Clinical and endocrinological profile of children with precocious puberty at a tertiary care center

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ABSTRACT

Introduction: Puberty is said to be precocious if it appears before chronological age of 8 years in girls and 9 years in boys. Untreated early puberty leads to early sexual maturation with growth and bone age advancement with early fusion, leading to the paradox of tall stature in childhood but short adult final height. **Objective:** The objective of this study was to study the profile of precocious puberty in children with respect to clinical and endocrinological outcome. **Materials and Methods:** This was a prospective study of 28 children (23 girls) who presented with precocious puberty in pediatric endocrine outpatient department. Presenting complaints, clinical findings including anthropometry, investigations (biochemical and radiological), treatment, and outcome with follow-up visits (every 3 monthly), were recorded. **Results:** Age at the presentation was 5.4±2.6 years. Most common presentation in girls was breast development (82.6%) followed by axillary hair development (39.13%), pubic hair development (30.43%), vaginal bleeding (13%), and clitoral hypertrophy (4.3%). History of recent height spurt was reported in 69.57% of girls. Boys presented with pubic hair growth and increased penile length (100%), change in voice (40%), seizures, or behavioral issues including aggressiveness. Etiology varied with the idiopathic cause constituting majority of the cases in girls (43.5%) with other causes being ovarian tumor (4.3%), adrenal adenoma (4.3%), and thelarche variant (4.3%). In boys, hypothalamic hamartoma (60%) was the most common cause followed by sex cord tumors (40%). The mean advancement in bone age on presentation was 3.4 years. Baseline luteinizing hormone (LH) was found to be high in patients with central causes like hypothalamic hamartomas than in children with other cause. Gonadotropin-releasing hormone (GnRH) stimulation test was positive (maximal stimulated LH after aqueous GnRH analog >3 mIU/ml by chemiluminescence immunoassay) in 61.5% of patients. Height velocity post-treatment showed a declining trend as compared to previous records before the onset of treatment and bone age advancement also slowed down. **Conclusions:** Increasing trend of precocious puberty and its adverse effect on final height and psychological profile of patients mandates the need for early referral and diagnosis and appropriate management.

Key words: *Gonadotropin-releasing hormone analogs, Growth velocity, Precocious puberty*

Puberty is a critical stage of development in an individual's life. Puberty occurs when a child develops into an adolescent. The onset of puberty is socially and culturally an important milestone and an indicator of public health [1]. Normal puberty begins between 8 and 13 years of age in girls and between 9 and 14 years of age in boys [2]. Precocious puberty is the appearance of appropriate secondary sexual characters before the age of 8 years in girls and before 9 years in boys [3]. As per data from the west, precocious puberty currently affects 1 in 5000 children and is 10 times more common in girls [4]. Increasing incidences of precocious puberty across cities and towns globally warrant detailed research. Majority of scientists think that the cause is idiopathic. Some studies have proved that secular trends are also the main cause of precocious puberty [5,6].

Untreated early puberty leads to early sexual maturation with growth and bone age advancement with early fusion, leading to the paradox of tall stature in childhood but short adult final height. Hence, it becomes important to arrest the progression of puberty and bring about regression of the sexual characters, increase the prospects for better adult height. Specific therapy could be offered once the underlying cause is identified. Various studies conducted show that factors such as obesity, consumption of junk food, lack of physical exercise, diet habits, low socioeconomic status, and education of parents have a major role in the development of precocious puberty [7-11].

It may be hard to diagnose precocious puberty in a child with minimal symptoms. Especially in girls, the diagnosis of precocious puberty should be confirmed by showing increase in gonadotropin and/or sex steroids, accelerated somatic development, and bone age advancement. The signs of sexual development also need to be regularly followed up. If the mentioned signs do not progress during the follow-up, then breast development can be accepted

as a normal variant. The objective of this study was to explore the precocious puberty in terms of clinical and endocrinological aspect.

MATERIALS AND METHODS

This was a cross-sectional observational study carried out at a tertiary care center over a period of 2 years. A total of 28 children (23 girls and 5 boys) with a history of precocity or clinical evidence of precocity, in boys <9 years and girls <8 years of age, were included. Children with a history or clinical evidence of precocity but not fitting into specific age group (boys above 9 years and girls above 8 years of age) were excluded from the study.

The study was conducted with approval from the institutional ethics committee. Informed consent was taken from the parents before enrolled for the study. Details regarding age, gender, and chronology of the appearance of secondary sexual characteristics before the age of 8 years in a girl (B2 stage as per tanner staging chart) or before the age of 9 years in a boy (G2 and/or testicular volume 4 ml as measured by Prader's orchidometer), and associated symptoms were noted. Physical examination was focused on quantifying puberty by Tanner staging and anthropometric measurements on new Indian Academy of Pediatrics 2015 growth charts.

Enrolled children then underwent radiological and biochemical investigations. Bone age assessment using Tanner-Whitehouse-3 method provided an indication of skeletal advancement from excess sex steroids and was used to estimate final height since bone age corresponds more to sexual maturity as compared to chronological age. Ultrasound of abdomen and pelvis was done to see uterine size and shape, endometrial thickness, fundocervical ratio, ovarian size, and volume. Magnetic resonance imaging (MRI) of the brain was done in all boys with central precocious puberty (CPP), given the high prevalence of organic causes in this group as well as in girls <6 years. Thyroid function tests were done to rule out hypothyroidism.

The key endocrine investigation was to determine the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) response to acute gonadotropin-releasing hormone (GnRH) stimulation to distinguish between central and non-central (peripheral) forms of precocious puberty. GnRH stimulation test is an important tool in the valuation of children with precocious puberty. The test was performed by measurement of LH and FSH at baseline and 20 and 60 min after 10 mcg/kg aqueous GnRH analog given subcutaneously [12].

Data were analyzed then using Microsoft Excel 2010. Data were presented as mean ± standard deviation or percentage. $p<0.05$ was considered statistically significant. All the statistical analyses were done with a 95% confidence interval. Entire data were statistically analyzed using Statistical Package for the Social Sciences (SPSS ver. 19, IBM Corporation, USA) for MS Windows.

RESULTS

A total of 28 children were registered for the study, of which 23 were girls. The mean age of the presentation of boys was 5.49±2.76 years while that among the girls was 5.31±2.65 years.

Presenting complaints with which these children were brought to the hospital are described in Table 1. Appearance of pubic hair, increased penile length, and change in voice were the concerned problems in boys, whereas breast development and excess in height gain were common in girls (Fig. 1).

Hypothalamic hamartoma (60%) and testicular tumor (40%) were the two major etiologies found in boys, whereas in the girls, the principle etiology observed was idiopathic.

The first investigation to be conducted was radiological and the bone age was advanced in all children. The mean advanced bone age was 3.43±2.1 years. The general value of the bone age is much higher in boys (4.66±2.21) than in girls (2.20±1.83). MRI was done in all boys and in girls <6 years of age with a mean age of 5.6±1.2 years. Ultrasonography was done in boys with testicular tumor to confirm the diagnosis and in 18 girls of whom, 9 showed changes of precocity.

Further, several biochemical investigations were also conducted as per the protocol. Baseline LH level in 24 children (5 boys) showed high values with mean LH levels of 1.4±0.87 mIU/mL in boys and 1.305±1.98 mIU/mL in girls. GnRH stimulation test was done in 13 children (1 boy) to confirm the diagnosis. About 61.5% had results >5 IU/L indicating precocious puberty. Serum estradiol

Table 1: Complaints of the study population

Presenting complaint	Boys (n=5) (%)	Girls (n=23) (%)
The appearance of pubic hair	100	30.4
Breast development	-	82.6
Increased penile length	100	
The appearance of axillary hair		39.1
Enlarged clitoris		4.3
Vaginal bleed		13.04
Excess height gain		69.5
Change in voice	40	

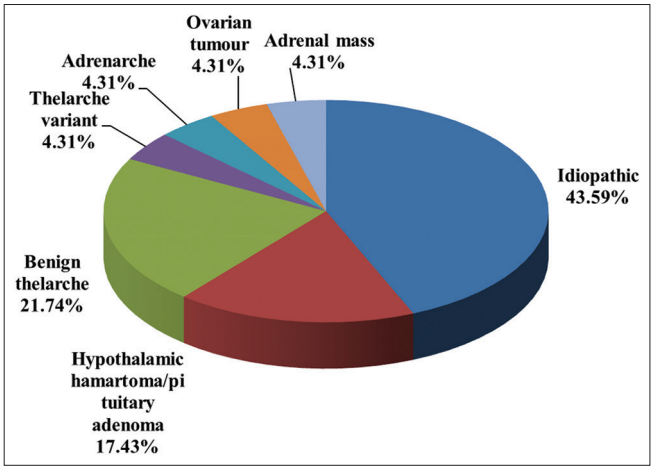

Figure 1: Distribution of etiology in girls

level was done in 14 girls and had mean value of 20.1±17.44 nmol/L (the normal range pubertal: >10 nmol/L) while serum testosterone in boys had mean value of 359.4±201.08 ng/dL (normal range pre-pubertal: 7–20 ng/dL, adult male: 300–1000 ng/dL) which were high for the age. Once diagnosed, 18 children (14 girls and 4 boys) were treated with inj. Leuprolide acetate I.M. monthly and the distribution in accordance with the treatment is presented in Table 2.

It was observed that the post-treatment height velocity showed a declining trend at the end of 19 months of treatment (Table 3) as compared to that before the initiation of the treatment. The bone age advancement slowed down as well; the LH levels on follow-up had a decreasing trend indicating the effectiveness of the treatment initiated (Table 4, $p<0.05$).

In boys, the distribution of mean follow-up z-score of height did not differ significantly compared to the mean z-score of height at the presentation ($p>0.05$). In girls, the distribution of mean follow-up z-score of height was significantly lower compared to the mean z-score of height at the presentation ($p<0.05$). The results thus supported the effectiveness of the intervention given (statistically significant in girls and through improved but not statistically significant in boys) as described in Table 5.

DISCUSSION

Precocious puberty is relatively uncommon but treatable pediatric endocrine disorder. In India, the data regarding precocious puberty are not well documented; hence, the frequency, prevalence, and exact magnitude of the problem are not known. No data were available to provide an estimate of the prevalence rate of precocious puberty until 1997 when Herman-Giddens *et al.* reported on the incidence of breast and pubic hair development by age and race in 17,000 US girls aged between 3 and 12 years [1].

Most of the studies done around the world were retrospective in nature and done over a longer duration. In this regard, a prospective observational study was designed with the aim to investigate the clinical and endocrinological profile of children with precocious puberty during a period of 2 years.

The concern with which children were brought to pediatric endocrine outpatient department varied a lot. Among boys, complaint of pubic hair growth and genital development was common, four boys had increased testicular size and one had a concern of increased penile length. Other complaints that gained parental attention were changes in the voice (40.0%). In girls, the common presentation was breast development (82.6%), followed by axillary hair development (39.1%), pubic hair development (30.4%), vaginal bleeding (13.0%), and clitoral hypertrophy (4.3%). A total of 12 girls (52.2%) also had a history of recent height spurt. Of all children, 8 (28.6%) had behavioral issues and seizures as a presenting complaint.

A review of this topic by Walvoord and Mazur concluded that CPP may become a risk factor for psychosocial problems, mainly in the setting of other risk factors. Authors cautioned against the use of medical therapy to avoid presumed negative psychological consequences of precocious puberty [13].

In terms of etiology, the data represent that 60.9% of girls had CPP with majority of them 71.4% being idiopathic in nature and 28.6% were diagnosed with hypothalamic hamartoma/pituitary adenoma which is consistent with the international data by Pescovitz *et al*., who reported out of 129 patients, of which 73.6% were female and 82.9% had CPP, 8.3% had peripheral precocious puberty (PPP), and remaining had combined precocious puberty [14]. 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 [14].

Table 2: Distribution according to treatment with injectable leuprolide acetate

Variable	Number of patients
Treatment (n=19) Inj. Leuprolide acetate	
Received	18
Not received	1
Dose in males (Mean±SD) (mcg/kg/dose)	190±18.3
Dose in females (Mean±SD) (mcg/kg/dose)	180±14.4
Mean duration (Months)	19±1.41

SD: Standard deviation

Table 3: Height velocity after treatment

Investigations	Baseline (at diagnosis)	1st follow-up (6 months)	2nd follow-up (12 months)	3rd follow-up (after 18–20 months)	p value
Height (cm)	119	126	130	133	<0.05

p-values calculated by paired t-test. $p<0.05$ is considered statistically significant

Table 4: Stimulated LH levels on follow-up

Investigations	Post-stimulation at presentation	3 h after leuprolide on the 1st follow-up	3 h after leuprolide on the 2nd follow-up	p value
LH	3.38	1.84	1.94	<0.05

p-values calculated by paired t-test. $p<0.05$ is considered to be statistically significant, LH: Luteinizing hormone

Table 5: Sex-specific comparison of mean height Z score at presentation and at follow-up

Parameters	Boys (n=5)			Girls (n=23)		
Mean±SD	Presentation	Follow-up	p value	Presentation	Follow-up	p value
Z score height	1.76±1.31	1.93±2.72	0.826^{NS}	1.10±1.50	−4.82±11.1	0.032*

p-values calculated by paired t-test. $p<0.05$ is considered to be statistically significant. SD: Standard deviation

Bajpai and Menon reviewed 140 cases of precocious puberty at a tertiary care center in Indian children and reported that majorities were female, 67% had CPP, 11.5% had PPP, and remaining had normal benign variants. The most common cause of precocious puberty in boys was secondary to adrenal causes while in girls, it was due to ovarian cysts [6]. In the current study, remaining 39.1% of girls had a peripheral cause for precocious puberty constituting ovarian tumor (11.1%), adrenal adenoma (11.1%), and benign thelarche (55.5%)/thelarche variant (11.1%). In boys, hypothalamic hamartoma was the cause of (60.0%) followed by Leydig cell tumors (40.0%). This could be attributed to the present tertiary care center, which is a referral center with pediatric endocrine facilities, and hence, an increased number of referrals were coming from the peripheries.

In the past decade, new gonadotropin assays with better sensitivity and specificity have been developed, which make them particularly useful to study the ontogenesis of LH secretion in normal and abnormal puberty [15]. The present results demonstrate that both basal and GnRH-stimulated levels of LH exhibit high specificity for the diagnosis of gonadotropin-dependent precocious puberty. The present study had mean baseline LH levels of 1.2 IU/L with post-stimulation levels significantly rising to mean 16.38 IU/L at the end of 60 min. Treatment with GnRH agonists resulted in the regression or stabilization of pubertal symptoms, decrease in the growth velocity, bone age advancement, and improved adult height [16].

This study had similar results on follow-up with the patients after a mean period of 18 months post-treatment with GnRH analog. There was a decrease in high velocity and bone age advancement and stabilization in pubertal symptoms. The LH levels documented on follow-up showed a decreasing trend as well. Significant benefit was observed in clinical as well as psychosocial domains. A major limitation of the present study was the small range of sample enlisted in the study population. A larger study sample would have validated the outcome of the study more efficiently.

CONCLUSIONS

An increasing trend of precocious puberty and its adverse effect on final height and psychological profile of patients mandates the need for early referral and diagnosis and appropriate management. The etiologies are heterogeneous, and treatment and prognosis differ according to the etiology. Detailed evaluation including radiological and biochemical tests is required. It is important to correct the underlying pathology based on the exact diagnosis. The medical treatment with monthly inj. Leuprolide acetate has shown a decline in a rapid progression of symptoms of precocious puberty and has improvement of height outcomes as well as in follow-up hormone levels.

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. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13-23.
3. Kaplowitz P. Precocious puberty: Update on secular trends, definitions, diagnosis, and treatment. Adv Pediatr 2004;51:37-62.
4. Cutler GB. Preccocious puberty. In: Hurst JW, editor. Medicine for Practicing Physics. 2nd ed. Woburn, MA: Butterworth; 1988. p. 526-30.
5. Grunt JA, Midyett LK, Simon SD, Lowe L. When should cranial magnetic resonance imaging be used in girls with early sexual development? J Pediatr Endocrinol Metab 2004;17:775-80.
6. Bajpai A, Menon PS. Contemporary issues in precocious puberty. Indian J Endocrinol Metab 2011;5:172-9.
7. Zhu M, Fu J, Liang L, Gong C, Xiong F, Lui G, *et al*. Epidemiological study on current pubertal development in Chinese school aged children. Zhejiang Da Xue Xue Bao Yi Xue Ban 2013;42:396-402.
8. Biro FM, Khoury P, Morrison JA. Influence of obesity on timing of puberty. Int J Androl 2006;29:272-7.
9. Ayele E, Berham Y. Age at menarche among in school adolescents in Sawala town, South Ethiopia. Ethiop J Health Sci 2013;23:189-200.
10. Yang YD, Ma J, Fu LG, Wang HJ, Dong B, Song Y, *et al*. Association between early onset of menarche and anthropometry measurements among adolescents in China. Zhonghua Yu Fang Yi Xue Za Zhi 2013;47:712-7.
11. Colmenares A, Gunczler P, Lans R. Higher prevalence of obesity and overweight without an adverse metabolic profile in girls with central precocious puberty compared to girls with early puberty, regardless of GnRH analogues treatment. Int J Pediatr Endocrinol 2014;2014:5.
12. Khadilkar V, Jahagirdar R, Khadilkar A, Lalwani S. Evaluation of GnRH analogue testing in diagnosis and management of children with pubertal disorders. Indian J Endocrinol Metab 2012;16:400-5.
13. Walvoord EC, Mazur T. Behavioral problems and idiopathic central precocious puberty: Fact or fiction? Pediatric Endocrinol Rev 2007;4 Suppl 3:306-12.
14. Pescovitz OH, Comite F, Hench K, Barnes K, McNemar A, Foster C, *et al*. The NIH experience with precocious puberty: Diagnostic subgroups and response to short-term luteinizing hormone releasing hormone analogue therapy. J Pediatr 1986;108:47-54.
15. Lee PA. Early pubertal development. In: Moshang T Jr., editor. Pediatric Endocrinology: The Requisites in Pediatrics. St. Louis: Mosby; 2004. p. 73-85.
16. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group, *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.

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