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Thyrotrophic status in patients with pituitary stalk interruption syndrome

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Abstract

Pituitary stalk interruption syndrome (PSIS) is associated with simultaneous or subsequent pituitary hormone deficiencies (PHDs). Although the clinical features of multiple PHDs are well known, the status of the thyrotrophic axis in PSIS has not been thoroughly investigated.

The clinical data of 89 PSIS patients and 34 Sheehan syndrome (SS) patients were retrospectively analyzed.

The prevalence of central hypothyroidism in the PSIS patients and the SS patients was 79.8% and 70.6%, respectively. The thyroid-stimulating hormone (TSH) levels in the PSIS patients were significantly higher in comparison with the SS patients (5.13 ± 3.40 vs 1.67 ± 1.20 mU/L, $P < .05$). TSH elevation (8.79 ± 3.17 mU/L) was noticed in 29 of 71 (40.85%) hypothyroid PSIS patients but not in the 24 hypothyroid SS patients. The TSH levels in the hypothyroid PSIS patients were significantly higher in comparison with the euthyroid PSIS patients (5.42 ± 3.67 vs 3.66 ± 1.50 mU/L). Thyroid hormone replacement significantly reduced the TSH levels in the PSIS patients with elevated TSH levels from 7.24 ± 0.98 to 1.67 ± 1.51 mU/L ($P < .05$). The logistic regression analysis suggested that TSH level was not significantly associated with pituitary stalk status and height of the anterior pituitary gland.

PSIS is a newly recognized cause of central hypothyroidism. The proportion and amplitude of TSH elevations are higher in PSIS than in other causes of central hypothyroidism.

Abbreviations: ACTH = adrenocorticotropic hormone, CH = central hypothyroidism, GH = growth hormone, HPA = hypothalamic = pituitary = adrenal, IGF-1 = insulin-like growth factor-1, ITT = insulin-induced hypoglycemia tolerance test, MRI = magnetic resonance imaging, PHDs = pituitary hormone deficiencies, PSIS = pituitary stalk interruption syndrome, SS = Sheehan syndrome, TRH = thyrotropin-releasing hormone, TSH = thyroid-stimulating hormone.

Keywords: central hypothyroidism, pituitary stalk interruption syndrome, Sheehan syndrome, thyroid-stimulating hormone

1. Introduction

Pituitary stalk interruption syndrome (PSIS) is a newly recognized disorder characterized by an absent or thin pituitary stalk, hypoplasia of the anterior pituitary gland, and ectopic location of the posterior pituitary on magnetic resonance imaging (MRI).[1] Patients with PSIS usually have either isolated growth hormone deficiency or multiple anterior pituitary hormone deficiencies (PHDs).[2]

Central hypothyroidism is a rare type of hypothyroidism due to impaired synthesis and secretion of thyroid-stimulating hormone (TSH). This disease is usually secondary to other conditions, although rarely it can be caused by mutation of various genes, such as *TSHβ*, TRH receptor, *Pit-1*, and *Prop-1*.[3–5] Hypothalamic-pituitary tumors and Sheehan syndrome (SS) are the most well-known causes of central hypothyroidism. PSIS is a newly recognized etiology of central hypothyroidism. Previous reports have summarized the endocrine hormone characteristics of PSIS. However, the status of the thyrotrophic axis in PSIS has not been thoroughly investigated.

Our study aimed to compare the thyroid function between PSIS patients and SS patients, examine the TSH status in PSIS, and identify the factors influencing the TSH levels in PSIS patients.

2. Materials and methods

2.1. Subjects

The clinical data of 89 PSIS patients and 34 SS patients followed at our institution from January 2000 to December 2013 were retrospectively analyzed. The diagnosis of PSIS was based on MRI findings (an absent or thin pituitary stalk, hypoplasia of the anterior pituitary gland, and ectopic location of the posterior pituitary), anterior pituitary functions, and clinical features. The

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Table 1

Clinical characteristics of the patients.

	PSIS			SS		
	All PSIS n = 89 (100%)	**Hypothyroid n = 71 (79.8%)**	**Euthyroid n = 18 (20.2%)**	**All SS n = 34 (100%)**	**Hypothyroid n = 24 (70.6%)**	**Euthyroid n = 10 (29.4%)**
Age, y	20.5 ± 6.1	20.6 ± 6.2	19.2 ± 6.3	46.6 ± 14.3	48.1 ± 12.4	42.8 ± 13.8
Sex (M/F)	79/10 (7.90:1)	63/8 (7.88:1)	16/2 (8.00:1)	0/34	0/24	0/10
Height, cm	147.6 ± 16.3	150.7 ± 15.5	137.0 ± 15.0	158.3 ± 12.3	162.7 ± 11.7	156.4 ± 12.7
Weight, kg	45.5 ± 16.2	47.8 ± 16.4	37.4 ± 13.3	59.7 ± 11.1	61.9 ± 10.2	58.3 ± 12.4
FT4, pmol/L	8.77 ± 2.40	7.90 ± 1.45	12.38 ± 2.07	7.82 ± 4.44	5.63 ± 2.70	13.08 ± 3.19
TSH, mU/L	5.13 ± 3.40	5.42 ± 3.67	3.66 ± 1.50*	1.67 ± 1.20†	1.82 ± 1.23†	1.34 ± 1.11*
GH deficiency (n, %)	89 (100%)	71 (100%)	18 (100%)	34 (100%)	24 (100%)	10 (100%)
ACTH deficiency (n, %)	67 (75.3%)	59 (83.1%)	8 (44.4%)	27 (79.4%)	21 (87.5%)	6 (60.0%)
LH deficiency (n, %)	77 (86.5%)	64 (90.1%)	13 (72.2%)	23 (67.6%)*	17 (70.9%)	6 (60.0%)
Anterior pituitary height, cm	0.25 ± 0.09	0.26 ± 0.09	0.22 ± 0.09	NA	NA	NA

ACTH = adrenocorticotropic hormone, FT4 = free T4, GH = growth hormone, LH = luteinizing hormone, PSIS = pituitary stalk interruption syndrome, SS = Sheehan syndrome, TSH = thyroid-stimulating hormone.
* $P < .05$.
† $P < .01$.

diagnosis of SS was based on history of postpartum hemorrhage, anterior pituitary functions, and clinical features.

2.2. Endocrine evaluation

The pituitary-thyroid function was evaluated using levels of the TSH (reference range, 0.5–5.5 mU/L), T4, T3, free T4 (FT4) (reference range, 10.4–24.3 pmol/L), and free T3 (FT3). Central hypothyroidism was diagnosed by a basal FT4 level equal to or lower than 10.4 pmol/L. Basal levels of the growth hormone and the insulin-like growth factor-1 were measured. Secretary status of the growth hormone was evaluated using the pyridostigmine stimulating test, arginine stimulating test, and insulin-induced hypoglycemia tolerance test (ITT). The gonadotrophic axis was evaluated using levels of the luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol, as well as the gonadotropin-releasing hormone stimulating test. The hypothalamicpituitary-adrenal (HPA) axis was evaluated using the cortisol and adrenocorticotropic hormone (ACTH) levels at 8 AM and the 24-hour urinary-free cortisol. ACTH response was determined with the ITT. All the hormone tests were performed by the same reference laboratory at our hospital.

2.3. Pituitary MRI evaluation

Enhanced sellar MRI images were taken in both the coronal and sagittal planes. The pituitary stalk, location of the posterior pituitary, and a normal or hypoplastic anterior pituitary gland (height less than -2SD for chronological age) were recorded. Height (mm) of the anterior pituitary gland was measured with a scale in the MRI images.

2.4. Statistical analysis

Data were expressed as means ± standard deviations or percentages. Univariate comparisons between groups were made using the Student *t* test for normally distributed variables. Correlations between the TSH levels and height of the anterior pituitary gland and pituitary stalk status were analyzed using the logistic regression. $P < .05$ was considered statistically significant. All statistical tests were performed using the SPSS11.0 statistical package.

3. Results

3.1. Characteristics of the patients

The ratio of male to female in the 89 PSIS patients was 7.9:1, while all the 34 SS patients were female. For the PSIS and the SS patients, the average age was 20.5 ± 6.1 and 46.6 ± 14.3 years, the mean height was 147.6 ± 16.3 and 158.3 ± 12.3 cm, and the mean body weight was 45.5 ± 16.2 and 59.7 ± 11.1 kg, respectively. The most common presentation was growth retardation in the PSIS patients and acratia in the SS patients. All PSIS and SS patients had growth hormone deficiency. ACTH deficiency appeared in 67 (75.3%) PSIS patients and 27 (79.4%) SS patients ($P > .05$), and gonadotrophin deficiency appeared in 77 (86.5%) PSIS patients and 23 (67.6%) SS patients ($P < .05$) (Table 1).

3.2. Thyroid function

The overall mean FT4 level in our patients was lower than the normal range. In comparison with the SS patients, the PSIS patients had similar FT4 levels (8.77 ± 2.40 vs 7.82 ± 4.44 pmol/L, $P > .05$) and significantly higher TSH levels (5.13 ± 3.40 vs 1.67 ± 1.20 mU/L, $P < .01$). Central hypothyroidism was found in 71 PSIS patients (79.8%) and 24 (70.6%) SS patients ($P > .05$). Both FT4 and TSH levels were significantly higher in the hypothyroid PSIS patients in comparison with the hypothyroid SS patients (7.90 ± 1.45 vs 5.63 ± 2.70 pmol/L, 5.42 ± 3.67 vs 1.82 ± 1.23 mU/L, respectively, both $P < .01$). The euthyroid PSIS patients had similar FT4 levels (12.38 ± 2.07 vs 13.08 ± 3.19 pmol/L, $P > .05$) and significantly higher TSH levels (3.66 ± 1.50 vs 1.34 ± 1.11 mU/L, $P < .05$) in comparison with the euthyroid SS patients. The hypothyroid PSIS patients had significantly higher TSH levels in comparison with the euthyroid PSIS patients (5.42 ± 3.67 vs 3.66 ± 1.50 mU/L, $P < .05$), which was near the upper limit of the reference range (Table 1).

A predominant proportion (21/24, 87.5%) of the hypothyroid SS patients had normal TSH levels, while only half (38/71, 53.5%) of the hypothyroid PSIS patients had normal TSH levels. The hypothyroid PSIS patients with normal TSH levels had significantly higher levels of FT4 in comparison with their counterpart SS patients (8.08 ± 1.42 vs 5.24 ± 2.63 pmol/L, $P < .05$). Interestingly, the FT4 levels did not differ significantly between the hypothyroid PSIS patients with decreased TSH levels

Table 2

Status of the thyrotrophic axis in the hypothyroid patients.

	Elevated TSH			Normal TSH			Decreased TSH		
Case	n (%)	TSH, mU/L	FT4, pmol/L	n (%)	TSH, mU/L	FT4, pmol/L	n (%)	TSH, mU/L	FT4, pmol/L
PSIS (n=71)	29 (40.9)	8.79±3.17	7.90±1.38	38 (53.5)	3.42±1.30	8.08±1.42*	4 (5.6)	0.02±0.01	6.15±1.44
SS (n=24)	0	–	–	21 (87.5)	2.04±1.49	5.24±2.63	3 (12.5)	0.23±0.08	8.45±0.94

FT4=free T4, TSH=thyroid-stimulating hormone.
* $P<.05$; † $P<.01$.

and their counterpart SS patients (6.15±1.44 vs 8.45±0.94 pmol/L, $P>.05$, Table 2).

Thyroid hormone replacement treatment significantly decreased the TSH levels in the hypothyroid PSIS patients from 7.24±0.98 to 1.67±1.51 mU/L ($P<.05$). Using TSH as the dependent variable, the height of the anterior pituitary gland, pituitary stalk status, and total number of PHDs as the independent variables, the logistic regression analysis suggested that the TSH level was not significantly associated with pituitary stalk status, height of the anterior pituitary gland, and the total number of PHDs ($P>.05$).

4. Discussion

PSIS was first reported by Fujisawa et al in 1987.[6] Patients with PSIS have varied anterior PHD and clinical presentations, while the posterior pituitary function is largely unaffected. Our study found that the prevalence of deficiencies in the growth hormone, gonadotropins, corticotropin, and thyrotropin was 100%, 86.52%, 75.28%, and 79.78% in the PSIS patients, respectively, which was consistent with previous findings.[7]

Central hypothyroidism is caused by insufficient stimulation of the thyroid gland by the TSH, which resulted from impaired secretion or activity at the hypothalamic or pituitary levels. The reported prevalence of central hypothyroidism is 1:80,000 to 1:120,000,[8] and hypothalamic-pituitary tumors and SS are the most frequent causes. Although severe hypothyroidism can arise, the serum TSH levels are within the normal limits in most patients with central hypothyroidism. Alexopoulou et al[9] reported that the serum TSH levels were normal in 84%, low in 8%, and elevated in 8% of the hypothyroid patients. Ferretti et al[10] found that the TSH levels were low in 19%, normal in 70%, and slightly increased in 11% of the hypothyroid patients. Our study found that there was no significant difference in the prevalence of hypothyroidism between the PSIS and the SS patients, but the TSH levels were significantly higher in the PSIS patients in comparison with the SS patients. In our study, the serum TSH levels were elevated in 40.9%, normal in 53.5%, and low in 5.6% of the hypothyroid PSIS patients. That is to say, the proportion and amplitude of TSH elevations were higher in PSIS than in other causes of central hypothyroidism once reported.

TSH secretion is mainly regulated by the negative feedback of thyroid hormone and the positive action of thyrotropin-releasing hormone (TRH). Hypothyroid patients with a predominant hypothalamic defect can have normal or elevated TSH levels because the circulating TSH is not completely metabolized in the absence of TRH action.[11] The pituitary TSH reserve is infrequently depleted and the anterior pituitary can secrete the immunoreactive TSH without full biological activity.[12]

The first proposed pathophysiological mechanism of PSIS was perinatal injury. Birth canal compression and prolonged labor process can cause neonatal hypoxia, which reduces the hypothalamic TRH secretion and damages the pituitary stalk. In this condition, the hormones secreted by the hypothalamus are not transported to the anterior pituitary. Our results showed that the PSIS patients had a high proportion and amplitude of TSH elevations, the TSH levels of the hypothyroid patients were higher than that of the euthyroid patients, and thyroid hormone replacement treatment decreased the TSH levels to the normal range. These results suggest that the TSH-producing cells in the anterior pituitary secreted more TSH with reduced biological activity. This hypothesis should be tested by detecting the bioactivity to immunoreactivity ratio of the basal TSH and the increment of serum levels of T3 or free T3 in response to TRH stimulating.[13] Another proposed pathophysiological mechanism of PSIS was mutations in the critical genes involved in the development of the anterior pituitary, such as *HESX1*, *LHX4*, *SOX3*, and *OTX2*.[14,15] Our results showed that only 4 out of 71 patients presented with low levels of TSH and TSH, which was not significantly associated with the pituitary stalk status and the height of the anterior pituitary gland. Our results do not support the theory of gene mutation in PSIS.

Our study has limitations. The PSIS patients and the SS patients in our study had very different age and sex ratio. The PSIS patients were much younger and the SS patients were all females. It has been reported that the TSH-FT4 relationship can be influenced by age, smoking, and thyroid peroxidase antibody status.[16] These differences in age and sex ratio may bias our results.

In conclusion, the proportion and amplitude of TSH elevations in PSIS patients are higher than in other hypothalamic pituitary defects causing central hypothyroidism. The specific mechanism underlying PSIS and central hypothyroidism needs further investigation.

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