ORIGINAL ARTICLE
YUJM 2013;30(2):90-4

pISSN 1225-7737/eISSN 2234-8042
http://dx.doi.org/10.12701/yujm.2013.30.2.90

The Utility of Basal Serum Luteinizing Hormone Levels for Screening Central Precocious Puberty in Girls

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Background: This study was conducted to examine if basal luteinizing hormone (LH) levels could be useful for screening central precocious puberty (CPP) in girls.

Methods: A total of 90 girls under the age of 8 years were included in this study. They underwent the gonadotropin-releasing hormone (GnRH) stimulation test at Good Gang-An Hospital from March 2008 to December 2012 for evaluation of premature sexual development. Patients were classified into two groups: the pubertal response group of patients who had 5 IU/L peak LH levels in the GnRH stimulation test, and the prepubertal response group of patients who had LH levels <5 IU/L. Chronological and bone ages, height, weight, body mass index, gonadotropin response to GnRH stimulation, and basal levels of LH, follicle-stimulating hormone, and estradiol were studied in both groups. The relationship between basal LH and peak-stimulated LH was evaluated using Spearman's correlation. To determine the optimal cut-off values of basal LH levels for differentiating between two groups, the receiver operating characteristic (ROC) curves were analyzed.

Results: When the correlation between basal LH levels and peak LH after GnRH stimulation was analyzed in all subjects (N=90), basal LH levels had a statistically significant positive correlation with peak stimulated LH levels (rs=0.493, p<0.001). The cut-off level of optimal basal LH was 0.1 IU/L, according to the ROC curves. Its sensitivity was 73.3%, and its specificity was 77.8%.

Conclusion: The study results showed that serum basal LH levels are useful for screening CPP in girls.

Key Words: Central precocious puberty, Luteinizing hormone, Gonadotropin-releasing hormone stimulation test

INTRODUCTION

Precocious puberty occurs when secondary sexual characteristics begin to appear before 8 years of age in girls or 9 years in boys.[1] Central precocious puberty (CPP) is a condition in which isosexual precocious puberty occurs due to the early activation of the hypothalamic-pituitary-gonadal (HPG) axis.[2] CPP sporadically occurs with a frequency of 1 in 5,000-10,000 and is known to occur 10 times more often in girls than boys.[3]

Received: September 2, 2013, Revised: October 2, 2013, Accepted: October 7, 2013

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CPP is diagnosed by confirming the activation of the HPG axis prior to a typical age for normal puberty.[4] However, measuring the gonadotropin-releasing hormone (GnRH) levels directly is technically difficult. As a result, the diagnosis emphasizes the confirmation of the pubertal levels of the luteinizing hormone (LH), follicle-stimulating hormone (FSH) and gonadal hormones.[5] The standard method measures the serum levels of the gonadotropins (LH and FSH) after injecting GnRH.[6]

However, this test is inconvenient for patients because it is time-consuming and requires multiple blood samples.[7] In addition, breast caused by accumulation of fat was increasingly difficult to be distinguished from breast areolar development, as the prevalence of obesity in children increased lately.[8] Therefore, it is necessary to develop a screening test which can detect girls with premature breast development who will

Table 1. Clinical and laboratory characteristics of girls who were evaluated for early pubertal signs

Characteristics	Prepubertal response group (n=45) Mean±SD	Pubertal response group (n=45) Mean±SD	*p*-value
Chronological age (yr)	7.33±0.41	7.39±0.46	0.25
Bone age (yr)	8.57±1.06	8.97±0.90	0.05
BA-CA (yr)	1.24±0.99	1.58±0.73	0.05
Height (cm)	129.62±5.29	128.19±5.08	0.08
Body weight (kg)	31.46±6.34	28.12±4.95	0.01
BMI (kg/m^2)	18.68±2.97	17.01±2.15	0.006

Comparisons between groups were made via the Mann-Whitney U test. BA-CA: the difference between the bone age and the chronological age, BMI: body mass index.

Table 2. Laboratory characteristics of girls who were evaluated for early pubertal signs

Characteristics	Prepubertal response group (n=45) Mean±SD	Pubertal response group (n=45) Mean±SD	*p*-value
Basal LH (IU/L)	0.12±0.20	0.39±0.57	<0.001
Basal FSH (IU/L)	1.65±0.74	2.69±1.25	<0.001
Basal LH/FSH ratio	0.12±0.25	0.18±0.44	0.009
Basal E2 (pg/mL)	15.34±12.32	15.83±12.02	0.87
Peak LH (IU/L)	2.78±1.12	10.58±7.06	<0.001
Peak FSH (IU/L)	14.24±5.51	17.52±7.32	0.028
Peak LH/FSH ratio	0.21±0.11	0.72±0.47	<0.001

Comparisons between groups were made via the Mann-Whitney U test. LH: luteinizing hormone, FSH: follicle stimulating hormone, E2: estradiol.

benefit from the GnRH stimulation test. Thus, this study was conducted to examine if the basal LH levels could be useful for screening CPP in girls.

MATERIALS AND METHODS

1. Subjects

We retrospectively analyzed the records of all girls with premature sexual development who underwent a GnRH stimulation test at Good Gang-An Hospital from March 2008 to December 2012. A total of 90 girls were included in this study. The inclusion criterion was objective breast budding before 8 years of age, defined as Tanner stage II. Girls who had chronic illnesses such as thyroid disease or who had taken any hormone drugs were excluded.

Patients with a peak LH greater than 5 IU/L in the GnRH stimulation test were diagnosed with CPP. They were classified as the 'pubertal response group'. Those with a peak LH less than 5 IU/L were classified as the 'prepubertal response group'. The chronological and bone ages, height, weight, body mass index (BMI), gonadotropin response to GnRH stimulation, and basal levels of LH, FSH, and estradiol (E2) were studied in both groups. The pubertal stage of the patients was classified based on Tanner stages II-V, and the bone age was evaluated using the Greulich and Pyle method. The respective standard deviation scores (SDS) were determined using the 2007 Korean National Growth Charts.

2. Hormone Measurements

The serum LH and FSH levels were measured by chemiluminescent microparticle immunoassay (Architect; Abbott Laboratories Diagnostics, Chicago, Illinois, USA) with an analytical sensitivity of ≤0.07 IU/L and 0.05 IU/L, respectively (2-3% of the intra-assay coefficient of variation values and 3-4% of the inter-assay coefficient of variation values). The E2 levels were measured by chemiluminescent microparticle immunoassay (Architect) with an analytical sensitivity of ≤ 10 pg/mL (4-5% of the intra-assay coefficient of variation values and 5-6% of the inter-assay coefficient of variation values).

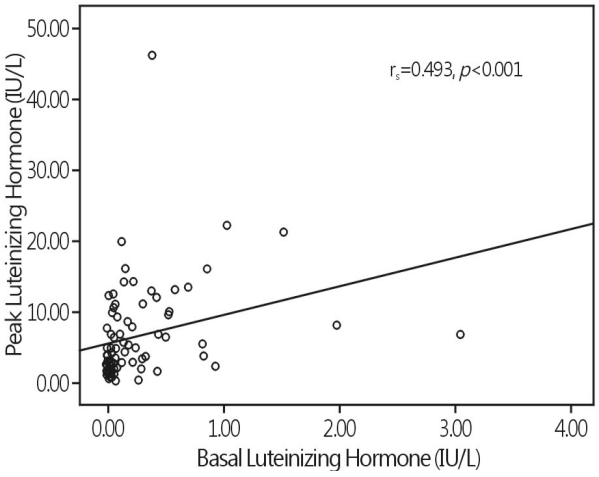

Fig. 1. Significant correlation between peak stimulated LH after GnRH injection and basal LH in girls evaluated for early pubertal signs.

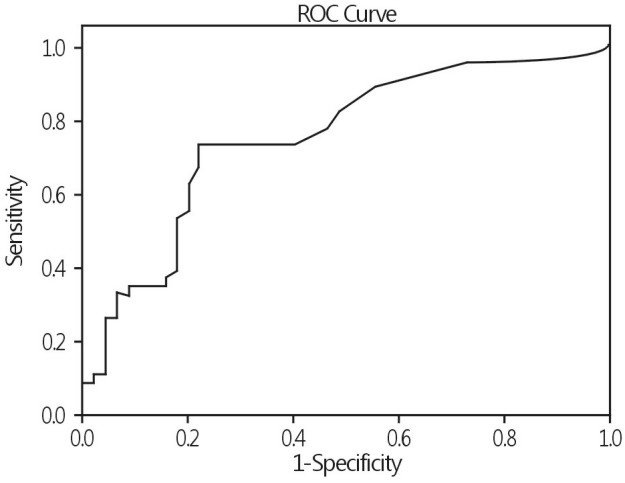

Fig. 2. Receiver operator characteristic (ROC) curve of various tresholds of basal LH levels (AUC: 0.754, 95% CI: 0.653-0.855) for predicting CPP.

3. GnRH Stimulation Test

The HPG axis activation was examined using the GnRH simulation test that was conducted during the day. The basal serum samples were drawn before the GnRH (100 μg; Relefact; Sanofi-Aventis, Frankfurt, Germany) injection. To measure the LH and FSH levels after the injection, the samples were taken after 30, 60, 90, and 120 minutes.

4. Statistical Analysis

For the statistical analysis, SPSS version 17.0 (SPSS Inc. Chicago IL, USA) was used. To compare the biochemical parameters between the pubertal response and prepubertal response groups, the Mann-Whitney U test was conducted. The relationship between the basal LH and the peak LH levels was evaluated using Spearman's correlation. The sensitivity and specificity of each basal LH level were determined using receiver operating characteristic (ROC) curves. To differentiate the pubertal response group from the prepubertal response group, the optimal LH cut-off levels from the ROC curves were determined using Youden's J index (=sensitivity +specificity -1). For all the data, a <0.05 p value was interpreted as statistically significant.

RESULTS

1. Subject Characteristics

A total of 90 subjects were registered in this study. Of these, Forty-five of them were consigned to the pubertal response group, and the remaining 45, to the prepubertal response group. The mean age in the pubertal response group was 7.39±0.46 years, and in the prepubertal response group, 7.33±0.41 years. There was no significant difference between the two groups with respect to age (p=0.251, Table 1).

There was no statistically significant difference in the heights, or bone ages between the pubertal response group and the prepubertal response group. The weight and BMI in the pubertal response group were significantly higher than in the prepubertal response group (p<0.05, Table 1).

2. Comparison of the biochemical Characteristics

The basal LH and FSH levels of the pubertal response group were significantly higher than those of the prepubertal response group (p<0.05, Table 2).

The peak-stimulated LH and FSH levels, and the basal LH/FSH and peak-stimulated LH/FSH ratios, in the pubertal response group were higher than in the prepubertal response group (p<0.05, Table 2).

However, there was no significant difference in the estradiol levels of the two groups (Table 2).

3. Correlation

The basal LH levels showed a statistically significant posi

tive correlation with the peak-stimulated LH levels after the GnRH stimulation (r_s=0.493, p<0.001, Fig. 1).

To differentiate the two groups, the optimal cut-off basal LH levels were determined using the Youden index. The analysis of the ROC curves (AUC=0.754) showed that the cut-off value was 0.1 IU/L, the sensitivity was 73.3% and the specificity was 77.8% (Fig. 2).

DISCUSSION

The study results suggest that the serum basal LH levels are useful as a screening test for CPP. The GnRH stimulation test is the gold standard to reveal premature activation of the HPG axis in patients with precocious puberty[9] When the peak-stimulated LH levels are 5 IU/L, it is considered a pubertal response.[10] However, blood must be taken 5-8 times after the GnRH injection to determine the highest concentration of LH and FSH. As a result, this test is costly, time-consuming and inconvenient for patients. Therefore, testing outpatients can be difficult and the diagnosis can be delayed.[7] Thus, studies searching have been conducted to find a test method that will complement the GnRH stimulation test.[9-14] Some studies maintain that the repeated sampling of blood is not necessary because the pubertal state and the prepubertal state can be distinguished only with the LH concentration, obtained either at 30, 45 or 60 minutes after the GnRH stimulation.[11,12] In addition, studies on the validity of using basal LH levels to diagnose CPP have been undertaken.[13,14] In our study, we found that the basal LH levels in the pubertal response group was significantly higher than in the prepubertal response group (p<0.05). The analysis of the correlation between the basal and peak-stimulated LH levels after the GnRH stimulation led to the detection of their statistically significant positive correlation (Fig. 1).

The estradiol levels in the prediction of the organic origin of CPP cases in girls has been widely studied.[15,16] To differentiate idiopathic CPP from organic CPP, a cut-off value of 45 pmol/L has been suggested.[17] However, 54% of girls with idiopathic CPP show normal estradiol levels.[15,16] Accordingly, estradiol levels do not appear to be useful in diagnosing CPP. This was also supported by our results, as there was no significant difference between the estradiol levels in the prepubertal response and pubertal response groups.

In this study, both the basal FSH level and the basal LH/FSH ratio in the pubertal response group were significantly higher than in the prepubertal response group (p<0.05). However, as it is generally accepted that there are similar FSH levels in prepubertal and pubertal girls, such levels are not helpful in diagnosing CPP.[17,18] Moreover, the limited relevance of the LH/FSH ratio seems to be due to the considerable variation in the FSH levels in both prepubertal and pubertal girls.[4] It has been reported that the mean peak-stimulated FSH does not distinguish between prepubertal and pubertal status.[19,20] Nevertheless, in our study, the mean peak-stimulated FSH levels in the pubertal response group were significantly higher than in the prepubertal response group (p<0.05).

Other studies reported that the peak-stimulated LH level of the pubertal response group was significantly higher than in the prepubertal response group.[21] Our study confirmed this result. Furthermore, in our study, the peak-stimulated LH/FSH ratio in the pubertal response group was significantly higher than in the prepubertal response group. Previous studies have indicated that analysis of the peak-stimulated LH/FSH ratio could lead to greater accuracy in diagnosing CPP.[22,23]

However, it has been reported that the peak-stimulated LH/FSH ratio is low from Tanner breast stage II to the early period of stage III, and therefore, it may not be a good diagnostic standard.[6,11] In our study, 25% of the girls with CPP had a peak-stimulated LH/FSH ratio >1, and there was no such case in the prepubertal response group.

In conclusion, the results of this study demonstrate that the serum basal LH levels can be used to initially screen CPP. We used ROC curves to confirm the predictive value of the basal LH levels for positive GnRH stimulation test results and the optimal statistical cut-off point was 0.1 IU/L. Therefore, our results showed that the GnRH stimulation test should be recommended for cases with serum basal LH levels greater than 0.1 IU/L.

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