LONGITUDINAL STUDY OF PATIENTS WITH IDIOPATHIC ISOLATED TSH DEFICIENCY: POSSIBLE PROGRESSION OF PITUITARY DYSFUNCTION IN LYMPHOCYTIC ADENOHYPOPHYSITIS

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Abstract. The relationship between isolated TSH deficiency and hypophysitis was studied. Six patients (five women and one man) with idiopathic isolated TSH deficiency were longitudinally investigated with an interval of 31 to 60 months. Clinical symptoms, laboratory results and endocrine function were investigated as well as pituitary magnetic resonance imaging (MRI) at the start and the end of the study. Clinically, initial symptoms due to hypothyroidism were ameliorated by the thyroid hormone replacement in all patients. Oligomenorrhea newly appeared during the study in three patients, although no other symptoms appeared. Serum fT3 and fT4 levels were within the reference ranges, and serum TSH level and its response to TRH stimulation remained low in all patients. Peak plasma GH level during GRH stimulation was significantly (p<0.03) decreased, at the end of the study as compared with the start. Peak plasma FSH level to LHRH stimulation was significantly (p<0.03) decreased as well as basal FSH level. In contrast, peak of prolactin during TRH stimulation was significantly (p<0.03) increased at the end of the study as compared with the start as well as basal prolactin level. Endocrine features at the end of the study were compatible with those of lymphocytic adenohypophysitis (LAH). MRI of the pituitary gland showed empty sella in one patient and slight swelling in two patients. These findings remained unchanged during the study period. One patient underwent pituitary biopsy, with histological examination showing atypical form of LAH. LAH can cause idiopathic isolated TSH deficiency and can functionally progress to combine dysfunction of the pituitary gland.

Key words: Pituitary, Thyroid

ISOLATED pituitary hormone deficiency can be induced by many causes including mechanical destruction of the hypothalamo-pituitary axis, neoplasm, inflammation, and injury and genetic defects of pituitary hormone production and secretion. In many cases, however, its etiology is still unknown. Isolated TSH deficiency has been considered to be a rare disease [1]. Patients with idiopathic isolated TSH deficiency sometimes show the presence of anti-pituitary antibody (APA) [1-3] and empty sella on magnetic resonance imaging (MRI) [1].

Patients with lymphocytic adenohypophysitis (LAH) frequently demonstrate the presence of APAs [2-6] and hypopituitarism to a variable degree [7-12]. To our knowledge, however, only one patient with isolated TSH deficiency associated with LAH has been reported [13]. This patient showed very gradual progression from isolated TSH deficiency to combined hypopituitarism. No series of isolated TSH deficiency has been longitudinally studied yet. We longitudinally investigated clinical features and pituitary function as well as pituitary imaging findings in six patients with idiopathic isolated TSH deficiency. Furthermore, we could histologically examine the pituitary gland in one patient. We tried to clarify the etiology of idiopathic isolated TSH deficiency.
Subjects and Methods

Subjects

We previously reported six patients with idiopathic isolated TSH deficiency [1]. We are able to follow up three of them, but not the remaining three patients because of their ceasing to visit our out-patient service by themselves or their admission to another hospital due to apoplexy. We diagnosed three new patients and started the thyroid hormone replacement. Accordingly, five women and one man with a mean age of 41.2 yr were investigated. The detailed data of Cases 1-3 at the initial diagnosis are described elsewhere [1]. Cases 4-6 were similarly diagnosed according to the procedure previously described [1]. Their clinical features are summarized in Table 1. Serum TSH levels were low and showed no nocturnal surge as well as a blunted response to stimulation with 500 μg TRH (Fig. 1-a). Serum fT3 and fT4 levels were low or within the reference ranges. No decrease in the secretion of pituitary hormones other than TSH was initially seen.

Materials and methods

The responses of plasma pituitary hormone levels to the administration of the respective hypothalamic stimulating hormones were examined initially and 31 to 60 months later. The procedure of the examinations is described elsewhere [1]. In brief, plasma samples for the measurement of each pituitary hormone level were obtained through a plastic cannula inserted into an antecubital vein before and 15, 30, 60, 90 and 120 min after the intravenous injection of the respective hypothalamic stimulating hormones following one-hour bed-rest early in the morning. Levothyroxine supplementation had been withdrawn four weeks before the stimulation tests at the end of the study. Plasma sampling for estradiol measurement and LHRH stimulation test were performed four to six days after the cessation of menstruation in the pre-menopausal women (Cases 2-4 and 6). The methods of measuring plasma or serum hormone levels and antibodies are described elsewhere [1]. APA was measured by the method using Western blotting as described previously by Crock et al. [14]. In short, normal human pituitary glands were homogenized in PBS and were centrifuged for the separation of the cytosol and the membrane fractions. The cytosol fraction was further fractionated onto SDS-polyacrylamide gels by electrophoresis. The separated proteins were transferred to polyvinylidene difluoride membranes and incubated overnight with diluted patients’ serum. Reactivity to pituitary proteins was detected using biotin-conjugated goat antihuman IgG antiserum and color reaction with enhanced chemiluminescence detection reagents.

In all cases, MRI of the pituitary gland was initially examined on the diagnosis and finally examined in the end of the follow-up study. Only Case 2 underwent MRI examination every year because of initially suspected pituitary tumor.

In Case 2, the pituitary gland was transsphenoidally biopsied 55 months after the initial diagnosis and was examined histologically and immunohistochemically according to the methods previously reported [15]. In the immunohistochemical examination, in short, the indirect immunoperoxidase method was applied, using antisera specific to TSH (Anti-TSH Monoclonal Antibody, Code #412701, Nichirei, Tokyo, Japan), PRL (Anti-Prolactin Polyclonal Antibody, Code #412601, Nichirei), GH (Polyclonal rabbit anti-human growth hormone (hGH) Code #A0570, Dako Cytomation, Glostrup, Denmark), LH (Anti-LH Monoclonal Antibody, Code #412481, Nichirei), FSH (Anti-FSH Monoclonal Antibody, Code #412231, Nichirei), and ACTH (Anti-Corticotropin Polyclonal Antibody, Code #412031, Nichirei).

Data are presented as individual values or mean +/- SEM. In the statistical analysis, TSH value less than 0.04 mIU/L (not detectable level) was calculated as 0 mIU/L. The results between tests were compared using intra-individual pair-wise analysis with Wilcoxon’s signed rank test computerized in StatView Version 5.0 (SAS Institute Inc., Cary, NC). A value of p<0.05 was considered statistically significant.
All examinations were performed after obtaining permission from the Ethics Committee of Matsunami General Hospital and informed consent from the patients according to the Declaration of Helsinki.

Results

Clinical and biochemical findings
Levothyroxine was replaced in all patients, because they complained of fatigability, cold intolerance, lethargy and sleepiness that were compatible with hypothyroidism. These symptoms disappeared with the thyroid hormone replacement therapy in all of them. However, in Cases 2, 4 and 6, oligomenorrhea newly appeared during the study period. Blood pressure, pulse rate, and other physiological examinations including the relaxation phase of Achilles tendon reflex remained unchanged during the study period. Total blood counts and biochemical data including serum total cholesterol and creatine phosphokinase remained unchanged during the study period. Serum APA titers were initially positive in Cases 2 and 3, but became negative by the end of the study in all patients (Table 1).

Pituitary function

Basal level
At the end of the study, basal TSH, fT3 and fT4 levels four weeks after the cessation of levothyroxine replacement were statistically unchanged as compared with the start of the study (Table 2). However, basal TSH levels in Cases 3 and 4 were slightly increased and in the reference range. Basal prolactin levels of Cases 4 and 6 at the end of the study were high and at the higher limit of the reference range, respectively, as compared with the reference range. Statistically, basal prolactin levels were significantly (p<0.03) higher at the end of the study than at the start. Basal FSH levels of a post-menopausal woman, Case 1, and a man aged 74 yrs, Case 5, were higher than the reference ranges of younger controls at both the start and the end of the study. A similar tendency was seen in basal LH levels in both cases, although the levels at the end of the study in Case 1 and at the start of the study in Case 5 were within the reference ranges. However, basal LH and FSH of other younger patients were within the respective reference ranges, at both the start and end of the study. Basal FSH level was significantly (p<0.03) lower at the end of the study than at the start. Similarly, plasma estradiol level in Case 1 was low as compared with the respective reference range of younger controls. Plasma free testosterone level in Case 5 was relatively low but within reference range. In the younger patients, Cases 2-4 and 6, estradiol levels were within the reference range and were not different between the start and end of the study. The basal levels of ACTH, cortisol, GH and LH were within the reference ranges at both the start and end of the study and unchanged statistically.

Stimulation tests
In all cases the TSH response to TRH stimulation was blunted at both the start and end of the study, although TSH slightly but subnormally increased in Cases 3 and 4. The peak levels of TSH during the TRH stimulation test did not differ between the start (1.34 ± 0.37 mIU/L) and end (2.19 ± 1.00) of the study (Fig. 1-a). However, the response of prolactin to TRH stimulation at the end of the study was exaggerated in Cases 2-6 in spite of the normal response at the start of the study. The peak of prolactin during TRH stimulation test at the end of the study (peak, 98.7 ± 11.6 μg/L) was significantly (p<0.03) higher than at the start (50.7 ± 5.3) (Fig. 1-b). The peak of GH during GRH stimulation in Case 3 was higher than the reference range both at the start and the end of the study. On the other hand, the responses in Cases 2, 4 and 5 were blunted at the end of the study. Statistically, the peak of GH during GRH stimulation test at the end of the study (15.5 ± 5.4 μg/L) was significantly (p<0.03) lower than at the start (35.9 ± 12.1) (Fig. 1-c).
responses of ACTH as well as cortisol to CRH stimulation were unchanged and within the reference ranges at both the start and end of the study. The peak of ACTH and cortisol during the CRH stimulation test was not different between the start (11.6 ± 1.0 pmol/L and 471 ± 27 nmol/L, respectively) and the end of the study (10.5 ± 1.4 and 515 ± 30, respectively) (Figs. 1-d and e). No difference was seen in the peak of LH during the LHRH stimulation test between the start (36.5 ± 9.8 IU/L) and the end of the study (39.7 ± 6.0), although a hyper-response was seen in the elderly woman (Fig. 1-f). However, the FSH response to LHRH stimulation was blunted in Cases 2-4, 6 at the end of the study. The peak of FSH during LHRH test was significantly (p<0.03) lower at the end of the study (15.5 ± 7.7 IU/L) than at the start (26.4 ± 12.7) (Fig. 1-g).

**MRI of pituitary gland**

In Case 1, MRI revealed an empty sella in the initial examination and showed no change in the end of the study (Fig. 2-a). In Cases 3, 5 and 6, MRI of the pituitary gland remained unremarkable both in the start and the end of the study. In Cases 2 and 4, a slightly enlarged pituitary gland enhanced with gadolinium was revealed in the initial examinations (Fig. 2-b, c). Pituitary adenoma was initially suspected in Case 2. In both cases, MRI demonstrated no change at the end of the study.

**Pituitary biopsy and histopathological examination of Case 2**

In Case 2, the pituitary gland was biopsied at the end of the study because of the swelling on pituitary MRI and hyper-response of prolactin to TRH stimulation and blunted responses of GH and FSH to GRH and LHRH stimulation tests combined with the new appearance of oligomenorrhea. During the transsphenoidal biopsy, no pituitary tumor but abnormal non-tumorous tissue was found. After the biopsy, the patient showed no change in her symptoms or the results of endocrine examinations. In the histopathological examination (Fig. 3, a and b), the anterior pituitary cells were arranged with a dilated capillary network. All cells, both eosinophilic and chromophobic ones, were swollen and had pyknotic nuclei and unclear cell membrane to varying degrees. In some of them, small vacuoles were found. Clusters of lymphocytes were seen in the peripheral region of the specimen and around the pituitary cells. However, almost no fibrosis or plasma cells infiltration was seen in the pituitary specimen. These findings were inconsistent with the typical findings of LAH, but an atypical form of LAH could be diagnosed. Immunohistochemically, almost no staining was found with anti-TSH antibody. Positive staining was found with antibodies for five other anterior pituitary hormones.

**Discussion**

The symptoms of idiopathic isolated TSH deficiency diagnosed in adults are not severe and are easily ameliorated by thyroid hormone replacement [1]. Despite the improvement in the symptoms of hypothyroidism noted during the study, a new symptom, oligomenorrhea, appeared in three patients. It is interesting that the response of pituitary hormones to the hypothalamic stimulating hormones deteriorated during the study period. The response of FSH to LHRH stimulation decreased and the response of prolactin to TRH stimulation increased at the end of this study as compared with the start. This endocrine change might be related to the new appearance of oligomenorrhea, although plasma estradiol levels remained unchanged. Although the responses of plasma GH to GRH stimulation decreased at the end of the study, no change was seen in the clinical symptoms and general laboratory results. Unfortunately, plasma IGF-1 level was not measured in any patients. On the other hand, in two patients, basal levels and the responses of TSH to TRH stimulation slightly increased at the end of the test. This phenomenon was of interest, because spontaneous recovery has been reported in idiopathic TSH deficiency [16].

In cases of hypopituitarism induced by pituitary tumor or irradiation, the decrease of
pituitary hormones secretion gradually progresses, but hyper-secretion of prolactin is not seen without tumor invasion or irradiation damage to hypothalamus [17]. When serum fT3 and fT4 levels decrease due to decreased TSH secretion, TRH increases and prolactin level may increase. However, hyperprolactinemia is observed only in up to 20% of cases even in hypothyroidism [14]. In our series, serum fT3 and fT4 levels were within the reference ranges, although serum TSH level was low. It is unlikely that hypothyroidism itself caused hyperprolactinemia and/or hyper-response of plasma prolactin to TRH stimulation. LAH frequently shows hyperprolactinemia [7-10], although the precise reason has not been clarified [9, 10]. The endocrinological features seen at the end of this study were compatible with LAH, decreased response of TSH, GH and FSH and increased response of prolactin to the respective stimulating hypothalamic hormones.

Several reports have suggested that LAH might have caused acquired isolated deficiency of pituitary hormones [1, 18-22]. Actually, several types of isolated pituitary hormone deficiency associated with LAH have been reported [13, 22-26]. However, ACTH secretion is most frequently impaired followed by impairment of TSH secretion in LAH [8-10]. In our study, basal ACTH levels and their response to CRH stimulation were intact and unchanged during the study, although TSH had been clearly damaged. It is unclear why the secretion of ACTH was intact in our series. Only in one patient, Case 3, GH response to GRH stimulation was exaggerated during the study, although basal GH level was within reference range. The cause of this hyper-response is unknown.

Although lymphocyte infiltration and pituitary cell degeneration were seen in the biopsy specimen of pituitary gland of Case 2, neither plasma cell infiltration nor fibrosis was seen. LAH shows lymphocyte and plasma cell infiltration, and cluster formation of these cells is seen as well as fibrosis and/or degeneration of the pituitary cells [8-10, 27]. The pathological findings in Case 2 were incompatible with typical LAH. However, the findings were inconsistent with other forms of hypophysitis, granulomatous hypophysitis, xanthogranulomatous hypophysitis, xanthomatos hypophysitis, and necrotizing hypophysitis [27]. An atypical form of LAH could be diagnosed histologically. According to Tashiro et al. [27], which represents the largest series of pathological investigations of hypophysitis, only very slight lymphocyte infiltration and fibrosis were seen in the two of five patients with isolated ACTH deficiency associated with LAH. With the progression of the disease, the lymphocyte infiltration may become more marked, and deficits of other hormones may develop in the future in these patients. It is conceivable that the functional and morphological findings reflected a midpoint in the inflammatory destruction of the pituitary gland due to LAH.

Considering the clinical course of LAH, the impairment of pituitary hormone secretion in LAH is restored spontaneously in a few cases [8, 28]. In some cases, however, no recovery was seen throughout the clinical course [8]. To our knowledge, only a single case [13] of slow progression of the disease has been reported. In this case, a small pituitary lesion of LAH had grown to a suprasellarly extended mass compressing the optic chiasm during an eight-year period [13]. Although the initial hypopituitarism was not adequately investigated, the hypopituitarism might have progressed from an isolated deficit of TSH to combined hypopituitarism of TSH, ACTH and gonadotropin. Glucocorticoid treatment was not attempted in this study, although the impaired pituitary function of LAH is frequently restored after such treatment [9, 10, 29].

Severe swelling, suggestive of a tumor, of the pituitary gland including pituitary stalk enhanced with gadolinium [9, 10, 30, 31] has frequently been reported in LAH [9, 10, 28, 32, 33]. MRI demonstrated a slight swelling of the pituitary gland, which was homogenously enhanced with gadolinium in Cases 2 and 4. MRI findings indicated the pituitary gland appeared unchanged in size during the study period in spite of the deterioration of pituitary function. The lack of any change in the size of pituitary gland might have been due to the absence of fibrosis and only slight infiltration of lymphocytes in the pituitary gland in Case 2. These findings are consistent with those of LAH.

APAs are often detected in several pituitary diseases [1-3]. However, it is unclear
whether the detected APAs are related to the etiology or are consequences of the disease. In our previous report [1], APA, the antibody to the human pituitary cytosol was detected in five of six patients with isolated TSH deficiency. APAs were detected also in patients with isolated ACTH deficiency [2, 4, 34, 35] and empty sella [34, 35]. It is suggested that LAH as an autoimmune disease contributed to the etiology of isolated TSH deficiency in some of the patients. The antibodies to 22-Kd [4] or 49-Kd [2, 5] protein of human pituitary gland were detected in patients with LAH. The antibody to α-enolase, which is a ubiquitous glycolytic enzyme, was frequently detected in the patients with LAH [3, 6], but it was frequently detected in patients with pituitary macroadenoma or other autoimmune diseases [3] as well. APA at the end of our study was negative in all patients, even in those who were APA positive at the start. According to a longitudinal study on APAs in patients with hypopituitarism [35], positive APA titers became negative in three of four initially positive patients during the observation period. In the longitudinal study of autoantibodies in patients with type I diabetes mellitus, the change of titers of the autoantibodies including decline at older ages was frequently seen [36]. The negative results during our longitudinal study might have been due to a similar phenomenon. However, the pathogenic role of APA detected in our patients is unknown at this point and the reason why APA disappeared during the study is also unknown. The diagnostic value of APA for LAH thus remain controversial.

In cases diagnosed with Sheehan’s syndrome seen after severe hemorrhage at the time of delivery, not only APA but also empty sella is frequently seen [35, 37]. In some cases of Sheehan’s syndrome, LAH, frequently seen during late pregnancy or in the postpartum period, may cause the disease and induce the hypopituitarism and empty sella [33, 38]. Although empty sella was seen in only one patient, Case 1, in our study, the association of empty sella with isolated ACTH deficiency [35] or isolated TSH deficiency [1] has been reported. Empty sella showing panhypopituitarism was also reported. Furthermore, some cases of LAH showed empty sella on MRI [9, 22].

It can be postulated that the functional course of LAH in some cases starts with isolated impairment of the pituitary hormone, ACTH or TSH, as seen in this study, progresses to combined deficiency of pituitary hormones, and eventually culminates in panhypopituitarism. Morphologically, the pituitary gland may be initially swollen and gradually shrink with the loss of pituitary cells with the extension of inflammation. In other patients, the disease can be transient and can recover spontaneously, while in the remaining ones, the disease can rapidly progress to panhypopituitarism and subsequently develop to empty sella. The etiology and natural course of LAH require further investigation.

References


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<th>Initial chief complaints</th>
<th>Newly appeared symptoms</th>
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<th>APA B</th>
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F, female; M, male; *, MRI findings were not changed during the study periods; Gd, gadolinium; APA, anti-pituitary antibody; A, at the start of the study; B, at the end of the study.
Table 2. Serum of plasma basal hormone levels in the longitudinal study

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<th>PRL (μg/L)</th>
<th>GH (μg/L)</th>
<th>ACTH (pmol/L)</th>
<th>Cortisol (nmol/L)</th>
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<td></td>
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<tr>
<td>A</td>
<td>3.64±0.21</td>
<td>14.6±0.98</td>
<td>0.10±0.03</td>
<td>5.49±1.04</td>
<td>0.62±0.08</td>
<td>3.13±0.38</td>
<td>217±32</td>
<td>5.82±2.48</td>
<td>15.1±8.0</td>
<td>73.4-312*</td>
</tr>
<tr>
<td>B</td>
<td>3.37±0.26</td>
<td>14.1±1.31</td>
<td>0.15±0.07</td>
<td>10.1±1.77#</td>
<td>1.02±0.13</td>
<td>2.7±0.27</td>
<td>144±53</td>
<td>5.9±1.6</td>
<td>2.8±5.2#</td>
<td>26.3-96.7**</td>
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</table>

A, at the start of the study; B, at the end of the study; *, reference ranges of women with follicular phase; **, reference ranges of men younger than 50 years of age, The serum TSH values less than 0.04 mIU/L were calculated as 0 in the statistical analysis. #, significantly different between A and B. ##, plasma estradiol level (E2) in female patients and plasma free testosterone (fTesto) level in male patient (Case 5)
Fig. 1. Peak of pituitary hormone levels during the stimulating test with respective hypothalamic stimulating hormones; X-axis, study periods; A, at the start of the study; B, at the end of the study; n.d., not significantly different; shadow area, reference ranges of peaks; a) TSH; b) prolactin; c) GH; d) ACTH; e) cortisol; f) LH; g) FSH.
Fig. 2. MRI image with gadolinium enhancement of pituitary gland at the end of the study period; a) Case 1 showed empty sella; b) and c) Cases 2 and 4 showed slight swelling of pituitary gland enhanced with gadolinium.

Fig. 3. Histological findings of pituitary gland in Case 2. a) Pituitary cells were swollen and had pyknotic nuclei and unclear cell membrane to varying degrees. b) Clusters of lymphocytes were seen in the peripheral region.