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ORIGINAL RESEARCH
Pediatric Endocrinology

Etiological distribution of cases of delayed puberty in a pediatric endocrinology outpatient clinic at a tertiary-care children's hospital

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ABSTRACT

Objective: Delayed puberty is a common condition with diverse causes, ranging from benign developmental delays to permanent hypogonadism. Accurate and timely diagnosis is essential to safeguard growth, psychosocial well-being, and fertility. This study aimed to identify the etiological distribution and diagnostic characteristics of patients diagnosed with delayed puberty at a pediatric endocrinology clinic.

Material and Methods: We retrospectively analyzed data from 180 patients diagnosed with delayed puberty at the Pediatric Endocrinology Clinic of Ankara Child Health and Diseases Hematology-Oncology Training and Research Hospital between 2005 and 2012. The parameters reviewed included chronological age, bone age, growth metrics, clinical findings, family history, and basal/stimulated gonadotropin levels. Patients were categorized into four main diagnostic groups: hypogonadotropic hypogonadism (HypoH), hypergonadotropic hypogonadism (HyperH), functional hypogonadotropic hypogonadism (FHH), and constitutional delay of puberty (CDP).

Results: Participants were aged 13–18 years. All diagnostic groups showed delayed bone age compared with chronological age, especially in the hypogonadotropic hypogonadism group. Height and BMI were reduced across groups, indicating impaired growth due to pubertal delay. Cases of constitutional delay of puberty often had a positive family history. Hypogonadotropic hypogonadism was the most common etiology in both sexes. Gonadotropin levels played a key role in the differential diagnosis. Benign causes were more prevalent in boys, whereas serious or permanent etiologies were more frequent in girls. Chromosomal analysis was necessary in selected cases.

Conclusion: This study highlights the clinical and etiological diversity among 180 cases of delayed puberty caused by 46 distinct conditions. Thorough history-taking, physical examination, bone age assessment, and hormonal evaluation are vital for accurate diagnosis. Prompt referral to pediatric endocrinology is crucial to prevent diagnostic and therapeutic delays.

Keywords: Delayed puberty; etiology; hypogonadism.

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Üçüncü basamak bir çocuk hastanesinin pediatrik endokrinoloji polikliniğinde gecikmiş ergenlik vakalarının etiyolojik dağılımı

ÖZET

Amaç: Ergenlik gecikmesi, iyi huylu gelişimsel gecikmelerden kalıcı hipogonadizme kadar çeşitli nedenlerle ortaya çıkabilen yaygın bir durumdur. Büyüme, psikososyal iyilik hali ve doğurganlığın korunması için doğru ve zamanında tanı şarttır. Bu çalışma, bir çocuk endokrinoloji kliniğinde ergenlik gecikmesi tanısı konulan hastaların etiyolojik dağılımını ve tanısal özelliklerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji-Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Endokrinoloji Kliniği'nde 2005–2012 yılları arasında ergenlik gecikmesi tanısı konulan 180 hastanın verileri retrospektif olarak analiz edildi. İncelenen parametreler arasında kronolojik yaş, kemik yaşı, büyüme ölçümleri, klinik bulgular, aile öyküsü ve bazal/uyarılmış gonadotropin düzeyleri yer aldı. Hastalar dört ana tanı grubuna ayrıldı: hipogonadotropik hipogonadizm (HypoH), hipergonadotropik hipogonadizm (HyperH), fonksiyonel hipogonadotropik hipogonadizm (FHH) ve konstitüsyonel ergenlik gecikmesi (CDP).

Bulgular: Katılımcılar 13–18 yaş aralığındaydı. Tüm tanı gruplarında, özellikle hipogonadotropik hipogonadizm grubunda, takvim yaşına kıyasla kemik yaşında gecikme görüldü. Boy ve BKİ tüm gruplarda azalmıştı ve bu durum pubertal gecikmeye bağlı büyüme bozukluğunu gösteriyordu. Konstitüsyonel ergenlik gecikmesi vakalarında genellikle pozitif aile öyküsü vardı. Her iki cinsiyette de en sık görülen etiyoloji hipogonadotropik hipogonadizmdi. Gonadotropin düzeyleri ayırıcı tanıda önemli bir rol oynadı. İyi huylu nedenler erkeklerde daha yaygınken, kızlarda ciddi veya kalıcı etiyolojiler daha sık görüldü. Seçilmiş vakalarda kromozom analizi gerekliydi.

Tartışma: Bu çalışma, 46 farklı duruma bağlı 180 ergenlik gecikmesi vakasındaki klinik ve etiyolojik çeşitliliği ortaya koymaktadır. Doğru tanı için kapsamlı öykü, fizik muayene, kemik yaşı değerlendirmesi ve hormonal değerlendirme hayati önem taşımaktadır. Tanı ve tedavi gecikmelerini önlemek için pediatrik endokrinolojiye derhal sevk edilmesi çok önemlidir.

Anahtar Kelimeler: Ergenlik gecikmesi; etiyoloji; hipogonadizm.

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INTRODUCTION

Puberty is a dynamic biological process marked by sexual and physical maturation and is influenced by genetic, environmental, nutritional, and socioeconomic factors. Delays in this process may result from individual variability or interactions among these factors (1).

In cases of suspected delayed puberty (DP), the primary clinical goal is to differentiate between physiological variants, in which growth and puberty are naturally slower, and pathological causes, in which the normal mechanisms triggering puberty are disrupted. Accurate diagnosis relies on anthropometric assessments, genital examination, and evaluation of secondary sexual characteristics and their progression over time (2).

Timely diagnosis and treatment are essential for supporting normal physical development, safeguarding psychosocial well-being, and preserving reproductive potential. Identifying the underlying causes and their distribution is key to guiding clinical evaluation, selecting appropriate tests, and making differential diagnoses (3).

This study aimed to identify etiological factors in patients presenting with DP at a tertiary care center, determine the distribution of diagnostic categories, and compare these groups based on clinical and laboratory findings. The findings are expected to contribute to a better clinical understanding of DP and improve diagnostic and management strategies for affected individuals.

MATERIAL AND METHODS

Study Population and Diagnostic Criteria

This retrospective observational study evaluated 180 patients (91 boys and 89 girls) diagnosed with DP who presented to the Pediatric Endocrinology Clinic at Ankara Children's Health and Diseases Hematology-Oncology Training and Research Hospital between December 1, 2005, and December 31, 2012. DP was defined using standard criteria: absence of breast development by age 13 years in girls and failure of testicular volume to reach 4 mL by age 14 years in boys.

Clinical Assessment and Anthropometry

Patients' medical histories were reviewed for prenatal and postnatal complications, birth weight, onset of pubertal delay, history of chronic illness, surgeries, medications, and nutritional habits. Family history of DP was also noted. Height was measured

using an AYRTON stadiometer and weight with a SECA® digital scale. Growth data were assessed using reference standards developed for Turkish children by Bundak et al. (4) Cases lacking adequate archival data for evaluation were excluded. Tanner-Marshall staging (5, 6) was used for pubertal evaluation, and bone age was assessed using the Greulich-Pyle atlas (7).

Laboratory Evaluations

Complete blood counts were performed using a Beckman Coulter Gen S analyzer. Biochemical parameters were measured with a Roche Hitachi Modular P800 using spectrophotometry. Screening for celiac disease included IgG and IgA anti-tTG antibodies analyzed via ELISA. Positive cases underwent stomach-duodenum biopsy for confirmation.

Hormonal Assays

Hormonal evaluations included thyroid function tests, insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), basal luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex steroids (estrogen/testosterone), prolactin, cortisol, and dehydroepiandrosterone sulfate (DHEA-S). These were analyzed using electrochemiluminescence on an Immulite 2000 autoanalyzer.

Patients without chronic illness, medication use, or nutritional deficiency and with low basal gonadotropin levels underwent a gonadotropin-releasing hormone (GnRH) stimulation test.

CDP was diagnosed in patients with bone age (BA) consistent with height but delayed relative to chronological age (CA), with no underlying chronic disease or endocrinopathy.

LHRH Stimulation Test: Initial blood samples were obtained for basal LH, FSH, and estrogen (E2) or total testosterone (TT). An intravenous LHRH dose of 60 mcg/m² (maximum 100 mcg/m²) was administered, and blood samples were collected at 30, 60, and 90 minutes after injection to assess stimulated hormone levels (8). Patients with a peak LH response <5 ng/mL and findings inconsistent with constitutional delay of puberty (CDP) were diagnosed with hypogonadotropic hypogonadism (HypoH). Although newer studies have proposed different thresholds, this cutoff was selected in accordance with the methodology applied during the study period. Chromosomal analysis was performed in patients with severe short stature, dysmorphic features, or clinical suspicion of chromosomal disorders, such as Turner syndrome or disorders of sex development.

Growth Hormone Testing: In patients with suspected hypopituitarism and marked short stature, growth hormone (GH) stimulation tests were performed using L-DOPA or clonidine following testosterone priming (100 mg IM) (9).

Clonidine Test: A baseline sample was obtained, followed by 150 mcg/m² oral clonidine. Samples were collected at 30, 60, 90, and 120 minutes (9).

L-DOPA Test: L-DOPA was administered orally at 10 mg/kg (maximum 500 mg), and samples were collected at the same intervals. GH deficiency was diagnosed if peak levels were insufficient (9).

Radiological and Additional Evaluations

Patients with HypoH underwent pituitary MRI. Elevated basal FSH and LH levels indicated hypergonadotropic hypogonadism (HyperH).

The differentiation between constitutional delay of puberty (CDP), functional hypogonadotropic hypogonadism (FHH), and permanent hypogonadotropic hypogonadism (HypoH) was based on a combination of clinical, auxological, and biochemical parameters. These included bone age delay relative to chronological age, family history of delayed puberty, presence of chronic illness or nutritional deficiency, and response to GnRH stimulation testing. CDP was considered in patients with delayed bone age consistent with height, positive family history, and a pubertal response to GnRH stimulation, whereas HypoH was diagnosed in patients with persistently low gonadotropin responses and no evidence of reversible underlying conditions.

Patients with chronic illness or malnutrition but no permanent hypothalamic or pituitary damage were classified under functional hypogonadotropic hypogonadism (FHH). Malnutrition-related DP was diagnosed in individuals below the 10th percentile for weight-for-height and with documented nutritional deficiencies.

Nutritional and Hematological Causes

Iron Deficiency Anemia: Diagnosed in patients with low hemoglobin and hematocrit levels, microcytic indices, and elevated red cell distribution width (10).

Macrocytic Anemia: Diagnosed based on high mean corpuscular volume, low vitamin B12 and folate levels, and low hematological parameters (10).

Tayanç-Prasad Syndrome: Diagnosed in patients with growth retardation, hepatosplenomegaly, iron/zinc deficiency, and DP. These patients improved following supplementation (11).

Genetic and Structural Diagnoses: Two patients were diagnosed with Turner syndrome through karyotype analysis, prompted by severe short stature and the absence of elevated basal gonadotropin levels. Additional patients with abnormal LHRH responses (stimulated LH >5 ng/mL but low baseline levels) and abnormal pituitary imaging findings, such as microadenoma or partial empty sella, were categorized as unclassifiable.

An otolaryngologist evaluated cases of hypopituitarism for anosmia.

For analytical purposes, patients were categorized into four main diagnostic groups: hypogonadotropic hypogonadism (HypoH), hypergonadotropic hypogonadism (HyperH), functional hypogonadotropic hypogonadism (FHH), and constitutional delay of puberty (CDP).

Statistical Analysis

Data were analyzed using SPSS for Windows, version 16.0. Continuous variables were expressed as mean±standard deviation (min–max). Group comparisons for continuous variables were performed using Student's t-test for two groups or one-way ANOVA with LSD post hoc test for multiple groups.

Table 1. Gender differences in cases of delayed puberty

	Girls (n=89)	Boys (n=91)	p
Height SDS[a]	-2.4±1.9 (-6.7–2.1)	-2.5±1.6 (-7.3–1.5)	0.600
BMI SDS[a]	-0.95±1.85 (-4.9–3.7)	-1.01±2.1 (-8.2–2.6)	0.800
Weight SDS[a]	-2.1±2.3 (-6.3–3.8)	-2.1±2.2 (-9.8–2.5)	0.800
Pubic hair[b]	44.9%	27.5%	**0.015**
Axillary hair[b]	41.6%	36.3%	0.560
Parental history[b]	8 (9)	24 (26.4)	**0.002**
Sibling history[b]	16 (18)	3 (3.3)	**0.001**
CDP[b] n (%)	15 (16.9)	31 (34.1)	**<0.05**
FHH[b] n (%)	20 (22.5)	18 (19.8)	>0.05
HypoH[b] n (%)	29 (32.6)	32 (35.2)	>0.05
HyperH[b] n (%)	23 (25.8)	9 (9.9)	**<0.05**

a: Results are presented as the mean±standard deviation (minimum–maximum); b: Results are given as percentages; CDP: Constitutional delay of puberty; FHH: Functional hypogonadotropic hypogonadism; HyperH: Hypergonadotropic hypogonadism; HypoH: Hypogonadotropic hypogonadism.

For non-normally distributed data, the Kruskal–Wallis test was used. Categorical data were compared using the chi-squared test. For pairwise comparisons of non-normally distributed variables between two groups, the Mann–Whitney U test was used. A p-value <0.05 was considered statistically significant.

Ethical Approval

This study was derived from a pediatric residency thesis and represents a retrospective analysis of data collected in 2013 at Ankara Children's Health and Diseases Hematology and Oncology Training and Research Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee.

RESULTS

The following results were obtained from the evaluation of 180 cases. Of these cases, 50.6% were male (n=91).

The mean CA was 14.5±1.2 (13–18) years, and the median BA was 12±1.5 (9.5–18) years. The mean difference between CA and BA (CA-BA) was 2.4±2.2 (-3.8±7.0) (p<0.05).

Although the difference in CA between male and female cases was significant (p<0.05), the differences in BA and ΔCA-BA values were not significant (p>0.05).

A significant difference in ΔCA-BA was found in the comparison between HypoH and HyperH (p<0.05). Among female cases, a significant difference in ΔCA-BA was observed between HypoH and HyperH, as well as between HypoH and FHH (p<0.05). Among FHH cases, the difference in ΔCA-BA between female and male cases was significant (p<0.05).

Pubic hair was present in 36.1% of cases. The prevalence of pubic hair was significantly higher in girls than in boys (p<0.05). However, no significant difference was found in axillary hair between the two groups (p>0.05).

A history of DP was present in at least one parent in 17.8% of cases and in at least one sibling in 10.6% of cases. The history of DP among parents and siblings differed significantly by sex and diagnostic group (p<0.05).

We categorized cases into four groups based on DP etiology. The most common diagnosis was HypoH. Hypogonadotropic hypogonadism and FHH occurred at similar rates in both sexes. Hypergonadotropic hypogonadism was more common in girls, whereas CDP was more frequent in boys. Table 1 presents the characteristics by sex, and Table 2 presents the characteristics by diagnostic group.

A total of 46 diagnostic subgroups were identified. Tables 3, 4, and 5 show the subgroup distributions for HypoH, HyperH, and FHH, respectively. Idiopathic HypoH was the most frequent subgroup and was more common in males.

Of all cases, patients with HypoH presented latest. The CA of the HypoH group differed from that of the CDP group (p=0.003). Patients with HyperH were found to have a BA that was older than that of patients with CDP (p=0.026). There was no difference in BA between the other groups.

IGF-1 showed better SDS values in the HyperH group than in the other three diagnostic groups (p<0.05). IGFBP-3 SDS values differed significantly between the HyperH and HypoH groups (p=0.026). However, there was no significant difference in BMI SDS among the diagnostic groups (p>0.05).

The HyperH group had significantly higher basal LH and FSH values than the other groups (p<0.0001). The CDP and FHH groups exhibited a pubertal LHRH response. The HypoH group had a significantly lower peak LH response than the other groups (p<0.0001). The CDP group had a significantly higher LH peak than the FHH group (p=0.009).

In males, chronological age and peak LH levels differed significantly between the HypoH and CDP groups (p=0.019 and p=0.0001, respectively).

Table 2. Differences between diagnostic groups

	CDP	HypoH	FHH	HyperH
ΔTY-KY (years)				
All cases[a]	2.3±0.9	2.9±1.5	2.3±1.7	2.0±1.5
Girls[a]	2.3±0.7	3.1±1.5	1.5±1.5	2.1±1.4
Boys[a]	2.3±1.01	2.7±1.6	3.1±1.6	1.8±1.9
Parental history[b]	**47.8**%*	11.5%	5.3%	3.1%
Sibling history[b]	4.3%	13.1%	7.9%	**18.8**%*

a: Results are presented as the mean±standard deviation (minimum–maximum); b: Results are given as percentages; *: A parental history was more frequent in CDP cases, whereas a sibling history was more frequent in HyperH cases. CDP: Constitutional delay of puberty; FHH: Functional hypogonadotropic hypogonadism; HyperH: Hypergonadotropic hypogonadism; HypoH: Hypogonadotropic hypogonadism.

Table 3. Diagnosis subgroups of hypogonadotrophic hypogonadism

	All cases	Girls	Boys
Idiopathic hypoH	18 (29.5)	4 (13.7)	14 (44.2)
Panhypopituitarism	10 (16.6)	8 (27.5)	2 (6.2)
Thalassemia major	7 (11.5)	3 (10.3)	4 (12.5)
Pituitary microadenoma	6 (9.8)	5 (17.2)	1 (3.1)
Craniopharyngeoma	5 (8.2)	3 (10.3)	2 (6.2)
Syndromic cases[a]	3 (4.9)		3 (9.2)
Empty sella	2 (3.3)	2 (7)	
Partially empty sella	2 (3.3)		2 (6.2)
Head trauma	2 (3.3)	1 (3.5)	1 (3.1)
Chemotherapy	1 (1.6)		1 (3.1)
Hypoxic ischemic encephalopathy	1 (1.6)		1 (3.1)
Hypophysitis	1 (1.6)		1 (3.1)
Pars intermedia cyst	1 (1.6)	1 (3.5)	
Severe iron deficiency anemia	1 (1.6)	1 (3.5)	
Ovarian dysgenesis and pituitary hypoplasia	1 (1.6)	1 (3.5)	
Total	61 (100)	29(100)	32 (100)

a: Bardet Biedl Syndrome, Lesch-Nyhan Syndrome, Nail Patella Syndrome Results are given as number of cases (%)

There was a significant difference between the HypoH and FHH groups in terms of IGF-1 SDS (p=0.016) and peak LH levels (p=0.028).

There was a significant difference between the FHH and HyperH groups in terms of bone age (p=0.042).

There was a significant difference between the FHH and CDP groups in terms of IGFBP-3 SDS (p=0.038) and peak LH levels (p=0.0001).

Table 4. Diagnosis subgroups of hypergonadotrophic hypogonadism

	All cases	Girls	Boys
Sexual differentiation defects	12 (37.7)	11 (47.8)	1 (11.1)
Turner syndrome	7 (21.8)	7 (30.4)	
Klinefelter syndrome	2 (6.25)		2 (22.2)
Ovarian dysgenesis	2 (6.25)	2 (8.7)	
Bone marrow transplantation	2 (6.25)	2 (8.7)	
Testicular atrophy	2 (6.25)		2 (22.2)
Radiotherapy	1 (3.1)		1 (11.1)
Testicular rest tumor	1 (3.1)		1 (11.1)
Vanishing testis	1 (3.1)		1 (11.1)
Anorexia nervosa	1 (3.1)	1 (4.4)	
Mitochondrial disease	1 (3.1)		1 (11.1)
Total	32 (100)	23 (100)	9 (100)

Results are given as number of cases (%).

Table 5. Diagnosis subgroups of functional hypogonadotrophic hypogonadism

	All cases	Girls	Boys
Obesity	6 (16)	2 (10)	4 (22.3)
Celiac disease	3 (7.9)	3 (15)	
Thalassemia major	3 (7.9)	2 (10)	1 (5.55)
Malnutrition	3 (7.9)	1 (5)	2 (11.1)
Familial Mediterranean fever	3 (7.9)	2 (10)	1(5.55)
Diabetes mellitus (Type 1)	2 (5.3)	2 (10)	
Tayanç Prasad syndrome	2 (5.3)	1 (5)	1 (5.55)
Immunodeficiency	3 (7.9)	1 (5)	2 (11.1)
Bronchiectasis	2 (5.3)		2 (11.1)
Profound iron deficiency anemia	1 (2.6)	1 (5)	
Asthma	1 (2.6)	1 (5)	
Adrenal insufficiency	1 (2.6)	1 (5)	
Inflammatory bowel disease	1 (2.6)		1 (5.55)
Chronic renal failure	1 (2.6)	1 (5)	
Nephrotic syndrome	1 (2.6)		1 (5.55)
Autoimmune thyroiditis	1 (2.6)	1 (5)	
Cardiomyopathy	1 (2.6)		1 (5.55)
Renal tubular acidosis	1 (2.6)		1 (5.55)
Mitochondrial disease	1 (2.6)		1 (5.55)
Hypothyroidism	1 (2.6)	1 (5)	
Total	38 (100)	20 (100)	18 (100)

Results are given as number of cases (%).

With the exception of the HyperH group, there were no significant differences in BMI SDS or basal LH or FSH values between the diagnostic groups (p>0.05).

In females, significant differences were found between the HypoH and CDP cases in terms of BA (p=0.007), IGFBP-3 SDS (p=0.038), and peak LH values (p=0.0001).

Significant differences were observed between the HypoH and FHH groups in terms of IGF-1 SDS (p=0.025), IGFBP-3 SDS (p=0.015), and peak LH values (p=0.0001).

CA and BA were significantly lower in the CDP group than in the HyperH group (p=0.038 and p=0.019, respectively).

BA was significantly lower in the CDP group than in the FHH group (p=0.022).

DISCUSSION

Our study represents one of the largest DP case series in the literature (12–14), comprising a retrospective analysis of 180 patients who presented to our pediatric endocrinology clinic over a seven-year period. These cases were classified into 46 different diagnostic subgroups, allowing for a comprehensive evaluation of the wide range of etiological factors underlying DP.

The mean age at presentation was 14.5 years, with a significant sex-based difference: boys presented later than girls, a finding consistent with previous studies (12, 13). This highlights the importance of assessing testicular volume during routine pediatric evaluations, as early detection of pubertal onset in boys may otherwise be overlooked.

Among female patients, the mean age at presentation was 14 years, and approximately half had pubic hair. This may have led to misinterpretation by families, who could have assumed that pubertal development had already begun. However, in girls, pubic and axillary hair growth is primarily driven by adrenal androgens and does not necessarily indicate pubertal activation (2, 15). In contrast, pubic hair development in boys is typically linked to increased testicular volume and mediated by testicular androgens (15). The lower prevalence of pubic hair among male patients in our cohort may therefore reflect a deficiency in these androgens.

Across all diagnostic groups, bone age (BA) was delayed relative to chronological age (CA). The difference between CA and BA (ΔCA-BA) is a standard parameter for assessing bone maturation delay (13). Although no significant sex-based differences were observed in ΔCA-BA values, the greatest delay was noted in patients with hypogonadotropic hypogonadism (HypoH), particularly those with panhypopituitarism. In this subgroup, in addition to sex steroid deficiency, patients also exhibited deficits in thyroid hormone and growth hormone. They were also older at the time of presentation, suggesting that prolonged and profound hormone deficiencies contributed to the greater skeletal maturation delay observed.

Conversely, the most advanced BA was seen in the hypergonadotropic hypogonadism (HyperH) group. This is expected, as most HyperH cases are syndromic, and in such patients, CA and BA typically progress in parallel (13). Additionally, these individuals often maintain normal thyroid and growth hormone function, which may help preserve BA progression.

The role of estrogen in bone maturation, particularly in its biphasic effects on epiphyseal growth plates, is well documented. In girls with DP, estrogen deficiency can result in delayed BA and decreased growth velocity by altering growth hormone responsiveness (1). Although previous research has suggested that BA delay is often more pronounced in girls than in boys, our study did not find significant sex-based differences in BA, height SDS, weight SDS, or BMI SDS. These findings suggest that sex-specific effects of DP may not always be evident and could vary depending on population characteristics. Moreover, the impact of DP on growth is likely influenced by multiple hormonal and environmental factors.

A positive family history of DP was identified in 17.8% of parents and 10.6% of siblings. In the CDP group, parental history was particularly common (47.8%), whereas in the HyperH group, sibling history was more frequent (18.8%). Parental history was more often reported in male patients, whereas sibling history predominated among females. This may be due to the higher prevalence of HyperH among female cases, a condition that can be genetically transmitted, such as primary ovarian insufficiency, and can manifest similarly among siblings (16). On the other hand, the high prevalence of CDP among males, which is often inherited in an autosomal dominant fashion, may explain the increased parental history in this group (17).

Basal gonadotropin levels were central to diagnostic classification (18). The highest LH and FSH levels were observed in the HyperH group, whereas the lowest levels were found in the HypoH group. When basal levels were inconclusive, the LHRH stimulation test provided critical diagnostic clarity (9). A pubertal LH response was observed in the CDP and FHH groups, whereas the HypoH group had significantly blunted responses. Notably, patients with CDP had higher peak LH levels compared with the FHH group, a distinction that can aid in differentiating these conditions (15).

Although CDP is often cited as the most common cause of DP in both sexes (1, 2), our study found that HypoH was the most frequently diagnosed etiology. This likely reflects the referral nature of our tertiary care setting, which tends to receive more complex or pathological cases. CDP was the second most common diagnosis. HyperH, although the least frequent overall, was the second most prevalent diagnosis among female patients. Within the HyperH group, disorders of sex development (DSD) and Turner syndrome were predominant. Among males, CDP was the second most frequent cause. This distribution aligns with previous studies suggesting that pathological causes are more common among girls, whereas benign etiologies, such as CDP, are more typical in boys (12, 13).

Similarly, Galal et al., (14) in a 15-year retrospective analysis conducted at a tertiary center in Sudan, also identified HypoH and FHH as the most prevalent etiologies. They emphasized

the influence of socioeconomic status, nutritional factors, and genetic background, including high rates of consanguinity, on the distribution of DP causes.

A total of 46 distinct etiologies for DP were identified in our study. The most common was idiopathic hypogonadotropic hypogonadism (IHH). All patients with IHH were screened for anosmia, and those with suspicious findings were referred for otolaryngology evaluation. No cases of anosmia were confirmed. It is worth noting that, during the study period, genetic and molecular diagnostics were not widely available. Since then, advances in these technologies have allowed for more accurate identification of underlying causes in IHH cases (19).

Mean BMI SDS values were low across our cohort, indicating that body weight, like height, is negatively affected in patients with DP. No significant differences in BMI SDS were observed between diagnostic groups or sexes. In boys, decreased IGF-1 levels were particularly noted in the FHH group, suggesting that chronic illnesses may induce secondary growth hormone resistance. Among females, both IGF-1 and IGFBP-3 levels were significantly lower in the HypoH group compared with the FHH and HyperH groups. Many of these HypoH cases involved panhypopituitarism, and combined deficiencies of thyroid and growth hormones likely contributed to the observed reductions in IGF-1 and IGFBP-3.

Basal LH and FSH levels were diagnostically elevated in patients with HyperH, while remaining low in the other groups. However, before BA reaches approximately 12 years, when the hypothalamic-pituitary-gonadal (HPG) axis typically activates, it can be difficult to distinguish between CDP and HypoH (2, 3). In such cases, stimulated LH values following LHRH administration offer important diagnostic insight (8). In our CDP group, stimulated LH reached pubertal levels, and patients generally developed secondary sexual characteristics either spontaneously or after short-term sex steroid therapy. The subsequent rise in endogenous sex hormones after treatment cessation served as an indicator of ongoing gonadal function.

In patients with FHH, pubertal development sometimes commenced after treatment of the underlying chronic illness and temporary sex steroid administration, indicating the potential for endogenous activation. In contrast, patients in the HypoH group had persistently low LH levels both at baseline and after stimulation, necessitating lifelong hormone replacement due to permanent gonadotropin deficiency (2, 20). Distinguishing between CDP and HypoH is therefore essential for clinical decision-making (20).

Among female patients, HypoH and HyperH were the most frequent causes of DP, whereas CDP was the least common, consistent with findings in the literature (1, 2, 13). The higher prevalence of pathological etiologies in girls supports the need for thorough diagnostic workup and, where appropriate, chromosomal analysis. In our study, 18 of 22 female patients with HyperH (81.8%) had either DSD or Turner syndrome. These patients exhibited more advanced BA and higher IGF-1 and IGFBP-3 levels compared with the other groups, likely due to relatively normal growth hormone function and the presence of androgen excess, which is known to stimulate bone maturation.

Given our hospital's status as a tertiary referral center, the high number of patients and prevalence of complex conditions likely contributed to the predominance of permanent and functional hypogonadotropic causes in our cohort. IHH was the most commonly diagnosed condition, yet the lack of genetic testing during the study period limited our ability to differentiate between congenital and acquired forms (21). This constitutes a major limitation of the study. Future genetic research will enhance diagnostic precision and facilitate the early identification of at-risk family members.

Differentiating CDP from permanent HypoH remains a well-recognized clinical challenge, particularly in early adolescence, when the hypothalamic-pituitary-gonadal axis has not yet fully activated. In our study, this distinction was made based on clinical findings, bone age, family history, and GnRH stimulation test results. However, the absence of long-term follow-up data represents an important limitation. Some patients initially classified as IHH may later exhibit spontaneous pubertal development, leading to potential reclassification as CDP. Therefore, longitudinal follow-up is essential for confirming the definitive diagnosis in such cases.

CONCLUSION

In conclusion, this study is among the most comprehensive case series investigating the etiology of delayed puberty (DP) in a tertiary pediatric unit. Our findings provide valuable insight into the distribution of underlying causes and highlight the clinical and laboratory features that aid differential diagnosis. Accurate diagnosis and individualized assessment are essential for effectively managing adolescents with DP. Even in cases of permanent hypogonadism, appropriate treatment can significantly improve physical and psychosocial outcomes. Genetic studies are increasingly important in evaluating DP and are expected to play a critical role in the future management of hypogonadism.

Ethics Committee Approval: This study was derived from a pediatric residency thesis and represents a retrospective analysis of data collected in 2013 at Ankara Children's Health and Diseases Hematology and Oncology Training and Research Hospital. The study was approved by the local ethics committee.

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Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Çalışmamızın üretim veya yazım aşamalarında yapay zeka kullanmadık.

Yazarlık Katkıları: Fikir – FD, Fİ; Tasarım – FD, Fİ; Denetlemeler – FD, Fİ; Kaynaklar – FD, Fİ; Malzemeler – FD, Fİ; Veri toplanması ve/veya işleme – FD, Fİ; Analiz ve/veya yorumlama – FD, Fİ; Literatür araştırması – FD, Fİ; Yazım – FD, Fİ; Eleştirel incelemeler – FD, Fİ.

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