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ORIGINAL ARTICLE

Precocious Puberty in Children

Irum Atta, Taj Muhammad Laghari, Yasir Naqi Khan, Saira Waqar Lone, Mohsina Ibrahim and Jamal Raza

Abstract

Objective: To determine the etiology of precocious puberty in children and to compare the clinical and laboratory parameters of central and peripheral precocious puberty.

Study Design: Cross-sectional study.

Place and Duration of Study: Endocrine Clinic at National Institute of Child Health, Karachi, from January 2009 to December 2011.

Methodology: Children presenting with precocious puberty were included. The age of onset of puberty was documented. Clinical evaluation, Tanner staging, height, height SDS, weight, weight SDS, body mass index, bone age, pelvic USG, plasma estradiol level and GnRH stimulation were done. Ultrasound of adrenal glands, serum level of 17 hydroxyprogesterone, ACTH, Renin, aldosterone and testosterone were performed in children with peripheral precocious puberty. MRI of adrenal glands and gonads was done in patients with suspected tumor of that organ and MRI of brain was done in patients with central precocious puberty. Skeletal survey was done in patients with Mc Cune-Albright syndrome.

Results: CAH (81.8%) indentified as a main cause in peripheral percocious puberty and idiopathic (67.74%) in central precocious puberty. Eighty five patients were registered during this period. The conditions causing precocious puberty were central precocious puberty (36.47%), peripheral precocious puberty (38.82%), premature pubarche (10.58%) and premature thelarche (14.11%). There was a difference in the age of onset of puberty in case of central precocious puberty (mean=3, 2-6 years) versus peripheral precocious puberty (mean=5.25; 3.62 - 7.0 years). Children with central precocious puberty showed higher height SDS, weight SDS, FSH, LH than those with peripheral precocious puberty.

Conclusion: Etiology in majority of cases with peripheral precocious puberty was congenital adrenal hyperplasia and idiopathic in central precocious puberty. Central precocious puberty children showed higher height SDS, weight SDS, FSH, LH than peripheral precocious puberty.

Key Words: *Precocious puberty. GnRH stimulation test. Premature thelarche.*

INTRODUCTION

The onset of puberty is socially and culturally an important milestone and an indicator of public health.[1] The age of onset of puberty varies, influenced by genetic and environment factors such as race, ethnicity, geographic location and nutrition.[2] Normal puberty begins between 8 and 13 years of age in girls with breast development as first sign followed by pubic hair appearance and later menarche. In boys, it begins between 9 and 14 years of age with testicular enlargement as first sign followed by penile growth, pubic hair and voice changes. Pubertal growth spurt occurs earlier in girls than in boys.[3] Tanner staging system is used worldwide to assess normal puberty, its variants and abnormal puberty. Precocious puberty is defined as the appearance of any sign of secondary sexual maturation at an age more than 2.5 standard deviation below the mean. The most widely used age limit for girls is 8 years and 9 years for boys.

Department of Pediatric Medicine, Unit II, National Institute of Child Health, Karachi.

Correspondence: Dr. Irum Atta, A-14, Younus Terrace, Block 13-B, Gulshan-e-Iqbal, Karachi.
E-mail: irumatta@yahoo.com

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Precocious puberty influences the psychosocial development and growth of child. Short adult stature is one of the most serious long-term consequence of precocious puberty. The behavioral changes like aggression, poor adjustment of the child with matched peers in the school and emotional distress in girls with early breast development and menarche are challenging issues. There is a high risk of sexual abuse in either gender.

The reported incidence of precocious puberty in the West is 1:5000 - 10,000 individual.[4] Girls are 5 - 10 fold more frequently affected with female to male ratio of a 3:1.

Precocious puberty is classified into two main types. True or Central Precocious Puberty (CPP) is gonadotropin dependent caused by premature activation of Hypothalamic Pituitary Gonadal (HPG) axis. It accounts for 80% cases of precocious puberty of which majority (90%) are girls with idiopathic variety.

Precocious puberty is a treatable pediatric endocrine disorder; there is sparse local published data on subject in Pakistan. True incidence of precocious puberty and frequency of types is unknown. This study may provide base line data which may help to guide pediatricians and family physicians for initial evaluation, referral and management of precocious puberty.

The objective of this study was to determine the etiology of precocious puberty and to compare the clinical and laboratory parameters of central and peripheral precocious puberty in children presenting at National Institute of Child Health, Karachi.

METHODOLOGY

This study was conducted after seeking approval from Hospital Ethical Review Committee. All the patients fulfilling the criteria of precocious puberty during January 2009 to December 2011 were included after taking informed consent from the parents. Precocious puberty is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.[5,6] Children with head trauma, cranial radiation, previous CNS infections (meningitis, encephalitis), neurofibromatosis, tuberous sclerosis and severe hypothyroidism were excluded. Premature thelarche was labeled on the basis of appearance of breast development before the age of 8 years, bone age within 2 SDs of the mean for the chronological age, prepubertal height velocity < 6 cm/year and prepubertal response to the GnRH test.[7] Premature pubarche diagnosed as the appearance of axillary hair, pubic hair or both before the age of 8 years, bone age within 2 SDs of the mean for the chronological age, prepubertal height velocity < 6 cm/year and prepubertal response to the GnRH test.[7]

The diagnosis of precocious puberty in girls was based on the following accelerated bone age (> 2 SDs of the mean for the chronological age), accelerated height velocity (> 6 cm/year), pubic/axillary hair or menarche and confirmed by pubertal response to the GnRH test.[7]

Precocious puberty for boys was labeled on the basis of following characteristics before 9 years of age; accelerated bone age (> 2 SDs of the mean for the chronological age), accelerated height velocity (> 6 cm/year), genital development (G2), pubic hair stage 2 or more or testicular enlargement > 3 ml volume measured by Prader orchidometer and confirmed by pubertal response to the GnRH test.[8,9]

Central Precocious Puberty (CPP) was labeled on the basis of normal pubertal development sequence and isosexual as in normal puberty. Peripheral Precocious Puberty (PPP) was labeled on the basis of abnormal pubertal development sequence with loss of synchronicity of pubertal development or contrasexual, (virilization in girls or feminization in boys).

In registered patients, age of onset of puberty was documented and clinical evaluation, Tanner staging, height, SDS (standard deviation score), weight SDS, body mass index, bone age, pelvic ultrasound, plasma estradiol level were recorded. GnRH stimulation was carried out in all the patients. USG of adrenal glands, 17 hydroxyprogesterone, ACTH, Renin, aldosterone, serum testosterone were performed in children with peripheral precocious puberty. MRI of adrenal gland and gonads were preceded in patients with suspected tumor of that side and MRI brain in patients with central precocious puberty. Skeletal survey was done in patient with Mc Cune Albright syndrome.

Pubertal status was staged according to Tanner.[12] Height was measured in centimeters with stadiometer in children more than 2 years of age and length was taken in less than 2 years. Weight was measured in kilograms with electronic scales. Both height and weight were taken by a single observer. Height, weight and BMI were expressed as standard deviation score with reference to UK standard.[11]

Bone age was estimated by one of the three consultant pediatric radiologists in the department of Radiology using the RUS (TW2) system.[12] Pelvic USG examination was performed by radiographer trained in pediatric ultrasound. The criteria for assigning appearances as pubertal as opposed to prepubertal were dependent on the appearance of the uterus, including the presence or absence of an endometrial echo.[13] MRI of brain, adrenal glands and gonads were reported by two consultant radiologists in radiology department.

GnRH stimulation test was interpreted using the criteria proposed by Ng *et al*.[14] After overnight fasting, blood sample for baseline values of FSH and LH was taken, then injection GnRH 100 ug was administered by intravenous or subcutaneous route and blood samples for values of FSH and LH was taken at 30 and 60 minutes. In CPP, it showed pubertal response, defined as peak LH/FSH ratio greater than 1 or peak LH greater than 5. In PPP this test showed prepubertal or flat response. Normal pre-pubertal FSH was taken as 0.26 - 3 mIU/ml in male and 1.0 - 4.2 mIU/ml in female; normal pre-pubertal LH was taken as 0.02 - 3.0 mIU/ml in male and 0.02 - 0.18 mIU/ml in female.

Data was entered and analyzed using SPSS version 17.0. Shapiro Wilks test was used to check the normality of data. Mean ± SD / Median (IQR) were computed for variables depending on the normality assumption. Independent sample t-test/ Mann-Whitney U-test were applied to check significant differences in quantitative variables among groups of central and peripheral puberty. Frequency and percentages were calculated for all the qualitative variables.

RESULTS

Total number of patients registered during this period were 85. Precocious puberty was classified as peripheral precocious puberty in 33 (38.82%), central precocious puberty in 31 (36.47%), premature thelarche in 12 (14.1%) and premature pubarche in 9 (10.6%). In the peripheral precocious puberty group, 21 (63.33%) were males and 12 (36.36%) were female. Less than 3

years were 4 (12.5%) children, 13 (40.62%) were between 3 to 5 years and 15 (46.87%) were more than 5 years. Etiology of peripheral precocious puberty is mentioned in Table I. In CAH, 8 (29.62%) were girls and 19 (70.37%) were boys. Adenocarcinoma was diagnosed in 3 and 7 years old boys and one-year girl. Ovarian teratoma was identified in 1.9 years and 7 years old girls. There was one 5 years female child who diagnosed as a case of McCune Albright syndrome. In the central precocious puberty group, children age less than 3 years and 3 to 5 years were 11 (35.84%); while children age more than 5 years were 9 (29.84%). There was female preponderance with 26 (83.87%) female and 5 (16.12%) male children.

Table II shows the etiology of central precocious puberty. Nineteen (90.47%) females and 2 (9.52%) males were identified as having idiopathic central precocious puberty. Hypothalamic hamartoma were seen in 3 girls of age one-year, 1.5 years and 6 years and one boy age one-year. Craniopharyngioma was seen in 2 female child of age 6 years and 6.5 years and one male age 8.5 years. Hypothalamic astrocytoma was diagnosed in a 2.8 years old girl, arachnoid cyst in a one-year boy and hydrocephalus in a 7 years old girl.

Table I: Etiology of peripheral precocious puberty.

CAH	27 (81.8%)
Adenocarcinoma	3 (9.1%)
Ovarian teratoma	2 (6.1%)
Mc Cune- Albright syndrome	1 (3%)
Total	33 (100%)

Table II: Etiology of central precocious puberty.

Idiopathic	21 (67.74%)
Hypothalamic hamartoma	4 (12.90%)
Craniopharyngioma	3 (9.67%)
Arachnoid cyst	1 (3.22%)
Hypothalamic astrocytoma	1 (3.22%)
Hydrocephalus	1 (3.22%)
Total	31 (100%)

Table III: Comparison between central and peripheral precocious puberty.

Variables / groups	Central puberty	Peripheral puberty	p-value
Onset age in years; median (IQR)	3 (2-6)	5.25 (3.62-7.0)	0.013*†
Height in cm; mean (SD)	110.38 (15.03)	108.53 (10.21)	0.549§
Height SDS; median (IQR)	2.65 (2.0-3.61)	-0.13 (-0.70-0.46)	0.000**†
Weight in kg; median (IQR)	16 (13-22)	21 (16-24.5)	0.060†
Weight SDS; median (IQR)	0.87 (0.53-1.2)	0.33 (-0.39-1.17)	0.020*†
BMI; median (IQR)	14.41 (13.36-15.5)	16.74 (15.05-18.91)	0.000**†
Bone age in years; median (IQR)	6.5 (4.8-8.9)	7.8 (6.25-9.15)	0.111†
FSH; median (IQR)	8.62 (6.7-14.23)	2.1 (1.2-2.99)	0.000**†
LH; median (IQR)	7.1(4.68-10.6)	1.32(0.28-2.65)	0.000**†

** P-value < 0.05, ** P-value < 0.0001 indicating significant differences between both the groups in that particular variable (p-value < 0.05). IQR = inter-quartile range. § P-value calculated using independent sample t-test, † P-value calculated using Mann-Whitney U-test.*

Table III shows the comparison between the variables of central and peripheral precocious puberty. There was a difference in the age of onset of puberty of central precocious puberty, 3 (2 - 6) versus peripheral precocious puberty, 5.25 (3.62 - 7.0) years. Central precocious puberty children showed higher height SDS, weight SDS, FSH and LH values than peripheral precocious puberty. All the parameters were significantly comparable with p-value < 0.05.

DISCUSSION

Precocious puberty is an uncommon but treatable pediatric endocrine disorder. In Pakistan, there is sparse local published data on precocious puberty, therefore, the exact magnitude of problem, the prevalence and frequency of various type of precocious puberty is unknown. This is due to lack of availability of facilities of pediatric endocrinologists and specialized pediatric endocrine centers in Pakistan.

This study is an effort about the determination of various types of precocious puberty within the local setup at National Institute of Child Health, Karachi, a tertiary care hospital with facility of pediatric endocrine clinic and an experienced pediatric endocrinologist.

The international data shows great variability regarding the prevalence and frequency of various types of precocious puberty in different study populations. This data shows children with PPP were 38.82% and CPP 36.47%. International data by Pescovitz *et al*. reported out of 129 patients (73.6%) were females and 82.9% had CPP, 8.3% had PPP and remaining had combined precocious puberty.[15] In a study at Middlesex Hospital UK, among 213 patients of precocious puberty, 197 (97.4%) were girls, 16 (7.6%) were boys; 40% girls had CPP, 5% had PPP, remaining had benign variants.[16] Midyett *et al*. in a series of 223 American children who presented with early pubertal development reported 47% CPP.[17] Cisternino *et al*. reviewed the etiology and age incidence in 430 girls over a period of 10 years. A vast majority of girls, (97.7%) had CPP and only 2.3% had PPP.[18] Bajpai *et al*. reviewed 140 cases of precocious puberty at a tertiary care center in Indian children and reported that majority were females, 67% had CPP, 11.5% had PPP and remaining had normal benign variants.[19]

Above studies shows girls had more central precocious puberty as compared to boys as seen in this study and central precocious puberty more common in these studies as compared to peripheral one. The reason could be that most of the studies were retrospective review of patients with precocious puberty with longer duration of study period. In the setup, peripheral precocious puberty is a significant problem and

underlying cause is CAH in majority of cases. This is due to lack of diagnosis and treatment at early age and later on they presented with peripheral precocious puberty. In a recent, Chinese retrospective review of 6 years period of 91 cases that showed peripheral precocious puberty in children was common and the underlying etiology was CAH.[20] Their results are similar to this study. The frequency of benign variants (premature thelarche and premature pubarche) in this study is 24.7% which are similar to Bajpai *et al*. results.[19] In a recent Korean review of 223 patients of precocious puberty, 39% had benign variant.[21] Kaplowtz evaluated 104 children, 91% had benign normal variants.[22] There is great variability in results of benign variants in different studies and factors which are responsible for it could be genetic, childhood dietary habits, physical activity and exposure to endocrine disrupting chemicals.

In CPP, the most common underlying cause in this study was idiopathic (67.74%) similar to studies reported by Cisternino *et al*. and Pescovitz *et al*.[16,19] The distribution of idiopathic precocious puberty in girls is 69% to 98% and in boys 0% to 60% reported by Partsch *et al*. in his article of management and outcome of central precocious puberty.[23] In this study, 90.47% girls and 9.52% boys have idiopathic central precocious puberty. Hypothalamic hamartoma (12.90%) was the second most common cause of central precocious puberty in this study. Hypothalamic hamartoma is responsible for CPP in 2 - 28%.[23] Cisternino *et al*. reported 2.3% cases and Pescovitz *et al*. 22.42% cases of hypothalamic hemartoma.[15,18] The younger the child, the higher the chance that hypothalamic hamartoma is the cause of CPP.[18] In the present study, the age range of patients having hypothalamic hamartoma was from 1 - 1.5 years.

In PPP, the common causes identified in this study were CAH (81.8%) and adrenal tumor (9.1%). Pescovitz *et al*. found that both CAH and adrenal tumor cases presented as combined central and peripheral precocious puberty.[15] McCune-Albright syndrome (5.6%) and familial male precocious puberty (5.6%) was the main causes of PPP in his study. In this study McCune-Albright syndrome was identified in 3% of cases. The low value in this study could be due to less number of patients as compared to Pescovitz *et al*. study.

In this study, the different parameters of central and peripheral precocious puberty was also compared. There was a difference in the age of onset of puberty. CPP patients showed higher height SDS, weight SDS, FSH, LH than those with PPP. Early maturation of hypothalamic centers in CPP results in exposure to sex steroids that leads to increase growth rate and accelerated bone age development.

CONCLUSION

Peripheral precocious puberty was more common than central precocious puberty in this study. Etiology in majority of cases with peripheral precocious puberty was CAH and idiopathic in central precocious puberty. Central precocious puberty children showed higher height SDS, weight SDS, FSH, LH than those with peripheral precocious puberty.

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REFERENCES

1. Herman-Giddens ME, Kaplowtz PB, Wasseman R. Navigating the recent articles on girls puberty in pediatrics: What do we know and where do we go from here? *Pediatrics* 2004; **113**: 911-7.
2. Parent AS, Teilman G, Juul A, Shakkebaek NE, Toopari J, Bourguigon JP. The timing of normal puberty and the age limits of sexual precocity: variation around the world, secular trends, and changes after migration. *Endocr Rev* 2003; **24**:668-93.
3. Papadimitrio A, Beri D, Tisiala A, fertzayas A, Psychou F, Nicolalaid P. Early growth acceleration in girls with idiopathic precocious puberty. *J Pedaitr* 2006; **149**:43-6.
4. Cutler GB. Preccocious puberty. In:Hurst JW, editor. Medicine for practicing physics, 2nd ed. Woburn, MA: *Butterworth*; 1988: 526-30.
5. Grumbach MM, Styne DM. Puberty: ontogeny neuro-endocrinology, physiology, and disorders. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, editors. Williams textbook of endocrinology. Philadelphia: *WB Saunders*; 1998:1509-625.
6. Styne DM. New aspects in the diagnosis and treatment of pubertal disorders. *Pediatr Clin North Am* 1997; **44**:505-29.
7. Badouraki M, Christoforidis A, Economou I, Dimitriadis AS, Katzos G. Evaluation of pelvic ultrasonography in the diagnosis and differentiation of various forms of sexual precocity in girls. *Ultrasound Obstet Gynecol* 2008; **32**:819-27.
8. Sørensen K, Mouritsen A, Aksglaede L, Hagen CP, Mogensen SS, Juul A. Recent secular trends in pubertal timing: Implications for evaluation and diagnosis of precocious puberty. *Horm Res Paediatr* 2012; **77**:137-45.
9. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009; **123**:e752-62.
10. Odel WD. Puberty. In: DeGroot LJ, ed. Endocrinology. Philadelphia: *Saunders;* 1989.
11. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross-sectional stature and weight reference curves for the UK. *Arch Dis Child* 1995; 73:17-24.
12. Tanner JM, Whitehouse RH. Prediction of adult height for height, bone age and occurrence of menarche at ages 4 to 16 with allowance for midparental height. *Arch Dis Child* 1975; **50**:14-26.
13. Griffin IJ, Cole TJ, Duncan KA, Hollman AS, Donaldson MD. Pelvic ultrasound measurements in normal girls. *Acta Paediatr* 1995; **84**:536-43.
14. NG SM, Kumar Y, Cody D, Smith CS, Didi M. Cranil MRI scans are indicated in all girls with central precocious puberty. *Arch Dis Child* 2003; **88**:414-8.
15. Pescovitz OH, Comite F, Hench K, Barnes K, Mc Neman A,

Foster C, *et al*. The NIH experience with precocious puberty: Diagnostic subgroups and response to short term leutinizing hormone releasing hormone analogue therapy. *J Pediatr* 1986; **108**:47-54.

16. Bridges NA, Christofer JA, Hindmash PC, Brook CGD. Sexual precocity sex incidence and etiology. *Arch Dis Child* 1994; **70**:118-20.
17. Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? *Pediatrics* 2003; **111**:47-51.
18. Cisternino M, Arrigo T, Pasquino AM, Tinelli C, Antoniazi F, Beduschil, *et al.* Etiology and age incidence of precocious puberty in girls: a multicenteric study. *J Pediatr Endocrinol Metab* 2000; **13** (suppl 1): 695-701.
19. Bajpai A, Sharma J, Kabra M, Kumar Gupta A, Menon PS. Precocious puberty: Clinical and endocrine profile and factors indicating neurogenic precocity in Indian children. *J Pediatr Endocrinol Metab* 2002; **15**:1173-81.
20. Zou CCC, Liang L, Zheng YZ. Peripheral precocious puberty: A retrospective study for six years in Hang Zhou China. *J Pediatr Child Health* 2008; **44**:415-8.
21. Kim SY, Chae HW, Kim HS, Kim DH. Incidence and etiologies of precocious puberty in Korea during last 10 years. Puberty disorders: *Horm Res* 2008.
22. Kaplowtz P. Clinical characteristics of 104 children reffered for evaluation of precocious puberty. *J Clin Endocrinol Metab* 2004; **89**:3644-50.
23. Partsch CJ, Heger S, Sippell WG. *J Clin Endocrinol Metab* 2002; **56**:129-48.