



Thyroid function in girls with central precocious puberty

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Purpose: Obesity is a well-known risk factor for central precocious puberty (CPP). Recently, elevated thyroid stimulating hormone (TSH) was reported in obese youth. However, few data regarding the relationship between CPP and TSH are available. The aim of this study was to evaluate thyroid function in girls with CPP and the relationship between CPP and serum TSH concentration.

Methods: This was a retrospective cross-sectional study. A total of 1,247 girls aged between 6.0 and 8.9 years who had undergone a gonadotropin-releasing hormone (GnRH) stimulation test to determine the presence of puberty were studied. Subjects were classified into CPP (n=554) and non-CPP (n=693) groups according to the results of the GnRH stimulation test. Characteristics and laboratory data of the CPP and non-CPP groups were compared and correlations between those characteristics and laboratory data and TSH concentration were evaluated. Serum TSH concentration in the CPP group was higher than that of the non-CPP group (3.19 ± 1.55 mIU/L vs. 2.58 ± 1.34 mIU/L, $P < 0.001$).

Results: Serum free thyroxine (fT4) concentration in the CPP group was notably lower than that of the non-CPP group (1.38 ± 0.14 ng/dL vs. 1.44 ± 0.18 ng/dL, $P < 0.001$). Across all subjects, 149 girls (11.9%) had hyperthyrotropinemia. The prevalence of hyperthyrotropinemia was higher in the CPP group compared to the non-CPP group (15.7% vs. 8.9%, $P < 0.001$). TSH concentrations were positively correlated with age, height, weight, BMI, bone age, bone age advance, insulin-like growth factor 1 (IGF-1), IGF-1 standard deviation score, basal luteinizing hormone (LH), peak LH and basal follicle-stimulation hormone. TSH concentrations were negatively correlated with fT4. Multiple linear regression analysis showed that age ($\beta = 0.548$, $P < 0.001$) and peak LH ($\beta = 0.019$, $P = 0.008$) were independently associated with serum TSH concentration.

Conclusion: Hyperthyrotropinemia in girls with CPP tends to be associated with pubertal LH elevation. In conclusion, pubertal onset may be associated with thyroid function.

Keywords: Precocious puberty, Thyroid hormone, Obesity

Received: 18 May, 2018
Revised: 25 July, 2018
Accepted: 21 August, 2018

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Introduction

Puberty is a period of physical and behavioral changes.¹ In this period, reproductive systems are matured by hypothalamic-pituitary-gonadal axis activation. The onset of puberty is affected by many hormones and genes and even the environment.² In healthy condition, genetic features tend to determine pubertal changes. Leptin and ghrelin are hormones that are supposed to affect to the beginning of puberty.^{1,2} Leptin, a hormone produced by adipocyte, is mainly thought to influence the pubertal onset. It has been found to have direct stimulatory effects on the secretion of gonadotropin-releasing hormone (GnRH) and gonadotropin.³

"Precocious puberty" is defined as the development of pubertal changes before the age of 8

in girls and 9 in boys and increasing numbers of children are being diagnosed with precocious puberty as childhood obesity is also increasing.⁴⁾ There have been many investigations about the factors that promote these early changes such as races, maternal menarche, child's body weight, and body mass index (BMI) including environmental influences.^{5,6)} There are clear associations between childhood obesity and early pubertal changes.³⁾ Although the cause of this relationship is still not fully understood, as excessive leptin level precedes the pubertal LH elevation and the timing of menarche is related to serum leptin level, it is thought that leptin plays a key role in pubertal onset.^{3,7)}

Obesity is a metabolic disease that affects the endocrinological system and a range of researches about the relationship between obesity and hormones has been conducted. In particular, there is much research about the relationship between obesity and thyroid function since thyroid hormones modulate metabolic pathways which is relevant to basal metabolic rate.⁸⁾ Most papers have reached the conclusion that thyroid function is usually normal in obese patients,⁹⁾ although thyroid stimulation hormone (TSH) and BMI are positively correlated.¹⁰⁾ The causal relationship between TSH and BMI is still unclear, however TSH levels are usually elevated and free thyroxine (fT4) levels are in the normal range in obese people.^{9,11)}

Central precocious puberty (CPP) is strongly affected by obesity and so it is reasonable to consider the relationship between CPP and thyroid function. However, few data regarding the relationship between CPP and thyroid function are available. Therefore, the aim of this study was to evaluate thyroid function in girls with CPP and the relationship between CPP and serum TSH concentration.

Materials and methods

1. Study population

This was a retrospective cross-sectional study. Subjects were girls who had visited the Pediatric Endocrinology Clinic at Korea University Ansan Hospital between March 2013 and February 2017 for precocious puberty evaluation. Subjects showed signs of the pubertal development such as breast development, pubic hair or relatively tall height comparing to peers. A total of 1,247 girls aged between 6.0 and 8.9 years who had undergone a GnRH stimulation test to determine the onset of puberty were included in this study. All the subjects showed Tanner breast scores \geq II before the age of 8 years old. All subjects showed neither clinical hypothyroidism, hyperthyroidism nor CPP caused by organic reasons.

2. Clinical data collection

Patient data was collected from medical records through a retrospective review. Measurement of height and weight had been performed in all subjects. Height was measured to the nearest 0.1 cm using a rigid stadiometer. Weight was measured

to the nearest 0.1 kg using a calibrated balance scale. Height standard deviation score (SDS), weight SDS and BMI SDS were calculated by using the Cole's Lambda Mu Sigma method according to 2007 Korean National Growth Chart. Bone age had been measured by a single pediatric endocrinologist using the Greulich and Pyle method.

To diagnose CPP, a GnRH stimulation test had been performed. Basal serum samples were obtained prior to GnRH injection. The GnRH (0.1 mg) was administered intravenously for 1 minute, and poststimulation samples were taken at 30, 45, 60, and 90 minutes to measure the luteinizing hormone (LH) and follicle-stimulation hormone (FSH) levels. Serum LH and FSH levels were measured using electrochemiluminescence technology (Cobas 6000, Roche Diagnostics, Indianapolis, IN, USA).

Serum concentration data for insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), thyroid stimulating hormone (TSH) and fT4 had been also collected. IGF-1 SDS and IGFBP-3 SDS was calculated based on the study by Hyun et al.¹²⁾ Serum IGF-1, serum TSH and fT4 levels were measured using radioimmunoassay methods (Gamma Pro, Seyeong NDS Co., Seoul, Korea). Serum IGFBP-3 was measured using radioimmunoassay methods (Cobra II 5010, Packard BioScience Co., Midland, ON, Canada).

3. Definition

CPP was diagnosed when LH levels during the GnRH stimulation test peaked at above 5 IU/L and bone age was advanced more than 1 year compared to chronological age.¹⁾ Subjects were classified into CPP (n=554) and non-CPP (n=693) groups according to the results of GnRH stimulation test. Hyperthyrotropinemia was defined as elevated TSH (TSH \geq 5.0 mIU/L) in serum concentration and normal fT4 level (0.8 ng/dL < fT4 < 1.9 ng/dL) based on the study by Cho et al.¹³⁾

4. Statistical analyses

IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used for the statistical analyses. Data are expressed as mean \pm standard deviation. An independent *t*-test was used to compare the CPP and non-CPP groups and Pearson's correlation test was used to analyze the relationship among multiple characteristics and TSH concentration; *P*-values under <0.05 were considered statistically significant. To compare the prevalence of hyperthyrotropinemia between the CPP and non-CPP groups, a chi-square test was conducted. Moreover, a multiple linear regression analysis test was used to investigate the independent factors influencing TSH levels by controlling confounding factors in CPP group.

Results

Comparing characteristics between the CPP and non-CPP

groups, there were significant differences in serum TSH and serum fT4 levels. TSH concentration in the CPP group was significantly higher than that of the non-CPP group (3.19 ± 1.55 IU/L vs. 2.58 ± 1.34 IU/L, $P < 0.001$). Serum fT4 concentration in the CPP group was significantly lower than that of the non-CPP group (1.38 ± 0.14 ng/dL vs. 1.44 ± 0.18 ng/dL, $P < 0.001$). Most importantly, the proportion of hyperthyrotropinemia was notably higher in the CPP group than in the non-CPP group (15.7% vs. 8.9%, $P < 0.001$).

Bone age, bone age advances, IGF-1, IGF-1 SDS, LH and basal and peak FSH were also significantly higher in the CPP than in the non-CPP group. Weight, weight- SDS, BMI and BMI SDS were higher in the non-CPP than the CPP group.

However, age, height, height SDS, IGFBP-3 and IGFBP-3 SDS showed no differences between the 2 groups. (Table 1)

We analyzed the correlation of these characteristics with TSH concentration. TSH concentration had a positive correlation with age, height, weight, BMI, bone age, IGF-1, IGF-1 SDS, basal LH, peak LH and basal FSH. Additionally, TSH concentration showed a negative correlation with fT4. Contrastingly, height SDS, weight SDS, BMI SDS, IGFBP-3, IGFBP-3 SDS and peak FSH showed no correlation with TSH level (Table 2).

To investigate the independent predictor factor of serum TSH level, a multiple linear regression test was used. Age, height, weight, BMI, IGF-1, basal LH, peak LH, basal FSH, and

Table 1. Comparison of characteristic and laboratory data between CPP and non-CPP groups

Variable	CPP (n=554)	Non-CPP (n=693)	P-value
Age (yr)	8.11±0.49	8.12±0.57	0.828
Height (cm)	129.7±5.7	129.6±5.8	0.853
Height SDS	0.69±0.87	0.68±0.91	0.821
Weight (kg)	29.8±5.6	30.7±6.2	0.009
Weight SDS	0.64±0.87	0.76±0.93	0.018
BMI (kg/m ²)	17.6±2.4	18.1±2.7	<0.001
BMI SDS	0.43±0.96	0.62±1.02	0.001
Bone age (yr)	10.28±0.54	9.07±0.77	<0.001
Bone age advance (yr)	2.17±0.54	0.95±0.68	<0.001
IGF1 (ng/mL)	303.02±104.17	258.01±85.35	<0.001
IGF1 SDS	0.78±1.19	0.26±1.00	<0.001
IGFBP3 (ng/mL)	2,881.79±607.93	2,855.63±588.56	0.457
IGFBP3 SDS	-0.01±1.14	-0.06±1.13	0.430
Basal LH (IU/L)	0.29±0.59	0.10±0.06	<0.001
Peak LH (IU/L)	11.46±9.07	3.20±1.43	<0.001
Basal FSH (IU/L)	2.42±1.46	1.58±0.85	<0.001
Peak FSH (IU/L)	13.94±4.67	12.09±3.70	<0.001
TSH (mIU/L)	3.19±1.55	2.58±1.34	<0.001
Free T4 (ng/dL)	1.38±0.14	1.44±0.18	<0.001
Hyperthyrotropinemia	87 (15.7)	62 (8.9)	<0.001

Values are presented as mean±standard deviation or number (%). CPP, central precocious puberty; SDS, standard deviation score; BMI, body mass index; IGF-1, insulin-like growth factor 1; IGFBP 3, insulin-like growth factor-binding protein 3; LH, luteinizing hormone; FSH, follicle stimulating hormone; Free T4, free thyroxine; TSH, thyroid stimulating hormone.

peak FSH were analyzed. Age ($\beta=0.548$, $P < 0.001$) and peak LH ($\beta=0.019$; $P=0.008$) were proven as independent factors to influence serum TSH concentration (Table 3).

Discussion

To the best of our knowledge, this study is the first research to investigate the relationship between TSH levels and CPP.

In this study, the prevalence of hyperthyrotropinemia was higher in the CPP group compared to the non-CPP group. Most importantly, age and peak LH were proven as independent predictor factors of serum TSH concentration. This means that pubertal onset may be associated with thyroid function.

Table 2. Correlation of characteristic and laboratory data with TSH concentration

Variable	r	P-value
Age	0.216	<0.001
Height	0.130	<0.001
Height SDS	0.009	0.758
Weight	0.122	<0.001
Weight SDS	0.041	0.153
BMI	0.082	0.004
BMI SDS	0.049	0.085
Bone age	0.245	<0.001
Bone age advance	0.121	<0.001
IGF1	0.104	<0.001
IGF1 SDS	0.083	0.003
IGFBP3	0.051	0.083
IGFBP3 SDS	0.024	0.418
Basal LH	0.086	0.002
Peak LH	0.138	<0.001
Basal FSH	0.115	<0.001
Peak FSH	0.030	0.285
Free T4	-0.133	<0.001

TSH, thyroid stimulating hormone; SDS, standard deviation score; BMI, body mass index; IGF-1, insulin-like growth factor 1; IGFBP 3, insulin-like growth factor-binding protein 3; LH, luteinizing hormone; FSH, follicle stimulating hormone; Free T4, free thyroxine; r, coefficient of correlation.

Table 3. Results of multiple linear regression analysis of factors associated with TSH concentration

Variable	Unstandardized coefficient β	S.E.	P-value
Age	0.548	0.078	<0.001
BMI	0.042	0.016	0.125
IGF1	0.001	0.000	0.129
Basal LH	-0.090	0.129	0.484
Peak LH	0.019	0.007	0.008
Basal FSH	0.065	0.041	0.110
Peak FSH	0.014	0.011	0.208

TSH, thyroid stimulating hormone; BMI, body mass index; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; FSH, follicle stimulating hormone; S.E., standard error (the standard deviation of its sampling distribution).

Puberty occurs when there is reactivation of the hypothalamic-pituitary-gonadal axis.²⁾ Several factors are considered to influence the onset of puberty such as race, maternal menarche, low birth weight, excessive weight gain or obesity and, even environmental factors.¹⁴⁾ There have been many investigations into obesity's effect on the onset of puberty but the exact mechanism is still unknown.¹⁵⁾ Some studies suggest that leptin appears to be a main promoting factor in pubertal development. As leptin increases proportionally according to the amount of adipocyte, obese children have high levels of leptin. Leptin seems to accelerate GnRH pulse frequency.^{3,4)}

Obesity also influences thyroid hormone levels.¹⁶⁾ Although thyroid function is usually normal in obese subjects, it is known that TSH and BMI are positively correlated.^{11,17)} Several studies have revealed that TSH, T3 is higher in obese children than in control groups and, contrastingly, that T4 has no significant difference between the 2 groups in the absence of thyroid antibodies.¹⁸⁻²⁰⁾ The causes of thyroid hormonal changes in obese patient are various; autoimmunity, mutation of the TSH receptor gene, leptin, thyroid hormone resistance, mitochondrial dysfunction, and an adaptation process to increase energy expenditure are considered to influence thyroid function.⁹⁾ So far, there are many conflicting views as whether elevated TSH induces obesity or obesity itself induces TSH elevation.^{9,11,16)} Winter et al.²¹⁾ proved that derangement in the hypothalamic-pituitary axis is a cause of increased TSH levels in obesity. Conversely, Reinehr et al.²²⁾ suggest that increased TSH levels in obesity are an adaptation mechanism to increased resting energy expenditure.

Considering the relationship between CPP, obesity, and TSH levels, it may be thought that because obese patients tend to have CPP, a CPP group may have high levels of TSH. It is easily thought that a tendency to obesity in a CPP group is relevant to TSH elevation. However, in this study, the CPP group had lower average of BMI SDS than the non-CPP group. This result is different to most of the related researches.⁴⁾ This difference may be related to the subject's characteristics. As the subjects in this study were girls who were suspected of precocious puberty as showing clinical symptoms of puberty such as breast budding.

In this study, age, height, weight, bone age, IGF-1, basal LH, peak LH, basal FSH and also BMI had positive relationships with TSH. However, only age and peak LH showed as independent factors in the multiple regression test, hence the older the patient and the higher the peak LH level, the higher the TSH level that was found. Therefore, it is not obesity but puberty that is related with an elevation in TSH.

This may be explained by the molecular similarity of these hormones. FSH, LH, human chorionic gonadotropin and TSH are glycoprotein hormones which are similarly composed with a common α subunit and specific β subunits.²³⁾ Thyrotropin releasing hormone (TRH) and GnRH have several common proteins that involve the regulation of TRH and GnRH receptors. This interaction may induce high levels of both LH and TSH.^{24,25)}

There are limitations to this study. Firstly, no sex and age-

matched healthy control group was included; only data from girls who were suspected of CPP were compared. In addition, the thyroid function test was only conducted once when the subjects first underwent the GnRH stimulation test. No follow-up data was taken. There is also a lack of data about thyroid hormone antibodies.

In conclusion, we suggest that hyperthyrotropinemia is relevant to pubertal onset. Elevated TSH in girls with CPP should be associated with pubertal LH elevation. Still, no association has been found between elevated TSH in CPP and obesity. Further longitudinal studies with normal control groups are needed to investigate the causal relationship between CPP and hyperthyrotropinemia.

Ethical statement

This was a retrospective study, and it was approved by the Institutional Review Board (IRB) at Korea University Ansan Hospital in Ansan, South Korea (approval number: 2018AS0080). Informed consent was waived by the IRB.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

An earlier version of this study has been presented at Endo-annual-meetings according to the following link: <https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=6094>.

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