Correlation between the Pituitary Size and Function in Patients with Asthenia

Takashi Yamada, Ken Nojiri*, Hideyuki Sasazawa*, Tomomichi Tsukui*, Yasuhiro Miyahara, Kazumi Nakayama, Mitsuhisa Komatsu**, Toru Aizawa*** and Ichiro Komiya#

Department of Medicine, Kashiwa City Hospital, Kashiwa, Chiba 277-0825, Japan
*Haruna Brain Surgery, Takasaki, Gunma 370-0871, Japan
**Department of Aging Medicine and Geriatrics, Graduate School of Medicine, Shinshu University, Matsumoto 390-8621, Japan
***Center for Health, Safety and Environmental Management, Shinshu University, Matsumoto 390-8621, Japan
#Second Department of Medicine, School of Medicine, Ryukyu University, Naha 903-0215, Japan

Abstract. To explore the relationship between pituitary morphology and function, we performed mid-sagittal MRI and endocrinological evaluation in 38 patients with asthenia. Six patients were diagnosed as having complete empty sella (ES) and 16 patients partial empty sella (PES). BMI, blood pressure, serum Na, ACTH, cortisol, TSH and T4 were lower in ES group and PES group than in the group with normal pituitary size. Age in the patients with ES was oldest. Multiple regression analysis revealed that serum cortisol level was independently correlated with the size of the pituitary (β = 0.586, p = 0.0069). Other variables, including age, BMI, blood pressure, serum Na, ACTH, TSH and T4, were not correlated with the pituitary size when multivariate analysis was employed. In conclusion, there is a close relationship between the reduction of size of pituitary gland and the degree of adrenocortical dysfunction in asthenic patients. It is suggested that the pituitary-adrenal axis is especially vulnerable in empty sella syndrome, and therefore, meticulous evaluation of the hypophysial adrenal axis is recommended in subjects with reduced pituitary size even in elderly population.

Key words: Empty sella syndrome, Asthenic patients, Adrenal insufficiency

Magnetic resonance imaging (MRI) has become an important tool for assessing morphology of the pituitary gland [1–3], and it is well established that there are age- and gender-related alterations in volume of the pituitary gland in the general population [2]. Incident diagnosis of reduction of the size of pituitary gland and/or empty sella are not uncommon [4]. It would be anticipated that the reduction of size of the pituitary gland is associated with pituitary dysfunction. However, it is not necessarily the case. In fact, symptoms and laboratory data of the patients with reduced pituitary size/empty sella syndrome are so variable from “no symptom and normal pituitary function” to “clear-cut signs and symptoms with overt hypopituitarism” [5–7]. The reason for such diversity is unknown. In this study, we re-evaluated the issue by performing a multivariate analysis of the size of pituitary gland, pituitary function, and clinical data in asthenic patients.

Subjects and Methods

The patients were referred to Kashiwa City Hospital for evaluation of such symptoms as weakness, fatigue, emaciation and low blood pressure. After exclusion of non-endocrine disorders including gastrointestinal, hepatic, hematologic, renal and cardiovascular disorders, basic endocrinological evaluation was performed in 38 patients as shown in Table 1.

Brain MRI examination was performed with a 1.5
Tesla GE Sigma system. The mid-sagittal image was used to determine length and height of the pituitary gland [8]. Based on the finding of MRI, the patients were divided into three groups: empty sella (ES), partial empty sella (PES), and normal (N) group. ES was defined as having little visible pituitary gland, or as having area of cerebrospinal fluid more than 90% of the sella turcica as shown in Fig. 1A–F. Apparent concavity of the upper surface of the pituitary gland was used as the diagnosis of PES. The size of the pituitary gland was determined by an index [pituitary height × pituitary length] on the mid-sagittal section.

Blood samples were withdrawn at 8:00–9:00 a.m., and serum ACTH, cortisol, TSH, T\textsubscript{4} and Na levels were determined. ACTH was measured by immunoradiometric assay, cortisol was measured by radioimmunoassay, and TSH and T\textsubscript{4} were measured by chemiluminescent immunoassay. Blood pressure was measured in the patients in a comfortable recumbent position, the cuff being placed on the arm at the level of the heart. Body mass index (BMI) was calculated as kg/m\textsuperscript{2}.

Statistical analysis was performed by one way ANOVA and multiple regression analysis (StatView, SAS, Cary, NC), and \( p \) values less than 0.05 were considered statistically significant.

**Results**

*Clinical characteristics of the patients*

The age of the patients was oldest in ES group, intermediate in PES group and youngest in N group. BMI, systolic blood pressure and diastolic blood pressure were lowest in ES group, intermediate in PES group and highest in N group. Three patients in ES group were diagnosed as Sheehan’s syndrome.

<table>
<thead>
<tr>
<th>Group</th>
<th>age (yr)</th>
<th>N</th>
<th>F/M</th>
<th>BMI (kg/m\textsuperscript{2})</th>
<th>systolic BP (mmHg)</th>
<th>diastolic BP (mmHg)</th>
<th>serum Na (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ES</td>
<td>68 ± 3</td>
<td>6</td>
<td>4/2</td>
<td>19.8 ± 0.3</td>
<td>117 ± 3</td>
<td>65 ± 4</td>
<td>126 ± 6</td>
</tr>
<tr>
<td>B. PES</td>
<td>56 ± 3</td>
<td>16</td>
<td>12/4</td>
<td>21.9 ± 0.9</td>
<td>127 ± 2</td>
<td>65 ± 3</td>
<td>137 ± 2</td>
</tr>
<tr>
<td>C. Normal</td>
<td>53 ± 2</td>
<td>16</td>
<td>11/5</td>
<td>24.4 ± 1.1</td>
<td>130 ± 4</td>
<td>77 ± 3</td>
<td>138 ± 1</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

<table>
<thead>
<tr>
<th></th>
<th>Age A vs B ( p = 0.0167 )</th>
<th>BMI A vs C ( p = 0.0115 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs C ( p = 0.0034 )</td>
<td>A vs C ( p = 0.0075 )</td>
</tr>
<tr>
<td></td>
<td>B vs C ( p = 0.0038 )</td>
<td>A vs C ( p = 0.0048 )</td>
</tr>
<tr>
<td></td>
<td>A vs B ( p = 0.0254 )</td>
<td>A vs C ( p = 0.0340 )</td>
</tr>
<tr>
<td></td>
<td>A vs C ( p = 0.0340 )</td>
<td>A vs C ( p = 0.0038 )</td>
</tr>
<tr>
<td></td>
<td>Na ( p = 0.0075 )</td>
<td>Na ( p = 0.0048 )</td>
</tr>
</tbody>
</table>

Table 1. Physical condition in patients with asthenia divided into three groups, empty sella (ES), partial empty sella (PES) and normal pituitary size (Normal).

**Fig. 1.** Mid-sagittal magnetic resonance images from 6 patients (A–F) with complete empty sella. Note that little pituitary tissue was seen in the pituitary fossas in patients A, B, D, E, and that more than 90% of the fossas were occupied by cerebro-spinal fluid in patients C and F.
Endocrine data

As shown in Table 2, serum ACTH and cortisol concentrations were lowest in ES group, intermediate in PES group and highest in N group. The same trend was observed in serum TSH and T4.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>ACTH (pg/ml)</th>
<th>Cortisol (µg/ml)</th>
<th>TSH (µU/ml)</th>
<th>T4 (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ES</td>
<td>6</td>
<td>5.30 ± 0.55</td>
<td>2.38 ± 0.86</td>
<td>0.95 ± 0.20</td>
<td>3.68 ± 0.89</td>
</tr>
<tr>
<td>B. PES</td>
<td>16</td>
<td>8.98 ± 1.02</td>
<td>11.01 ± 0.54</td>
<td>1.49 ± 0.30</td>
<td>7.11 ± 0.29</td>
</tr>
<tr>
<td>C. Normal</td>
<td>16</td>
<td>12.27 ± 1.20</td>
<td>16.43 ± 1.48</td>
<td>1.71 ± 0.27</td>
<td>7.09 ± 0.28</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

Morphological abnormality of the pituitary gland was found in 22 out of 38 patients (58%) with asthenia: 6 had ES and 16 had PES. This is clearly higher than the reported incidence of ES in the previous studies [2, 4] where MRI was performed as a routine examination of the CNS abnormalities. Of note is the significantly higher age in those with ES among patients with asthenia. The finding indicates a possibility that ES progresses insidiously in elderly subjects, and seemingly non-specific symptoms as asthenia is overlooked as “senile” changes. Previously reported “age-related” decrease of the volume of pituitary gland [1, 2, 8, 9] might have to be re-considered in light of the current findings.

In the univariate analysis, size of the pituitary was correlated with many clinical and laboratory data including age, BMI, BP, serum Na, cortisol, FT4, TSH, and ACTH. However, in the multivariate analysis, the pituitary size was correlated with serum cortisol levels but not other variables. Thus, it is strongly suggested that the primary event associated with atrophy of the pituitary gland is adrenal dysfunction, and that clinical and other laboratory abnormalities develop secondarily to hypothalamic hypothyroidism. Absence of independent relationship between the size of pituitary gland and ACTH was rather unexpected in face of the significant relationship between the pituitary size and serum cortisol. It is more likely that serum ACTH fluctuates more than serum cortisol in a given patient, hence the degree of secondary hypothalamic hypothyroidism may be more faithfully evaluated by serum cortisol than ACTH. The other possible explanation is that decreased cortisol concentration induced variable compensatory elevation of ACTH in those with residual secretory capacity of
corticotrophs.
In general, it is assumed that more than 90% reduction of the pituitary volume is associated with hypopituitarism [10]. However, degree of reduction of the pituitary size was not well correlated with the degree of hypopituitarism [6, 11]. In these studies, the morphology of pituitary was evaluated for various reasons such as obesity, hypertension, ophthalmologic/neurologic abnormalities and positive anti-pituitary antibodies. In the present study, however, we selectively analyzed patients with asthenia suggestive of hypoadrenocorticism and hypothyroidism. Thus, homogeneity of the patient population in the current study may have yielded the correlation between the pituitary size and the pituitary function.

In conclusion, there is a correlation between the pituitary size and clinical and endocrine abnormalities in asthenic patients. It is suggested that the pituitary-adrenal axis is especially vulnerable in patients with empty sella. Therefore, meticulous evaluation of the hypophysial adrenal axis is highly recommended in subjects with reduced pituitary size even in elderly population.

References