ORIGINAL ARTICLE

Celiac Disease in Short Stature Pediatric Population Presenting to Endocrinology Clinics: A Cross-Sectional Study from a Tertiary Care Hospital in Karachi

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Abstract

Background: Among many reasons, short stature is one of them for referring children to paediatric endocrinology. The most frequent extra-intestinal symptom of celiac disease is short stature (SS). A very high probability of celiac disease is reported among children with SS for non-endocrinological reasons.

Objective: To ascertain the frequency of celiac diseases among short-stature children presenting in endocrinology clinics in a tertiary care hospital.

Methods: This descriptive cross-sectional study was performed in pediatric endocrinology clinics at the National Institute of Child Health for a six-month duration from February 2022 to July 2022. All short-stature children of any gender and age from 2 to 12 years were included in the study. Short stature was defined as height for age < -2 standard deviation for the corresponding age and gender. Serological investigation including Immunoglobin A (IgA), anti-tissue-transglutaminase antibodies (TTG IgA) and TTG IgG test was done by ELISA (enzyme-linked immunosorbent assay) method for all of the patients recruited into the study.

Results: A total of 149 children with short stature were studied. The mean age of children was 10.2 ± 3.1 years. The majority of patients were males 53.7%. Average height and height for age z-score were 104.8 ± 8.9 cm and -5.1 ± 1.9 respectively. Out of 149 children, only 6.7% had positive serology for celiac diseases. None of the patients' factors was significantly different among patients with and without celiac disease.

Conclusion: The current investigation discovered that patients with low stature had a substantial frequency of celiac disease. It was discovered that none of the patients' demographics were linked to celiac disease. For prompt diagnosis and treatment of celiac disease, people with short height should undergo screening.

Keywords: *Celiac disease, short stature, pediatrics, endocrinology problems, growth hormone deficiency.*

INTRODUCTION

Short stature (SS) is the situation in which a person's height falls inside the third percentile for the average height of that person's age and gender. There are various anthropometric measurements for SS assessment. Genetic causes and hormonal and developmental pathology are responsible for leading to SS in children [1]. Growth deceleration and SS are frequent concerns in pediatric endocrinology. However, its pathogenesis is not clearly understood yet. Most likely, the etiology is multifactorial and may occur because of malabsorption, growth hormone deficiency and irregularities in the hypothalamus-pituitary axis [2]. This condition may be a sign of social stigma contributing to mental distress. Although SS is not a disease itself it may be the manifestation of various diseases. Hence the timely diagnosis and evaluation of underlying causes are essential [3].

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Among many reasons, SS is one of them for referring children to paediatric endocrinology [4]. The purpose of initial management is to alleviate the primary causes of SS and do management of associated distress [1]. The most frequent extra-intestinal symptom of celiac disease (CD) is SS [5]. The first step in the evaluation of an SS child is to rule out CD as only SS may be a manifestation in CD. CD may be viewed as a systemic immune-mediated disorder caused by ingestion of dietary gluten, which is a component in wheat, rye and barley. It is ingestion in the upper gastrointestinal (GI) tract among a genetically vulnerable population that results in impairment of small intestinal function [6].

As per the Oslo classification, CD may be classic with symptoms of malabsorption or non-classic with extra-intestinal symptoms [7]. In previous decades, a CD was merely suspected in patients having malabsorption and gastrointestinal symptoms such as chronic diarrhea, abdominal pain and distention, vomiting, constipation and nausea [8]. However, presently many cases present with no classical symptoms but extra-intestinal symptoms such as growth failure, and iron deficiency anemia, may present with SS. Even the pattern of clinical presentation

of CD cases has gone beyond GI signs and symptoms [9].

The prevalence of CD among pediatric SS cases varies from 2-10.9%. A very high probability of CD is reported among children with SS of non-endocrinological reasons. Almost 8-10% of SS cases as a cause of idiopathic SS are reported to have serological evidence of CD [2]. Though many of the cases are presently undiagnosed which is greater than the existing burden in absence of serological testing, mainly due to the existence of CD cases with unusual symptoms and poor disease awareness [10]. Furthermore, most of the studies have been conducted in Pakistan during the last two decades for investigating the causes of SS and the burden of CD in SS children [11, 12]. However, limited studies were conducted in the present decade [13, 14]. Since there is a shift in CD presentation from classical to non-classical symptoms, therefore it is highly essential to uncover the existing CD burden in SS children in our settings.

METHODOLOGY

The National Institute of Child Health's paediatric endocrinology clinics carried out this descriptive cross-sectional investigation. The study was commenced once approval was sought from Hospital Ethics Board (IRB#: IERB¬-45/2021). The data was collected for six months of duration from February 2022 to July 2022. After receiving parents' or guardians' written informed consent, children were enrolled in the study. Children of either gender ages 2 to 12 years presenting with short stature were included in the study. Attendants not approving to recruit their children into the study were excluded from the study.

A previously conducted study reported a 10.9% frequency of celiac disease in SS children [15]. Open-Epi, an online calculator, estimated a sample of 150 patients with a 95 percent confidence interval and a 5 percent precision at a prevalence of 10.9%. SS was defined as height for age < -2 standard deviation for the corresponding age and gender. Serological investigation including Immunoglobin A (IgA) and anti-tissue-transglutaminase antibodies (TTG IgA) and TTG IgG test was done by ELISA (enzyme-linked immunosorbent assay) method was done for all of the patients recruited into the study. A serum sample containing TTG IgA > 10 U/mL was considered a positive case of CD. The assigned data collectors recorded the demographic data; age, gender, height and clinical data; causes of short stature and results of the serological investigation.

The collected data were entered into the statistical package SPSS version 21. Frequencies and percentages were calculated for categorical variables. Mean ± standard deviation was computed to summarize numerical variables after assessing the assumption of normality with the Shapiro-Wilk test. Patients' features were compared among positive and negative cases of CD using a chi-square test for categorical variables whereas an independent t-test was applied for comparing continuous variables. P-value less than or equal to 0.05 was taken as statistically significant.

RESULTS

A total of 149 children with short stature were studied. The mean age of children was 10.2 ± 3.1 years. The majority of patients were males 53.7% (n=80). The average height and height-to-age z-score were 104.8 ± 8.9 cm and -5.1 ± 1.9 respectively. None of the patients presented with any gastrointestinal symptoms.

Out of 149 children, only 6.7% (n=10) had positive serology for celiac diseases. **Fig. (1)** displays the causes of short stature among study subjects. Among endocrinological causes were growth hormone deficiency (87.5%), congenital adrenal hyperplasia (6.3%) and primary hypothyroidism (3.6%) and Cushing syndrome (2.7%). Non-pathological variants included familial short stature (60%) and constitutional growth delay (40%). Among non-endocrinological reasons, the most frequent were celiac disease (58.8%), turner syndrome (23.5%) and idiopathic (17.6%).

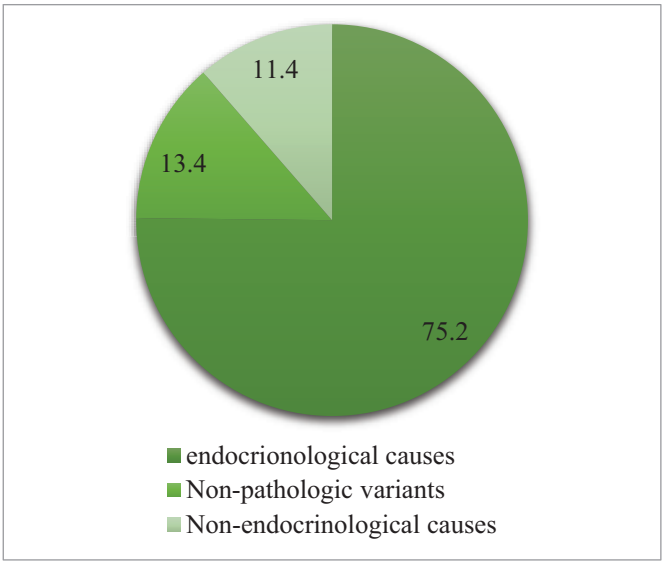

Fig. (1): Frequency of etiology of short stature among study subjects.

Table **1** shows the comparison of life years and sex distribution among the patients with positive and negative serology results. The prevalence of positive serology was rising with age but statistically, it was not significant. Gender distribution also did not differ among patients with and without celiac disease. Average height and height to age z-score were not significantly different among patients classified as with and without celiac disease.

DISCUSSION

CD is genetically gluten-sensitive damage to the small intestine causing malabsorption with a globally rising incidence [16]. Infants affected with CD show symptoms of diarrhea, abdominal distension and impaired growth.

Table 1: Comparison of socio-demographic features among patients with and without celiac diseases.

Variables	Positive Serology	Negative Serology	p-value
Age groupst			
4-5 years, n (%)	0 (0)	12 (100)	0.144
6-8 years, n (%)	1 (3)	32 (97)	
9 – 17 years, n (%)	9 (8.7)	95 (91.3)	
Gender			
Male, n (%)	6 (7.5)	74(92.5)	0.752
Female, n (%)	4 (5.8)	65(94.2)	
Height, mean ± standard deviation	104.5±17.7	104.8±8.1	0.949
Height to age z-score, mean ± standard deviation	-3.7±1.3	-2.1±1.2	0.345

CD is a disease of wide spectrum GI and extra-intestinal symptoms with asymptomatic cases as well. Diseases of atypical nature are generally prevalent in older children or teenagers who often show no overt signs of malabsorption. Extra-intestinal features including rickets, dental enamel defect, delayed puberty and SS may occur as mono symptomatic features [17]. If the GI symptoms are absent, SS may present in CD patients as a clinical manifestation. It has been reported that 10%-47.5% of pediatric celiac patients have short stature at the time of diagnosis [18-19].

The average age of SS patients in our study was around ten years. Another Pakistani study investigating SS causes among 169 children reported that nearly half of the patients were in the age group of 5-11 years (48.5%) [12]. A similar study from Egypt analyzing the etiology of short stature demonstrated the finding that the majority of the children with short stature were belonging to the age category of 6-12 years (63.8%)[3]. Manji *et al.* [20] also reported a closer median age of 9 years among children of short stature. It could be perceived that parents of older children as compared to younger children of age within five years are more cautiously monitoring the height pattern of their children. Short stature could indicate psychological issues caused by disease, inability, or social embarrassment. It is crucial to receive a prompt diagnosis and begin treatment. It is alarming that parents of younger children are not much concerned about short stature or may be less aware because this ignorance may cause further progression of undiagnosed underlying diseases which are causing short stature among children.

There are wide-ranging SS causes, but luckily, the typical variant of SS does not require any clinical attention or hormonal management. Contrariwise, related emotional anxiety should be addressed promptly [12]. The reasons for short stature may be categorized as genetical, endocrinological, non-pathological and chronic diseases [3, 17]. Genetic SS includes a constitutional delay of growth and development and familial SS. Frequent endocrine disorders, which are based on SS, are growth hormone deficiency, hypothyroidism and Cushing's syndrome. Other notable causes are skeletal dysplasias and Turner's syndrome. Chronic infantile diseases, if quite serious, may lead to SS and development failure. Some of the significant diseases include cardiac problems, pulmonary, cystic fibrosis, renal, malignancy, and celiac disease [21]. In the present study, the most frequent cause was growth hormone deficiency which is a contrary finding as compared to other studies. The most plausible reason for this finding could be the study setting as the study was conducted in endocrinology clinics. Most likely the finding could be changed if the study was conducted in primary care or other settings. In the present study, among genetic causes frequency of familial SS was higher than constitutional growth delay which is consistently reported in available literature [3, 12, 17]. Other less likely causes in our study were Turner's syndrome, Cushing syndrome adrenal hyperplasia, and idiopathic SS, which is in line with other similar studies [3, 12, 17].

The CD frequency has amplified drastically in the past three decades. This is caused by both the extensive use of accurate diagnostic tests for CD and the improved understanding and awareness of clinicians regarding celiac disease [22, 23]. In the present study, 6.7% CD prevalence was observed in this study. Rabbani *et al.* found a 3.6% frequency of celiac diseases in the same population [12]. A similar prevalence of celiac diseases (6.6%) in short-stature children was reported in Egypt [3]. Our finding is also consistent with the Saudi study reporting a 5.8% prevalence of celiac diseases in SS [21]. Another Saudi study reported a 4.5% CD prevalence in SS [17]. The pooled prevalence of CD based on positive anti-tissue transglutaminase and anti-endomysial antibody results was reported in a meta-analysis to be 11.2%, compared to 7.4% for biopsy-confirmed CD; however, there was a severe risk of selection discrimination and considerable heterogeneity in computed results [24].

The present study enrolled only 149 patients in a single center. A multi-center evaluation with a larger sample size will be more helpful to determine the factors associated with celiac diseases in short stature, particularly in case-control or cohort studies. The generalizability of results in our population may be assumed with a larger sample size study.

CONCLUSION

The current investigation discovered that patients with low stature had a substantial frequency of celiac disease. It was discovered that none of the patients' demographics were linked to celiac disease. For prompt diagnosis and treatment of celiac disease, people with short height should undergo screening.

ETHICS APPROVAL

The ethics committee of the hospital approved the study protocol (IRB#: IERB-45/2021). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

The data will be accessible from the corresponding author upon a judicious appeal.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

MJ gave the study concept. MNI and MJ were involved in designing the study protocol. SA and SD were involved in data collection and drafted the initial version of the manuscript. UT and MR performed data analysis and wrote the study results. MNI critically reviewed and revised the initial draft of the manuscript. All authors read and approved the manuscript.

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