RESEARCH PAPER

Gonadotropin-Dependent Precocious Puberty: Single-Center Experience From Western India

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Objective: To describe the characteristics of gonadotropin-dependent precocious puberty (GDPP) in Indian children. **Methods**: Clinical profiles of GDPP (*n*=78, 61 females) and premature thelarche (*n*=12) from a single center in Western India were retrospectively studied. **Results**: Pubertal onset was earlier in boys than girls (29 vs 75 months, respectively; *P*=0.008). The basal luteinizing hormone (LH) was ≥0.3 mIU/mL, except 18% of GDPP girls. At 60 minutes after GnRHa-stimulation, all patients (except one girl) had LH ≥5 mIU/mL. The GnRHa-stimulated LH/FSH ratio was ≥0.34 at 60 minutes in girls with GDPP unlike premature thelarche. Only one girl had an allergic reaction to long-acting GnRH agonist. Among GnRH agonist-treated girls (*n*=24), the predicted final adult height was -1.67±1.5 SDS, whereas the attained final height was -0.25±1.48 SDS. **Conclusion**: We establish the safety and efficacy of long acting GnRH agonist therapy in Indian children with GDPP. The 60-minute stimulated serum LH/FSH of ≥0.34 differentiated GDPP from premature thelarche.

Keywords: *GnRHa stimulation test, Management, Premature thelarche, Pubarche*.

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Precocious puberty is defined as the onset of secondary sexual characteristics before 8 years in girls and 9 in boys [1]. It is classified as gonadotropin-dependent (GDPP) or independent (GIPP). Most cases (>90%) of GDPP in girls are idiopathic, whereas 40-90% of boys have an identifiable central nervous sys-tem (CNS) pathology [1]. GDPP should be differentiated from premature thelarche, a normal pubertal variant. Basal serum luteinizing hormone (LH) ≥0.3 mIU/mL is indicative of pubertal onset but may not be diagnostic of GDPP and hence, necessitates the gonadotropin-releasing hormone analog (GnRHa)-stimulation test [2,3]. Magnetic resonance imaging (MRI) of the brain helps to rule out organic causes of GDPP. The goal of treatment in GDPP is to halt pubertal advancement, mitigate adverse psychosocial issues and improve final adult height (FAH). Long-acting GnRH agonists have been the gold standard of treatment in GDPP over the last few decades [1].

Only a few studies on GDPP reported from India describe this condition. However, most of these include both GDPP and GIPP [4-6]. The data on FAH outcome with GnRH agonists and the utility of the GnRHa-stimulation test to differentiate GDPP and premature thelarche are lacking in Indian cohorts. Hence, we aimed to retrospectively evaluate the clinical, biochemical, radiological, treatment, and outcome profiles of GDPP patients from a single center in Western India.

METHODS

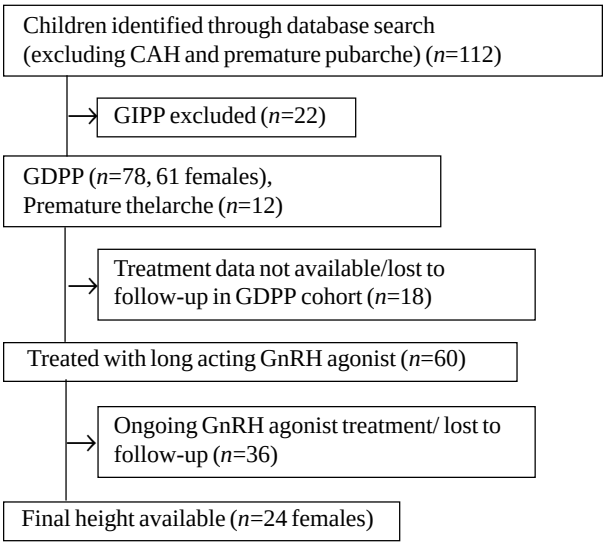
A retrospective case-record review of children with precocious puberty managed at a tertiary care center from January, 2000 to February, 2021 was done after clearance from Institutional Ethics Committee.

Clinical details and anthropometry were noted for all cases. Bone age was determined by the Tanner-Whitehouse-3 method. Predicted adult height was calculated by using Bayley and Pinneau tables [7]. Hormones [LH, follicle-stimulating hormone (FSH), testosterone (boys), and estradiol (girls)] were measured by chemiluminescence immunoassay (ADVIA Centaur XP, Siemens). Intra- and inter-assay coefficients of variation were <10% for all assays. GnRHa stimulation test was performed if basal LH was <0.3 mIU/mL. Serum LH and FSH were estimated at baseline and 30, 60, 90, 120, and 180 min after 20 µg/kg subcutaneous aqueous leuprolide. Peak-stimulated serum LH ≥5 mIU/mL with an LH/FSH ratio >0.6 was used to define GDPP [3,8]. Patients with an initial diagnosis of premature thelarche were followed up, and if pubertal

progression was noted with suggestive biochemistry, the diagnosis was revised to GDPP.

Magnetic resonance imaging (MRI) of the brain was performed in all patients with GDPP, and an ultrasonogram (USG) of the pelvis was performed in all GDPP girls. Most GDPP patients were treated with a standard dose of 11.25 or 22.5 mg depot leuprolide acetate intramuscularly every three months (140-300 µg/kg/month). Few patients were treated with triptorelin: 3.75 mg monthly or 11.25 mg every three months intramuscularly. Clinical parameters moni-tored at 3-6 months intervals included growth velocity and Tanner staging. Bone age was determined yearly. Basal serum LH <0.3 mIU/mL and/or 3 hours postleuprolide depot serum LH of <3.3 mIU/mL suggested adequate treatment response. Treatment was stopped at a bone age of ~12 years in girls and ~13 years in boys unless indicated to continue for psychosocial reasons till 10.5 and 11.5 years of chronological age in girls and boys, respectively.

Statistical analysis: Statistical analyses were performed using IBM SPSS software version 26.0 (SPSS Inc.) software. Categorical data were expressed as absolute numbers and percentages, and continuous data were expressed as mean (SD) or median and ranges as appropriate. Chi-square and Fisher exact tests were used to compare categorical variables, *t* test and Mann-Whitney *U* tests were used to compare continuous variables, as appropriate. A two-sided *P*-value <0.05 was considered statistically significant.



CAH: congenital adrenal hyperplasia; GDPP: gonadotropin-dependent precocious puberty; GIPP: gonadotropin-independent preco-cious puberty.

Fig. 1 Flow chart for case-record review of precocious puberty.

RESULTS

Fig. 1 summarizes the selection of patients for the study. The baseline characteristics of GDPP patients (*n*=78, 61 females) are summarized in **Table I**. Pubertal onset and presentation age were earlier in boys. The typical presentation was genitalia growth (76.5%) in boys and thelarche (75.4%) in females, followed by height spurt (boys: 17.6%, girls: 11.4%), pubic hair development (boys: 5.8%, girls: 6.5%) and vaginal bleeding (6.5%). Median testicular volume was 8.0 cc (range:4-20). Pubarche was present in all boys, and absent in 31.6% of girls. In girls below 6 years, 18/28 (64.3%) had pubarche. In females, the breast stage was 2, 3, 4, and 5 in 21.3%, 34.4%, 29.5%, and 14.8%, respectively, and the vaginal mucosa was dull pink in 82.1%.

Basal serum LH of ≥0.3 mIU/mL was seen in all boys but <0.3 mIU/mL in 11 girls (age: 82-99 months). All girls with GDPP except one reached a stimulated serum LH of ≥5 mIU/mL at 60 minutes. The comparison of girls with GDPP and premature thelarche who had low basal LH and under-went GnRHa-stimulation test is shown in **Table II**. When compared with premature thelarche (*n*=8), girls with GDPP (*n*=11) were significantly older, had a com-parable GnRHa-stimulated (60-minute) serum LH but a higher LH/FSH ratio. Uterine length ≥3.2 cm, corpus-to-cervix ratio >1, and endometrial echo were found in 84.2%, 80%, and 68.1% of GDPP (*n*=38) and 37.5%, 50%, and 41.6% premature thelarche (*n*=11), respectively. Median (range) ovarian

Table I Baseline Characteristics of Patients with Gonadotropin Dependent Precocious Puberty

	Boys (n=17)	*Girls (n=61)*
Age of onset of symptoms (mo)[c]	29 (0,102)	75 (0,102)
Age at presentation (mo)[c]	58 (7,114)	82 (11,123)
Height at presentation (SDS)	1.02 (-1.52,4.97)	0.75 (-1.9,3.6)
Target height (SDS)	-0.77 (-2.12, 0.09)	-0.82 (-2.6, 1.07)
Pubarche <6 y of age[a,c]	13 (100)	18 (64.3)
Pubarche >6 y of age[a]	4 (100)	24 (72.7)
BA/CA ratio at presentation	1.88 (0.87, 3.14)	1.40 (1.02, 4.61)
Basal serum LH (mIU/mL)	2.67 (0.52, 10.0)	2.2 (0, 15.8)
Basal serum FSH (mIU/mL)[b,c]	2.48 (0.42, 5.7)	5.24 (1.03, 9.8)
Basal serum LH ≥0.3 mIU/mL[a,c]	17 (100)	50 (81.9)
MRI brain abnormality[a,d]	12 (80)	12 (23.5)

Data are expressed as median (range) or [a]no. (%). BA: bone age; CA: chronological age; FSH: follicle stimulating hormone; LH: luteinizing hormone; MRI: magnetic resonance imaging; [b]n=13 in boys, n=57 in girls; [c]P<0.05; [d]P<0.001.

Table II Baseline Characteristics of Girls

	GDPP girls (n=11)	*Premature thelarche (n=8)*	*P value*
Age of onset of symptoms (mo)	83 (10,91)	14.5 (0,64.5)	0.001
Age at presentation (mo)	90 (14,99)	20.5 (15,65)	0.002
Height at presentation (SDS)	0.61 (-0.58,1.42)	-0.55 (-1.66,1.20)	0.091
Target height (SDS)	-0.67 (-2.6,0.99)	-0.385 (-3.26,0.43)	0.762
Basal serum LH (mIU/mL)	0.13 (0.05,0.29)	0.10 (0,0.25)	0.600
Basal serum FSH (mIU/mL)	3.06 (0.24,6.51)	2.8 (0.41,4.62)	0.002
GnRHa stimulated 60 min serum LH (mIU/mL)	9.64 (3.97,16.8)	7.16 (3.51,9.69)	0.129
GnRHa stimulated 60 min serum FSH (mIU/mL)	15.66 (5.7,28.3)	29.97 (13,40.75)	0.005
GnRHa stimulated 60 min serum LH/FSH	0.66 (0.34,1.62)	0.21 (0.13,0.30)	<0.001

Data expressed as median (range). Patients included with GDPP and premature thelarche with basal serum luteinizing hormone <0.3 mIU/mL who underwent gonadotropin-releasing hormone stimulation test. FSH: follicle stimulating hormone; GDPP: gonadotropin-dependent precocious puberty; GnRHa:gonadotropin-releasing hormone analogue; LH: luteinizing hormone.

volume was 2.3 (0.35-6.6) cc in GDPP and 1 (0.1-2) cc in girls with premature thelarche.

MRI brain abnormality was seen in 12/15 (80%) boys and 12/51 (23.5%) girls; 9/12 (75%) of those were newly diagnosed lesions in both groups. Hypothalamic hamartoma was the most common abnormality (*n*=7 each in boys and girls), followed by optic glioma (*n*=3), sellar suprasellar pilocytic astrocytoma (*n*=2), hypothalamic glioma, pineal cyst, Rathke cleft cyst, aqueduct stenosis with congenital hydrocephalus and healed tuberculoma (*n*=1 each). Of the three patients (2 boys) with optic glioma, both boys had a prior history of neurofibromatosis type 1. The proportion of girls with MRI brain abnormality with pubertal-onset before 6 years was significantly higher (34.6 vs 12.0%; *P*=0.038) than in those with later onset.

Fifty-five patients were treated with GnRH agonists [monthly 3.75 (*n*=2) or 7.5 mg (*n*=1), three monthly 11.25 mg (*n*=27) or 22.5 mg (*n*=25)] whereas five patients were treated with triptorelin. None had drug-related side effects, except one girl who had an allergic reaction to leuprolide and was switched to triptorelin. Except for a boy with hypothalamic hamartoma, none showed clinical pubertal progression on therapy. All tested children had adequate treatment response. The median (range) duration of treatment in those with final adult height available was 57.5 (33-120) months. The median (range) bone age to chronological-age ratio at two years, five years, and the end of treatment was 1.22 (1.18-1.27), 1.09 (0.93-1.27), and 1.1 (1-1.25), respectively. Among GnRH agonist treated girls (*n*=24), the predicted adult height was -1.67±1.5 SDS, whereas the attained final adult height was -0.25±1.48 SDS.

Four out of eight girls with premature thelarche who underwent the GnRHa-stimulation test had predicted adult height of -0.69 (-3.26 to 0) SDS, and attained final adult height of 0 (-0.88 to 0.36) SDS.

DISCUSSION

In this single centre study from a tertiary care center in western India, the pubertal onset and presentation age in GDPP were earlier in boys than girls. The stimulated serum LH/FSH ratio at 60 minutes was ≥0.34 in all girls with GDPP vs none in premature thelarche. Boys and younger girls (<6 years) more frequently had an organic etiology, hypothalamic hamartoma being the most common. Long acting GnRH agonist therapy was safe and beneficial in halting pubertal progression and improving final adult heights in children with GDPP.

Most boys presented before six years of age, unlike girls, with a higher frequency of organic etiology. Organic etiology was frequent in boys and girls with pubertal onset <6 years but not in those with later pubertal onset. Hence, routine CNS imaging may be optional in girls with pubertal onset >6 years [9]. As observed in our cohort, pubarche is reported in most boys with GDPP [10]. In contrast to the conventional belief, almost two-thirds of girls before 6 years had pubarche, probably due to ovarian androgen production despite low DHEAS [11].

The biochemical diagnosis of GDPP was based on basal LH of ≥0.3 mIU/mL in all boys and most of the girls. A basal LH >1.0 mIU/mL was considered as confirmatory of GDPP, whereas levels between 0.1-1.0 mIU/mL prompted a GnRHa-stimulation test [2]. Most of the patients in this study with basal LH between 0.3-1.0 mIU/mL had ≥2 definitive evidence of GDPP (height velocity >7 cm in the preceding year, bone age SDS >2, breast stage ≥4, uterine length ≥3.2 cm) at presentation.

The 60-minute serum LH/FSH ratio accurately discrimi-nated premature thelarche from GDPP in girls. Hence, a single sampling at 60 minutes after GnRHa stimulation may provide comparable diagnostic accuracy to

multiple conventional samplings. A recent large (*n*=1492) study also supported the diagnostic accuracy of GnRHa-stimulated LH and LH/FSH ratio at 60 minutes [8]. A GnRHa-stimulated serum LH of ≥5 mIU/mL criterion to diagnose GDPP is not applicable in early childhood. Peak serum LH may be >10 mIU/mL in ~16% girls with premature thelarche [12,13]. A discriminatory characteristic of premature thelarche in this study was a robust FSH response and 60-min LH/FSH ratio <0.34. Such observations have been reported previously [12,14,15]. Hence, serum LH levels should always be interpreted in relation to FSH response in early childhood. Uterine length of ≥3.2 cm predicted precocious puberty, which is as reported in a recent meta-analysis [16].

The rarity of allergic reactions in our study reiterates the safety of long acting GnRH agonist in GDPP [17]. Most patients had regression/stabilization of puberty despite the majority receiving three-monthly preparations, similar to the literature [18]. In patients whose final adult height was available, GnRH agonist therapy significantly improved the height outcome. However, data were inadequate to analyze the final height outcomes in boys, and girls with pubertal onset between 6 and 8 years of age. The etiological profile might have been affected by referral bias.

To conclude, this study reports the clinical and treatment outcomes of Indian children with GDPP. This study also establishes the safety and efficacy of long acting GnRH agonist therapy in improving final adult height in Indian with GDPP girls.

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