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Underlying Causes of Short Stature in Children Aged 4 to 16 Years Presenting at the Endocrine Clinic of a Tertiary Care Hospital in Pakistan

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ABSTRACT

Short stature is a frequent pediatric presentation that may arise from normal growth variants or underlying pathological conditions. In Pakistan, its burden is heightened by malnutrition, infections, and delayed healthcare-seeking behaviors. Identifying the underlying causes is crucial for timely intervention and better outcomes. **Objectives:** To determine the underlying causes of short stature in children aged 4–16 years presenting at the Endocrine Clinic of a Tertiary Care Hospital in Pakistan. **Methods:** This descriptive cross-sectional study was conducted at the Pediatric Endocrinology Clinic, Aga Khan University Hospital, Karachi, from March 2023 to March 2024. All children aged 4–16 years with short stature, defined as height <-2 SD for age and sex or below the 3rd centile, were enrolled. Participants were evaluated for normal variants (familial short stature and constitutional delay of growth and puberty) and pathological causes (endocrine and non-endocrine). **Results:** Among 384 children, 128 (33.3%) had normal variants, most commonly familial short stature (70.3%). Pathological short stature was found in 256 (66.7%) children, with endocrine disorders predominating (60.9%), mainly growth hormone deficiency, hypothyroidism, panhypopituitarism, and hypogonadism. Non-endocrine causes included rickets, celiac disease, and genetic syndromes. No significant gender differences were observed in the distribution of short stature types. **Conclusions:** Pathological conditions were the leading cause of short stature, accounting for two-thirds of cases, with endocrine disorders being the most frequent contributors. These findings underscore the importance of timely endocrine evaluation in children presenting with growth concerns.

INTRODUCTION

Short stature, a prevalent issue in the paediatric population of developing countries, is defined as a height more than 2 standard deviations (SD) below the mean for age and sex, or below the 3rd percentile on standardized growth charts, in accordance with international pediatric endocrinology guidelines [1-3]. According to the United Nations Children's Fund (UNICEF) report, globally, 23.2% of children under five were stunted in 2024, amounting to 150.2 million affected children [4]. Short stature can result from various underlying etiologies, including genetic, endocrine, nutritional, and systemic disorders. Understanding the causes of short stature is crucial for appropriate diagnosis, management, and timely intervention [5-7]. In Pakistan, where malnutrition and infectious diseases are common, short stature is prevalent and represents a manifestation of several underlying diseases rather than a condition itself [7, 8]. Various studies have shown variations in the magnitude of different causes. Studies have identified several common factors in Pakistan contributing to short stature in children [2, 9]. These include familial short

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stature (FSS), hypothyroidism, growth hormone deficiency (GHD), insulin-dependent diabetes mellitus (IDDM), and constitutional delayed growth and maturation (CDGM). Despite the availability of studies at the national and international levels, there is a need to continuously monitor the specific etiological factors contributing to short stature in Pakistani children. We hypothesize that nutritional and endocrine causes, particularly hypothyroidism and growth hormone deficiency, along with familial short stature, account for the majority of cases.

Despite the high burden of short stature in Pakistan, particularly in the context of malnutrition and infectious diseases, there remains limited updated hospital-based data delineating the current etiological spectrum among children presenting to specialized endocrine services. Most local studies are either outdated, region-specific, or lack detailed stratification by pubertal status and pathological subtypes. Furthermore, evolving diagnostic capabilities and referral patterns may have shifted the relative contribution of endocrine versus non-endocrine causes. Therefore, contemporary data from tertiary care settings are needed to better characterize underlying etiologies and guide timely diagnostic evaluation. This study aims to analyze the etiological spectrum of short stature in children aged 4 to 16 years presenting at a Tertiary Care Endocrine clinic in Pakistan.

METHODS

This cross-sectional study was conducted at the Endocrinology Clinic of Aga Khan University Hospital, Karachi, Pakistan, from March 2023 to March 2024. Ethical approval was granted by the Institutional Review Board of the Aga Khan University Hospital (Ref. No. 2023-8357-24166). Consecutive sampling was used to recruit all eligible children with short stature during the study period. As the study involved a retrospective review of medical records without direct patient contact, informed consent was not required. Patient confidentiality and anonymity were strictly maintained. The sample size was estimated for a descriptive cross-sectional study using the single-population proportion formula, assuming a prevalence of 50% (to maximize variance), 95% confidence level, and 5% margin of error. This yielded a minimum required sample size of 384 children. Our study included 384 cases, thereby fulfilling this requirement. The formula applied was: $n = (Z^2 \times p(1-p)) / d^2$, where n = required sample size, Z = standard normal deviate at 95% confidence level (1.96), p = expected prevalence (0.50), and d = margin of error (0.05) [10]. The inclusion criteria were children aged 4 to 16 years presenting with short stature. While children with missing information regarding short stature were excluded, all eligible cases meeting the inclusion criteria during the study period were included. Short stature was defined as a height more than 2 standard deviations (SD) below the mean for age and sex, or below the 3rd percentile on standardized growth charts, in accordance with international pediatric endocrinology guidelines [1-3]. A pre-structured proforma was used to collect all the data. Data were extracted from patient records, which included baseline characteristics, clinical histories, physical examination findings, growth measurements, and results of diagnostic tests. Information regarding variant (normal/abnormal), sub-categories of normal variant such as familial short stature and constitutional delay of growth and puberty (CDGP), pathological short stature, endocrine and non-endocrine causes, and idiopathic short stature were observed. Pubertal development was assessed using the Tanner staging system, based on clinical examination of breast development in girls and genital development in boys, supplemented by pubic hair assessment. Examinations were performed by trained pediatric endocrinologists to ensure reliability. For analytical purposes, participants were stratified into three groups: Group 1: Tanner Stage 1 (prepubertal); Group 2: Tanner Stage 2 (early pubertal); Group 3: Tanner Stages 3–5 (mid to late pubertal). This classification allowed comparison of etiologies of short stature across different phases of pubertal maturation [11]. Recorded heights measured by healthcare professionals using a stadiometer and plotted on WHO growth charts were noted. Parental heights mentioned in the medical records were used to calculate mid-parental height. Normal variant short stature included familial short stature (parental height <3rd percentile, with consistent mid-parental height prediction) and constitutional delay of growth and puberty (delayed bone age with expected pubertal catch-up). Pathological short stature included endocrine causes (e.g., GHD, hypothyroidism) and non-endocrine causes (e.g., celiac disease, renal insufficiency, systemic disorders). Statistical analysis was performed using RStudio (version 4.4.0). Quantitative variables were summarized as mean ± SD, while categorical variables were presented as frequencies and percentages. Associations between categorical variables were assessed using Chi-square or Fisher's exact tests, as appropriate. Test statistics (χ^2 values, degrees of freedom, and corresponding p-values) are reported in the tables. A p-value of ≤0.050 was considered statistically significant.

RESULTS

The study included 384 children with a mean age of 10.0 ± 3.5 years, with almost equal distribution between children aged 4–10 years (50.3%) and those older than 10 years (49.7%). Gender distribution was also balanced (51.8% females vs. 48.2% males). The majority were term births

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(95.3%) and had appropriate birth weight (88.0%). A positive family history of short stature was reported in 40.6% of cases, most commonly maternal (31.5%) and less frequently paternal (18.0%). Most participants were prepubertal or in early puberty, with only 20.8% reaching mid to late pubertal stages (Table 1)

Table 1: General Characteristics of the Population

Characteristics	Overall N=384	Group 1 N=158	Group 2 N=146	Group 3 N=80
	N (%)			
Age, Years				
4-10 Years	193 (50.3%)	128 (81%)	62 (42.5%)	3 (3.8)
>10 Years	191 (49.7%)	30 (19%)	84 (57.5%)	77 (96.3)
Gender				
Male	185 (48.2%)	74 (46.8%)	79 (54.1%)	32 (40%)
Female	199 (51.8%)	84 (53.2%)	67 (45.9%)	48 (60%)
Gestational age at Birth				
Preterm	18 (4.7%)	9 (5.7%)	8 (5.5%)	1 (1.3%)
Term	366 (95.3%)	149 (94.3%)	138 (94.5%)	79 (98.8%)
Low Birth Weight (<2.5kg)	46 (12%)	23 (14.6%)	17 (11.6%)	6 (7.5%)
Family history of short stature	156 (40.6%)	62 (39.2%)	59 (40.4%)	35 (43.8%)
Mother's history of short stature	121 (31.5%)	48 (30.4%)	47 (32.2%)	26 (32.5%)
Father's history of short stature	69 (18%)	26 (16.5%)	25 (17.1%)	18 (22.5%)
Maternal family's history of short stature	36 (9.4%)	18 (11.4%)	13 (8.9%)	5 (6.3%)
Paternal family's history of short stature	29 (7.6%)	13 (8.2%)	9 (6.2%)	7 (8.8%)
Sibling's history of short stature	30 (7.8%)	14 (8.9%)	10 (6.8%)	6 (7.5%)
Maternal history of delayed puberty	23 (6%)	6 (3.8%)	10 (6.8%)	7 (8.8%)
Paternal history of delayed puberty	26 (6.8%)	11 (7%)	10 (6.8%)	5 (6.3%)

Group 1 = children at Tanner Stage 1 (prepubertal); Group 2 = children at Tanner Stage 2 (early pubertal); Group 3 = children at Tanner Stages 3–5 (mid to late pubertal)

Among the participants, 128 (33.3%) exhibited normal variant short stature, which includes non-pathological growth delays such as familial short stature affecting 90 (70.3%) and CDGP 38 (29.7%). In contrast, a significant proportion, 256 (66.7%), were diagnosed with pathological short stature. Of the 256 children with pathological short stature, endocrine causes were the most frequent, observed in 156 cases (60.9%), while non-endocrine causes accounted for 90 cases (35.2%), with a small subset showing combined etiologies (3.9%). These findings highlight that endocrine disorders represent the leading contributors to pathological short stature in this population (Table 2).

Table 2: Categories of Causes of Short Stature among the Study Population, Stratified by Gender

Characteristics	Overall N=384	Male N=185	Female N=199	p-Value
	N (%)			
Normal variant, N=128	128 (33.3%)	61 (33%)	67 (33.7%)	0.885
Familial Short Stature (FSS)	90 (70.3%)	40 (65.6%)	50 (74.6%)	0.263
Constitutional delay in growth and puberty (CDGP)	38 (29.7%)	21 (34.4%)	17 (25.4%)	0.354
Pathological ShortStature, N=256	256 (66.7%)	123 (66.5%)	133 (66.8%)	0.942
Endocrine	156 (60.9%)	78 (63.4%)	78 (58.6%)	0.435
Non-endocrine	90 (35.2%)	38 (30.9%)	52 (39.1%)	0.170
Both Endocrine and Non-endocrine	10 (3.9%)	7 (5.7%)	3 (2.3%)	0.185
Groups				
Group 1	158 (41.1%)	74 (40%)	84 (42.2%)	0.116
Group 2	146 (38%)	79 (42.7%)	67 (33.7%)	
Group 3	80 (20.8%)	32 (17.3%)	48 (24.1%)	

Chi-square or Fisher's exact test applied as appropriate: normal variants (χ^2=0.021, df=1, p=0.885); familial short stature vs. CDGP (χ^2=1.254, df=1, p=0.260); pathological subcategories (χ^2=0.005, df=1, p=0.942).

Within endocrine causes, growth hormone deficiency was the most frequent diagnosis, followed by panhypopituitarism and hypothyroidism. Non-endocrine causes included rickets, chronic systemic diseases, and syndromic conditions, while a small subset had combined etiologies. Gender differences across these subcategories were not statistically significant (Table 3).

Table 3: Subcategories of Causes of Short Stature Among the Study Population, Stratified by Gender

Characteristics	Overall N=384	Male N=185	Female N=199	p-Value
	N (%)			
Normal variant, N=128	128 (33.3%)	61 (33%)	67 (33.7%)	0.885
Familial Short Stature (FSS)	90 (70.3%)	40 (65.6%)	50 (74.6%)	0.263
Constitutional delay in growth and puberty (CDGP)	38 (29.7%)	21 (34.4%)	17 (25.4%)	0.354

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Pathological Short Stature, N=256	256 (66.7%)	123 (66.5%)	133 (66.8%)	0.942
Endocrine, N=156	156 (60.9%)	78 (63.4%)	78 (58.6%)	0.435
Growth Hormone Deficiency/Resistance	118 (75.6%)	61 (78.2)	57 (73.1%)	0.748
Hypothyroidism	2 (1.3%)	0 (0.0%)	2 (2.6%)	0.217
Panhypopituitarism (GHD and Hypothyroidism)	20 (12.8%)	9 (11.5%)	11 (14.1%)	0.807
Diabetes Mellitus	2 (1.3%)	2 (2.6%)	0 (0.0%)	0.155
Hypogonadism	6 (3.8%)	3 (3.8%)	3 (3.8%)	0.604
Growth Hormone Deficiency & Hypogonadism	1 (0.6%)	1 (1.3%)	0 (0.0%)	0.316
Post Chemotherapy/ Radiotherapy in childhood malignancy	1 (0.6%)	1 (1.3%)	0 (0.0%)	0.316
Others	6 (3.8%)	1 (1.3%)	5 (6.4%)	0.086
Non-endocrine, N=90	90 (35.2%)	38 (30.9%)	52 (39.1)	0.170
Dysmorphic Syndrome, N=11	11 (12%)	4 (11%)	7 (13%)	0.675
Down Syndrome	1 (9%)	1 (25%)	0 (0%)	0.165
Turner Syndrome	5 (45%)	0 (0%)	5 (71%)	0.022
Others	5 (45%)	3 (75%)	2 (29%)	0.137
Rickets	35 (39%)	17 (45%)	18 (35%)	0.331
Skeletal Dysplasia	2 (2%)	1 (3%)	1 (2%)	0.822
Chronic Systemic Disease, N=36	36 (40%)	13 (34%)	23 (44%)	0.078
Celiac Disease	14 (39%)	3 (23%)	11 (48%)	0.403
Malnutrition/Malabsorption	12 (33%)	6 (46%)	6 (26%)	0.107
Chronic Liver Disease	2 (5%)	1 (8%)	1 (4%)	0.486
Malignancies	2 (5%)	1 (8%)	1 (4%)	0.486
Chronic Anemia	2 (5%)	1 (8%)	1 (4%)	0.486
Chronic Infections	2 (5%)	1 (8%)	1 (4%)	0.486
Others	10 (28%)	3 (23%)	7 (30%)	0.901
IUGR	6 (7%)	3 (8%)	3 (6%)	0.690
Both Endocrine and Non-endocrine, N=10	10 (3.9%)	7 (5.7%)	3 (2.3%)	0.185
Growth Hormone Deficiency & Rickets	5 (50%)	4 (57%)	1 (33%)	0.569
Growth Hormone Deficiency & Chronic Systemic Disease	2 (20%)	2 (29%)	0 (0%)	0.467
Growth Hormone Deficiency, Rickets & Chronic Systemic Disease	1 (10%)	0 (0%)	1 (33%)	0.373
Post Chemotherapy/ Radiotherapy & Chronic Systemic Disease	1 (10%)	1 (14%)	0 (0%)	0.467
Growth Hormone Deficiency & Intra-uterine growth retardation	1 (10%)	0 (0%)	1 (33%)	0.373
Groups				
Group 1	158 (41.1)	74 (40)	84 (42.2)	0.116
Group 2	146 (38)	79 (42.7)	67 (33.7)	
Group 3	80 (20.8)	32 (17.3)	48 (24.1)	

Chi-square or Fisher's exact test applied as appropriate: endocrine vs. non-endocrine causes (χ^2=0.61, df=1, p=0.435); chronic systemic disease subtypes (χ^2=3.105, df=1, p=0.078); dysmorphic syndromes (χ^2=0.176, df=1, p = 0.675)."

DISCUSSION

Pathological causes accounted for two-thirds of cases, underscoring the predominance of endocrine and systemic disorders in this tertiary care cohort. This contrasts with community-based studies from Pakistan, where normal variants are more frequent, but is consistent with findings from referral centers in Pakistan and Egypt. These differences likely reflect referral bias, availability of diagnostic facilities, and healthcare-seeking behaviors. Normal variants comprised one-third of cases (33.3%), comparable to previous Pakistani reports, where normal growth variations were seen in 38.35% of cases, and familial short stature was observed in 11.0% [12, 13]. However, our prevalence of familial short stature was lower than in previous studies, which may reflect differences in referral populations or diagnostic thresholds. Endocrine causes, particularly growth hormone deficiency and hypothyroidism, were more frequent in our cohort and other tertiary-based studies [14, 15]. This difference likely reflects referral bias, since our study was conducted in a tertiary endocrine clinic where suspected hormonal cases are preferentially directed. Improved diagnostic availability and physician awareness may also contribute, a pattern consistent with other hospital-based reports. Interestingly, a retrospective study found that 69% of short stature cases were attributed to growth hormone deficiency, which is substantially higher than what was observed in our population and underscores the variability in growth hormone deficiency prevalence across different clinical settings [13, 14]. Celiac disease contributed to 3.6% of cases, consistent with other regional estimates (3–6%), underscoring its role as an underdiagnosed yet important etiology of growth failure. The mean age at presentation (10 years) suggests delayed recognition of growth concerns compared with an Indian cohort, where the mean age was 12 years [15, 16]. This highlights the importance of improving parental and physician awareness to facilitate earlier referral and intervention. Recent advances emphasize the role of genetic evaluation, including chromosomal microarray and next-generation sequencing, which provide diagnostic yields of up to 30–40% in children with idiopathic or syndromic short stature [17-20]. Studies have identified novel variants in growth plate and GH–IGF axis genes, improving etiological precision and guiding personalized management [21, 22]. Although genetic testing was not undertaken in our cohort, future incorporation of such tools could substantially enhance diagnostic accuracy. The current study has both strengths and limitations. Strengths include the robust sample size (n=384) and detailed categorization of short stature, which enhance the validity of the findings. The inclusion of gender-based analysis also provides insights

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into differences between male and female children, relevant for personalized medical approaches. Limitations include its single-center, retrospective design, absence of a control group of children with normal stature, and limited biochemical or genetic evaluation, which restricts generalizability and causal inference. Since only children with short stature were included, the findings mainly describe etiological distribution within this subgroup and do not fully capture determinants of growth in the general pediatric population. Future research should incorporate appropriate control groups, multicenter prospective cohorts, and long-term follow-up. Advanced diagnostic tools, such as genetic profiling and detailed hormonal assays, could further refine etiological identification and improve management strategies. By addressing these areas, future research can significantly strengthen our understanding of short stature in children and improve management strategies.

This study has certain limitations, including its single-center, retrospective design and referral-based population, which may limit generalizability to the broader pediatric community. The absence of a control group and limited incorporation of advanced genetic and molecular diagnostic testing may have led to under-recognition of certain etiologies. Additionally, longitudinal growth outcomes and treatment responses were not assessed. Future multicenter prospective studies incorporating genetic profiling, comprehensive hormonal evaluation, and long-term follow-up are warranted to refine etiological classification and optimize individualized management strategies for children with short stature.

CONCLUSIONS

Approximately one-third of cases of short stature in this cohort were attributable to normal growth variations, including familial short stature and constitutional delay of growth and puberty (CDGP), while two-thirds were pathological. Among the pathological causes, endocrine disorders particularly growth hormone deficiency and hypothyroidism were the most frequent contributors. These findings confirm that the etiological spectrum of short stature in Pakistani children is dominated by endocrine conditions. They underscore the importance of timely recognition, and comprehensive medical assessment of children with growth disturbances, with particular attention to endocrine evaluation, to facilitate early diagnosis, targeted management, and improved growth outcomes.

Authors' Contribution

Conceptualization: FN, IN, KNH
Methodology: MA, IN, KNH
Formal analysis: AU, MFQ
Writing and Drafting: FN, MA, IN, KNH
Review and Editing: FN, MA, IN, KNH, AU, MFQ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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