IGF-I levels throughout the study, also indicate that tissue IGF-I probably generated by GHRH-induced GH release does not significantly inhibit pituitary somatotrophs in these patients (Berelowitz et al. 1981b; Rosenfeld et al. 1984).

All IGHD patients examined in this study had severe GH deficiency and did not show GH response to arginine and L-dopa. Group B and A (11/19, 58% of IGHD), however, showed good or improved response to 1st or 3rd GHRH administration, respectively. Regarding the first GHRH administration, group B showed much greater GH response than group A, i.e., peak GH was above 5 μg/liter in all patients in group B while it was below 4 μg/liter in all group A. Therefore, it is conceivable that hypothalamic lesions of GHRH neurons might have important roles for the GH deficiency in these two groups, and the lesions are less severe in group B than in group A. It seems that peak GH of 5 μg/liter after the 1st GHRH administration is the critical value for determining the two response patterns mentioned above, and that activation of hypofunctional somatotrophs overcame the hypothalamic somatostatin inhibition in group A whereas hypothalamic somatostatin inhibition overcame the recovery of somatotrophs in group B.

On the contrary, group C (8/19, 42% of IGHD) did not show any significant changes of GH response patterns. Such unchanged response patterns were similar to the patterns in secondary GHD with severe hypothalamo-pituitary lesions as was reported by Hizuka et al. (1984). This group showed the more subtle improvement of the GH resposiveness to arginine compared to group A and B. Therefore, group C might have severe pituitary damages as well as severe damages of hypothalamic somatostatin neurons. The fact that the basal GH in this group was higher than other two groups and GH response to the first GHRH was larger in this group than that in group A indicates the possibility of almost maximally activated somatotrophs by the reduced somatostatin tone and of absolutely fewer somatotroph populations responsible to GHRH.

Although, group B patients, who might have least hypothalamic lesions, showed decreased GH response patterns to sequential GHRH administration, NSC did not show significant GH decreases to the administration. GH response to arginine was, however, clearly enhanced after the sequential GHRH administration in both subjects, suggesting the activation of hypothalamic somatostatin
Sequential GHRH in Idiopathic GH Deficiency

neurons. The reason why GH response was significantly suppressed only in group B is not clear at present. However, it is conceivable that GH response to GHRH is mainly dependent on the numbers and activities of somatotrophs and the magnitude of GHRH or somatostatin actions. Therefore, the major difference between the group B and NSC might be the above all factors except GHRH or the concentrations of somatostatin per each somatotroph.

When GHRH priming was pursued several times per day for more than 3 days, Romer et al. (1991) observed an improvement of GH responsiveness after 6 months, but not 2 months, whereas many authors did not observe such priming effects (Borges et al. 1984; Gelato et al. 1985; Takano et al. 1985; Ross et al. 1987; Low et al. 1988). When GHRH was administered once a day as in the present study, incremental GH response pattern frequently turns to decremental pattern after 3 days (Hizuka et al. 1984; Chihara et al. 1985). This may arise from the mutual interaction between the recovery of somatotrophs and the elevated somatostatin tone as mentioned above. Therefore, 3 days sequential administration of GHRH seems to be a reasonable method for the study of hypothalamo-pituitary axis in IGHD patients. The reproducibility of GH responses to GHRH in the majority of severe IGHD patients were considerably good as we previously reported (Hanew et al. 1988).

We could not observe any tendency between the 3 GH response patterns and MRI findings of pituitary area or delivery state at birth in patients with severe IGHD. This may imply that MRI findings and delivery state do not always reflect the degrees of humoral connections between hypothalamus and pituitary gland and of functional somatotroph activities (Kikuchi et al. 1988; Hanew et al. 1991).

In conclusion, sequential administrations of GHRH did not induce uniform GH response patterns, but three GH response patterns, namely increased, decreased and unchanged were observed after the administration in patients with IGHD. These patterns may reflect the degrees of hypothalamic lesions of GHRH and somatostatin neurons. The combined studies with the sequential GHRH and arginine using highly sensitive GH IRMA kit (Ishiwatari et al. 1990) seem to be useful for the evaluation of the activities of hypothalamic GHRH and somatostatin neurons in these patients.

Acknowledgments

We are grateful to Dr. Rich A. Brown for his careful review of our manuscript. We thank Miss Kumi Arai and Rie Aizawa for their technical assistance.

References


