Coeliac disease in patients with short stature: A tertiary care centre experience

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ABSTRACT

**Background.** We aimed to determine the prevalence of coeliac disease among children with short stature at a tertiary care centre and to define the predictors for coeliac disease, if any, in them.

**Methods.** In this retrospective study, we reviewed the case records of children and adolescents with growth retardation attending the Paediatric Endocrinology Clinic from January 2008 to June 2011. All patients underwent the multi-tier stratified diagnostic protocol for complete evaluation of short stature. Coeliac disease was screened using IgA-anti-tissue transglutaminase antibody. The diagnosis of coeliac disease was made on the basis of the modified European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria.

**Results.** Of 432 patients (238 boys) who presented with short stature, 72 (16.7%) had physiological, while 360 (83.3%) had pathological causes. Endocrine causes were growth hormone deficiency (86 patients, 19.9%), hypopituitarism (31, 7.2%), hypothyroidism (22, 5.1%) and others (7, 1.6%). The systemic causes were: coeliac disease (47, 10.9%), haematological diseases (14, 3.2%) and others (83, 19.3%). The most common systemic cause of short stature was endocrine disease, followed by haematological disease.

**Conclusion.** Nearly 11% of patients presenting with short stature have coeliac disease. In these patients chronic diarrhoea and anaemia were significant predictors of coeliac disease.


INTRODUCTION

Coeliac disease is considered uncommon in India. However, a recent large survey of the general population showed the prevalence of coeliac disease to be approximately 1% in northern India.1,2 There is a wide spectrum of clinical manifestations of coeliac disease and approximately half the patients present with atypical manifestations such as short stature, chronic anaemia unresponsive to haematinics, infertility or metabolic bone disease.3,4 Though coeliac disease is a known cause of short stature and failure to thrive, it was not well recognized in many countries including India.7–13 Globally, the prevalence of coeliac disease among short-statured persons ranges from 2% to 8%.12,13 Bhadada et al. studied 176 patients with short stature and reported that 15.3% of them were due to coeliac disease.14 Another study from northern India found that almost one-fifth of children with short stature were seropositive for tissue transglutaminase (tTG).15

Of the causes of pathological short stature, endocrine diseases are the commonest.7,8,11 Other causes of pathological short stature are systemic diseases of the gastrointestinal system (coeliac disease, Crohn’s disease), and infectious diseases such as tuberculosis and metabolic bone disorders. Timely diagnosis and treatment of some of these diseases can lead to an increase in growth velocity with a potential for attaining near normal height.

We aimed to determine the prevalence of coeliac disease among children with short stature at a tertiary care centre and to determine in them predictors for coeliac disease, if any. We assessed whether patients with short stature due to coeliac disease were different from those with short stature due to other causes, and also ascertained the predictors, if any, of coeliac disease among patients with short stature.

METHODS

We reviewed the case records of children and adolescents who presented with complaints of short stature to the Paediatric Endocrinology Clinic from January 2008 to June 2011. We included only those patients who had at least 6 months of follow-up after the initial visit for evaluation. Height and weight were measured using Holtain’s stadiometer (Holtain Inc, Cymrych, Pembs, UK) and a digital weighing machine, respectively. Height and weight percentiles were calculated using the Agarwal chart (height SDS=[observed height–mean height for that age and sex]/standard deviation of height for that age and sex) was calculated.16 As per our clinic protocol, a child was considered as having short stature if the height of child was (i) below the 5th
between those with and without coeliac disease were done using Statistical analysis was done using SPSS version 17.0. Comparisons regularly about compliance with GFD.

and calcium were added. Patients and their family were counselled disease about taking a gluten-free diet (GFD). Supplemental iron short stature. A nutritionist counselled patients with coeliac disease about the need to be on a normal growth velocity over at least 6 months of follow-up, and bone age estimation. Radiological evaluation at first visit included X-ray of the chest (postero-anterior view), skull lateral view (cone down view of sella) and anteroposterior view of the left hand for estimation of bone age. Serum follicular stimulating hormone (FSH) level was measured in all girls on their first visit. If these investigations failed to reveal the cause for short stature, the next set of investigations included tests for malabsorption (as assessed by D-xylose test) and renal tubular acidosis (using urinary pH). If both these were normal, the child was followed up for documentation of growth velocity. Children with delayed bone age and subnormal growth velocity were evaluated for growth hormone deficiency using standard growth hormone stimulation test (clonidine and glucagon stimulation test). They underwent evaluation of the pituitary hormone axis if clinically indicated. Girls suspected to have Turner syndrome or unexplained short stature underwent karyotyping studies.

During the early part of the study (2008), if the children had gastrointestinal manifestations they were screened for coeliac disease using serum anti-tissue transglutaminase antibodies (anti-tTG Ab). However, from January 2009, all children presenting with short stature were screened for coeliac disease using anti-tTG Ab at the initial clinic visit. Anti-tTG Ab was done using ELISA kits procured from Binding Site Limited, Birmingham, UK (cut-off value <10 U/ml) and AESKU, Wendelsheim, Germany (cut-off value <18 U/ml). Anti-endomysial antibody (EMA) test was done for one patient. All those with a positive serological test had a detailed evaluation for coeliac disease, including oesophago-gastro-duodenoscopy (EGD) and duodenal mucosal biopsies. Multiple biopsies were taken from the post-ampullary part of the duodenum during endoscopic examination. The Modified Marsh grading system was used for grading mucosal changes. Based on the presence of clinical manifestations, positive coeliac serology and presence of villous atrophy, a provisional diagnosis of coeliac disease was made. Familial short stature was diagnosed if the patients met the following criteria: the height percentile falling within the target height range, normal growth velocity over at least 6 months of follow-up, and bone age corresponding to the chronological age. Constitutional delay of growth and puberty (CDGP) was diagnosed if the children were short for target height, had a bone age delay of >2 years, and had a normal growth velocity over the past 6 months.

All patients were treated appropriately as per the cause of their short stature. A nutritionist counselled patients with coeliac disease about taking a gluten-free diet (GFD). Supplemental iron and calcium were added. Patients and their family were counselled regularly about compliance with GFD.

Statistical analysis
Statistical analysis was done using SPSS version 17.0. Comparisons between those with and without coeliac disease were done using Chi-square test for categorical variables and Student t test for continuous variables. Multivariate logistic regression was used to assess predictors of coeliac disease. Results are expressed as mean (SD). A p value of <0.05 was considered significant.

RESULTS
Between January 2008 and June 2011, a total of 1042 children were registered in the Paediatric Endocrine Clinic (Fig. 1). Of the 432 short-statured children included in the analysis (238 boys, M:F ratio 1:1.2), 415 children (96.1%) were below the 5th percentile of the height for age while 11 were between the 5th and 10th centile (2.5%), 5 between the 10th and 25th centile (1.2%) and 1 was between the 25th and 50th centiles. Along with 415 short-statured children, these 17 children were also considered to have short stature on the basis of either poor growth velocity or height less than MPH.

Among girls, Tanner staging was pre-pubertal in 112 patients (57.7%), peri-pubertal in 77 (39.7%) and pubertal in the remaining 5 (2.6%). Among boys, 152 patients (63.9%) were pre-pubertal, 72 (30.2%) were peri-pubertal and 14 (5.9%) were pubertal.

Cause of short stature
Seventy-two patients (16.7%) had physiological causes of short stature while the remaining 360 patients (83.3%) had pathological causes. Endocrinological diseases were the most common (33.8%) cause of short stature. Nine patients had more than one cause of short stature—4 had growth hormone deficiency with hypothyroidism, 1 each had growth hormone deficiency with coeliac disease, Turner syndrome with coeliac disease, hypothroidism with coeliac disease and Turner syndrome with hypothroidism (Table I). There was no difference in the cause of short stature among boys and girls (p=0.07).

Clinical presentations of children with coeliac disease
In 2008, when only those with diarrhoea or anaemia were screened for coeliac disease, of 147 patients, 11 (7.5%) had coeliac disease. From 2009 onwards when every patient was screened, 36 of 285 patients (12.6%) were found to have coeliac disease. Overall, of the 432 children with short stature, 47 (10.9%) were diagnosed to have coeliac disease (22 boys). The mean (SD) age at presentation was 13.9 (2.6) years and the mean (SD) height SDS score was −3.4 (1.5). All 47 children were below the 5th centile of height except for 2 who were short for MPH. Forty children (85.1%) were below the 5th centile of weight for age.

The mean (SD) duration of symptoms at the time of presentation was 68.9 (60.3) months. The most common symptoms were fatigue (29, 61.7%) and chronic diarrhoea (25, 53.2%; Table II). Eight children (17%) with coeliac disease had other autoimmune disorders (autoimmune hypothyroidism in 4, type 1 diabetes mellitus in 3 and alopecia areata in 1).

Haematological and biochemical investigations in patients with coeliac disease
Anaemia was present in 42 patients (89.4%), while 5 patients (10.6%) had a normal of haemoglobin level. None of these 5 patients were receiving iron or vitamin supplements at the time of presentation. Severe anaemia (haemoglobin <7 g/dl) was present in 11 patients (23.4%). Seven patients (14.9%) each had hypoalbuminaemia (albumin <3.5 g/dl) and elevated (>1.5 times upper limit of normal) serum transaminases. Hypocalcaemia (serum calcium <8 mg/dl) was present in 2 and hypophosphataemia was present in 1 patient.
Endoscopic features in patients with coeliac disease
On oesophago-gastro-duodenoscopic examination, duodenal folds were normal in 6 (12.8%), scalloped in 24 (51%) and attenuated in 17 (36.2%) patients.

Duodenal mucosa: Histological features
While 27 (57.4%) patients had severe villous atrophy/modified Marsh grade 3c, 20 (42.6%) patients had moderate villous atrophy/modified Marsh grade 3b.

Coeliac serology
IgA anti-tTG Ab was positive in all patients except one who was serum IgA-deficient. This patient had severe villous atrophy (Marsh grade 3c). Since clinical suspicion was high in this patient,
a provisional diagnosis of coeliac disease was made even in the absence of a positive coeliac serology. The diagnosis of coeliac disease was confirmed once there was unequivocal response to GFD.

Follow-up of patients with coeliac disease
Of 47 patients with coeliac disease, 10 were lost to follow-up. In all 37 patients, a definite improvement was observed in one or more clinical and/or laboratory manifestations. The mean (SD) growth velocity measured over at least 6 months of GFD was 8.1 (3.0) cm/year. Of 37 patients, 17 (45.9%) had chronic diarrhoea at the time of presentation, which resolved in all within 6 months of starting GFD. Thirty-four of 37 (91.9%) patients had anaemia at the time of presentation and the haemoglobin level became normal or increased by at least 2 g/dl in 14 (41.2%) and 16 (47.1%) patients, respectively. The serum albumin level normalized in all 6 patients who had hypoalbuminaemia at the time of diagnosis.

Comparison between patients with short stature with or without coeliac disease
The mean height SDS of children with short stature without (385 patients) and with coeliac disease (47 patients) were –3.36 and –1.71, respectively (p=0.1). The mean weight SDS of children with short stature without and with coeliac disease were –3.41, respectively (p=0.345). The mean weight SDS between patients (n=47) and –1.96, respectively (p<0.001). The serum albumin level normalized in all 6 patients who had hypoalbuminaemia at the time of diagnosis.

Predictors of coeliac disease
Chronic diarrhoea (OR 15.7, 95% CI 7.8–31.5) and anaemia (OR 4.9, 95% CI 1.9–12.7) were significant predictors of coeliac disease in children with short stature (Table III).

DISCUSSION
We found the most common cause of short stature to be endocrine diseases (33.8%); these findings are consistent with those of other retrospective studies.3–6,14 Coeliac disease was the cause of short stature in 10.9% of cases. The prevalence of coeliac disease among patients with short stature varies widely from 4.7% to 15.2% in various countries.11,14,16–23 The prevalence of coeliac disease among patients with idiopathic short stature has been reported to vary from 21% to 48.7%.15,24–29 Most earlier reports from India in children with short stature have not reported coeliac disease as a cause of short stature.7–10 Bhadada et al. reported that the aetiology of short stature changed over a decade due to high suspicion of coeliac disease and the availability of screening tests.30

Unlike many of the other causes of short stature such as genetic and familial short stature that do not respond to specific therapeutic interventions, the growth velocity improves after starting GFD in children with coeliac disease.31 Aydogdu et al. showed a negative correlation between height SDS at the end of 4 years of follow-up and the age of diagnosis of coeliac disease.32 Studies have reported a complete catch-up in height if coeliac disease is diagnosed early.33,34 It is therefore important to diagnose all treatable causes of short stature, including coeliac disease and to start treatment.

In absolute numbers, 6–10 million Indians are expected to have coeliac disease. Patients with atypical manifestations may report to endocrinologists (with short stature, hypothyroidism or type 1 diabetes), haematologists (with anaemia resistant to haematinics), or to gynaecologists (with infertility or delayed menarche).1 Unless coeliac disease is considered in the differential diagnosis of short stature, the diagnosis will be missed. In 2009, after we realized that some of our patients with short stature had coeliac disease, we introduced screening for coeliac disease in the first set of investigations for short stature.

Though the presence of chronic diarrhoea and anaemia are predictors of coeliac disease in patients with short stature, only 50% of patients with short stature and coeliac disease had chronic diarrhoea. Bhadada et al. also reported the absence of gastrointestinal manifestations in about 30% of their patients with coeliac disease presenting as short stature.33 Similarly, anaemia is considered to be universal in patients with coeliac disease, but 10% of patients in the present cohort and 12% in the previous study did not have anaemia.14

On the basis of our findings and those of previous studies, we suggest that all patients with short stature should be screened for coeliac disease. The absence of chronic diarrhoea and anaemia do not rule out coeliac disease in patients with short stature. Given the high prevalence of coeliac disease among patients with short stature and the low cost of serological tests for coeliac disease as compared to other investigations such as growth hormone assay, which may be available only at specialized centres, the serological test should be included as an initial investigation in the diagnostic algorithm of short stature.

Of the 572 patients diagnosed with short stature, 432 (75.5%)...
patients could be adequately followed and screened for coeliac disease. Almost 25% of our patients were lost to follow-up, which is a limitation of our study. However, it is unlikely to impact the prevalence rate but may influence the risk factors of coeliac disease in patients with short stature. A referral bias can be expected as the study was done at a tertiary care centre; this again may limit generalization of the results. The results, however, may be applicable only to regions with a higher prevalence of coeliac disease, such as northern India. We might have missed a few patients with coeliac disease since our protocol for screening patients with short stature changed during the study period.

The pathogenesis of short stature due to coeliac disease is not well defined but appears to be multifactorial. Earlier, it was thought that coeliac disease-related malnutrition was the only factor responsible for short stature. There is new evidence that not all patients with coeliac disease have gastrointestinal manifestations and/or malnutrition.6 A study has shown a high prevalence of short stature (18.8%) even among patients with non-diarrhoeal coeliac disease.8 Patients with coeliac disease have been reported to have lower levels of both basal and hypoglycaemia-induced growth hormones, lower levels of insulin-like growth factor (IGF)-1, IGF-2, insulin-like growth factor binding protein (IGFBP)-1 and IGFBP-3.9,10 The imbalance in growth hormone and its downstream signalling pathways are known to cause short stature. Additionally, these patients might have partial insensitivity to growth hormone.11 Surprisingly, introduction of GFD normalizes many imbalances in the somatotropic axis in the form of increased growth hormone sensitivity as well as increased IGF-1, IGF-2 and IGFBP-1.12

Conclusions

The prevalence of coeliac disease among patients with short stature is 10.9%. The presence of chronic diarrhoea and anaemia are predictors of coeliac disease in children with short stature. All patients with short stature should be screened for coeliac disease.

Contributions

PRA SHANT SINGH: Data entry, analysis and interpretation of data; drafting the manuscript.

PYU SHI KUMAR SHARMA: Data entry, analysis and interpretation of data; drafting the manuscript.

ABHISHEK AGNIHOTRI: Data entry, analysis and interpretation of data; drafting the manuscript.

VIVEKA P. JYOTSA NA: Analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

PRA SE NIT DAS: Histopathology.

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