Etiologies of Precocious Puberty: 15-Year Experience in a Tertiary Hospital in Southern Thailand

Somchit Jaruratanasirikul and Maethanee Thaiwong

Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, 90110, Thailand

ABSTRACT

Background: Precocious puberty (PP) is defined as the appearance of secondary sex characteristic at an age <8 years in girls and <9 years in boys, or menarche <9 years in girls.

Objective: To determine the etiologies and clinical characteristics of children presenting with PP.

Subjects and method: The medical records of 307 children (292 girls, 15 boys) with PP (1995-2009) were reviewed.

Results: The most common etiology of PP in girls was premature thelarche (35.5%), followed by early puberty (25.4%) and central precocious puberty (23.8%). All boys had underlying pathologic etiologies. The average age of girls with premature thelarche was significantly younger than those with any other etiologies (2.8±1.6 vs 6.7±1.7 years, p <0.001). Height and weight SDSs of girls with central precocious puberty and early puberty were significantly greater than those with premature thelarche.

Conclusions: The most common etiologies of PP in girls are premature thelarche in girls <6 years and early puberty in girls >6 years. PP in boys has to be investigated for underlying etiologies.

KEY WORDS

central precocious puberty, congenital adrenal hyperplasia, early puberty, ovarian cyst, precocious puberty, premature adrenarche, premature thelarche

INTRODUCTION

Precocious puberty is defined as the appearance of secondary sex characteristic at an age younger than 8 years in girls and 9 years in boys, or the presence of menstruation before 9 years in girls1-3. The incidence of precocious puberty is estimated to be 1 in 5,000 to 1 in 10,000 children with a high female to male ratio4. The etiologies of precocious puberty can be classified into 3 categories: gonadotropin-dependent precocious puberty or central precocious puberty (CPP), gonadotropin-independent precocious puberty or pseudoprecocity, and variants of puberty such as premature thelarche and premature adrenarche. The clinical presentations in each category are different which leads to distinct laboratory investigations for definite diagnosis1-5. At present, there are only a few published studies regarding the etiologies of precocious puberty from Asian countries which may be different from western countries6-8. The aims of this present study were to identify the etiologies of patients referred to Songklanagarind Hospital, the major tertiary care institution and only university hospital in southern Thailand, for evaluation of precocious puberty and to compare the clinical presentations in each category of patients in terms of the age incidence, growth, duration of signs of puberty before initial evaluation, and the diagnostic investigations of patients with precocious puberty over the 15 years period.

SUBJECTS AND METHODS

The medical records of 307 children referred for evaluation of precocious puberty at the Pediatric Endocrinology Clinic at Song-
Klanagarind Hospital, the major tertiary care institution and only university hospital in southern Thailand, from January 1995 to December 2009 were reviewed. According to the recently revised 2008 criteria of the Thai Pediatric Endocrine Society (TPES), precocious puberty is considered as the appearance of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys, or the presence of menstruation before 9 years in girls. History intake included the age and the duration of the presence of breast development or pubic hair as first noticed by parents or caregivers before the initial evaluation, as well as exploring the possibility of exposure to exogenous hormones (in the form of tablets, syrup, topical cream, or inhalation). All the patients were evaluated for height, weight, Tanner stage of breast and pubic hair (according to Marshall and Tanner), skin lesions (café-au-lait spots, neurofibroma, hemangioma, nevus, etc), and given a neurological examination. Height and weight were measured in the standard position using a Harpenden stadiometer and a beam balance scale. The height and weight were expressed in cm and kg, respectively, and were transformed to a standard deviation score (SDS) based on chronological age using growth data of the Thai population as a reference.

The presence of breast development was defined as at least 1.0 cm in diameter of palpable glandular tissue when held between the thumb and index finger.

The extent of investigations for each patient was decided based on the various criteria:
1. height at initial evaluation >P90 for chronological age
2. accelerated height velocity more than 1 standard deviation above the mean for chronological age
3. the rapid progression of breast development or pubic hair
4. the presence of menstruation before 9 years of age.

For patients with isolated breast development without an increase in growth rate, generally no testing was done. For patients who showed growth acceleration or progression in breast development, a bone age was ordered to compare with the chronological age and height age.

Abdominal ultrasonography was performed in girls with breast development and vaginal bleeding. For patients suspected of central precocious puberty because of having 2 signs of puberty or rapid progression of pubertal development aged <6 years or girls who began menarche before 9 years, a basal of luteinizing hormone (LH) and follicle stimulation hormone (FSH), or a luteinizing hormone releasing hormone (LHRH) stimulation test, and estradiol were performed. Patients with isolated pubic hair development with or without other signs of virilization and growth acceleration were given a 1-microgram adrenocorticotropin (ACTH) stimulation test and blood samples were collected for cortisol, 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS) and testosterone measurements. Brain magnetic resonance imaging (MRI) was obtained in all cases diagnosed as central precocious puberty.

**DIAGNOSIS**

**Premature thelarche**

Appearance of breast tissue, at least Tanner II, in a girl without evidence of rapid progression over at least 12 months and no evidence of a central nervous system problem.

**True precocious puberty**

Patients with 2 signs of puberty or who had progressive pubertal development associated with rapid growth in girls <7 years and <9 years in boys or girls who began menarche <9 years.

**Early puberty**

Girls with breast development at age 7.0-8.0 years with advanced bone age and height age whose predicted adult height was close to their target height.

**Premature adrenarche**

Early appearance of pubic hair without breast development. ACTH stimulation test revealed
slightly elevated 17-OHP level.

**Congenital adrenal hyperplasia**

Appearance of virilization and growth acceleration in boys or girls during the childhood period with marked elevation of 17-OHP level (>10,000 ng/dL) after ACTH stimulation test.

**Ovarian cyst**

In some girls with breast development and vaginal bleeding with or without evidence of rapid growth, abdominal ultrasonography revealed a large cyst >1.0 cm in diameter in the ovary.

**Exogenous estrogen exposure**

Appearance of breast tissue in one girl who had a history of exogenous estrogen exposure (in forms of tablets, syrup, topical cream, or inhalation) was linked to probable exogenous exposure.

**No puberty**

No breast tissue or breast tissues <1.0 cm by palpation, no pubic hair found on examination, and no other clinical signs indicating early or precocious puberty.

**STATISTICAL ANALYSIS**

Data were expressed as mean ± standard deviation. ANOVA and student t-test were used to compare differences of variables between groups for continuous data. Statistical differences were considered significant at a p value of <0.05.

The protocol for this study was approved by the Ethics Committee of our institution, Songklanagarind Hospital. Written informed consent of the patients was not judged necessary for this kind of retrospective study.

**RESULTS**

During the 15-year period, 307 children were referred to our clinic for evaluation of precocious puberty (signs of puberty <8 years or menarche <9 years in girls, or signs of puberty <9 years in boys). The age of the children at the time of referral ranged from 9 months to 9 years. The most common clinical presentation was breast

<table>
<thead>
<tr>
<th>Etiology</th>
<th>N (%)</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature thelarche</td>
<td>109 (35.5)</td>
<td>-/109</td>
<td>2.8 ± 1.6</td>
<td>0.5 – 5.8</td>
</tr>
<tr>
<td>Early puberty</td>
<td>78 (25.4)</td>
<td>-/78</td>
<td>7.6 ± 0.3</td>
<td>7.0 – 8.0</td>
</tr>
<tr>
<td>Central precocious puberty</td>
<td>73 (23.8)</td>
<td></td>
<td>7.4 ± 1.6</td>
<td>6.9 – 8.2</td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>58</td>
<td>-/58</td>
<td>4.5 ± 2.3</td>
<td>1.6 – 6.5</td>
</tr>
<tr>
<td>- Hypothalamic hamartoma</td>
<td>8</td>
<td>2/6</td>
<td>6.9 ± 2.2</td>
<td>3.6 – 9.0</td>
</tr>
<tr>
<td>- CNS abnormalities</td>
<td>7</td>
<td>3/4</td>
<td>6.1 ± 0.4</td>
<td>5.2 – 6.6</td>
</tr>
<tr>
<td>No puberty</td>
<td>16 (5.2)</td>
<td>-/16</td>
<td>5.8 ± 2.3</td>
<td>2.8 – 8.3</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>13 (4.2)</td>
<td>9/4</td>
<td>6.7 ± 1.2</td>
<td>5.3 – 7.8</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>7 (2.3)</td>
<td>-/7</td>
<td>3.5 ± 0.4</td>
<td>1.6 – 4.0</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>7 (2.3)</td>
<td>-/7</td>
<td>1.9 ± 0.5</td>
<td>1.5 – 2.3</td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>2 (0.65)</td>
<td>1/1</td>
<td>2.6 ± 0.2</td>
<td>2.0 – 2.8</td>
</tr>
<tr>
<td>Exogenous estrogen exposure</td>
<td>2 (0.65)</td>
<td>-/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>15/292</td>
<td>4.7 ± 2.9</td>
<td>0.5 – 9.0</td>
</tr>
</tbody>
</table>
development (81.4%), followed by vaginal bleeding (7.5%), presence of pubic hair (8.8%), and phallus enlargement (2.3%). Basal LH and FSH were evaluated in 68 patients who were suspected of having central precocious puberty, and an LHRH stimulation test was performed in 38 patients. Abdominal ultrasonography was done in 14 girls who had breast development Tanner stage III. Of these, 4 had vaginal bleeding. Cysts (diameter >1.0 cm) were detected in 7 girls which led to a diagnosis of ovarian cyst. All of the girls who presented with apparent early breast development, 16 (5.2%) were found to have only fatty tissue at the breast area which was mistaken by the parents as breast tissue, thus the original diagnosis of possible early development was not confirmed. All of these girls were obese, with an average weight SDS of 3.03 ± 1.54. An ACTH stimulation test was performed in 22 patients, which revealed the marked elevation of 17-OHP level consistent with the diagnosis of congenital adrenal hyperplasia in 13 patients and no significant elevation of 17-OHP level consistent with the diagnosis of premature adrenarche in 9 patients. Two patients with an initial presentation of pubic hair had rapid progression of pubic hair staging and phallus enlargement during the 3-month follow-up. Abdominal MRI demonstrated right adrenal mass in these two patients which led to the diagnosis of adrenal carcinoma. The pathological result confirmed the diagnosis.

The distribution of diagnoses of patients referred for evaluation of precocious puberty is shown in Table 1. The most common diagnosis was premature thelarche (35.5%), followed by early puberty (25.4%), true precocious puberty (23.8%), no puberty (5.2%), congenital adrenal hyperplasia (4.2%), premature adrenarche (2.3%), ovarian cyst (2.3%), adrenal carcinoma (0.65%), and exogenous estrogen exposure (0.65%). The clinical presentations and the duration of the symptoms from the first being noticed by the parents to the time of the first visit to the doctor are shown in Table 2.

Premature thelarche was the most common diagnosis of girls referred for evaluation of precocious puberty. The mean age at the time of first visit was 3.0 ± 1.6 years. These girls had comparable average growth to the general population, with weight and height SDSs of 0.01 ± 1.09 and 0.19 ± 0.91, respectively. Six girls

### Table 2

Clinical presentations of patients who presented with precocious puberty

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Duration of puberty (months)</th>
<th>Breast</th>
<th>Pubic hair/ phallus</th>
<th>Vaginal bleeding</th>
<th>Height SDS</th>
<th>Weight SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature thelarche</td>
<td>3.0 ± 1.6</td>
<td>109/109</td>
<td>-</td>
<td>-</td>
<td>0.01 ± 0.91</td>
<td>0.01 ± 1.09</td>
</tr>
<tr>
<td>Early puberty</td>
<td>6.4 ± 2.5</td>
<td>78/78</td>
<td>-</td>
<td>-</td>
<td>1.11 ± 0.99</td>
<td>1.60 ± 1.18</td>
</tr>
<tr>
<td>Central precocious puberty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Idiopathic</td>
<td>7.8 ± 6.5</td>
<td>38/58</td>
<td>-</td>
<td>20/58</td>
<td>1.69 ± 1.31</td>
<td>1.72 ± 1.18</td>
</tr>
<tr>
<td>- Hypothalamic hamartoma</td>
<td>10.1 ± 4.0</td>
<td>4/6</td>
<td>2/2 boys</td>
<td>2/6</td>
<td>2.49 ± 2.05</td>
<td>2.48 ± 1.98</td>
</tr>
<tr>
<td>- CNS abnormalities</td>
<td>4.8 ± 4.1</td>
<td>3/4</td>
<td>3/3 boys</td>
<td>1/4</td>
<td>0.81 ±1.37</td>
<td>0.98 ± 1.72</td>
</tr>
<tr>
<td>No puberty</td>
<td>4.2 ± 1.2</td>
<td>16/16</td>
<td>-</td>
<td>-</td>
<td>1.22 ± 1.07</td>
<td>3.03 ± 1.54</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>16.8 ± 5.0</td>
<td>-</td>
<td>13/13 (9 boys, 4 girls)</td>
<td>-</td>
<td>2.20 ± 0.90</td>
<td>2.56 ± 1.72</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>5.8 ± 3.2</td>
<td>-</td>
<td>7/7</td>
<td>-</td>
<td>1.42 ± 0.66</td>
<td>1.68 ± 0.87</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>1.5 ± 0.8</td>
<td>3/7</td>
<td>-</td>
<td>4/7</td>
<td>0.20 ± 1.27</td>
<td>0.02 ± 1.24</td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>11.0 ± 1.4</td>
<td>-</td>
<td>2/2 (1 boy, 1 girl)</td>
<td>-</td>
<td>1.70 ± 1.44</td>
<td>1.91 ± 1.82</td>
</tr>
<tr>
<td>Exogenous estrogen exposure</td>
<td>1.0 ± 0.1</td>
<td>2/2</td>
<td>-</td>
<td>-</td>
<td>0.18 ± 0.32</td>
<td>0.03 ± 0.40</td>
</tr>
</tbody>
</table>
TABLE 3
Laboratory investigations of patients at the time of initial presentation.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Bone age (yr)</th>
<th>Basal LH (mU/mL)</th>
<th>Basal FSH (mU/mL)</th>
<th>Peak LH (mU/mL)</th>
<th>Peak FSH (mU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>premature thelarche</td>
<td>0.07 ± 0.10</td>
<td>2.10 ± 1.80</td>
<td>2.17 ± 0.82</td>
<td>19.3 ± 7.01</td>
<td></td>
</tr>
<tr>
<td>Early puberty</td>
<td>10.0 ± 1.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Central precocious puberty</td>
<td>11.1 ± 1.8</td>
<td>2.06 ± 2.31</td>
<td>3.90 ± 2.44</td>
<td>39.97 ± 18.68</td>
<td>21.74 ± 10.22</td>
</tr>
<tr>
<td>- Idiopathic</td>
<td></td>
<td>(n = 30)</td>
<td>(n = 30)</td>
<td>(n = 30)</td>
<td>(n = 30)</td>
</tr>
<tr>
<td>- Hypothalamic hamartoma</td>
<td>8.1 ± 3.9</td>
<td>3.29 ± 2.04</td>
<td>5.25 ± 1.91</td>
<td>31.96 ± 28.64</td>
<td>18.22 ± 10.42</td>
</tr>
<tr>
<td>CNS abnormalities</td>
<td>11.0 ± 2.0</td>
<td>3.50 ± 1.58</td>
<td>6.60 ± 3.74</td>
<td>33.93 ± 17.28</td>
<td>19.38 ± 5.89</td>
</tr>
<tr>
<td>- No puberty</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Con genital adrenal hyperplasia</td>
<td>9.5 ± 2.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>6.9 ± 1.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>3.0 ± 1.2</td>
<td>0.16 ± 0.50</td>
<td>1.90 ± 1.00</td>
<td>2.09 ± 1.25</td>
<td>11.75 ± 2.48</td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>2.5 ± 0.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exogenous estrogen exposure</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

were given LHRH stimulation test due to weight and height for age over 90th percentile, all of which revealed low levels of LH (2.1 ± 1.8 mU/mL) and elevated FSH (19.3 ± 7.0 mU/mL) (Table 3). Abdominal ultrasonography in 3 cases revealed 1 - 2 tiny cysts. All girls showed no progression in breast tissue and no rapid growth during 2 years of follow-up. The average duration from first evaluation to the time of regression of breast to Tanner I was 12.5 ± 7.5 months (range 0.5 – 36 months).

The second most common diagnosis was early puberty in girls referred for evaluation of breast development at age 7.0-8.0 years. The average age at the time of initial evaluation was 7.6 ± 0.3 years. About half of these girls were obese with an average weight SDS of 1.60 ± 1.18 which was greater than their average height SDS of 1.11 ± 0.99. Their bone age was also advanced and was about the same as their height age resulting in a predicted height at or 2 - 3 cm above their target height.

True precocious puberty was diagnosed in 73 patients (5 boys, 68 girls). Seven patients (3 boys and 4 girls) had underlying central nervous system abnormalities (3 with congenital hydrocephalus, 2 with cerebral palsy, and 2 with post cranial irradiation for brain tumors). An MRI brain scan in 68 cases revealed hypothalamic hamartoma in 8 cases (2 boys, 6 girls). Brain pathology was identified in all boys with CPP (100%), but only 10 (15%) girls. The mean age at the time of diagnosis of cases with hypothalamic hamartoma was significantly younger than patients with idiopathic central precocious puberty (4.5 ± 2.3 and 7.4 ± 1.6 years, p < 0.01). The growth rate in patients with both idiopathic central precocious puberty and hypothalamic hamartoma was greater than in the general population with both weight and height SDSs >1.00 (Table 2), and were significantly greater than patients who had underlying CNS abnormalities (p < 0.01). The main clinical presentations were breast development (45 of 68 girls or 66.2%) and menstruation at age <9 years (23 cases or 33.8%) in girls and penile enlargement with presence of pubic hair in all 5 boys (100%). The LHRH stimulation test revealed average marked elevation of LH (39.97 ± 28.68 mU/mL) and FSH (21.74 ± 10.22 mU/mL), with a ratio of LH to FSH more than
The average basal LH and FSH were 2.06 ± 2.31 and 3.90 ± 2.44 mU/mL, respectively.

Twenty-two patients were referred for evaluation of the early presence of pubic hair with or without growth acceleration. Of these, 13 were diagnosed as congenital adrenal hyperplasia (the average level of 17-OHP after ACTH stimulation test was 35,317 ± 9,820 ng/dL), and 9 were premature adrenarche (average level of 17-OHP after ACTH stimulation test was 410 ± 127 ng/dL). The weight and height of patients with congenital adrenal hyperplasia were significantly greater than those with premature adrenarche (p < 0.01). Two patients had rapid progression of pubic hair staging and phallus enlargement during the 2-month follow-up. Adrenal carcinoma was diagnosed after adrenal masses were demonstrated by abdominal MRI.

Ovarian cyst was diagnosed in 7 girls presenting with breast development for an average period of 1.5 ± 0.8 months and 4 also had vaginal bleeding. Two girls, aged 2 and 3 years, had a history of exogenous estrogen exposure (both with a history of using topical premarin for labial adhesion treatment for 4 - 6 weeks). The girls with ovarian cyst and exogenous estrogen exposure were at average weight and height for the general population.

**DISCUSSION**

In our study, the three most common etiologies of precocious puberty were premature thelarche (35.5%), early puberty (25.4%) and CPP (23.8%) which was different from studies in western countries. For example, a study by Bridges et al. in 213 patients over a 15-year period (1975-1990) in Middlesex Hospital, United Kingdom, found that the three most common etiologies of precocious puberty were CPP (40%), premature thelarche (24.5%) and thelarche variants (14%)7. A multicenter study in 438 girls in Italy over a 10-year period (1988-1998) found that the etiologies of precocious puberty were CPP (97.7%) and gonadotropin-independent precocious puberty (2.3%)8. In the USA, a study by Kaplowitz et al. in 104 patients with precocious puberty in a 3-year period from 1999-2002 found that the most common etiology of precocious puberty was premature adrenarche (46%), followed by premature thelarche (18%) and CPP (9%)6. What was common in our study and most others is that precocious puberty is much more common in girls than in boys with an average ratio of girls to boys of 10 - 20 : 1. The major difference in our study was that CPP and premature adrenarche were not as common as in western countries. The different etiologies of precocious puberty might be at least partially explained by noting that the cut-off age for diagnosis in our study of CPP in girls was <7 years and early puberty 7 - 8 years, whereas the cut-off age for diagnosis of CPP in the other studies was <8 years, and thus those studies might have identified more girls with early puberty. In a study by Cisternini et al., the average age of girls with CPP was 6.5 ± 1.5 years and 60% of these girls were aged 7 - 7.9 years8, which in our study was diagnosed as early puberty.

Premature thelarche was the most common etiology of precocious puberty in our study. The girls presented with breast development Tanner II-III without other signs of puberty and had average growth for their age. Seventy percent of these girls presented at <3 years old. Only 10% of the girls had weight and height >1.5 SDS which made it difficult to differentiate between CPP and premature thelarche, and an LHRH stimulation test was needed. A finding of suppressed LH and elevated FSH was helpful in making a definite diagnosis12. Long term observation showed that 90% of our patients had regression of breast to Tanner I within 12 months. In 10% of them, their breasts remained the same size for 3 years and their growth rate was normal for age. Our findings of premature thelarche were the same as the findings in the study by Pescowitz et al.13, and we believed it is safe to proceed on the premise that a young girl who presents with isolated breast development Tanner II – III stage with otherwise normal growth rate requires no further endocrine investigations. The observation of a clinical course of regression in breast tissue size or no further progression of breast tissue size in 6-12 months is helpful for the diagnosis of premature thelarche.

Early puberty was the second most common
etiology for girls who presented with breast development without signs of virilization at ages 7 - 8 years, the age of the beginning of normal physiological pubertal development in 10 - 15% of most female populations. Several previous studies before the year 2000 used a cut-off age for CPP diagnosis in girls of <8 years which might have included 40 - 50% of girls with early puberty. The studies regarding GnRH analog treatment in girls who entered puberty aged 7.0-7.9 years revealed no beneficial effect of GnRH analog to increase final height. The observation of girls with early puberty in our study found that these girls attained their final height an average of 1 cm above their target height which indicated that the early puberty experienced by these girls had no negative effect on their overall physical growth. There has been some concern that using a cut-off age for diagnosis of precocious puberty at an age <7 years might lead to the misdiagnosis of some patients with endocrine disorders. A study by Midyett et al. in 212 girls aged 6 - 8 years referred for evaluation of precocious puberty found that 12.3% had an endocrine pathology such as congenital adrenal hyperplasia or hyperinsulinism. However, the sequences of puberty in girls who had endocrine pathology were not consonant with normal puberty as they had pubic hair before having breast development.

CPP was the third most common etiology of precocious puberty in our study. Girls outnumbered boys at a the ratio of 14 : 1. MRI brain scan found lesions in 100% of boys and 15% of girls. Using the cut-off age of 6 years, we found no brain lesions in girls with CPP who were >6 years old at the time of initial evaluation. Hence, an MRI brain scan is indicated in all boys and girls <6 years with CPP, which was also recommended in previous studies. All of our patients were found to have advanced bone age. The majority of patients with CPP, except those with underlying CNS diseases, had greater weight and height than in the general population of the same age and sex. Thus, growth acceleration and advanced bone age are additional clinical signs indicating a diagnosis of CPP. Hormonal evaluation regarding the activation of the HPG axis is necessary for the diagnosis of CPP. The standard test used to verify HPG activity has been the gonadotropin response to a GnRH test. Using a chemiluminescent assay, a peak LH level of >5.0 mU/L after a GnRH test indicates pubertal development in both boys and girls with a sensitivity of 88%.

Among 307 patients referred for evaluation of precocious puberty, 16 girls (5%) were found to have no signs of pubertal development. These girls were all moderately to severely obese, and in all cases the fatty tissue deposits in the breast area were misinterpreted by their parents as breast development. Thus, a careful physical examination and evaluation of growth and pubertal development is important in differentiating the actual breast tissue from simple fat deposits.

Twenty-two patients presented with virilization, the presence of pubic hair and phallus enlargement without testicular enlargement in 10 boys, and the presence of pubic hair without breast enlargement in 12 girls. Virilization without consonant pubertal development is a suggestive sign of pseudoprecocity caused by the overproduction of androgens. Serious conditions such as the virilizing form of congenital adrenal hyperplasia or an androgen-producing adrenal tumor must be distinguished from less serious conditions such as premature adrenarche, the benign condition resulting from adrenal overactivity. In western countries, premature adrenarche is a common etiology of patients presenting with precocious puberty. A study by Kaplowitz in mainly African-American patients found that the most common etiology of precocious puberty was premature adrenarche. Premature adrenarche is less common in Asian populations. At present, there have been no studies of premature adrenarche from Asian countries, but studies of virilization in Asian females have found that the etiologies were from virilizing and nonclassical congenital adrenal hyperplasia and polycystic ovarian syndrome. Therefore, patients who present with virilization in boys or girls should be investigated for adrenal and ovarian diseases. 17-hydroxyprogesterone (17-OHP) is markedly elevated in patients with congenital adrenal hyperplasia and is required for definite diagnosis. Mild elevation of 17-OHP in patients who have rapid progression of phallus enlargement or pubic hair development should
have an abdominal MRI to look for an androgen-producing adrenal tumor. The height and weight in patients with virilization in our study were greater than those in the general population, which was caused by the growth stimulation effect of excess androgen exposure. However, patients with congenital adrenal hyperplasia had significantly greater weight and height than those with premature adrenarche due to the much longer duration of androgen exposure in patients with congenital adrenal hyperplasia.

In our study, we found 7 girls with an ovarian cyst and 2 girls with a history of exogenous estrogen exposure. The presence of vaginal bleeding with breast development in young normal stature girls is an important clinically suggestive clue for ovarian cyst. The finding of suppressed LH and elevated FSH after an LHRH stimulation test is helpful to exclude central precocious puberty. The detection of small cysts in ovaries by ultrasonography can be found in premature thelarche. Nonetheless, premature thelarche and ovarian cyst are benign conditions and almost all the patients have spontaneous remission over time. Two girls with ovarian cyst had 2 episodes of vaginal bleeding before complete remission in 1 year. History taking of exogenous estrogen exposure is necessary in all girls presenting with precocious breast development. In our two patients, breast development was secondary to prolonged use of estrogen cream prescribed for treatment of labial adhesion.

In summary, our study, based on 307 patients with precocious puberty in a single center over a 15-year period, found that the most common etiology of isolated breast development in young girl with average height and weight was premature thelarche, a benign condition that requires no hormonal investigation and usually ends in spontaneous regression in 6 - 12 months. Breast development in girls aged 7 - 8 years is a variant of normal puberty. Children with rapid progression of normal sequence of puberty and accelerated growth should have full endocrine investigations and cranial radio imaging for central precocious puberty, particularly in boys and girls <6 years old. Children who have virilization without consonant puberty should be investigated for overproduction of androgens. History taking, complete physical examination and review of growth data are important clinical tools to separate patients who have a pathologic condition and need a full endocrine work-up.

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