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ORIGINAL ARTICLE

Etiological profile and clinical spectrum of delayed puberty in adolescents at a Tertiary Care Center.

Mariam Bibi[1], Mohsina Noor Ibrahim[2], Zubair Ahmed Khoso[3], Maira Riaz[4], Versha Rani Rai[5], Roshia Parveen[6]

ABSTRACT… Objective: To determine the etiological profile and clinical spectrum of delayed puberty among adolescents presenting to a tertiary care center. **Study Design:** Descriptive, Cross-sectional study. **Setting:** Department of Paediatric Endocrinology, National Institute of Child Health (NICH), Karachi, Pakistan. **Period:** 1st November 2025 to 15th January 2026. **Methods:** A total of 125 adolescents aged 12–18 years with delayed puberty were included. Clinical assessment included Tanner staging, anthropometry, hormonal profiling, and bone age evaluation. Data were analyzed using SPSS v26, while chi-square test or fisher's exact test was applied to determine association between categorical data, taking p<0.05 as significant. **Results:** Among 125 adolescents, the median age was 15.0 (14.0–16.0) years, and 74 (59.2%) were boys. Underweight was recorded in 30 (24.0%), short stature 78 (62.4%), family history of delayed puberty 61 (48.8%), growth faltering 44 (35.2%), and dysmorphic features in 21 (16.8%) adolescents. Etiologies included constitutional delay of growth and puberty (CDGP) in 43 (34.4%), hypogonadotropic hypogonadism 32 (25.6%), hypergonadotropic hypogonadism 28 (22.4%), chronic disease related delay 13 (10.4%), and hypothyroidism 9 (7.2%). CDGP was significantly more frequent among boys 33 (44.6%), than girls 10 (19.6%) (p=0.007). Family history had significant association with CDGP (p<0.001), systemic symptoms with chronic disease (p<0.001), dysmorphism with hypergonadotropic hypogonadism (p<0.001), and bone age delay ≥2 years with CDGP (p<0.001). **Conclusion:** Delayed puberty in adolescents presenting to tertiary care showed a heterogeneous etiological profile and a wide clinical spectrum, ranging from constitutional delay to hypogonadism, and secondary causes related to chronic systemic illness, and thyroid dysfunction.

Key words: Adolescents, Dysmorphism, Hypogonadism, Hypergonadism, Puberty.

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INTRODUCTION

Delayed puberty is a relatively common reason for referral to paediatric endocrine services and affects an estimated 2–3% of adolescents globally.[1,2] It is typically defined as the absence of breast development by 13 years in girls or lack of testicular enlargement by 14 years in boys.[3] Although many cases represent constitutional delay of growth and puberty (CDGP), delayed pubertal onset may also signal underlying endocrine disorders, chronic systemic disease, or genetic conditions that require timely recognition and specialist management.[4]

CDGP remains the most frequently reported etiology of delayed puberty, particularly among boys, and is often associated with familial clustering, supporting a genetic influence on pubertal timing.[5] Delayed puberty is not always a benign variant. Functional hypogonadotropic hypogonadism may occur secondary to chronic illness, nutritional deficiency, or excessive exercise, whereas permanent hypogonadotropic hypogonadism reflects impaired hypothalamic–pituitary gonadotropin secretion requiring sustained endocrine follow-up.[6,7] Hypergonadotropic hypogonadism results from primary gonadal failure and includes chromosomal disorders such as Turner syndrome and Klinefelter syndrome.[8] Sex-specific differences have also been observed, with girls more likely to present with hypergonadotropic hypogonadism, while boys more commonly exhibit CDGP or hypogonadotropic hypogonadism.[9] Distinguishing CDGP from pathological causes requires careful attention to clinical red flags, including growth faltering, systemic symptoms, and neurological features, particularly in referral-level practice where the presentation may be complex.[10]

1. MBBS, Post-graduate Resident Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan.
2. MBBS, FCPS (Pediatric Medicine), Professor Pediatrics, National Institute of Child Health, Karachi, Pakistan.
3. MBBS, FCPS (Pediatric Medicine), Associate Professor Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan.
4. MBBS, FCPS (Pediatric Medicine), FCPS (Pediatric Endocrinology), Assistant Professor Pediatric Endocrinology, National Institute of Child Health, Karachi, Pakistan.
5. MBBS, FCPS (Pediatric Medicine), FCPS (Pediatric Endocrinology), Assistant Professor Pediatric Endocrinology, National Institute of Child Health, Karachi, Pakistan.
6. MBBS, FCPS (Pediatric Medicine), Senior Registrar Pediatric Endocrinology, National Institute of Child Health, Karachi, Pakistan.
Correspondence Address:
Dr. Mariam Bibi
Department of Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan.
mariambibi369@gmail.com

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Despite the clinical and psychosocial burden of delayed puberty, there is limited local evidence describing its etiological distribution and clinical presentation in Pakistani adolescents attending tertiary endocrine services. This study was conducted to determine the etiological profile and clinical spectrum of delayed puberty among adolescents presenting to a tertiary care center.

METHODS

This descriptive, cross-sectional study was conducted at the Department of Paediatric Endocrinology, National Institute of Child Health (NICH), Karachi, a tertiary care referral center for paediatric endocrine disorders. The study was conducted during 1st November 2025 to 15th January 2026, following approval from Institutional Ethical Review Board (IERB-53/2025). Non-probability consecutive sampling technique was employed. Adolescents of both genders aged 12–18 years were included if they fulfilled the operational definition of delayed puberty, defined as absence of breast development (Tanner stage II) by 13 years or absence of menarche by 16 years in girls, and testicular volume <4 mL measured using a Prader orchidometer or testicular length <2.5 cm by 14 years in boys.[3] Participants were excluded if they or their parents/guardians were unwilling to be part of this study, or had been previously diagnosed with chronic renal failure, uncontrolled diabetes mellitus, or any kinds of malignancy. Written informed consent was obtained from parents or guardians, and assent was taken from participants. A sample size of 125 adolescents was calculated using the single-proportion formula ($n=Z^2 \times p \times [1-p]/d^2$), assuming a 95% confidence level (Z=1.96), an expected CDGP proportion of 29.2% (p=0.292) based on published tertiary-care data,[3] and a margin of error of 8% (d=0.07).[11] The primary outcome of the study was the etiological profile of delayed puberty, while the clinical spectrum at presentation was assessed as a secondary outcome.

Among all eligible study participants, clinical evaluation was performed by a same-gender paediatric endocrinologist or a trained resident in a private examination setting, with a parent present. Each participant underwent structured history taking and physical examination, including documentation of presenting complaints, anthropometric measurements (height, weight, and body mass index), and pubertal staging using Tanner criteria. Associated systemic features and syndromic characteristics were assessed and documented at the time of presentation to capture the clinical spectrum. Relevant hormonal evaluation were performed and bone age assessment was done using radiography where necessary / required. CDGP was defined as delayed puberty in an otherwise healthy adolescent, typically associated with short stature and/or family history of delayed puberty, normal baseline laboratory evaluation, and expected spontaneous pubertal progression.[12] Hypogonadotropic hypogonadism was defined by low sex steroid levels (testosterone <100 ng/dL in boys or estradiol <20 pg/mL in girls) with low or inappropriately normal gonadotropins for age, whereas hypergonadotropic hypogonadism was defined by low sex steroid levels with elevated LH and FSH above pubertal reference ranges, consistent with primary gonadal failure. All study data were recorded using a structured proforma. Participant confidentiality was maintained through de-identification of all recorded information, and electronic data were stored and accessible only to authorized research personnel.

Statistical analysis was performed using IBM-SPSS Statistics, version 26.0. Quantitative variables were assessed for normality using the Shapiro–Wilk test and were summarized as mean with standard deviation (SD) or median with interquartile range (QR), as appropriate. Categorical variables were presented as frequencies and percentages. Associations between categorical variables were assessed using the chi-square test or Fisher's exact test where appropriate. A two-sided p value <0.05 was considered statistically significant.

RESULTS

In a total of 125 adolescents, the median age was 15.0 (14.0–16.0) years. There were 74 (59.2%) boys, and 51 (40.8%) girls. Underweight status was recorded in 30 (24.0%) participants, while short stature was documented in 78 (62.4%). A positive family history of delayed puberty was present in 61 (48.8%), and growth faltering was noted in 44 (35.2%). Dysmorphic or syndromic features were

observed in 21 (16.8%) (Table-I).

TABLE-I

Characteristics of study participants (N=125)

Characteristics		Frequency (%)
Gender	Boys	74 (59.2%)
	Girls	51 (40.8%)
Underweight		30 (24.0%)
Short stature		78 (62.4%)
Positive family history of delayed puberty		61 (48.8%)
Growth faltering		44 (35.2%)
Systemic symptoms suggestive of chronic illness		
Dysmorphic or syndromic features		21 (16.8%)

The etiological spectrum included CDGP in 43 (34.4%), hypogonadotropic hypogonadism in 32 (25.6%), hypergonadotropic hypogonadism in 28 (22.4%), chronic systemic disease related pubertal delay in 13 (10.4%), and hypothyroidism in 9 (7.2%). Etiological distribution differed by gender, with CDGP documented in 33 (44.6%) boys, and 10 (19.6%) girls, hypergonadotropic hypogonadism in 10 (13.5%) boys, and 18 (35.3%) girls, while hypogonadotropic hypogonadism was present in 21 (28.4%) boys, and 11 (21.6%) girls, chronic systemic disease related delayed puberty in 6 (8.1%) boys, and 7 (13.7%) girls, and hypothyroidism in 4 (5.4%) boys, and 5 (9.8%) girls. The details of etiological profile of delayed puberty with respect to gender distribution are given in Table-II.

Significant association of positive family history of delayed puberty was recorded in 32 (74.4%) adolescents with CDGP ($p<0.001$). Systemic symptoms were documented in all adolescents with chronic systemic disease related delayed puberty ($p<0.001$). Dysmorphic or syndromic features were observed in 15 (53.6%) adolescents with hypergonadotropic hypogonadism ($p<0.001$). Bone age delay ≥2 years was noted in 39 (90.7%) adolescents with CDGP ($p<0.001$). Details about the association of various clinical correlates and etiological profile are shown in Table-III.

DISCUSSION

The CDGP was identified in 34.4% adolescents, supporting its standing as a frequent diagnosis among tertiary care referrals for delayed pubertal milestones. Zahra et al.[13], reported CDGP in 42 (24.6%) participants presenting with delayed puberty, showing a comparable pattern within the same regional context, though with a lower proportion than the present cohort.

TABLE-II

Etiological profile with respect to gender distribution (N=125)

Etiology	Total (N=125)	Boys (n=74)	Girls (n=51)	P-Value
Constitutional delay of growth and puberty	43 (34.4%)	33 (44.6%)	10 (19.6%)	0.007
Hypogonadotropic hypogonadism	32 (25.6%)	21 (28.4%)	11 (21.6%)	
Hypergonadotropic hypogonadism	28 (22.4%)	10 (13.5%)	18 (35.3%)	
Chronic systemic disease related to puberty	13 (10.4%)	6 (8.1%)	7 (13.7%)	
Hypothyroidism	9 (7.2%)	4 (5.4%)	5 (9.8%)	

TABLE-III

Association of clinical correlates with etiological profile (N=125)

	Constitutional delay of growth and puberty (n=43)	Hypogonadotropic hypogonadism (32)	Hypergonadotropic hypogonadism (n=28)	Chronic diseases (n=13)	Hypothyrodism (n=9)	P- Value
Positive family history of delayed puberty	32 (74.4%)	12 (37.5%)	9 (32.1%)	2 (15.4%)	1 (11.1%)	<0.001
Systemic symptoms suggestive of chronic Illness	5 (11.6%)	4 (12.5%)	-	13 (100%)	2 (22.2%)	<0.001
Dysmorphic or syndromic features	1 (2.3%)	3 (9.4%)	15(53.6%)	2 (15.4%)	-	<0.001
Bone age delay ≥ 2 years	39 (90.7%)	18 (56.3%)	6 (21.4%)	6 (46.2%)	5 (55.6%)	<0.001
Underweight	9 (20.9%)	11 (34.4%)	4 (14.3%)	5 (38.5%)	1 (11.1%)	0.209
Short stature	30(69.8%)	18(56.3%)	19(67.9%)	7 (53.8%)	4 (44.4%)	0.477

A large retrospective study analyzing 232 subjects from USA found CDPG as the most common etiology of dealyed puberty, affecting 53% participants.[14] Contemporary literature on delayed puberty emphasise that CDGP remains a dominant diagnosis in referral practice, particularly when delayed bone age and familial clustering support a self limited tempo of maturation.[3] Differences in CDGP frequency across clinic cohorts can reflect variation in age at referral, thresholds for endocrine consultation, and the proportion of patients in whom diagnostic separation from hypogonadotropic hypogonadism remains uncertain at first presentation. A structured evaluation focusing on growth pattern, pubertal staging, family history, and bone age can prevent unnecessary escalation of investigations in adolescents whose presentation aligns with CDGP, while maintaining follow up to confirm pubertal progression.[15]
Hypogonadotropic hypogonadism was diagnosed in 25.6% adolescents, indicating that impaired gonadotropin secretion is a substantial contributor in delayed puberty. Regional data reported hypogonadotropic hypogonadism in 19.3% and functional hypogonadotropic hypogonadism due to non endocrine illness in 9.4%, highlighting the heterogeneity within this category in routine clinical practice.[13] Large body of evidence supports the need to differentiate self limited delay from congenital hypogonadotropic hypogonadism using clinical trajectory and targeted markers, since biochemical testing alone may overlap at early puberty.[16] The clinical importance of hypogonadotropic hypogonadism burden lies in its management implications, where permanent deficiency warrants planned pubertal induction and long term endocrine follow up, while functional suppression may improve with correction of systemic illness and nutritional status.

Hypergonadotropic hypogonadism accounted for 22.4% cases, showing that primary gonadal failure is a key diagnostic category in adolescents presenting with delayed puberty. The Sudanese hospital based cohort described by Galal et al.[17], reported hypergonadotropic hypogonadism in 11.7% of patients, with a higher representation in females. The implications extend beyond pubertal induction, since primary gonadal failure frequently requires broader counselling on fertility potential, bone health preservation, and syndrome specific surveillance where applicable.[18]

Chronic systemic disease related pubertal delay was identified in 10.4% adolescents and systemic symptoms suggestive of chronic illness were present in 100% participants within this group, reinforcing the link between systemic disease burden and delayed pubertal onset. The pattern mirrors observations from Sudan where functional hypogonadotropic hypogonadism contributed 36% and chronic illness was frequently implicated, with type 1 diabetes mellitus and coeliac disease among reported causes.[17] Hypothyroidism was documented in 7.2% adolescents, supporting thyroid dysfunction as a consistent secondary cause of delayed puberty. Thyroid function testing remains an essential first line investigation in delayed puberty pathways, since timely diagnosis provides a direct treatment pathway with expected improvement in growth velocity and pubertal progression after correction of thyroid hormone deficiency.[19,20]

Gender based differences in etiology were evident as CDGP was documented in 44.6% boys, and 19.6% girls, while hypergonadotropic hypogonadism was present in 13.5% boys, and 35.3% girls. Local data reported delayed puberty in 70.0% males, with short stature as a frequent presenting symptom in males and amenorrhoea related complaints in females, supporting the clinical observation that referral triggers and diagnostic categories differ by gender distribution.[13] A Thai tertiary care cohort by Udomratn et al., reported self-limited delayed puberty as the leading diagnosis in boys at 38.3%, and hypergonadotropic hypogonadism as the leading diagnosis in girls at 57.1%, reflecting a comparable direction of sex stratification despite differences in absolute proportions.[21] These patterns emphasize that sex informed pretest probability can improve diagnostic efficiency.

The clinical correlates observed in this cohort provide important diagnostic linkage. A positive family history of delayed puberty was present in 48.8% overall and was strongly associated with CDGP, recorded in 74.4% ($p<0.001$). Family history has been highlighted as a recorded parameter

within clinical assessment, reinforcing its role as a discriminator when combined with growth pattern and bone age.[13] CDGP is widely recognized to cluster in families, supporting the utility of structured family history taking in outpatient endocrine pathways.[22] These findings have direct counselling value, since adolescents with CDGP and familial clustering can be reassured regarding expected progression, while retaining follow up plans to verify development and to ensure that pathological causes are not missed when progression fails to occur.

Regarding limitations of this study, the single center design and non-probability consecutive sampling reduces generalizability to community settings and primary care populations. The cross-sectional framework captured presentation and initial classification, without longitudinal confirmation of pubertal progression in CDGP or follow up outcomes after therapeutic interventions. Comprehensive genetic testing and imaging were not described as universal components of classification

CONCLUSION

Delayed puberty in adolescents presenting to tertiary care showed a heterogeneous etiological profile and a wide clinical spectrum, ranging from constitutional delay to hypogonadism and secondary causes related to chronic systemic illness and thyroid dysfunction. The findings support a structured diagnostic approach that integrates careful phenotypic assessment, growth evaluation, bone age interpretation, and hormonal profiling to enable timely differentiation between constitutional delay and endocrine or systemic disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Mariam Bibi:** Data collection, drafting.
2	**Mohsina Noor Ibrahim:** Concept, design, literature review.
3	**Zubair Ahmed Khoso:** Data analysis, methodology.
4	**Maira Riaz:** Proof reading.
5	**Versha Rani Rai:** Critical revisions.
6	**Roshia Parveen:** Data collection, literature review.