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Original Research Article

Clinical spectrum of premature sexual developments in a tertiary care center of South India

Durai Arasan G.[1]*, Hemachitra J.[2]

[1]Department of Pediatrics, Govt. Tiruvannamalai Medical College, Tiruvannamalai, Tamil Nadu, India
[2]Department of Pediatrics, Govt. Tiruvarur Medical College, Tiruvarur, Tamil Nadu, India

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***Correspondence:**
Dr. Durai Arasan G.,
E-mail: drdurai_07@yahoo.com

ABSTRACT

Background: The clinical spectrum of precocious sexual development and its etiology are varied and we need to know our own data regarding this. The objective of the study was to study the clinical spectrum of premature sexual developments and the usefulness of imaging modalities in understanding the ongoing insult.
Methods: Female child of less than 8 years of age and male child of less than 9 years of age with development of secondary sexual characteristics were registered and analyzed. After through clinical examination the children were subjected to investigations, which included radiological and hormonal.
Results: Majority of cases 54% (14 cases) had symptoms before 2 years of age. Premature thelarche was seen in 58% and the majority 71% was less than 2 years of age. 17% of the female children with sexual precocity had true precocious puberty. Hypothyroidism as a cause of true precocious puberty is 8%. Heterosexual precocious puberty was seen in 16%. Among male children peripheral cause of isosexual precocious puberty was seen in two cases. Congenital adrenal hyperplasia as a cause of sexual precocity among both sexes was seen in 15%. All four children (100%) with true precocious puberty showed uterine length of > 3.5 cm and 93% of the children with isolated premature thelarche showed a uterine length of < 3.5 cm.
Conclusions: Sexual precocity is most common among female children. Isolated premature thelarche is the most common type of sexual precocity. Ultrasound visualized uterine length helps in the differentiation of isosexual precocious puberty and isolated premature.

Keywords: Adrenarche, Menarche, Precocious puberty, Thelarche

INTRODUCTION

The onset of pubertal changes at an earlier than normal age comprises a fascinating but still poorly understood group of disorders. The development of secondary sexual characteristics before the age of 8 years in girls and before the age of 9 years in boys constitutes "precocious puberty".[1,2,4] There are two major classes of "precocious puberty", those that result from early reactivation of the hypothalamic pituitary-gonadal axis, generally referred to as "gonadotropin dependent or central or true precocious puberty", and those that do not result from early reactivation of the hypothalamic pituitary-gonadal axis, referred to as "gonadotropin independent or pseudo or peripheral precocious puberty".[1,2,4]

True precocious puberty is always isosexual and the physical signs of sexual development are in keeping with the phenotypic gender of the child. In precocious pseudopuberty the sex characteristics may be "isosexual" or "heterosexual". Precocious pseudopuberty may induce

maturation of the hypothalamic pituitary - gonadal axis and trigger the onset of true sexual precocity.

Incomplete sexual precocity or variants of pubertal developments refers to those disorders in which pubertal development is mild or non-progressive resulting in premature thelarche or premature adrenarche or premature menarche".[3]

The disorders that cause sexual precocity are multiple and successful management of these cases depends on the identification of precise etiological factors. Though there are many reports regarding the sexual precocity from the west, there are very few studies from India and most of them are case reports. We want to study our own population. The present study reveals the clinical variants presenting as sexual precocity. This study also focuses on the importance of imaging modalities in the diagnosis of precocious puberty.

Aim of the study were,

- The Clinical spectrum of premature sexual developments
- Role of imaging modalities in understanding the on-going insult.

METHODS

Design of the study was descriptive study. Study Setting was Endocrinology Division, ICH and HC, Egmore. The period of the study was from June 2010 to May 2011. All cases attending endocrinology OP and diagnosed as premature sexual development.

Female child of less than 8 years of age and male child of less than 9 years of age with development of secondary sexual characteristics.

Total no of children analysed were 26.

Manoeuvre

All cases satisfying the case definition were registered in the study. A detailed prenatal, perinatal and postnatal history, the type of premature sexual development, the age of onset, the course of the disorder, associated problem were recorded in a proforma.

A detailed history of previous illness with special emphasis on CNS infections (meningitis / encephalitis), shunt surgery for hydrocephalus, radiation exposure to brain, head injury, ingestion of steroids, external application of steroid cream, in the proforma. A detailed family history for premature sexual developments and/ or precocious puberty is also recorded.

The child was then subjected to a through clinical examination and the presence or absence of acne, goiter, hoarse voice, axillary hair, breast development (as per Tanner staging), galactorrhea, public hair (as per Tanner staging), clitoromegaly, menstruation, stretch penile length and testicular volume as assessed by prader's orchidometer were recorded in the proforma.

Anthropometric measurements like height, weight, head circumference, upper segment and lower segment ratio were recorded and compared with standard charts, for age and sex matched percentiles. The vital parameters like, pulse, blood pressure, respiratory rate and temperature were recorded.

After the clinical assessment, the child was subjected to investigations, which included radiological and hormonal. The radiological investigations being (i) x-ray for bone age assessed with help of radiographic atlas of skeletal developmental, (ii) ultrasound abdomen and pelvis, for evaluation of length and morphology of uterus, ovaries, adrenals and testes, (iii) MRI brain, for selective patients and (iv) CT scan abdomen for selective patients who warranted.

The hormonal investigation done were (i) TSH, (ii) T_4, (iii) LH, (iv) FSH and (v) 17 B estradiol for female patients, (vi) testosterone for male patients (vii) 17 hydroxy progesterone in cases suspected to have congenital adrenal hyperplasia and (viii) DHEA, DHEAS and cortisol in female patients with heterosexual precocious puberty.

Blood samples were collected and pooled and sera were separated for hormonal assay.

RESULTS

Registered total children were 26.

Sex distribution was as below.

Male: 2

Female: 24

Age distribution

The mean age of onset is 3.4 years and the mean age of presentation to hospital is 4.06 years. Majority of children 54% (14) had symptoms before 2 years of age, and 46% (13) presented to us before the age of 4 years (Table 1).

Symptoms and signs

Breast development was the most common presenting symptom, present in 83.3% (20 children), Public hair growth was present in 29.16% (7 children) and menarche was present in 20.08% (5 children) (Figure 1).

Public hair growth, increase in weight gain and increase in penile length were present in both the males. There

was no increase in testicular volume in both children (Figure 2).

Table 1: Age distribution at onset of symptom and at presentation of children with sexual precocity.

Age group (in years)		Age of onset of symptoms		Age of presentation	
		(n)	Percentage	(n)	Percentage
Birth	6 Months	8	30.7	0	
6 Months	1 yr	6	23	8	30.7
2 yrs	3 yrs	3	11.5	4	15.38
4 yrs	5 yrs	6	23	4	15.38
6 yrs	7 yrs	3	11.5	10	38.46
8 yrs	9 yrs	0		0	
		26		26	

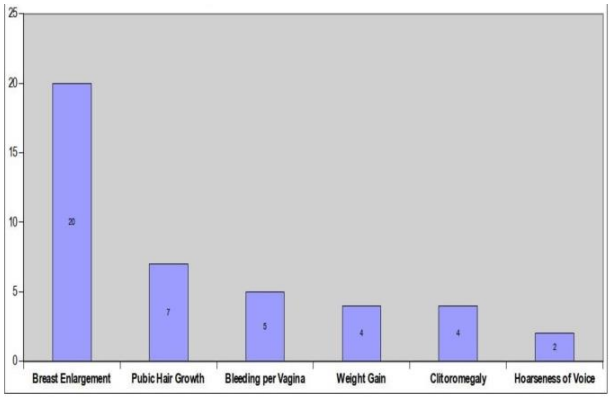

Figure 1: Signs and symptoms in children with sexual precocity.

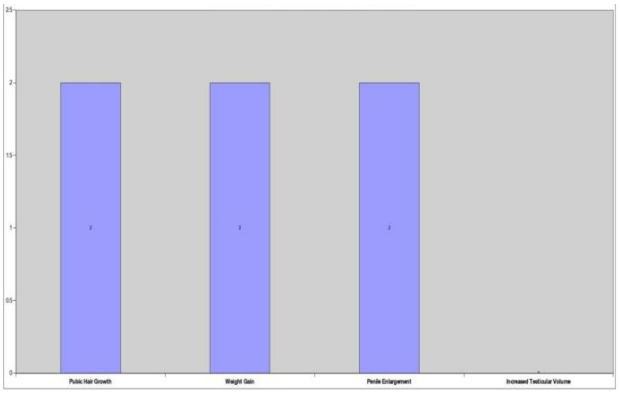

Figure 2: Symptoms and signs in male children with sexual precocity.

Height age distribution

Height age > 90th percentile 12 cases

Height age normal for age 14 cases

Height age < 10th percentile Nil

26 cases

Height of more than 90th percentile was found in 46.15% (12) children who signify increased somatic growth. Out of these 12 cases, 4 children had true isosexual precocious puberty, 4 children had congenital adrenal hyperplasia, 2 adrenal tumors, (8.3%) 1 child premature thelarche and (8.3%) 1 child was hypothyroidism.

Thelarche

Thelarche was noticed in 20 children (83.33%). Out of the 20 children with thelarche, 80% (16) were bilateral. 10 children (62.5%) were premature thelarche, 4 children (25%) were true isosexual precocious puberty and 12.5% (2 cases) were hypothyroidism. Unilateral thelarche constituted 20% and all 4 were premature thelarche. The breast development varied between tanners stages II and IV.

Pubarche

Pubic hair development was noticed in 9 children, of which, 7 were females and 2 were males. Out of the 7 females with pubarche, 42.8% (3) were true isosexual precocious puberty, 28.5% (2) were congenital adrenal hyperplasia and 28.5% (2) were adrenocortical tumor. The public hair development varied between tanner stages II and III.

In males pubarche was seen in 2 children and both were congenital adrenal hyperplasia. Both the male child had an increase in phallic length, > 2SD for their age, and the testicular volume was < 3.5 ml as measured by Prader's orchidometer.

Thelarche and menarche without pubarche was noticed in 8.33% (2 children). One was a true isosexual precocious puberty and the other was a case of hypothyroidism. Thelarche, pubarche and menarche, all three were present in 12.5% of female children and all of them were true isosexual precocious puberty.

Investigations

Radiological

X- ray for bone age

An acceleration of > 2 years above the chronological age was found in 46.15% (12 cases). Out of these 12 cases, 33.33% (4 cases) were true isosexual precocious puberty, 33.33% (4 cases) were congenital adrenal hyperplasia, 16.6% (2 cases) were heterosexual precocious puberty due to adrenocortical tumour, 8.3% (1 case) were premature thelarche and 8.3% (1 case) were hypothyroidism.

Ultrasound abdomen and pelvis

The upper limit of uterine length in the prepubertal age group is 3.5cm. Excluding hypothyroidism, of all the 18 female children with signs and symptoms of isosexual maturation, the four children with true precocity had enlarged uterine segment. Enlarged uterine segment was also observed in one case of premature thelarche (Table 2).

Table 2: Uterine length in prepubertal and pubertal girls.

	Uterine segment >3.5 cm	Uterine segment <3.5 cm	Total
True precoccity	4	0	4
Premature thelarche	1	13	14
	5	13	18

The association of enlarged uterine segment with central precocity is statistically significant (p-0.001634).

Hormonal

Luteinizing hormone (LH) and Follicular stimulating hormone (FSH)

LH and FSH were done in 20 cases. It was not done in 4 cases of congenital adrenal hyperplasia and 2 cases of adrenocortical tumor, where peripheral cause is established.

Table 3: LH and FSH.

	< 3 mIU/ml No. of cases	> 3 mIU/ml No. of cases	Total
LH	15	5	20

Out of the 20 cases LH was elevated significantly i.e., above 3 mIU/ ml in 25% (5 cases), and FSH was elevated significantly in 45% (9 cases). Both LH and FSH were elevated in 5 children, 4 of them were true isosexual precocious puberty and one child was found to be a hypothyroid. FSH alone was elevated in 4 cases, all the four being premature thelarche and all cases were below 2 years of age. This FSH elevation can be a part of the gonadotropin surge in the infancy which normally can last up to 2 years of age. In the rest of the 11 cases, both LH and FSH were below 3 mIU/ml and all the cases had premature thelarche.

17 β Estradiol

Estradiol estimation was done in 22 cases, except in 4 cases of congenital adrenal hyperplasia.

Estradiol values	Number of cases
Not detectable	10
< 10 pg/ml	7
> 10 pg/ ml	5

Out of the 22 cases, estradiol was elevated significantly in 22.7% (5 cases). Out of these 5 cases, 4 were true isosexual precocious puberty and 1 case was hypothyroidism. In the rest of the 17 cases estradiol levels were within normal limits.

T_4 and TSH

Thyroid function test was done in all the 26 cases. Elevated TSH and decreased T_4 were observed in 2 cases. In all other children the values were within normal limits.

Adrenal androgens

Dehydroepiandrosterone sulphate (DHEAS), cortisol and testosterone were measured in two cases of adrenocortical tumor and both cases showed significant elevation of DHEAS and testosterone. Cortisol was within normal limits in both cases. Both the patients underwent adrenalectomy and the HPE showed adrenocortical adenoma.

All the girl children in our study were found to be LHRH dependent and none had LHRH independent isosexual precocious puberty. None of the male child had Testicular cause of peripheral isosexual precocious puberty.

All the 2 children with heterosexual precocious puberty were girls.

Adrenal tumor

Two female children had suprarenal mass, one of them had on the right and the other on the left side. Both were confirmed with hormonal assays and CT scan abdomen and subjected to adrenalectomy.

Diagonsis

After a through clinical examination and investigation the cases were classified into three major groups.

- Isosexual precocious puberty
- Heterosexual precocious puberty
- Variants of sexual precocity.

The isosexual precocity can be classified further into a) LHRH dependent precocious puberty, b) LHRH independent precocious puberty and c) hypothyroidism (Table 4).

Table 4: Final diagnosis in the study population.

	Female	Male
I. Isosexual precocious puberty		
A. LHRH dependent (true or central		
i. Idiopathic	3	-
ii. CNS disorder Hydrocephalus	1	-
B. LHRH independent (Pseudo or peripheral)		
i. Boys Congenital adrenal hyperplasia	-	2
C. Hypothyroidism	2	-
II. Heterosexual precocious puberty		
i. Girls		
a. Congenital adrenal hyperplasia	2	-
b. Adrenocortical tumors	2	-
III. Variants of sexual precocity		
i. Premature thelarche	14	-
	24	2

Out of the 24 girls, 25% (6) had isosexual precocious puberty. Out of these 6 cases, 50% (3) idiopathic, 33.3% (2) hypothyroidism and 16.6% (1) CNS disorder. Heterosexual precocious puberty was seen in 16.6% (4) of female children. Out of these 4 cases, 50% (2) were congenital adrenal hyperplasia and 50% (2), virilising adrenocortical adenoma.

Premature thelarche was seen in 58.3% (14) of female children. Male children constituted 7.7% of the cases i.e., 2 and both were isosexual precocious puberty of peripheral cause. Both were due to congenital adrenal hyperplasia.

DISCUSSION

Wide variation exists in the clinical spectrum of premature sexual developments. Its etiology is multifactorial and successful management of these cases depends on the identification of the primary process which leads on to premature sexual developments. The most common age group was 6-7 years seen in 39% of children, followed by 6 months - 1 year seen in 30% of children. The mean age of onset of symptoms was 3.4 years in our study, whereas it was 3.37 years by Meena Desai et al, 4.8 years by K.M Prasanna Kumar et al, observations of these studies were comparable with our study.[5,7] In a study by Farzaneh Rohani from Tehran the mean age of onset for girls and boys was 7.43±1.4 and 5.8±2.1 years respectively.[8] This difference may be because of different ethnicity. Among the female children, premature thelarche was seen in 58% of our study, compared to 34% by Meena Desai et al, 21.7% by S. Khandekar et al, 14.2% by K. M. Prasanna Kumar et al and 34.1% by Farzaneh Rohani et al.[5-8] The higher percentage of premature thelarche in our study may be due to the difference in the study population. In our study 71% of the premature thelarche were less than 2 years of age compared to 80% in the study by Volta C et al, this observation was comparable to our study.[9]

Table 5: Isosexual precocious puberty comparison of our study with other studies.

	ICH and HC		Meena Desai et al[5]		S. Kandhekar et al[6]		KM Prasanna Kumar et al[7]		Farzaneh Rohani et al[8]	
	F	M	F	M	F	M	F	M	F	M
I. Isosexual precocious puberty										
A. Central or true										
i. Idiopathic	3	-	15	-	11	4	5	2	20	1
ii. CNS disorder										
Hydrocephalus	1	-	1	-	1	1	1	1	1	2
Hamartoma	-	-	3	4	-	-	-	1		
Post meningitic	-	-	10	3	-	-	-	-		
Pinealoma	-	-	-	1	-	-	-	-		
Suprasellar cyst	-	-	-	-	-	1	-	-		
B. Peripheral or pseudo										
i. In Boys										
Congenital adrenal hyperplasia		2	-	6	-	-	-	4		3
Adrenal tumour	-	-	-	1	-	1	-	-		
Virilising hepatoblastoma	-	-	-	-	-	1	-	-		
ii In girls										
Ovarian cyst									2	
McCune- Albright syndrome									1	
C. Hypothyroidism	2	-	-	1	1	-	-	-		

17% of the female children with sexual precocity had true precocious puberty, compared to 50% by Meena Desai et al, 52% by S. Khandhekar et al, 86% by K. M. Prasanna kumar et al and 47.7 % by Farzaneh Rohani et al.[5-8] Idiopathic true precocious puberty constituted 12.5% in our study, compared to 51% by Meena Desai et al, 48% by S. Khandhekar et al and 71% by K. M. Prasanna Kumar et al, and a majority 95 % of girls in the Tehran study by Farzaneh Rohani et al.[5-8] CNS disorder as a cause of true precocious puberty was seen in 4% of our study, compared to 4% by S. Khandhekar et al, 14% by K. M. Prasanna Kumar et al, 48% by Meena Desai et al and 66.6% of boys in the Tehran study by Farzaneh Rohani et al. [5-8] Among male children peripheral causes of isosexual precocious puberty was seen in two cases i.e. 100% of males in our study, compared to 25% of males in the study by S. Khandhekar et al and 14% of males in the study by Meena Desai et al.[5,6] The difference between our study and other studies, may be due to the ethnic variability.

Hypothyroidism as causes of precocious puberty is 8% in our study, compared to 3% by S. Khandhekar et al.[6] In the other two studies from North India hypothyroidism among females with sexual precocity was not reported. This increased percentage of hypothyroidism in our study may be due to increased prevalence autoimmune thyroiditis among the South Indian population (Table 6).

Table 6: Heterosexual precocious puberty comparison of our study with other studies.

	ICH and HC		Meena Desai et al[5]		S. Kandhekar et al[6]		KM Prasanna Kumar et al[7]		Farzaneh Rohani et al[8]	
	F	M	F	M	F	M	F	M	F	M
II. Heterosexual precocious puberty										
In Girls										
Congenital adrenal hyperplasia	2	-	-	-	3	-	-	-		
Adrenocortical tumor	2	-	-	-	-	-	-	-	1	

Heterosexual precocious puberty was seen in 16% of our cases, compared to 13% by S. Khandhekar et al.[6] This study was comparable to our study. Adrenocortical tumor as causes of sexual precocity was seen in 7.69% of our study, compared to 3.2% by S. Khandhekar et al and 12.5% by Meena Desai et al.[5-6] Congenital adrenal hyperplasia as a cause of sexual precocity among both sexes was seen in 15% of our study compared to 8% by Meena Desai et al, 10% by S. Khandhekar et al and 27% by K. M. Prasanna Kumar et al, Among male children congenital adrenal hyperplasia was seen in 2 cases, i.e 100% of males in our study, compared to 50% by K. M. Prasanna Kumar et al and 32% by Meena Desai et al.[5-7] These studies were comparable with our study, showing an increased occurrence of congenital adrenal hyperplasia among male children.

All four children (100%) with true precocious puberty showed uterine length of >3.5 cm and 93% of the children with isolated premature thelarche showed an uterine length of < 3.5 cm. Uterine length as a diagnostic parameter in the differentiation of isosexual precocious puberty and isolated premature thelarche was first done in our study. It was found to be highly useful and a reliable diagnostic parameter.

CONCLUSION

Sexual precocity is most common among female children. The disorders that cause sexual precocity are multiple. Isolated premature thelarche is the most common type of sexual precocity. Bone age skiagram and ultrasound visualized uterine length formed an important diagnostic tool in the differentiation of isosexual precocious poverty and isolated premature thelarche amongst pediatric population. Further studies in large numbers are needed to unravel the real magnitude of this problem.

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REFERENCES

1. Peter A. Lee. Central precocious puberty: An overview of Diagnosis, Treatment and outcome, Endocrinology and metabolism clinics of N.A. 1999;28:901-17.
2. Wheeler MD, Styne DM. Diagnosis and management of precocious puberty, Pediatric clinics of North America. 1990;37:1255-70.
3. Herman-Giddens PA, Slora EJ, Wasserman RC. Secondary sexual characteristics and menses in young girls. New York. Pediatrics. 1997;99:505-12.
4. Grumbach MM, Styne DM. Puberty: Ontogeny, Neuroendocrinology, Physiology and Disorders. Williams Text book of Endocrinology 8th edition. W. B. Saunders. 1994:1572-1603.

5. Desai M, Colaco MP, Choksi CS. Isosexual precocity: The clinical and Etiological profile. Indian Pediatr. 1993;30:607-23.
6. Khandekar S, Dash RJ. Clinical and Hormonal Studies in Precocious puberty, Indian J Pediatr. 1990;57:411-9.
7. Kumar KMP, Amminin AC, Menon PSN. Sexual precocity: Clinical profile and laboratory evaluation. Indian J Pediatr. 1987;54:897-902.
8. Farzaneh R, Salehpur S, Saffari F. Etiology of precocious puberty, 10 years study in Endocrine Reserch Centre (Firouzgar), Tehran. Iranian J Repro Med. 2012;10(1):1-6.
9. Volta C, Bernasconi S. Cisternino M. Clinical and auxological followup of premature thelarche. J Endocrinol Invest. 1998;21(3):180-3.

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