The relation between pituitary magnetic resonance imaging findings and GH, TSH, PRL dynamics in patients with idiopathic GH deficiency

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Abstract. The relation between pituitary magnetic resonance imaging (MRI) findings and anterior pituitary function was studied in 36 patients with classic idiopathic GH deficiency. These patients were divided into three groups based on MRI findings which were compared with those of 14 normal short children; i.e. normal stalk (N=6), narrowed stalk (N=20), and transected stalk (N=10). The transected and narrowed stalk groups showed significantly delayed TSH responses to TRH compared with the normal stalk group and with the normal short children. Further, the mean maximal TSH increment in the narrowed and transected stalk group was slightly greater than that in normal short children. In contrast, there were no differences in basal plasma GH and PRL levels and their responses to GHRH and TRH among the three groups. When the patients were divided into normal anterior pituitary and atrophic pituitary groups regardless of stalk changes or when they were divided into groups of stalk changes (narrowing and transection) with and without pituitary atrophy, no differences in GH, TSH and PRL dynamics between the groups were observed. These results indicate that pituitary thyrotrope functions, but not somatotrope and lactotrope functions, in patients with idiopathic GH deficiency are more closely correlated to stalk changes than to anterior pituitary changes observed on MRI.

Recently it has been reported that patients with idiopathic GH deficiency frequently show pituitary atrophy and transection of the pituitary stalk on magnetic resonance imaging (MRI) (1,2). Kikuchi et al. observed stalk transection in all 12 patients with idiopathic GH deficiency using MRI (2). They divided these patients into two groups, one with a normal anterior pituitary gland and the other with a atrophic pituitary gland, but did not find any difference in GH, TSH and PRL responses to GHRH and TRH between the two groups.

Patients with idiopathic GH deficiency, however, do not always show complete stalk transection, but often show narrowing of the stalk (3) and less frequently a normal stalk. The hypothalamus regulates pituitary functions through the pituitary stalk, and stalk lesion exerts serious effects on pituitary function (4-6). It is well known that patients with hypothalamic lesions have elevated basal PRL levels, and often show delayed and prolonged TSH and PRL responses to TRH administration (7-13). To elucidate which lesion (i.e. pituitary stalk or anterior pituitary) is related to pituitary dysfunction, we divided patients with idiopathic GH deficiency in three different ways on the basis of MRI findings and compared these findings with those of normal short children, first: patients with a normal pituitary stalk, narrowed stalk, and transected stalk; second: patients with a normal anterior pituitary gland and an atrophic anterior pituitary gland regardless of stalk changes; and third: patients with stalk changes (narrowing or transection) with a normal anterior pituitary gland or an atrophic anterior pituitary gland. The basal levels of plasma...
GH, TSH and PRL as well as the responses to GHRH or TRH were studied in these three major categories of idiopathic GH deficiency.

Patients and Methods

Thirty-six patients with idiopathic GH deficiency (25 males and 11 females, aged 6.8 to 27.8 years) were studied. The diagnosis of idiopathic GH deficiency was based on the following criteria: 1. height less than 2 SD of the mean of matched normal children; 2. bone age less than 80% of chronological age; 3. maximal plasma GH response to two provocative stimuli (arginine and L-dopa) below 5 μg/l, and 4. absence of known causes of GH deficiency, such as genetic, organic, metabolic, or psychic abnormalities (14). Twenty-five patients were under treatment with hGH and the remaining 11 had terminated the treatment. As controls, 23 short but endocrinologically normal children (so-called normal short children: 15 boys, 8 girls; aged 7.8 to 16.5 years, mean 12.2±0.6) were studied. Informed consent was obtained from all subjects included. Synthetic human GHRH(1-44)NH2 (GHRH; Sumitomo-Seiyaku, Osaka), 100 μg, and TRH (Tanabe, Osaka), 500 μg, were given between 08.00 and 09.00 h after an overnight fast. In patients receiving hGH treatment, a GHRH test was performed 2 weeks after discontinuation of the treatment, and a TRH test was performed at the time of diagnosis. Adrenal function was normal in all patients, as was thyroid function except in 2 patients (No. 16 and 32) at the time of diagnosis. Mild hypothyroidism (lowering of T1 level) was observed during hGH treatment in other 11 patients and they received small doses of thyroxine (Table 1). Gonadotropic function was impaired in 18 out of 25 patients with idiopathic GH deficiency (more than 13 years of age). Vasopressin secretion was normal in all patients except 2. These patients suffered from diabetes insipidus and showed no high signal intensity at the posterior lobe. Their central diabetes insipidus was properly controlled by desmopressin.

Plasma GH, TSH, and PRL were measured in duplicate using commercial RIA kits (GH, Dinabot; TSH, Daiichi RI, Tokyo, Japan; PRL, Sorin, Gif-sur-Yvette, France). The minimal detectable levels of GH, TSH, and PRL were 0.2 μg/l, 0.15 mU/l, and 1 μg/l, and the intra- and inter-assay coefficients of variance were 4.1 and 4.7%, 4.2 and 5.9%, and 1.9 and 2.1%, respectively (14).

MR studies were performed on a 1.5 Tesla superconducting unit (Magnetom, Siemens, Erlangen); 3-mm thick contiguous T2-weighted images (SE pulse sequence, 500/20) were acquired 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, as in 14 normal short children of prepubertal maturation (7.3-16.5, mean 11.6±0.8 years) its thickness was between 1.0 and 1.9 mm (mean 1.5±0.07 mm). An anterior pituitary gland less than 2.5 mm high was considered small, as in the normal short children its height, was between 3.1 and 5.8 mm (mean 4.1±0.2 mm). The size of the pituitary stalk and the pituitary gland in the normal short children did not differ from that reported in adult subjects (15-19).

Statistical analysis was carried out using analysis of variance followed by the Student-Newman-Keul's test or Chi-square analysis, and all data were expressed as mean ± SEM.

Results

MRI findings in the pituitary region in 36 patients with idiopathic GH deficiency

On MRI, the pituitary stalk was normal in 6 (range 1.2-1.8; mean 1.5±0.1 mm), narrow in 20 (range 0.2-0.9; mean 0.6±0.05 mm), and transected in 10 patients (Table 1).

In the 3 groups, the high signal intensity occurring at the proximal stalk stump correlated with the stalk changes, namely in 1 patient (17%) in the normal group, in 11 (55%) in the narrowed stalk group, and in 10 (100%) in the transected stalk group. Anterior pituitary atrophy also correlated with the stalk changes, in 1 (15%), 12 (60%), and 9 (90%) patients, respectively (Table 1). Pituitary atrophy was significantly more frequent in the transected stalk group (N=10) than the non-transected group (normal and narrowed, stalk N=26) (p=0.017). Abnormal delivery (breech and asphyxia) was observed in none of the normal stalk group, but frequently in the narrowed stalk group (16/20) and transected stalk group (6/10) (Table 1).

Regarding the occurrence of pituitary atrophy, there was no statistical difference between the normal delivery (8/14=57%) and the abnormal delivery patients (13/22=59%). As a control, MRI was performed in 14 normal short children, and all of these children showed a normal pituitary gland, normal stalk and no ectopic posterior lobe.

Relationship of GH, TSH, PRL dynamics and pituitary stalk changes

The mean basal GH levels in the patients were slightly or significantly lower than those in normal short children (normal stalk, 1.0±0.2, N=6, NS; narrowed stalk, 0.6±0.1, N=20; p<0.05; transected stalk, 0.8±0.1, N=10; p<0.05 vs normal short children, 2.2±0.4 μg/l, N=23). No statistical differences were observed in the three groups of patients. The mean GH increments after GHRH from basal in the patients (normal stalk, 4.6±2.0,
Table 1.
Clinical data and MRI findings in 36 patients with idiopathic GH deficiency.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Pubertal state (PH)</th>
<th>Abnormal delivery</th>
<th>Thyroid replacement therapy</th>
<th>MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Normal stalk</td>
<td>4M/2F</td>
<td>14.6±1.8</td>
<td>138.6±7.6</td>
<td>40.5±8.1</td>
<td>2.8±0.6</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(N=6)</td>
<td></td>
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</tr>
<tr>
<td>2. Narrowed stalk</td>
<td>12M/8F</td>
<td>17.1±1.3</td>
<td>139.7±3.4</td>
<td>38.9±2.7</td>
<td>1.6±0.2</td>
<td>16</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>(N=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>3. Transected stalk</td>
<td>9M/1F</td>
<td>16.6±2.0</td>
<td>144.8±5.9</td>
<td>42.8±4.0</td>
<td>2.0±0.5</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>(N=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

PH: Tanner pubic hair stage. High signal: high signal intensity at the proximal portion of pituitary stalk.

N=6; narrowed stalk, 3.3±0.6, N=20; transected stalk, 3.8±0.8 μg/l, N=9) were all significantly lower than in normal short children (31.1±4.5 μg/l, N=23) (p<0.01). However, there were no differences between the normal, narrowed and transected stalk groups (Table 2). The mean time to peak after GHRH injection was not different between patient groups (normal stalk, 42.5±11.2; narrowed stalk, 55.0±3.6; transected stalk, 61.7±5.8) and normal short children (58.0±6.1 min) (Table 2).

Plasma TSH response (max. Δ TSH) to TRH was slightly greater in the transected (17.2±2.4, N=7) and narrowed stalk groups (17.3±3.1, N=19) than in the normal stalk group (13.3±2.9, N=6) or normal short children (11.7±0.9 mU/l, N=16) (p=NS, Table 2). Although the mean time to peak was similar in the normal stalk group (25.0±3.1) and the normal short children (29.1±2.9), it was significantly delayed in narrowed (58.3±7.8) and transected stalk groups (81.4±18.2 min) (vs normal stalk, p<0.05; vs normal short children, p<0.01) (Table 2). The mean basal TSH levels did not differ in the three groups of patients and the normal short children (normal stalk, 3.3±0.9; narrowed stalk, 2.1±0.3; transected stalk, 2.2±0.3; normal short children, 2.2±0.3 mU/l).

Plasma PRL response (max. Δ PRL) to TRH in the three patient groups did not differ from each other.

Table 2.
Mean increment of GH, TSH and PRL from the basal and mean time to peak after GHRH or TRH administrations in 36 patients with idiopathic GH deficiency.

<table>
<thead>
<tr>
<th>Group</th>
<th>GHRH</th>
<th>TRH</th>
<th>TRH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>max. ΔGH (μg/l)</td>
<td>Peak time (min)</td>
<td>max. ΔTSH (mU/l)</td>
</tr>
<tr>
<td>1. Normal stalk</td>
<td>4.6±2.0a</td>
<td>42.5±11.2 (N=6)</td>
<td>13.3±2.9</td>
</tr>
<tr>
<td>2. Narrowed stalk</td>
<td>3.3±0.6a</td>
<td>55.0±3.6 (N=20)</td>
<td>17.3±3.1</td>
</tr>
<tr>
<td>3. Transected stalk</td>
<td>3.8±0.8a</td>
<td>61.7±5.8 (N=9)</td>
<td>17.2±2.4</td>
</tr>
<tr>
<td>4. Normal short children</td>
<td>31.1±4.5</td>
<td>58.0±6.1 (N=23)</td>
<td>11.7±0.9</td>
</tr>
</tbody>
</table>

a: vs normal short children, p<0.01. b: vs Normal stalk, p<0.05.
other (normal stalk, 14.6±5.0, N=6; narrowed stalk, 22.1±3.6, N=18; transected stalk, 17.6±5.9, N=7); however, the responses were significantly lower than that of normal short children (45.0±5.0 μg/l, N=15, p<0.01) (Table 2). While the mean time to peak was almost similar in the 3 patient groups (normal stalk, 37.5±11.4; narrowed stalk, 30.0±2.7; transected stalk, 38.6±6.4), it was considered but not significantly delayed when compared with that of the normal short children (22.0±3.5 min) (Table 2). There was no statistical difference in basal PRL levels between the patients and normal short children (normal stalk, 6.2±1.4; narrowed stalk, 7.3±0.9; transected stalk, 13.1±5.1; normal short children, 8.9±0.8 μg/l), although two patients with a transected stalk showed a slight elevation (No. 32, 40.7; No. 34, 19.9 μg/l). These two patients showed normal PRL increments to TRH (20.8 and 41.2 μg/l).

**Discussion**

In 36 patients with classic idiopathic GH deficiency, transection of the pituitary stalk was observed on MRI in 28%, narrowing of the stalk in 55%, and a normal stalk in 17%. All the transected stalk patients showed a high signal intensity at the proximal stump of the pituitary stalk and these patients more frequently showed pituitary atrophy than did patients with a non-transected stalk.

Surgical transection of the pituitary stalk results in nerve and vascular regeneration, with a resultant enlargement of the proximal stump (so-called ectopic posterior lobe), and also causes variable degrees of infarction within the anterior lobe (3-5,20-22). However, if the stalk is transected at a higher level, such as the median eminence or nearby, no ectopic posterior lobe develops (20). The high signal intensity on MRI is thought to be dependent on accumulation of secretory materials (ADH, neurophysin and oxytocin) at the enlarged stump (3,19,21-23).

When the patients were divided into three groups on the basis of their stalk changes, i.e. normal stalk, narrowed stalk, transected stalk, each group showed significantly lower responses to GHRH or TRH in their plasma GH and PRL than those found in normal short children. Further, GH and PRL response and the mean time to peak did not differ from each other. There were no consistent GH response patterns to sequential 3-day administration of GHRH in either group of patients (unpublished observation).

In contrast, the time to peak TSH after TRH injection was significantly delayed in the transected and narrowed stalk group compared with that in the normal stalk group and normal short children. In addition, TSH increment in the narrowed and transected stalk group was significantly greater than that in normal short children. It has been reported that patients with hypothalamic lesions often show delayed, prolonged, and exaggerated TSH responses to TRH administration (7-13). However, patients with idiopathic GH deficiency with atrophic and normal pituitary glands have similar responses of TSH as well as GH and PRL regardless of stalk changes.

No difference in the basal levels of GH, TSH and PRL was observed in the three major groups mentioned above, and it is worth noting that the PRL levels were not elevated, even in the stalk transected groups.

**Relationship of GH, TSH, PRL dynamics and changes in the anterior pituitary gland**

On MRI, 21 of the 36 patients showed atrophy of the anterior pituitary gland (range: 0.5-2.4; mean, 1.5±0.1 mm) and the remaining 15 presented a normal anterior pituitary (range: 2.5-6.4; mean, 3.5±0.3 mm). There was no difference in maximal increment of GH, TSH and PRL or the time to peak after GHRH or TRH administration between patients with normal pituitary and those with an atrophic pituitary gland (data not shown). We could observe no difference in the mean basal levels of GH, TSH and PRL in these two patient groups (data not shown).

**GHRH and TRH tests in patients with idiopathic GH deficiency with stalk changes associated and not associated with pituitary atrophy**

In 30 patients with stalk changes (transection or narrowing), 10 demonstrated a normal anterior pituitary and 20 an atrophic pituitary gland. However, there were no differences in maximal increment of GH, TSH and PRL or the time to peak after GHRH or TRH administration between the normal pituitary and the atrophic pituitary groups (data not shown). Again, there were no statistical differences in the mean basal levels of GH, TSH and PRL in the two patient groups (data not shown).
These findings indicate that pituitary somatotrope and lactotrope functions in patients with idiopathic GH deficiency are not always correlated to anterior pituitary and stalk changes on MRI, but that thyrotrope functions (in terms of TSH responsiveness to TRH) are more closely correlated to stalk changes than to pituitary changes.

Six out of 20 patients in the narrowed stalk group and 7 out of 10 in the transected stalk group required thyroid replacement therapy before or during hGH therapy, whereas this was not required in the normal stalk group. This finding also suggests that an abnormality of the hypothalamo-pituitary-thyroid axis is closely related to the degree of stalk change. It is plausible that the extent of hypothalamic lesions is much greater in the transected stalk group than in narrowed and normal stalk groups.

It is well known that patients with classic idiopathic GH deficiency frequently have experienced perinatal insults such as breech delivery and asphyxia (24-26). In our study, 22 of 36 patients had such a history. We were not able to observe any clear correlation between the abnormal delivery and the presence of pituitary atrophy. However, an abnormal delivery was not observed in any patient with a normal stalk, but it was frequently observed in patients with stalk changes (narrowing and transection). Therefore, abnormal delivery may be one of the main causes of pituitary stalk change (1,2), but the etiology of idiopathic GH deficiency with stalk changes and normal stalks may be different.

An examination as to whether or not there are any genetic defects in these patients is necessary. However, Mullis et al. (27) could not observe any specific defects in the GHRH gene and the GH gene cluster in 53 patients with isolated GH deficiency.

There were no patients with panhypopituitarism in our series, even though some patients had stalk transection and pituitary atrophy. This strongly indicates the humoral connections between the hypothalamus and the anterior pituitary gland and the functional capacity of pituitary cells in these patients (2). In relation to this, if no barrier is placed between the cut end of the stalk at the time of stalk transection, the hypothalamo-hypophyseal portal circulation is restored (4,21,22). With the exception of 2 patients, the basal PRL levels in the transected stalk group were within normal ranges. It is considered that the PRL levels in the transected stalk group are determined by the mutual relation between the degree of hypothalamo-pituitary humoral connections and the degree of lactotrope damage.

In conclusion, a narrowing of the pituitary stalk was common in patients with idiopathic GH deficiency, whereas stalk transection and normal stalk were less common findings on MRI. The occurrence of pituitary atrophy correlated with the degree of the stalk lesion. Patients with stalk changes (narrowing and transection) showed delayed TSH response patterns to TRH, and stalk transection was often associated with subclinical hypothyroidism during hGH treatment. It is expected that MRI of the pituitary area will be a valuable procedure for the diagnosis and analysis of etiologies in patients with idiopathic GH deficiency.

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