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PRECOCIOUS PUBERTY

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Inhibin B as a screening tool for early detection and treatment monitoring of central precocious puberty

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ABSTRACT

Anti-Müllerian hormone (AMH) and inhibin B are considered possible biomarkers of central precocious puberty (CPP). The aim of this study was to evaluate serum levels of AMH and inhibin B, to investigate their regulatory patterns, and to study their clinical significance in girls with CPP. In total, 48 girls with CPP and 35 age-matched prepubertal control girls were enrolled in the study. AMH and inhibin B levels were determined in the CPP and control groups. In the patient group, AMH and inhibin B levels were evaluated during 1 year of gonadotropin releasing hormone analog (GnRHa) treatment. The mean inhibin B level in the CPP group was significantly higher than that in the control. AMH levels were not different between the two groups. After GnRHa treatment. AMH and inhibin B levels decreased significantly. Based on the ROC analysis, the cutoff value for inhibin B to determine CPP was 19.59 pg/mL, with 83.3% sensitivity and 82.9% specificity, and the area under the curve was 0. 852. Inhibin B was useful for determining CPP and the therapeutic effects of GnRHa treatment in girls with CPP. AMH interacted, in part, with the hypothalamo-pituitary gonadal axis, but its clinical implications in CPP should be further investigated.

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Introduction

Puberty is initiated by the secretion of high amplitude pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus. The pulsatile GnRH secretion pattern increases release of the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and these gonadotropins stimulate the production of gonadal steroids by testicular Leydig cells in boys or in the ovarian granulosa cells in girls. The increase in FSH induces gonadal maturation, such as follicular maturation in girls, and spermatogenesis in boys. Central precocious puberty (CPP) is caused by early activation of the hypothalamo–pituitary–gonadal (HPG) axis. It is defined as the appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Early maturation of the ovaries may be a possible outcome in girls with CPP, but evaluating the ovarian maturation process is insufficient. Although it is difficult to know the exact mechanism of ovarian maturation, anti-Müllerian hormone (AMH) and inhibin B are indirect indicators of ovarian function. AMH and inhibin B are gonadal hormones secreted by the ovaries in women that may change depending on the physiological condition and may help to identify girls at risk of developing CPP or to predict ovarian maturation.

Anti-Müllerian hormone is a glycoprotein hormone produced by granulosa cells in small antral follicles that plays a key role in folliculogenesis [1–3]. AMH is also critical for sex differentiation during fetal development, as its expression inhibits development of the female reproductive tract in the male embryo [4]. AMH regulates folliculogenesis by inhibiting recruitment of follicles from the resting pool to select the dominant follicle [5]. In healthy girls, serum AMH levels remain largely unchanged during childhood and adolescence, except for a temporary decline after pubertal onset [6].

Inhibin B is a heterodimeric glycoprotein hormone produced by developing ovarian follicles that downregulates FSH synthesis and inhibits FSH secretion [7,8]. Inhibin B levels rise rapidly during the early follicular phase of the menstrual cycle and fall to a low or undetectable concentration during the luteal phase in adult women [9]. Serum levels of inhibin B are low or undetectable in prepubertal girls and increase sharply through Tanner stage II to peak in stage Tanner III, above the adult level. Thereafter, inhibin B levels decline through Tanner stages IV and V [10]. These results indicate that AMH and inhibin B are somewhat in line with the HPG axis.

In patients with CPP, increased secretion of gonadotropins and sex steroids is downregulated by GnRHa treatment, which return to prepubertal levels and secondary sexual characteristics regress or slow down. Similarly, if AMH and inhibin B are dependent on pubertal status, it can be predicted that these hormones will change to prepubertal levels in response to GnRHa treatment in patients with CPP.

The purpose of this study was to measure the levels of AMH and inhibin B in girls with CPP, and to determine whether they could be used as a biomarker to determine CPP. We also investigated changes in serum AMH and inhibin B levels during 1 year of GnRH agonist treatment and their clinical significance during precocious puberty.

Subjects and methods

Subjects

A total of 48 girls with idiopathic CPP were included in this study. Clinical data were collected retrospectively *via* chart review of patients treated in the pediatric endocrine unit at

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Kangdong Sacred Heart Hospital between March 1, 2013 and August 31, 2015.

CPP was diagnosed according to the following criteria: (1) objective breast enlargement appearing before the age of 8 years, (2) bone age that exceeded chronological age by at least 1 year, and (3) increased pubertal LH response (cutoff value ≥5.0 mIU/mL) on a GnRH stimulation test. All patients were treated with GnRHa. The standard treatment regimen was the administration of subcutaneous leuprolide acetate, at a dose of 100 μg/kg every 4 weeks.

To evaluate changes in serum levels of AMH and inhibin B in girls with CPP, we included 35 age-matched healthy girls who were referred for health screening. Inclusion criteria for the normal control group were: no evidence of breast budding and the difference between bone age and chronological age < 1 year. No prior medical history of conditions associated with altered pubertal timing, gonadal diseases, or intake of medications was reported.

Measurements

The GnRH stimulation test was performed to assess pubertal status in all patients. GnRH (100 μg; Relefact, LHRH, Sanofi-Aventis, Germany) was given i.v., and blood sampling was performed 0, 30, 45, 60, and 90 min later for the LH and FSH measurements. Blood samples were withdrawn at baseline and after 6 and 12 months of treatment. Blood samples were centrifuged, and the plasma was immediately stored at −80 °C until analyses.

Data on height, weight, body mass index (BMI), pubertal status, and bone age were collected every 6 months from clinical charts and electronic medical records. Pubertal status (Tanner stage for breast development) and bone age were assessed and documented by one pediatric endocrinologists. Patients were categorized based on their pubertal stage (Tanner I–V) [11]. Bone age was interpreted by one pediatric endocrinologist according to Greulich and Pyle [12], and BMI was calculated as body mass (kg) divided by height squared (m^2). Standard deviation (SD) scores (SDSs) were calculated based on the 2007 Korean National Growth Charts [13]. This study protocol was approved by the Institutional Review Board of the Hallym Medical Center (KANGDONG 2013-01-022).

Serum LH, FSH, and 17β-estradiol (E_2) concentrations were measured only in the patient group. Serum LH and FSH levels were measured by chemiluminescent microparticle immunoassay (Abbot Diagnostics, Ireland). The detection limits for the LH and FSH assays were 0.09 and 0.05 mIU/mL, respectively. E_2 levels were determined by an electrochemiluminescence immunoassay, with a detection limit of 5 pg/mL (Roche Diagnostics GmbH, Germany). Serum AMH was assayed using a Gen II enzyme-linked immunosorbent assay (ELISA) (Immunotech, Beckman Coulter Inc., USA), with a detection limit of 0.08 ng/mL. The intra- and inter-assay coefficients of variation were 5.4% and 8.5%, respectively. Serum inhibin B was measured using a Gen II ELISA (Immunotech, Beckman Coulter), with an assay sensitivity of 2.6 pg/mL. Intra- and inter-assay coefficients of variation were 5.4% and 6.7%, respectively.

Statistical analyses

All values are expressed as mean ± SD or as counts. The endocrine parameters of the patients and controls were compared with Student's *t*-test. Comparisons between time points (at baseline and after 6 and 12 months) were performed using the paired *t*-test. The correlations between AMH, inhibin B, and the endocrine parameters were evaluated using Pearson's correlation coefficient. A receiver operating characteristic (ROC) analysis was carried out to establish the best cutoff value for inhibin B to distinguish between those with and without CPP. The area under the curve (AUC) was calculated with 95% confidence intervals (CIs). *p*-values <.05 were considered significant. All statistical analyses were performed with SPSS software (ver. 20.0; SPSS Institute, Chicago, IL, USA) and the *R* package (R Foundation for Statistical Computing, Austria).

Results

A total of 83 subjects (48 CPP patients and 35 normal controls) were included in this study. Table 1 shows the baseline characteristics of the subject at the beginning of the GnRHa treatment. Serum AMH levels of the patients and controls were 7.73 ± 6.34 and 6.90 ± 2.62 (ng/ml) ($p = .469$), respectively. Serum inhibin B level of the patients was 54.82 ± 48.65, which was higher than the control group (16.17 ± 7.01) pg/ml ($p < .001$). Figure 1 shows the changes in the mean serum AMH and inhibin B levels at pretreatment, after 6 months, and after 12 months of GnRHa. The mean serum AMH level was the highest at pretreatment (7.73 ± 6.34 ng/mL) and decreased significantly, after 6 months (5.75 ± 4.12 ng/mL) and after 12 months (4.89 ± 3.75 ng/mL) of GnRHa treatment. Similarly, the mean serum inhibin B was the highest at pretreatment (54.82 ± 48.65 pg/mL) and decreased significantly after 6 months (31.59 ± 27.08 pg/mL) and 12 months (19.73 ± 17.17 pg/mL) of GnRHa treatment. Serum AMH and inhibin B levels were the lowest during this study after 12 months of GnRHa treatment.

Baseline inhibin B levels were positively correlated with bone age, Tanner stage (breast), height SDS, BMI SDS, and bone age advancement in the subjects (data not shown). However, chronological age, basal LH/FSH, peak LH/FSH, and AMH were not correlated with inhibin B levels. Serum AMH was not correlated with any of the endocrine parameters presented above. To determine the inhibin B level for screening precocious puberty in the early stage, we assessed the predictive value of inhibin B levels in diagnosing CPP by ROC curve analysis in 31 patients with Tanner stage II (breast) and the controls (Figure 2). The area under the curve (AUC) for differentiating those with and without CPP was 0.852 (95% CI: 0.772–0.93, $p < .001$). The cutoff value for serum inhibin B that best differentiated between those

Table 1. Pretreatment clinical characteristics of 48 girls with CPP and 35 normal control girls.

	Patient ($n = 48$)	Control ($n = 35$)	*p*
Age at diagnosis (years)	8.40 ± 0.46	8.20 ± 0.54	.08
Bone age (years)	10.48 ± 0.67	7.79 ± 0.74	<.001
BA − CA (years)	2.05 ± 0.74	−0.22 ± 0.76	<.001
Height SDS	1.25 ± 0.91	−0.24 ± 0.71	<.001
Weight SDS	1.16 ± 0.82	−0.23 ± 0.76	<.001
BMI (kg/m^2)	18.79 ± 2.30	16.24 ± 1.67	<.001
BMI SDS	0.86 ± 0.85	−0.15 ± 0.86	<.001
Tanner stage	II 31 (64.6%) III 17 (35.4%)	I 35 (100%)	<.001
Basal LH (mIU/mL)	1.32 ± 0.96	ns	ns
Peak LH (mIU/mL)	12.69 ± 8.94	ns	ns
Basal FSH (mIU/mL)	3.25 ± 1.75	ns	ns
Peak FSH (mIU/mL)	17.37 ± 6.68	ns	ns
E_2 (pg/mL)	6.52 ± 5.43	ns	ns
AMH (ng/mL)	7.73 ± 6.34	6.90 ± 2.62	.469
Inhibin B (pg/mL)	54.82 ± 48.65	16.17 ± 7.01	<.001

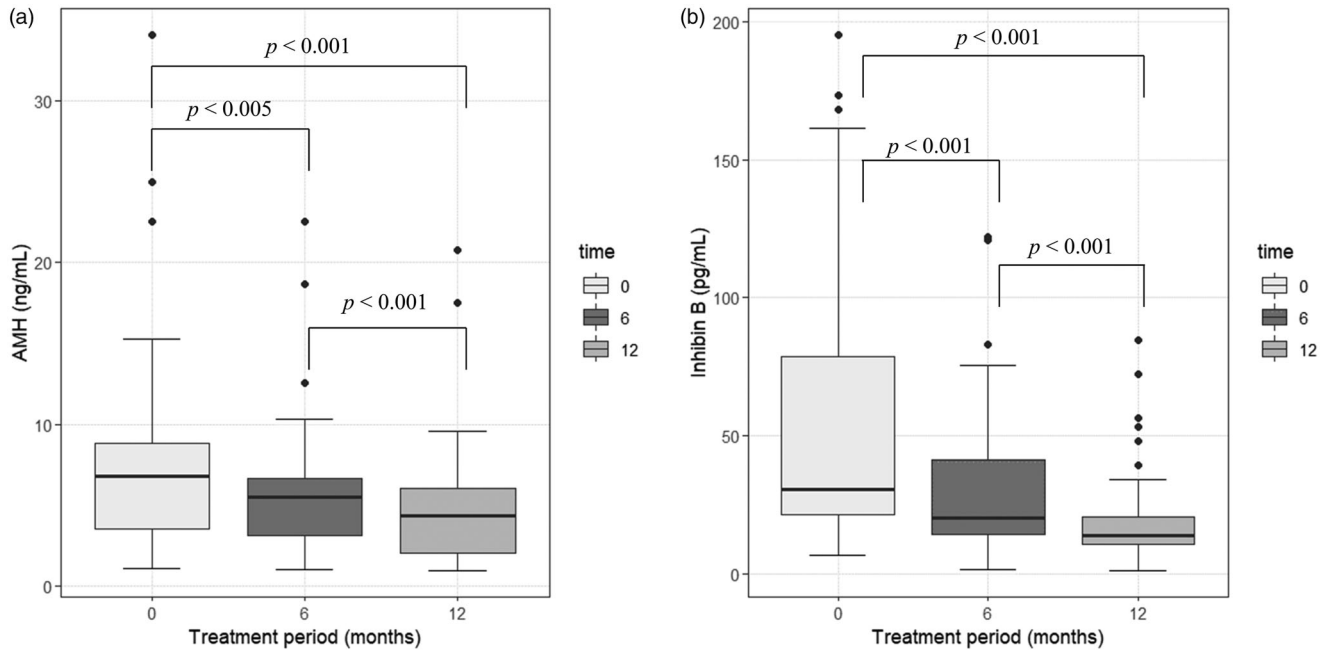


Figure 1. Changes in mean serum AMH and inhibin B levels at pretreatment and after 6 and 12 months of GnRHa treatment.

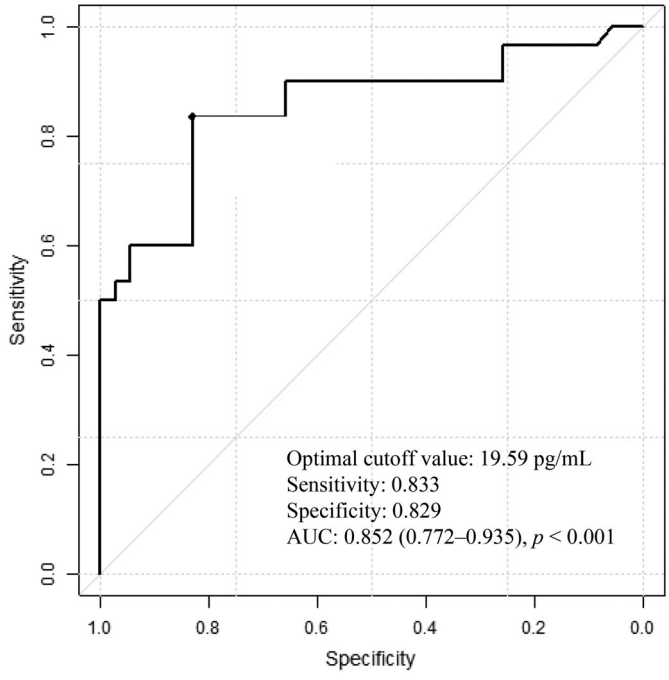


Figure 2. An indicative ROC curve of the inhibin B level for predicting CPP.

with and without CPP was 19.59 pg/mL, with 83.3% sensitivity and 82.9% specificity.

Discussion

In this study, serum inhibin B levels increased significantly in girls with CPP compared to normal prepubertal girls, but AMH did not. After the GnRH agonist treatment, inhibin B and AMH levels decreased significantly compared to pretreatment. The inhibin B level was correlated with various clinical indicators of CPP, and it could be an excellent tool for distinguishing patients with CPP at the early stage.

Serum inhibin B levels increase sharply as puberty begins [10]. Inhibin B is specific to the ovary, principally being produced by small antral follicles; therefore, an increasing inhibin B level reflects that more follicles are being recruited as puberty progress [14]. In our study, inhibin B increased significantly in girls with CPP and it was positively correlated with parameters representing pubertal status, such as Tanner stage, bone age, height SDS, and bone age advancement. These results suggest that inhibin B increases with the progression of puberty and reflects pubertal status. Therefore, we considered that inhibin B could be used to distinguish CPP during the early pubertal stage, especially Tanner breast stage II and analyzed its diagnostic value for determining precocious puberty. The ROC curves showed a significant AUC (0.852), and different cutoff points (19.59 pg/mL) were evaluated. We observed that inhibin B levels decreased more sharply after the GnRHa treatment. Inhibin B was useful, therefore, to determine the therapeutic effects of GnRHa treatment in girls with CPP.

Many previous studies have suggested inhibin B as a potential biomarker of CPP. Shested et al. reported that inhibin B is not superior to E_2 and LH for predicting pubertal progress, but it reflects the level of follicular maturation, and could be used to evaluate puberty in combination with ovarian ultrasound [14]. De Fililppo et al. found that adding basal inhibin B values to basal LH levels provides a reliable method for identifying a progressive form of CPP in girls [15]. Chen et al. reported that serum AMH and inhibin B levels could be potential biomarkers to discriminate between the progressive form and the nonprogressive form of CPP in girls [16].

In males, AMH and inhibin B are considered indicative of Sertoli cell function. The pattern of inhibin B and gonadotrophin levels during childhood is sexually dimorphic, with inhibin B levels distinctively higher in boys than girls [17]. Romina et al. suggested that inhibin B might be useful as for diagnosing CPP in boys and to monitor GnRHa treatment efficacy [18]. These findings suggest that inhibin B sensitively reflects pubertal status and progression, so the clinical implications of inhibin B as a diagnostic marker to determine pubertal initiation in children with precocious puberty need to be validated in more patients.

In contrast, no significant difference was observed in baseline AMH level between the CPP and control groups, but AMH levels decreased significantly 6 and 12 months after GnRHa treatment, compared to pretreatment in the patient group, which is consistent with previous findings [16,19–21]. Previous studies showed a negative correlation between AMH and FSH in prepubertal healthy girls [19,22]. Savas-Erdeve et al. reported that AMH levels did not differ between a CPP group and a control, but increased in premature thelarche [21]. They also reported that AMH levels were negatively correlated with LH in a premature thelarche group. In our study, pituitary gonadotropins, including basal LH/FSH and peak LH/FSH were not correlated with the basal AMH level in the CPP group. Our results differ from previous studies because we investigated the correlation between AMH and gonadotropins only in the CPP group, not in a prepubertal control or premature thelarche group. Our study was conducted retrospectively by chart analysis, so we could not obtain gonadotropin concentrations in the controls. Nevertheless, the correlation between AMH and FSH levels was inconsistent according to previous studies and remains inconclusive [23–25].

Several limitations in our study should be discussed. The age of the study subjects was relatively concentrated around 8 years old, making it difficult to understand the association between AMH, inhibin B, and age, and the relationship between these hormones and gonadotropins. Second, our study was carried out in Korean girls; thus, data may differ from other population groups. Third, our study was conducted within a short time frame with a small sample size, so it was not sufficient to observe long-term changes. Our study may help to expand and establish the basis of medical knowledge by analyzing and presenting the regulatory patterns of ovarian hormone in girls with CPP.

Taken together, our results show that (a) the inhibin B level increased faster at the beginning of CPP and decreased significantly after GnRHa treatment, which may help determine the onset of CPP in the early stage and the therapeutic effectiveness of GnRHa treatment. (b) The AMH level was insufficient to distinguish the beginning of CPP, but AMH interacted with the HPG axis, in part, given that the GnRHa treatment reduced AMH levels. (c) The clinical implications of AMH and inhibin B in precocious puberty need further validation, and (d) further investigation is warranted in girls with CPP to assess long-term reproductive function.

Disclosure statement

The authors have no conflicts of interest to declare.

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