ISOSEXUAL PRECOCITY: 
THE CLINICAL AND 
ETIOLOGIC PROFILE

Meena Desai
M.P. Colaco
C.S. Choksi
M.C. Ambedkar
F.E.E. Vaz
C. Gupte

ABSTRACT

Eighty children (58 girls and 22 boys) with isosexual precocity seen in the past eight years were evaluated clinically and investigated to identify the underlying cause. Of these, 50% (29 girls and 11 boys) had centrally mediated true precocious puberty (TPP). The girls could be classified into five major groups (I) Central precocious puberty 29 - subclassified into idiopathic (ITPP, 15) and organic or neurogenic (NTPP, 14), (II) Premature thelarche (PT, 20), (III) Premature menarche (PM, 2), (IV) Premature adrenarche (PA, 5), and, (V) Others: hypothyroid (n = 1), and McCune Albright Syndrome (n = 1). ITPP as a cause of precocity in girls was seen less often (52%) and NTPP more often (48%) compared to most Western series, with tubercular meningitis as the cause in 31% and hypothalamic hamartomas in 10%. Though the LH and estradiol levels were significantly higher (p < 0.05) in TPP, compared to PT, these were not helpful in differentiating because of considerable overlap. LH-predominant-response (LH/FSH ratio > 1) to LHRH testing was seen in TPP. Amongst the 22 boys, 11 (50%) had TPP, ITPP in 27% and NTPP in 73%. Hamartomas (n = 4) and TBM (n = 3) contributed equally to NTPP; pineal tumor was seen in one. The adrenal (n = 7) and testicular (n = 2) causes together involved 41% of the boys

One of the most fascinating and least understood disorders of maturation is the syndrome of sexual precocity. Complete or true precocious puberty (TPP) mediated by gonadotropins is isosexual and in its evolution similar to normal puberty with some differences in the pace and pattern of maturation. In incomplete or pseudoprecocious puberty sexual maturation may be iso- or hetero-sexual with only some of the sexual characteristics appearing early.

There are wide variations in the onset of puberty in various parts of the world. The acceptable definition of sexual precocity considers breast development before the age of eight years and menarche before the age of ten years in females, and enlargement of the testes before the age of nine years in male as

with precocity, congenital adrenal hyperplasia (CAH) CAH, 11-β hydroxylase being the commonest cause. Of the 6 boys with deficiency was found in four and nonsalt losing form of 21-hydroxylase deficiency in 2. Testicular and adrenocorticotropic testotoxicosis were noted in one case each. The etiologic factors were more varied in boys.

Key words: Sexual precocity, Hypothalamic hamartoma, Thelarche, Menarche, Adrenarche, Congenital adrenal hyperplasia, Testicular tumor, Testotoxicosis, LHRH test.

From the Division of Pediatric Endocrinology and Department of Pediatric Medicine, Bai Jerbai Wadia Hospital for Children and Institute of Child Health, and Sir H.N. Medical Research Society, Bombay.

Reprint requests: Dr. Meena Desai, Honorary Professor and Head, Department of Pediatric Medicine, and Division of Pediatric Endocrinology, B. J. Wadia Hospital for Children; Bombay 400 012.

Received for publication: September 9, 1992; Accepted: February 24, 1993
precocious. In the absence of other secondary sex characters the appearance of pubic hair in girls less than eight years and in boys less than nine years in boys also warrants evaluation(1).

Some of the large series have outlined various aspects of precocious puberty in children(2-5). The data on isosexual precocity from this country is limited(6,7). The present series is a retrospective analysis of eighty children of both the sexes with isosexual precocity, seen during the past eight years till December 1991.

Material and Methods

Eighty children, 58 girls and 22 boys with sexual precocity constituted the subject of this study. Detailed history, including the age of onset, the sequence of appearance and the rapidity of progression of various secondary sex characters, associated symptoms, birth history, milestones, past history of medication or intracranial infection, were all noted. Family history of consanguinity and early puberty was also recorded. Careful clinical examination was carried out and pubertal development was assessed by Tanner’s method(8,9). Testicular volume was assessed by Prader’s orchidometer.

The skeletal maturation was assessed by Greulich and Pyle’s atlas method(10). Other imaging studies included ultrasonography of abdomen for evaluation of size and morphology of uterus, ovaries, adrenals and testes. Plain skiagram of skull, and computerised tomographic and Magnetic Resonance Imaging of head (when indicated) was carried out.

Vaginal cytology for estrogen effect was obtained in 31 girls. Hormonal evaluation included basal serum leutinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol or testosterone. Thyroid hormones, thyroid stimulating hormone (TSH), prolactin, 17 alpha-hydroxyprogesterone (17-OHP basal and post ACTH stimulated when indicated) dehydroepiandrosterone sulphate (DHEAS) and androstenedione (AD) were estimated as required. Dexamethasone suppression test was carried out when necessary. LH releasing hormone (LHRH) stimulation test was done by administering 50 to 100 µg intravenously and measuring LH and FSH at 0, 15, 30, 45, 60, 90 and 120 minutes(11). A pubertal type of LH predominant response to LH/RH test with a peak LH/FSH ratio exceeding 1 was interpreted as favouring centrally mediated complete form of puberty as against isolated thelarche(11,12). All hormonal estimations were done by standard RIA using appropriate standards and controls. The 24 hours urinary 17 ketosteroid (17-KS) excretion was determined by the standard method.

Results

Of the 80 children presenting with isosexual precocity 58 (72.5%) were girls and 22 (27.5%) were boys (ratio of 2.65). Based on their clinical and investigative findings these children could be classified into specific clinical and etiologic groups. Follow up evaluation also helped in confirming the nature of the disorder.

Sexual Precocity in Girls (n=58) (Table I)

The mean age at presentation was 4.5 ± 2.67 years (0.66 - 8.5 years), and the mean age at onset of symptoms was 3.37 ± 2.43 years (0.25 - 7 years).

Presence of more than one secondary sex characteristics, enhanced physical growth and advanced bone age, current or past evidence of CNS involvement, and demonstrable CNS pathology on imaging, favoured TPP. These findings were further supported by marked estrogenization on
vaginal cytology, rise in basal gondotropin levels (when present) and/or pubertal LH-predominant response to LHRH (tested in 10 girls).

Girls presenting with isolated breast development with no enhancement of growth or advanced bone age, prepubertal vaginal cytology and absent or minimal evidence of estrogenization, and little progression on follow up, could be categorized as premature thelarche (PT). LHRH testing in six of these girls showed an FSH predominant response. Girls presenting with premature menarche (PM) or premature pubic hair growth or premature adrenarche (PA) had no other secondary sex characters or associated clinical findings.

**Group I - Girls with Central Precocious Puberty (TPP)**

Twenty nine (50%) of the fifty eight girls with sexual precocity (*Table I*) could be classified as having TPP. The mean age at the onset of symptoms for this group was 3.85 ± 2.17 years (0.25 to 7 years). Fifteen (52%) had an idiopathic true precocious puberty (ITPP) with no demonstrable intracranial pathology, and 14 (48%) had an organic or neurogenic cause (NTPP). The mean age at onset or presentation did not differ significantly between these subgroups. Amongst the causes of NTPP (*Table II*), post meningitic precocious puberty was the commonest (9 of the 14, 64%) and hypothalamic hamartomas were next (3 of the 14, 21%). Neurologic sequelae like mental subnormality, behavioural disorders, or motor deficits were evident in 10 of the 14 girls with NTPP.

Development of breast was the first noticeable abnormality in all, and at the time of presentation the development varied from Tanner stage II to V (22/29 with stage II to III). Presence of pubic hair Grade II to V was seen in 19 (with majority having Grade II), and axillary hair was present in 8. Ten of the 29 girls had attained menarche. The rate of progression of pubertal signs varied a great deal. The duration between the initial breast development and menarche ranged from 2 months to 5½ years. Rapid evolution of sexual precocity with breast development in very early infancy and onset of menarche by 3 months to 3 years was noted in three girls with hypothalamic hamartomas. In rest of the girls with NTPP the rate of progression was not as rapid. In three of the 15 girls with ITPP, evolution of secondary sex characters was slow with menarche occurring 5 to 5½ years after initial breast development.

All the fifteen girls with ITPP had weights and heights at or above 50th percentile of Tanner (heights above 90th percentile of ICMR) in comparison with 11 of the 14 with post asphyxial or post meningitic NTPP with weights and heights below 25th percentile of Tanner (*Fig. I*). The three girls with NTPP due to hypothalamic hamartomas had heights above 50th percentile. The growth velocity (data available in 50%) was above normal for age. The skeletal maturity was ahead of chronologic age by 1.5 to 7 years (mean 2.6 years); there was no significant difference between ITPP and NTPP. The mean height age in ITPP was significantly more (p<0.01) than that in NTPP (*Table I*).

Pelvic ultrasonography in 20 demonstrated, uterine size larger than in normal prepubertal girls in 8, and an ovarian size of pubertal age in 9. In 11 multiple small cysts were noted in ovaries. Vaginal cytology(21) showed a marked estrogen influence in fifteen.

Basal serum FSH levels ranged between 1.44 and 26 mIU/ml (mean 6.94±5.75 mIU/ml) and LH levels ranged between 0.1 and 13 mIU/ml (mean 5.52±3.49 mIU/ml)
### TABLE I—Sexual Precocity in Girls \((n=58)\)

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>No. of cases (n)</th>
<th>Percentage</th>
<th>C.A. (yrs) Mean ± SD</th>
<th>Age at onset (yrs) Mean ± SD</th>
<th>Height age (yrs) Mean ± SD</th>
<th>Bone age (yrs) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I CPP</td>
<td>29</td>
<td>50</td>
<td>5.87±2.66</td>
<td>3.85±2.17</td>
<td>5.75±2.81</td>
<td>8.38±3.56</td>
</tr>
<tr>
<td>ITTPP</td>
<td>15</td>
<td>52</td>
<td>5.96±2.13</td>
<td>4.30±1.99</td>
<td>7.13±2.53</td>
<td>8.85±3.04</td>
</tr>
<tr>
<td>NTTPP</td>
<td>14</td>
<td>48</td>
<td>5.78±3.15</td>
<td>3.41±2.34</td>
<td>3.95±2.12</td>
<td>7.91±4.08</td>
</tr>
<tr>
<td>II PT</td>
<td>20</td>
<td>34.5</td>
<td>2.66±2.20</td>
<td>1.54±2.27</td>
<td>2.45±2.12</td>
<td>2.71±2.32</td>
</tr>
<tr>
<td>III PM</td>
<td>2</td>
<td>3.5</td>
<td>2.30±0.71</td>
<td>1.80±0.94</td>
<td>2.80±0.99</td>
<td>2.13±0.88</td>
</tr>
<tr>
<td>IV PA</td>
<td>5</td>
<td>8.5</td>
<td>5.83±2.87</td>
<td>4.70±2.79</td>
<td>5.04±2.51</td>
<td>5.31±2.13</td>
</tr>
<tr>
<td>V Others*</td>
<td>2</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One patient with hypothyroidism due to thyroiditis. One patient with McCune Albright.
The mean age at onset and presentation was significantly lower in girls with PT \((p<0.005)\) as compared to CPP.
The bone age in CPP was significantly advanced than chronologic age \((CA) = (p<0.01)\).
Statistical evaluation by Student’s ‘t’ test.

### TABLE II—Etiology of Central Precocious Puberty (CPP) Amongst 40 Children.

<table>
<thead>
<tr>
<th>Nature of TPP</th>
<th>Girls ((n=29))</th>
<th>%</th>
<th>Boys ((n=11))</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td></td>
<td>No. of cases</td>
<td></td>
</tr>
<tr>
<td>Idiopathic (ITPP)</td>
<td>15</td>
<td>52</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Neurogenic (NTPP)</td>
<td>14</td>
<td>48</td>
<td>8</td>
<td>72</td>
</tr>
<tr>
<td>Post meningitic</td>
<td>11</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Cong. hydrocephalus</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Post asphyxial</td>
<td>4</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>3</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Pinealoma</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

(Table III). The mean serum estradiol level was \(44.39±40.92\) pg/ml. LHRH stimulation\((10)\) \((Fig. 3)\) showed a predominant LH response with a peak LH/FSH ratio more than 1 (peak FSH response 5.1 to 80 mIU/ml, mean 32.91±23.55 mIU/ml; and peak LH 5.6 to 249, mean 93.8±67.77 mIU/ml) \((Table III)\).

**Group II: Girls with Premature Thelarche (PT)**

Twenty of the 58 girls \((34%)\) presented with isolated progressive breast development starting between 0.25 and 6.5 years. The mean age at presentation was \(2.66±2.2\) years \((Table I)\), being significantly younger.
TABLE III—Basal FSH, LH, Estradiol and Peak FSH, LH Levels after LHRH test in Girls with True Precocious Puberty (TPP) and Premature Thelarche (PT)

<table>
<thead>
<tr>
<th></th>
<th>No. of cases (n)</th>
<th>Basal FSH mIU/ml Mean ± SD</th>
<th>Basal LH mIU/ml Mean ± SD</th>
<th>Estradiol pg/ml Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPP</td>
<td>29</td>
<td>6.94 ± 5.75</td>
<td>5.52 ± 3.49</td>
<td>44.4 ± 40.92</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>32.91 ± 23.55</td>
<td>93.8 ± 67.77</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>20</td>
<td>5.31 ± 4.19</td>
<td>2.08 ± 1.15</td>
<td>16.05 ± 9.87</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>68.08 ± 30.72</td>
<td>19.86 ± 9.39</td>
<td></td>
</tr>
</tbody>
</table>

No significant difference between basal levels of FSH in TPP and PT (p > 0.05) but LH and estradiol differ significantly (p < 0.01).

Peak FSH significantly higher in PT (0 < 0.05).
Peak LH significantly higher in TPP (p < 0.05).

No significant difference between basal levels of FSH in TPP and PT (p > 0.05) but LH and estradiol differ significantly (p < 0.01).

Peak FSH significantly higher in PT (0 < 0.05).
Peak LH significantly higher in TPP (p < 0.05).

Fig. 1. Height and weight percentile (Tanner's) in girls (n = 29) with TP and NT. The three girls with NT above 50th percentile for height had hypothalamic hamartomas.

than the group with TPP (p < 0.05). Unlike the TPP, the PT had a mean height age and bone age close to the chronologic age.

Past history and family history were non-

contributory. Breast development varied between Stages II and III. There were no other secondary sex characteristics. Vaginal cytology (10) showed minimal estrogen effect in two. Pelvic sonography in (15) showed normal uterine size in all, and normal ovaries in eleven; three cases showed two to three small ovarian follicles. One 6.5 year-old-girl had a large cyst 17 × 10 mm in left ovary. On follow up the cyst regressed, breast development, however, persisted.

Basal FSH and LH levels of 5.31 ± 4.19 mIU/ml and 2.08 ± 1.15 mIU/ml, respectively (Table III) were significantly lower (p < 0.01) than TPP. The LHRH stimulation test (6) showed predominant FSH peak response of 68.08 ± 30.72 mIU/ml with LH peak of 19.86 ± 9.39, and LH/FSH ratio of less than 1 (Table III and Fig. 3). The mean basal estradiol level of 16.05 ± 9.87 pg/ml was significantly (p < 0.01) lower than in girls with TPP (Table III). The basal hormonal profile was not always helpful in distinguishing PT from early TPP presenting with isolated breast enlargement due to overlap of values (Fig. 2).
Group III: Premature Menarche

In the present series two girls aged 1.75 years and 2.75 years (Table I) presented for cyclical vaginal bleeding in absence of any history of medication, and without any sign of sexual precocity. Their linear growth was at 90th percentile of Tanner’s and the skeletal maturity close to chronologic age. The younger patient presented for six episodes of monthly bleeding beginning at 1.5 years. Her pelvic sonography and brain CT scan were normal and vaginal cytology showed minimal estrogen influence. Basal serum gonadotropins, estradiol, thyroid hormones and TSH were normal but prolactin was high (62 mIU/ml). The second patient presented with 7 episodes of vaginal bleeding over a four month period. Her pelvic sonography demonstrated 2-3 mm cyst in the right

Fig. 2. Serum FSH, LH and estradiol values in girls with central precocious puberty - CPP (n = 29) and premature thelarche - PT (n = 20).

Fig. 3. Mean ± SD, FSH and LH values after IV LHRH (50-100 µg) in girls with TPP (n = 10) and PT (n = 6), showing a predominant LH response in TPP and FSH response in PT.
ovary. Hormonal profile was normal. Over the next few months of observation bleeding stopped in both. Bleeding has not recurred in the past five years in any of them and no other secondary sex characters have developed as yet.

**Group IV: Premature Adrenarche (PA)**

Five of the fifty girls presented with slowly progressive pubic hair growth, (Stage II to III) without virilization; three of them had axillary hair with adult type sweat odor. None of them had any other secondary sex characters. The age at onset of pubic hair growth was between 4 and 7 years (Table IV). One of these patients (RK) with rapid weight gain was found to have retardation of skeletal maturation by 2.5 years and was confirmed to have hypothyroidism due to thyroiditis (Table IV). DHEAS was elevated in two, and urinary 17 ketosteroids were marginally elevated (for their age) in three. 17-OHP response to ACTH stimulation was unequivocal. Basal FSH, LH and estradiol were in the pubertal range. On subsequent follow up over the past four years puberty has progressed normally in the four older girls and the fifth one is growing normally.

**Group V: Hypothyroidism and McCune Albright Syndrome with Sexual Precocity**

One of the patients (Table I), aged 5 years and 10 months presented with 2 episodes of vaginal bleeding over two months. She had pallor, puffiness of eyes, and breast development (Stage II with pigmented nipples and areola but no galactorrhea). Her height was below 3rd percentile Tanner’s with retardation in skeletal maturation by 18 months. Pelvic ultrasonography was normal except microcystic changes in the left ovary. Her T4 was 5.2 μg/dl with TSH > 90 mIU/ml, and a high antimicrosomal antibody titre. The LHRH test showed a predominant FSH response up to 16 mIU/ml with no rise in LH. Serum estradiol was 30 pg/ml (prepubertal < 20) and prolactin 16 mIU/ml. With institution of levothyroxine therapy all signs of puberty regressed.

The patient with McCune Albright syndrome had extensive unilateral skin pigmentation involving face and trunk, fibrous dysplasia in the fibula, and development of breast (Stage IV) and pubic hair (Stage II). Her skeletal maturation was advanced by 12 months. Her CT scan of head and pelvic ultra-sonography were normal. LHRH stimulation test showed a predominant LH response with a LH/FSH ratio of 3.48.

**Sexual Precocity in Boys (n=22)**

Boys constituted 27.5% (22/80) of the present series. The mean age at the time of presentation was (5.79 ± 3.93 years, range 6.5 to 12 years). The mean age at onset (3.56 ± 2.58 years) ranged between 2 months and 8 years. History of past intracranial infection was elicited in two. Two boys with CAH due to 11-β hydroxylase deficiency were first cousins.

Based on the history and clinical examination this group could be classified into TPP and pseudoprecocious puberty (PPP). The presenting features (Table V) in the 21 boys with precocity were pubic hair growth and increase in penile size. One subject presented with only pubic hair growth and was confirmed to have premature adrenarche. Physical features like increased growth, generalized musculature, and deepening of voice were often not noted by parents. The pubic hair development ranged from Tanner II to IV. Bilateral testicular enlargement (4 to 20 ml) was noted in 11/22 (TPP) the size correlated with the duration of symptoms and rapidity of progression. One patient
TABLE IV—Girls with Premature Adrenarche (n=5)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Subject</th>
<th>C.A. Age at Height</th>
<th>B.A. FSH</th>
<th>LII</th>
<th>E2</th>
<th>TESTO</th>
<th>17-OHP</th>
<th>DHEAS</th>
<th>URINARY 17-KS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(yrs)</td>
<td>(years)</td>
<td>(yrs)</td>
<td>(mIU/ml)</td>
<td>(mIU/ml)</td>
<td>(Pg/ml)</td>
<td>(ng/ml)</td>
<td>(ng/ml)</td>
</tr>
<tr>
<td>1</td>
<td>AJ</td>
<td>6-11m</td>
<td>5-5m</td>
<td>25-50</td>
<td>6-10m</td>
<td>1.9</td>
<td>1</td>
<td>8.4</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>KS</td>
<td>6-6m</td>
<td>4</td>
<td>50</td>
<td>5-9m</td>
<td>1.1</td>
<td>2.2</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>RK*</td>
<td>7-8m</td>
<td>6-10m</td>
<td>3-10</td>
<td>5</td>
<td>2.1</td>
<td>1</td>
<td>-</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>SP</td>
<td>7-5m</td>
<td>7-7m</td>
<td>3-10</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>9.5</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>RM</td>
<td>4-8m</td>
<td>4-6m</td>
<td>25-50</td>
<td>4</td>
<td>3</td>
<td>1.8</td>
<td>2.19</td>
<td>0.04</td>
</tr>
</tbody>
</table>

In prepubertal children, 17-OHP < 2.5 ng/ml, DHEAS (250-350 ng/ml) and 24 hr Urinary Ketosteroids are <3 mg between 3 and 7 years.

* RK - Hypothyroid patient (see text).

17-OHP response to ACTH stimulation in 3 cases (AJ, KS, SP) was unremarkable.

TABLE V—Symptoms and Signs in Male Children with Sexual Precocity (n=22)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubic hair growth</td>
<td>22</td>
</tr>
<tr>
<td>Increased penile size</td>
<td>21</td>
</tr>
<tr>
<td>Deepening of voice</td>
<td>10</td>
</tr>
<tr>
<td>Aggressive behavior and hyperactivity</td>
<td>13</td>
</tr>
<tr>
<td>Increased physical growth</td>
<td>7</td>
</tr>
<tr>
<td>Testicular size increase</td>
<td>11</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>6</td>
</tr>
<tr>
<td>Generalized muscularity</td>
<td>14</td>
</tr>
<tr>
<td>Acne</td>
<td>5</td>
</tr>
<tr>
<td>Mental subnormalcy</td>
<td>5</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
</tbody>
</table>

with testicular tumor had unilateral increase in testes (6 ml).

The weight of 20/22 patients were above the 50th percentile of Tanner and heights exceeded 50th percentile of Tanner's (90th percentile of ICMR) in all except one with hypothyroidism (<3rd percentile). In 11 of 22 (50%) the heights exceeded 97th percentile of Tanner's. Bone age advance in the group ranged between 1½ to 7 years with a mean advance of 4 years except in the patient with hypothyroidism.

These children could be classified into five etiologic groups after appropriate clinical assessment and investigation (Table VI).

**Group I: Boys with True Precocious Puberty**

TPP was suspected and confirmed in 11/22 (50%) boys (Table V). Eight of the eleven children (73%) had NTPP, more often than in girls (48%) (Table II). ITPP involved 27% of boys (52% in girls) (Table II). The causes of NTPP are listed in Table II. Hamartomas were noted in 4/11 boys (36%) with TPP. The mean age at onset of sexual precocity was 3.62 ± 2.59 years but the onset of symptoms was much earlier (3-10 months) in three of the four boys with hamartoma and progression more rapid; two of them had delayed milestones and developed seizures. One of the three boys with TBM had mental subnormality. An eleven-year-old boy with pineal tumor presented for increased intracranial pressure besides progressive sexual precocity since the age of 8 years. The age at onset was
| Nature of Disorder | No. of Cases | Percent | Age at onset (Yrs) | C.A. (Yrs) | H.A. (Yrs) | B.A. (Yrs) | FSH (mIU/ml) | IH (mIU/ml) | TESTO (ng/ml) | 17-OHP (ng/ml) | DHEAS (ng/ml) | URINARY 17-KS (mg/24 h) |
|-------------------|-------------|---------|--------------------|------------|------------|------------|--------------|------------|---------------|----------------|---------------|----------------|---------------------------|
| I CPP             | 11          | 50      | ±2.59              | ±3.84      | ±3.94      | ±4.69      | 5.28         | 7.10       | 4.32          | -              | -              | -                         |
| NTPP              | 8           |         |                    |            |            |            |              |            |               |                |                |                |                           |
| ITPP              | 3           |         |                    |            |            |            |              |            |               |                |                |                |                           |
| II Adrenal        | 7           | 32      | ±1.44              | ±4.28      | ±4.65      | ±4.09      | <3           | <1         | 2.14          | 6.6            | 20.56          | ±12.94                     |
| CAH               | 4           |         |                    |            |            |            |              |            |               | ±1.1           | ±2.3           | ±12.94                     |
| 11-OH             | 2           |         |                    |            |            |            |              |            |               |                |                |                |                           |
| 21-OH             | 2           |         |                    |            |            |            |              |            |               |                |                |                |                           |
| Carcinoma         | 1           |         | 8                  | 9          | 10.5       | 12         | <3           | <1         | 3.5           | 28.5           | 2590           | 45                          |
|                  |             |         | ±2.5               | ±2.5       |            |            |              |            |               | ±2.5           | ±2.5           | ±2.5                       |
| III Testicular    | 2           | 9       |                    |            |            |            |              |            |               |                |                |                |                           |
| Tumor             | 1           |         | 3.5                | 4          | 6          | 10         | 2            | 2.5        | 4.2           | <1             | 460            | 6.9                        |
| Testotoxicosis    | 1           |         | 2                  | 3.67       | 5.5        | 7          | 1            | 2          | 1.7           | <1             | 50             | 6.5                        |
| VI Hypothyroidism | 1           | 4.5     |                    | 7          | 12         | 7          | 5            | 8          | 4             | -              | -              | -                          |
| V Premature       | 1           | 4.5     |                    | 7.5        | 8.5        | 9.5        | 10           | 6.5        | <3            | 0.3            | 0.3            | 750                        |
| Adrenarche        |             |         |                    |            |            |            |              |            |               | 0.3            |                | 750                        |

CAH - Congenital adrenal hyperplasia due to 11-Hydroxylase (11-OH) and 21-Hydroxylase (21-OHP) deficiencies. The mean ± SD normal values for boys for the age group between 1 and 10 years in our laboratory are: FSH and LH < 3 mIU/ml; Testosterone < 0.1 ng/ml, 17-OHP: 0.25 to 2.5 ng/ml; DHEAS range: 250-350 ng/ml; Urinary 17-Ketosteroids - up to 3 mg.
between 3-4 years in children confirmed to have ITTP.

The mean basal FSH and LH were significantly above the prepubertal levels and higher than in boys with adrenal or testicular pathology (Table VI). The serum testosterone levels were very significantly higher than in prepubertal boys (p<0.001).

**Group II: Sexual Precocity Due to Adrenal Causes**

The second important cause of sexual precocity in boys was related to adrenals. This peripheral form of pseudo puberty was seen in seven boys (32%) of the series (Table IV). Six of these seven boys were confirmed to have CAH with an early onset of symptoms, mean age 2.45 ± 1.44 years. Testicular size was prepubertal in all. None had salt wasting symptoms, but hypertension ranging between 130 and 150 mm systolic by 90 to 100 mm diastolic was noted in four. All were well grown, muscular with height age and bone age exceeding the chronologic age (Table VI). Marked generalized darkening of the skin was observed in one. The gonadotropins were in the prepubertal range with elevation of serum testosterone as well as 24 hours urinary 17-ketosteroids (Table VI). The serum (17-OHP) level was moderately-elevated mean 6.6 ± 2.3 ng/ml (4.2 to 7.2 ng/ml) in the 4 children with the hypertensive form (presumed 11-β hydroxylase deficiency) as compared to the 2 with the classical CAH due to 21 hydroxylase deficiency (Table VI), with elevation up to 28 ± 5 ng/ml. Serum 11-deoxy cortisol elevation characteristic of CAH with 11-hydroxylase deficiency could not be estimated. The hypertension responded to steroid therapy.

One of these seven boys aged 9 years presenting with adrenogenital syndrome and a left adrenal mass had marked elevation of adrenal androgens, DHEAS and androstenedione (Table IV) with very high (45 mg/24 hours) urinary 17 ketosteroids. CT scan confirmed large mass which proved to be an adrenal carcinoma on surgery.

**Group III: Sexual Precocity due to Testicular Causes**

Testicular pathology affected two boys (9%). A four year old boy had testicular tumor with unilateral testicular enlargement (volume 6 ml). His height age and bone age were markedly advanced (Table VI). Imaging studies of the gonads confirmed a well defined unilateral well encapsulated mass. Hormonal assays were confirmatory with well marked serum testosterone elevation and minimal increase in DHEAS (Table VI). Histopathology confirmed a Leydig cell tumor on orchidectomy. On follow up one year later this patient developed a slowly progressive TPP.

One patient (MG) presented at 3 years 8 months, with progressive penile growth and pubic hair since the age of two years. The pubic hair was Tanner Stage III with penile size OS and prepubertal testes (between 2-3 ml). His height age (5.5 yea) and bone age (7 years), were both markedly advanced, (Table VI). His 17-OHP and adrenal hormones (DHEAS and androstenedione) were normal, urinary 17 ketosteroids were moderately elevated and nonsuppressible by dexamethasone. Serum testosterone was elevated to 1.7 ng/ml and gonadotropins were suppressed. The response to LHRH testing was prepubertal. Early morning ACTH level of 10 pg/ml was normal (norml 12-60 pg/ml). 17-OHP response to intravenous ACTH was equivocal. Testicular biopsy was refused. There was no history of medication and family history was noncontributory. This patient probably had gonadotropin inde-
ependent precocious sexual development now described as testicular testotoxicosis.

Groups IV and V

One 12-year-old boy with moderate mental subnormalcy and growth failure had progressive sexual maturation since the age of 7 years. He had TPP as indicated by bilateral increase in testicular size (12 ml), with retarded height age (7 years) and bone age (5 years) (Table VI). His hypothyroid state was confirmed by low T3, T4 and TSH >100 mIU/ml with prolactin elevation to 110 mIU/ml.

Another 8½-year-old boy presenting for progressive pubic hair growth Stage III since the age of 7½ years had slightly advanced bone age and moderate obesity. His serum LH and testosterone were in prepubertal range with slight elevation of serum DHEAS and urinary 17 ketosteroids (Table VI). CT scan of the adrenals was normal. 17-OHP and DHEAS response to ACTH stimulation test was unequivocal. These findings and follow up confirmed the diagnosis of premature adrenarche.

Discussion

A variety of etiologic factors cause isosexual precocity by premature elaboration of sex steroids in response to gonadotropins of pituitary origin or rarely from other sources or intrinsic disease of the gonads or adrenals. Besides being classified as complete or incomplete, true or pseudo, sexual precocity is also referred to as central or peripheral and occasionally as combined peripheral and central when the latter supervenes over the former. Sexual precocity in girls is often a variation of normal; in its extreme form as in idiopathic TPP, or as with premature thelarche and adrenarche or uncommonly-isolated prepubertal menses. Forms of sexual precocity in girls which are slowly pro-

gressive variants(13) or transient(14,15) are now described. An inherited gonadotropin independent disorder in boys also designated familial testotoxicosis, is now known (16). Hypothalamic hamartomas have now been identified with MRI in the so called ITPP in both the sexes(5).

Precocious puberty is encountered more commonly in girls than boys. In a large series of 772 cases reviewed by Seckel there were 591 girls and 181 boys (17). The present series of 80 children had a female to male ratio of 2.65 : 1.

Central form of True Precocious Puberty in Both the Sexes

The central form of TPP is most commonly encountered and involves more than 50% of children presenting with sexual precocity(2-5). It is reported to be five times more frequent in girls than in boys(18). In the present series centrally mediated TPP involved 40 of the 80 children (50%) with a female to male ratio of 2.64:1 (29 girls and 11 boys).

More than one sign of sexual maturation with advanced physical growth and bone age in girls is indicative of central form TPP though isolated breast development may be an early sign of TPP for as long as 6 months, and hence diagnostic difficulties arise in distinguishing early TPP from premature thelarche. In boys bilateral testicular enlargement suggests central form of puberty.

Amongst the girls with ITPP wide variation in the age of onset and rate of progression was observed with a relatively slow progression in majority of girls with the post meningitic form and an onset during infancy or early childhood with a rapid progression in those with hamartomas. A slowly progressive variant as described recently(14) was noted in three of the fifteen girls with ITPP. Interestingly increased physical growth
and height age advance was significantly more (p<0.05) in girls with ITPP as compared to NTTP.

Till recently TPP was considered to be idiopathic in 95 to 75% of girls(2,19,20) in contrast to 60% in boys(21). With the advent of high resolution CT Scans and MRI, higher frequency of organic form of TPP is recognised and hypothalamic hamartomas account for 16 to 33% in girls(5,22) and 50% in boys(5). In the present series amongst the 29 girls with TPP, only 52% had the idiopathic form and 48% had organic neurogenic pathology (NTTP). Amongst the 11 boys with TPP 27% were idiopathic and 73% had an organic cause. Two series from India report the incidence of ITPP in boys as 14%(6) and 25%(7) as compared to 6% from the USA(5). Postmeningitic form of TPP involved 31% of girls and 27% of boys, thus contributing to almost two thirds (64%) of the girls and one-third (36%) of the boys with NTTP. Similar high incidence of postmeningitic precocious puberty involving over 25% and ITPP in 57% in a series of 21 girls with TPP has been reported(6). However, other Indian series reported the incidence of ITPP in girls as 71%(7) and 85%(23).

In the present series hamartomas were detected in 10% of girls and 36% of boys with TPP. Of the tumors causing precocious puberty, hypothalamic hamartomas are now believed to be the most common. Hamartomas constitute an accessory hypothalamus with neurones releasing pulsatile GnRH bringing about early onset and rapid progression of sexual development with relatively higher LH and FSH levels(22,24). Of the seven children (3F and 4M) with hamartomas in the present series all had onset of symptoms by the age of 3 months to three years; in girls menarche was attained by the age of 3 months to 3½ years. A variety of seizure disorders are also described in children with hamartomas(24). Two of the boys in this series developed seizures, on follow up.

In girls basai levels of gonadotropins and estradiol are not always helpful in differentiating early TPP from PT as individual values overlap due to inclusion of girls at varying stages of sexual development both early and late. However, the mean levels of LH and estradiol were significantly elevated (p<0.05) in girls with TPP. LH predominant response to LHRH with LH/FSH ratio exceeding one is more likely to be encountered in TPP(11,12,25). Follow up evaluation of these girls confirmed the initial diagnosis.

Sex Precocity As Variants of Normal

These variations are more commonly encountered in females; premature thelarche/gonadarche and premature pubarche/adrenarche and a related but rare disorder isolated prepubertal menses(19,20). These are incomplete forms of isosexual precocity where breast development (thelarche) or sexual hair development (pubarche) is of a degree appropriate for an early stage of adolescence and most often non-progressive. In the present series, 27/58 girls (46%) belonged to this category of variants of normal. Amongst the 22 male children only one had PA.

Premature Thelarche

The term premature thelarche (PT) was first coined by Wilkins to refer to the isolated development of breasts in young girls(2). In these girls growth and skeletal maturation are unaffected and there is no significant estrogen effect on vaginal cytology or changes in hormonal levels. This constituted the next largest group (20/58 - 34%) amongst girls presenting with sexual precocity. The mean age at onset was significantly lower than
girls with CPP. Mills et al. (26) described the natural history of 46 girls with PT and on 3-5 years follow up noted no change in 57%, progressive enlargement in 11% in absence of any other symptoms and complete regression in 32%. In the present series skeletal maturation as expected was unaffected and pelvic ultrasound and vaginal cytology was non-contributory except the detection of ovarian cyst in one. Since breast development is often the first sign of TPP in majority of girls, careful evaluation and follow up is essential to distinguish PT from TPP for prognostic and therapeutic reasons. Basal levels of gonadotropins and estradiol were unremarkable and within the prepubertal range. The FSH predominant response to GnRH with peak LH/FSH ratio was less than one and was helpful in supporting the diagnosis of PT, when tested.

The precise pathophysiological mechanisms causing thelarche are still unknown. It was hypothesized to result from increased breast sensitivity to estrogen (27) or as summarized by Pescovitz (12) due to transient estrogen secretion by ovarian follicular cysts, or increased estrogen production from adrenal precursors. Partial activation of the hypothalamic-pituitary-ovarian axis with excessive FSH secretion, is also postulated (12,28). The FSH-predominant response typical of girls with PT is probably consistent with early activation of hypothalamic LHRH neurones (12). Thus, Pescovitz et al., postulated that PT and CPP may represent different positions along a continuum of hypothalamic LHRH neuron activation (12).

**Isolated Vaginal Bleeding**

Isolated cyclic vaginal bleeding in otherwise normal prepubertal girls in the absence of sexual development or any detectable uterine or vaginal abnormalities is uncommon and seldom reported (29,30). In recent report of seventeen girls with isolated menses, the plasma gonadotropins were normal but the estradiol level was significantly above the normal prepubertal range suggesting transient ovarian activity and instability of the pituitary gonadal axis (31). These authors also speculate seasonal variations of hormonal regulation (31). One of our patients showed a predominant FSH response with unexplained prolactin elevation. Similar brisk response of FSH to GnRH is described in one of four patients with premature menarche suggesting a transient activation of the hypothalamic pituitary-gonadal (HPG) axis (29). Vaginal cytology showed little estrogen effect in both our patients in presence of normal serum estrogen levels. Increased sensitivity of the endometrium to circulating estrogen levels too low to produce breast development has been postulated (29). A long term follow up of these girls to adulthood had shown no abnormality (30). It is important to exclude local causes and conditions like hypothyroidism, McCune Albright syndrome, ovarian pathology and NTTP in girls presenting with isolated vaginal bleeding.

**Premature Adrenarche**

Premature adrenarche (PA)—growth of public and/or axillary hair in children is usually a nonprogressive benign condition caused by precocious release of adrenal androgens and is seen more commonly in girls. It may be confused with TPP or pathologic virilizing disorders. High levels of DHEAS are described in PA but the correlation between pubic hair status and DHEAS, cannot always be established. Racial (predominance in black girls) and individual difference in the sensitivity of pubic hair follicles to androgenic stimulation is postulated (32). In the present series four girls and
one boy presented between 5.5 to 8 years of age. Adult type axillary odor as emphasized by Kaplowitz(32) was noted in all girls. Minimal elevation of adrenal androgens and urinary 17-ketosteroids with normal gonadotropins and gonadal steroids, supported early activation of adrenals.

Though breast development and early menarche are known in untreated hypothyroids, isolated premature adrenarche as a presenting feature of hypothyroidism is uncommon as seen in one of our patients. Adenal hormonogenesis is usually unaffected(33).

Hypothyroidism and McCune Albright syndrome causing precocious puberty

Of these 80 children two girls with thyroiditis (1 precocious puberty and 1 with adrenarche) and one boy with congenital hypothyroidism presented with sexual precocity. It is presumably caused by hyperprolactinemia and/or increased gonadotropins in response to excessive production of thyrotropin releasing hormone(34,35). Adrenal hormonogenesis is not increased, therefore, pubic hair and axillary hair are usually absent or sparse(33).

The association of sexual precocity with McCune Albright Syndrome in girls is well known. The mechanism is controversial; usually due to autonomous ovarian cysts or occasionally early activation of the hypothalamic-pituitary-gonadal axis(36). In our patient the presence of other sexual characteristics and a LH predominant response to LHRH testing supported central activation.

Incomplete (Peripheral) Forms of Sexual Precocity in Boys

Virilization in absence of activation of the HPG axis occurs due to autonomous secretion of adrenal androgens or testosterone or by production of chorionic gonadotropins from other sources causing stimulation of Leydig cells. Lack of testicular enlargement as in TPP, suppressed LH<FSH levels and prepubertal gonadotropin response to GnRH is characteristic. In a compiled data on 348 boys with sexual precocity 65% had complete and 35% had the incomplete form with adrenal disorders accounting for 65% of the boys with incomplete form(21)

Sexual Precocity and Disorders of the Adrenals

The most common cause of early pseudopuberty in boys is usually nonsalt loosing form of CAH-21 hydroxylase deficiency (18,21). Rapid physical growth and signs of sexual precocity in the absence of testicular growth are often noticed by 2 to 3 years of age. In the present series, CAH was an important underlying cause and involved 27% of boys with sexual precocity and 55% with the incomplete form. Four of them had 11-β hydroxylase deficiency associated with hypertension. The estimation of specific adrenal androgens in blood/urine help in confirming the diagnosis. Marked elevation of 17-OHP in blood is typical of 21 hydroxylase deficiency while as 11-deoxycortisol estimation helps the diagnosis of 11-β hydroxylase deficiency. The presence of hypertension with virilization, dexamethasone suppressibility of 17-ketosteroids and control of hypertension with corticosteroids are useful aids. The clinical picture is occasionally confused by the superimposed onset of true puberty(2). In children diagnosed late, TPP may supervene with the institution of glucocorticoid therapy(37).

Adrenal tumors, adenomas or carcinomas are uncommon but most often are virilizing, and occur in the first decade(38). The patient in the present series had adrenal carcinoma. It is important to differentiate
adrenal virilizing tumor from congenital adrenal hyperplasia. Very high levels of circulating adrenal androgens as also seen here and nonsuppressible markedly elevated urinary 17-ketosteroids are characteristic of the former. Part of these androgens are converted to testosterone.

**Sexual Precocity and Disorders of the Testes**

Only 2 of the 22 boys (9%) in this series had sexual precocity due to testicular involvement. Tumors of the testicle are rare in childhood and usually present as unilateral painless scrotal mass. In contrast with other testicular neoplasms which occur during the first year of life, functioning Leydig cell or sertoli cell tumors tend to occur after 2 years of age and majority have occurred in males five years of age or older (39,40). Leydig cell neoplasms in contrast to other testicular germinal neoplasms follow a benign course. As with CAH or adrenal virilizing tumors, rapid onset of true puberty may follow the removal of the tumor as was also noted in the present case.

Leydig cell hyperplasia can occur independent of gonadotropin control (13,41). The disorder is familial, apparently transmitted as an autosomal sex limited trait manifested only in males. Virilization may be evident at birth and usually distinct by age of five years. Gonadotropins are low, HCG undetectable, serum testosterone is elevated and plasma LH response to LHRH is prepubertal. Little increase in testicular size inappropriate for the degree of sexual maturation may be seen. This disorder is uncommon and only one patient in this series was suspected to have this. Testicular biopsies show a spectrum of changes from incipient pubertal development of the tubules and proliferation of Leydig cells to the appearance of normal adult testes (13,41). A circulating testis stimulating factor has been recently identified in the plasma of boys with this disorder (42).

Thus isosexual precocity is more commonly encountered in girls and in this series was almost three times more common than in boys. The underlying causes also differ a great deal between the two sexes. In females it is more often the variations of normal, ranging from idiopathic true precocious puberty to premature thelarche, menarche and adrenarche, which involved 41 of the 58 girls (71%). Adrenal causes are important in boys. Central form of the disorder is common in both the sexes and involved 50% of the whole series and in both the sexes. A much higher frequency of organic neurogenic causes (48%) leading to centrally mediated TTP was noted in girls, with 2/3 of these attributable to TBM. We are not aware of similar high incidence of NTPP from other developing countries or elsewhere. Hamartomas are now being identified with increasing frequency in the so called ITTP and were seen in 10% of girls and 36% of boys with TPP in this series. A careful clinical evaluation, growth monitoring and follow up with appropriate investigations is helpful in planning appropriate managing strategies.

**Acknowledgements**

The authors would like to thank the Dean, B.J. Wadia Hospital for Children and Institute of Child Health for his kind permission to publish this paper. They are also grateful to the Research Society of B.J. Wadia Hospital and Sir H.N. Medical Research Society for supporting this study, and Mr. B.N. Rao, Biostatistician for statistical evaluation.

**REFERENCES**

1. Kulin HE. Disorders of sexual maturation: Delayed adolescence and precocious


