Precocious Pubarche in Thai Children

Somchit Jaruratanasirikul MD*
Maethanee Thaiwong MD*

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

Objective: To describe the etiologies, clinical characteristics, and laboratory investigations of young Thai children being evaluated for precocious pubarche.

Material and Method: The medical records of 41 children referred for evaluation of precocious presence of pubic hair at Songklanagarind Hospital between 1995 and 2011 were retrospectively reviewed.

Results: The etiologies of precocious pubarche in young Thai children were congenital adrenal hyperplasia (n = 19, 46.3%), isolated premature adrenarche without pathology (n = 12, 29.3%), hypothalamic hamartoma (n = 7, 17.1%), adrenocortical carcinoma (n = 2, 4.9%), and Leydig cell tumor (n = 1, 2.4%). The weight and height of patients with pathological etiologies were significantly greater than those with isolated premature adrenarche (p < 0.001). Patients with congenital adrenal hyperplasia had significantly greater levels of basal and peak 17-hydroxyprogesterone than those with isolated premature adrenarche (p < 0.001). Patients with adrenocortical carcinoma had significantly greater level of DHEAS than those with congenital adrenal hyperplasia and isolated premature adrenarche (p < 0.001).

Conclusion: The precocious presence of pubic hair in young Thai children should be investigated for an underlying pathological etiology. The most common underlying pathology of precocious presence of pubic hair is congenital adrenal hyperplasia.

Keywords: Precocious pubarche, premature adrenarche, congenital adrenal hyperplasia

Precocious pubarche is defined as the appearance of pubic hair at an age younger than eight years in girls and nine years in boys(1). The basic principle of precocious pubarche is adrenal androgen oversecretion for the chronological age, which can be caused by pathological oversecretion of androgen (such as congenital adrenal hyperplasia, adrenal tumor, and gonadal tumor) or early maturation of the adrenal cortex without any pathological etiology. Premature adrenarche is the specific terminology for the early maturation of the adrenal cortex and this condition can be diagnosed after other pathological causes of androgen overproduction and central precocious puberty are excluded(2,3).

In Western countries, premature adrenarche is a common diagnosis of patients referred for evaluation of precocious puberty. A study in 104 American children referred between October 1999 and October 2002 for evaluation of precocious puberty found that 46% of the cases were premature adrenarche(3). In contrast, precocious pubarche has rarely been reported in Asian populations. A retrospective study in 307 Thai children referred to Songklanagarind Hospital for evaluation of precocious puberty between January 1995 and December 2009 found that nine patients (2.9%) were diagnosed as isolated premature adrenarche(4). Hence, the aim of this present study was to focus on the etiologies of patients referred to Songklanagarind Hospital for evaluation of the early appearance of pubic hair and to compare the clinical presentations in each category of patients in terms of the age at presentation, physical growth, and the diagnostic investigations of patients with precocious presence of pubic hair over the 17 years period.

Material and Method

Three hundred sixty two children were referred for evaluation of precocious puberty at the Pediatric Endocrinology Clinic at Songklanagarind Hospital, the major tertiary care institution, and only university hospital in southern Thailand, between January 1995 and December 2011. There were only 41 patients (11.3%) referred for evaluation of the presence of pubic hair before age eight in girls and
age nine in boys. History taking included the age of first appearance and the duration of the presence of pubic hair as first noticed by parents or caregivers before the initial evaluation, as well as questions designed to explore the possibility of exposure to exogenous hormones. Height and weight were recorded, and all the patients were evaluated for Tanner stage of breast, pubic hair, and genitalia (according to Marshall and Tanner)\(^5\), skin lesions (café-au-lait spots, neurofibroma, hemangioma, nevus, hyperpigmentation, hirsutism, etc.). Height and weight were measured with the nearest of 0.1 cm and 0.1 kg, respectively, and transformed into a standard deviation score (SDS) based on chronological age using growth data of Thai population as a reference\(^6\).

For patients suspected of central precocious puberty because of having two signs of puberty by physical examination or a rapid progression of pubertal development aged < 7 years, a basal luteinizing hormone (LH), and follicle stimulating hormone (FSH) levels, or a luteinizing hormone releasing hormone (LHRH) stimulation test, was performed. Patients with isolated pubic hair development with or without other signs of virilization and growth acceleration were given a standard 250 \(\mu\)g of adrenocorticotropin (ACTH) stimulation test and blood samples were collected for cortisol, 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEAS) and testosterone measurements. The tests were performed between 8 and 11 a.m. Serum samples were drawn at 0 and 60 minutes. Brain magnetic resonance imaging (MRI) was obtained in all cases diagnosed as central precocious puberty. For patients who had rapid progression of pubic hair development or phallus enlargement (clitoromegaly or penile enlargement), an abdominal MRI was performed to look for an androgen-producing adrenal or gonadal tumor.

**Hormone measurements**

LH, FSH, cortisol, testosterone, and DHEAS levels were measured using the chemiluminescent assay method. The lowest levels detected by this method were 0.1 mU/mL for LH and FSH, 0.02 \(\mu\)g/dL for cortisol, 0.02 ng/mL for testosterone, and 15 \(\mu\)g/dL for DHEAS. 17-OHP level was measured by radio-immunoassay with the lowest level detection at 0.1 ng/mL.

**Statistical analysis**

Data were expressed as median and interquartile ranges. Kruskal-Wallis test was used to compare the differences of variables among groups. Statistical difference was considered significant at a p-value of < 0.05.

The protocol for the present study was approved by the Ethics Committee of Faculty of Medicine, Prince of Songkla University. Written informed consent of the patients was not judged necessary for this kind of retrospective study.

**Results**

Forty-one children (15 boys and 26 girls) were referred to our clinic for evaluation of the presence of pubic hair at age < 8 years in girls and < 9 years in boys. Seven children were found to have other signs of puberty, four girls with breast Tanner 2 (which was not the parental concern at the initial presentation), and three boys with bilateral testicular volume 6 to 8 mL. The median levels of basal and stimulated LH after the LHRH stimulation test were elevated at 3.29 and 31.96 mU/mL, respectively, which were consistent with the diagnosis of central precocious puberty. Hypothalamic hamartoma was diagnosed in those seven patients on the basis of a demonstrated pedunculated mass at hypothalamus on the MRI brain study. An ACTH stimulation test was performed in 34 patients, which revealed a marked elevation of 17-OHP level in 19 patients (median level 353.2, range 45.0-545.0 ng/mL), consistent with a diagnosis of congenital adrenal hyperplasia, and no significant elevation of the 17-OHP level (median 4.1, range 1.5-7.5 ng/mL) in 15 patients. Of these 15 patients with no significant elevation of 17-OHP level, 12 had clinical course of non- or slowly progressive development of pubic hair without other signs of precocious puberty, and were diagnosed as isolated premature adrenarche. Three patients (2 boys, 1 girl) had rapid progression of pubic hair staging and phallus enlargement during a 2-month follow-up. An abdominal MRI demonstrated a right adrenal mass in two of these patients which led to a diagnosis of adrenocortical carcinoma, and the third, a boy, was found to have asymmetrical testicular volume, 2 mL in the right testis and 6 mL in the left testis, which led to a diagnosis of testicular tumor. After tumor removal, the pathological results confirmed the diagnosis of adrenocortical carcinoma in the first two patients\(^7\) and Leydig cell tumor in the third patient\(^8\).

After the full investigation, the distribution of diagnoses of patients referred for evaluation of the precocious presence of pubic hair were congenital adrenal hyperplasia (n = 19, 46.3%), followed by
isolated premature adrenarche (n = 12, 29.3%), hypothalamic hamartoma (n = 7, 17.1%), adrenocortical carcinoma (n = 2, 4.9%), and Leydig cell tumor (n = 1, 2.4%). The clinical presentations of patients in each diagnosis are shown in Table 1. The weight and height SDSs, and the ratio of bone age to chronological age of patients with congenital adrenal hyperplasia and hypothalamic hamartoma were significantly greater than those with isolated premature adrenarche (p < 0.001 and p = 0.03, respectively). Patients with congenital adrenal hyperplasia had significantly greater levels of basal 17-OHP than those with isolated premature adrenarche (p < 0.001). Patients with adrenocortical carcinoma had significantly greater levels of DHEAS than those with congenital adrenal hyperplasia and isolated premature adrenarche (p < 0.001).

All these patients were followed-up at the Pediatric Endocrine Clinic every three to six months. Of all the participants, seven girls with isolated

Table 1. Clinical presentations of 40 patients who presented with pubic hair (patient with Leydig cell tumor was not included in this table). Data were presented in median and interquartile ranges

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Hypothalamic hamartoma</th>
<th>Congenital adrenal hyperplasia</th>
<th>Isolated premature adrenarche</th>
<th>Adrenocortical carcinoma</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>7</td>
<td>19</td>
<td>12</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Male/female</td>
<td>3/4</td>
<td>10/9</td>
<td>-12</td>
<td>1/1</td>
<td>-</td>
</tr>
<tr>
<td>Chronological age (yr)</td>
<td>(4.2, 6.2)</td>
<td>(2.8, 8.0)</td>
<td>(5.5, 7.5)</td>
<td>(1.5, 2.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of having pubic hair (months)</td>
<td>7.0</td>
<td>15.5(^a)</td>
<td>6.0(^a)</td>
<td>8.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Height SDS</td>
<td>(3, 10)</td>
<td>(1.80, 4.55)</td>
<td>(0.75, 2.10)</td>
<td>(1.50, 1.90)</td>
<td></td>
</tr>
<tr>
<td>Weight SDS</td>
<td>2.48</td>
<td>2.70(^a)</td>
<td>1.68(^a)</td>
<td>1.91(^a)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone age (yr)</td>
<td>(19.6, 3.94)</td>
<td>(1.80, 4.20)</td>
<td>(0.98, 2.25)</td>
<td>(1.70, 2.10)</td>
<td></td>
</tr>
<tr>
<td>Bone age/chronological age</td>
<td>7.7</td>
<td>9.4</td>
<td>3.5</td>
<td>2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Basal 17-OHP (ng/mL)</td>
<td>-</td>
<td>31.9(^a)</td>
<td>1.5(^a)</td>
<td>2.9(^a)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Basal cortisol (μg/mL)</td>
<td>-</td>
<td>5.62</td>
<td>7.84</td>
<td>6.57</td>
<td>0.29</td>
</tr>
<tr>
<td>Peak 17-OHP (ng/mL)</td>
<td>-</td>
<td>353.2(^a)</td>
<td>3.7(^a)</td>
<td>4.8(^a)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak cortisol (μg/dL)</td>
<td>-</td>
<td>18.96(^a)</td>
<td>33.45(^b)</td>
<td>28.11(^b)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DHEAS (μg/dL)</td>
<td>-</td>
<td>82.6(^c)</td>
<td>44.3(^c)</td>
<td>412.0(^c)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>-</td>
<td>2.48(^d)</td>
<td>0.29(^d)</td>
<td>3.47(^d)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^a\) Significantly greater level in patients with congenital adrenal hyperplasia than those with isolated premature adrenarche and adrenal tumor  
\(^b\) Significantly lower level in patients with congenital adrenal hyperplasia than those with isolated premature adrenarche and adrenal tumor  
\(^c\) Significantly greater level in patients with adrenal tumor than those with congenital adrenal hyperplasia and isolated premature adrenarche  
\(^d\) Significantly lower level in patients with isolated premature adrenarche than those with congenital adrenal hyperplasia and adrenal tumor
premature adrenarche and 10 patients (5 boys and 5 girls) with congenital adrenal hyperplasia reached their final height (defined by height velocity < 0.5 cm/year for 2 consecutive 6-month visits). The median final height SDS of girls with isolated premature adrenarche was -0.40 (range -1.13 to 1.07), which was not different to their median target height of -0.21 (range -0.97 to 1.25). The median final height SDS of patients with congenital adrenal hyperplasia was -1.85 (range -3.52 to 0.21) which was significantly lower than their median target height of -0.22 (range -1.06 to 2.09) (p < 0.01).

Discussion

The results of the present study showed that the majority of young Thai children with the precocious presence of pubic hair had pathological etiologies and the most common pathological etiology was virilizing congenital adrenal hyperplasia. Seventeen percent of the presented patients had other signs of precocious puberty that were not noticed by their parents or did not cause concern as much as the presence of pubic hair. The authors’ finding that only 29.3% were diagnosed as isolated premature adrenarche and 71.7% of the presented patients had a pathological etiology which was different from most studies in Western countries, which found that isolated premature adrenarche was common in the Caucasian and African children presenting with precocious puberty and that only 4-35% of young children with early appearance of pubic hair had a pathological etiology (Table 2)(9-14).

A study for the age of onset of secondary sex characteristics by Herman-Giddens et al in primary care practitioner settings in the USA, published in 1997, found that Tanner 2 pubic hair was present in 1.4% of white girls and 9.5% of black girls at six years, and the percentages were 7.7% of white girls and 34.3% of black girls at the eight years(15). Our revealed study that only 41 young children were evaluated for the presence of pubic hair over the period of 17 years and only 29.3% of them were diagnosed with isolated premature adrenarche indicates that isolated premature adrenarche are less common in Thai children, and that young children who present with pubic hair should be investigated for pathological etiologies. To date, there have been rarely published studies of precocious pubarche in Asian countries, although studies of Asian adolescent female patients with virilization have found that the main etiologies were virilizing and non-classical congenital adrenal hyperplasia and polycystic ovarian syndrome(16-19). The marked elevation of 17-hydroxyprogesterone (17-OHP) is required for definite diagnosis of virilizing 21-hydroxylase deficiency congenital adrenal hyperplasia(20), and the marked elevation of the DHEAS level in young children who also have rapid progression of pubic hair development or phallus enlargement should have an abdominal MRI performed to check for an androgen-producing adrenocortical carcinoma(21).

In the present study, the clinical characteristics of the patients with a pathological etiology explaining the presence of pubic hair were different from those with isolated premature adrenarche. Patients with a pathological etiology were of significantly younger age, and had greater weight and height and more advanced bone age at the time of initial presentation, which was caused by the growth stimulation effect of markedly excess androgen exposure from the pathological underlying etiology than those with isolated premature adrenarche. Further evidence of pathology was the extremely high levels of testosterone and DHEAS. To our knowledge, there have been no published studies of normal levels of 17-OHP, DHEAS and testosterone for Asian children in different age

<table>
<thead>
<tr>
<th>Study, year of study</th>
<th>Number of patients</th>
<th>Levels of 17-OHP for diagnosis of CAH after 250 μg ACTH test</th>
<th>Number (%) of patients with CAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkins(9), 1992</td>
<td>46</td>
<td>&gt;10 ng/mL</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Siegel(10), 1992</td>
<td>69</td>
<td>&gt;10 ng/mL</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Balducci(11), 1994</td>
<td>171</td>
<td>&gt;2 SD of normal (&gt;10 ng/mL)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Dacou-Voutetakis(12), 1999</td>
<td>48</td>
<td>Molecular diagnosis</td>
<td>17 (35%)</td>
</tr>
<tr>
<td>Accenta(13), 2004</td>
<td>28</td>
<td>&gt;12 ng/mL</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Armengaud(14), 2009</td>
<td>238</td>
<td>&gt;10 ng/mL</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>This study, 2012</td>
<td>41</td>
<td>&gt;12 ng/mL</td>
<td>19 (46%)</td>
</tr>
</tbody>
</table>

CAH = congenital adrenal hyperplasia; ACTH = adrenocorticotrop hormone
groups, and therefore, the levels of 17-OHP, DHEAS and testosterone of the presented patients were compared using the reference levels for Caucasian populations (22). In the presented patients, the stimulated 17-OHP level was extremely greater than that cut-off level and the DHEAS level in patients with adrenocortical carcinoma was 5 and 10 times greater than those with virilizing congenital adrenal hyperplasia and isolated premature adrenarche, respectively.

Isolated premature adrenarche is a benign phenomenon. The pathophysiological basis is an early isolated maturation of the zona reticularis, which leads to a transient increased adrenal androgen secretion resulting in the appearance of pubic hair in prepubertal children (1,2). The cause of transient isolated maturation of the zona reticularis and adrenal androgen oversecretion in these young children is still unclear. Adrenal androgens, such as DHEAS, androstenedione, and testosterone are at moderately increased levels for their chronological age but are within the expected ranges according to the pubertal stage of pubic hair. In some patients, the early development of premature adrenarche is associated with normal androgen level for chronological age suggesting that there is an increased peripheral sensitivity to adrenal androgen. In our patients, the average level of DHEAS was 44.3 μg/dL, which was about the same level reported in Caucasian children with isolated premature adrenarche (23-25).

The clinical course of isolated premature adrenarche has been reported to be non- or slowly progressive development of pubic hair without other signs of central precocious puberty or other signs of virilization. The long-term follow-up in children with isolated premature adrenarche until they attained their final height found that this transient adrenal oversecretion had no negative effects on the beginning and progression of puberty and final height in the target ranges was reached in almost all affected girls (22,23-25). In contrast, undiagnosed or untreated patients with pathological androgen overproduction can cause premature closure of epiphyses resulting in shorter adult height (26-28). In our 12 patients with isolated premature adrenarche, their growth velocity was slightly increased over chronological age with mildly advanced bone maturation, but was about compatible with the height age. Although the median final height of our seven girls with isolated premature adrenarche was -0.19 SD lower than their target height, this was still within the acceptable range. The final height of the presented patients with congenital adrenal hyperplasia was significantly lower than the target height indicating that significant height deficit must be a concern with long duration of high androgen exposure.

In conclusion, isolated premature adrenarche is not a common etiology in young Thai children presenting with precocious pubarche and the early presence of pubic hair in young children indicates that investigations should be undertaken for pathological etiologies, particularly virilizing congenital adrenal hyperplasia, and adrenal tumor. Patients with a pathological etiology were of significantly younger age, and had greater weight and height and more advanced bone age at the time of initial presentation, which was caused by the growth stimulation effect of markedly excess androgen exposure from the pathological underlying etiology than those with isolated premature adrenarche.

Potential conflicts of interest
None.

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การมีขนหัวหน่าก่อนวัยในเด็กไทย

สมจิตร องรัตนสิริฤกษ์, เนทณี ไทยวงษ์

วัตถุประสงค์: เพื่อศึกษาสาเหตุ, ลักษณะทางคลินิกและผลการตรวจทางห้องปฏิบัติการในเด็กไทยที่ได้รับการประเมินการมีขนหัวหน่าก่อนวัย

วัสดุและวิธีการ: การศึกษาย้อนหลังจากเวชระเบียนของผู้ป่วยเด็กไทย 41 ราย ที่ส่งต่อมาเพื่อประเมินการมีขนหัวหน่าก่อนวัยที่โรงพยาบาลสงขลานครินทร์ในช่วง พ.ศ. 2538-2554

ผลการศึกษา: สาเหตุของการมีขนหัวหน่าก่อนวัยในเด็กไทย ได้แก่ โรคเปลือกต่อมหมวกไตหนาแต่กำเนิด (จำนวน 19 ราย, ร้อยละ 46.3) การมีขนหัวหน่าก่อนวัยเพียงอย่างเดียวโดยไม่มีพยาธิสภาพอื่น (จำนวน 12 ราย, ร้อยละ 29.3) เนื้องอกต่อมหมวกไต (จำนวน 7 ราย, ร้อยละ 17.1) และเนื้องอกอัณฑะ (จำนวน 1 ราย, ร้อยละ 2.4) เด็กที่มีขนหัวหน่าก่อนวัยที่เกิดจากการมีพยาธิสภาพน่าจะเกิดจากความสูงของการเจริญเติบโตที่มีขนหัวหน่าก่อนวัยที่ไม่มีพยาธิสภาพอย่างมีนัยสำคัญทางสถิติ (p < 0.001) การตรวจทางห้องปฏิบัติการพบว่า 17-hydroxyprogesterone ที่เริ่มต้นและสูงสุดในผู้ป่วยโรคเปลือกต่อมหมวกไตหนาแต่กำเนิดมีระดับสูงมากกว่าเด็กที่มีขนหัวหน่าก่อนวัยเพียงอย่างเดียวโดยไม่มีพยาธิสภาพ อีกทั้งมีนัยสำคัญทางสถิติ (p < 0.001) ผู้ป่วยโรคเปลือกต่อมหมวกไตหนาแต่กำเนิดมี dehydroepiandrosterone sulfate สูงมากกว่าผู้ป่วยโรคเปลือกต่อมหมวกไตหนาแต่กำเนิดและเด็กที่มีขนหัวหน่าก่อนวัยเพียงอย่างเดียวแต่ไม่มีนัยสำคัญทางสถิติ (p < 0.001)

สรุป: การมีขนหัวหน่าก่อนวัยในเด็กไทยควรจะได้รับการตรวจทางห้องปฏิบัติการให์มีผลลัพธ์ที่เหมาะสมโดยที่พยาบาลเป็นคนที่มีความรู้ดีในการตรวจต่อมหมวกไตหนาแต่กำเนิด