

GASTROENTEROLOGY

Does every short stature child need screening for celiac disease?Sanjay Bhadada,* Anil Bhansali,* Rakesh Kochhar,[†] Anil Shankar Menon,* Saroj Kant Sinha,[†] Pinaki Dutta* and Chander Kanwal Nain[†]Departments of *Endocrinology and [†]Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India**Key words**

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Correspondence

Dr Anil Bhansali, Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. Email: anilbhansali_endocrine@rediffmail.com

Abstract**Aim:** To study the etiological profile of short stature at a tertiary care hospital in north India.**Methods:** In this prospective study, 176 children with short stature were enrolled from January 2005 to December 2006. Appropriate screening and definitive tests were performed to establish the etiology of short stature.**Results:** Celiac disease (CD) emerged as the single most common (15.3%) cause of short stature, followed by various endocrine disorders. It was interesting to note that none of the CD patients presented with gastrointestinal symptoms.**Conclusion:** All short children should be screened for CD irrespective of gastrointestinal symptoms.**Introduction**

The prevalence of celiac disease (CD) has a wide geographic variation with the highest incidence in western Europe.¹ In Scandinavian and Celtic populations, its prevalence is as high as 1:99.² In northern Europe, its prevalence in Denmark is 40-fold lower than in neighboring Sweden.³ It has been said that factors such as predominant Human leukocyte antigen (HLA) haplotype and timing of the introduction of gluten in the diet are responsible for the variation in prevalence.⁴ There are no epidemiological studies in the general population regarding the prevalence of CD in any of the Asian countries, including India. Celiac disease is being increasingly reported from India, although reports from the rest of the South and South-East Asia are sparse. Most reports from India are from the north Indian states of Punjab, Delhi and Uttar Pradesh where the population are predominantly wheat eaters.⁵⁻⁸ Data on HLA haplotypes from India are even more limited. All the reports on adult CD from India are from gastroenterology units and hence non-gastrointestinal manifestations do not figure prominently in them.⁵⁻⁷ The three major series on short stature from India have failed to report CD as a cause,⁹⁻¹¹ whereas CD accounts for 1-5% of short stature (SS) in the West.^{12,13} The present report from the departments of Endocrinology and Gastroenterology from a tertiary referral center from north India details our observations on SS seen by us over a 2-year period.

Methods

This prospective study was conducted from January 2005 to December 2006 at Endocrine Clinic of the Postgraduate Institute

of Medical Education and Research, Chandigarh. A total of 176 patients were enrolled who fulfilled the criteria of SS. The criteria for diagnosis of short stature were:¹⁴ (i) height \geq 2.5 SD below the mean for chronological age; (ii) growth rate below the fifth percentile for chronological age; and (iii) height \geq 2 SD below the mean for chronological age when corrected for mid-parental height.

The height of all children was measured by keeping the head in the Frankfurt plane while occiput, shoulders, buttocks and heels touched a vertical board.¹⁴ The children were drawn up to their full height by upward pressure on the mastoids. The height of each patient was assessed by the National Center for Health Statistics (NCHS) growth weight chart¹⁵ and correlated with mid-parental height using the recommended method of evaluation.¹⁴ Children who were short for their target height and had slightly delayed bone age but had normal growth rate velocity and normal relevant investigations were labeled as having constitutional delay of growth.¹⁴ Weight was recorded by a digital weighing machine in all patients. The patients were followed for a minimum period of 6-9 months to study the growth rate velocity.

The etiological evaluation of the 176 children included a detailed history (antenatal, perinatal and postnatal) and clinical examination. Investigations were planned according to the available clues from the history and the initial clinical evaluation. If the history and examination did not reveal a cause for short stature, the following screening tests were carried out: bone age (as assessed from X-ray of the hands with the help of Greulich and Pyle's standards),¹⁶ complete blood count, urine and stool examination and biochemical tests (fasting blood glucose, blood urea, serum creatinine, liver function tests, electrolytes, fasting serum calcium,

Table 1 Etiological profile of short stature ($n = 176$)

Etiology	Number	Percentage
Celiac disease	27	15.3
Pituitary disorder	25	14.2
Hypothyroidism	24	13.6
CDGP and FSS	18	10.6
Metabolic bone disease	16	9.1
Turner syndrome	10	5.7
Adrenal disorders	8	4.5
Diabetes mellitus	7	3.9
Nutritional deficiency	6	3.4
Chronic disease	5	2.8
Dysmorphic syndromes	9	5.1
Miscellaneous	7	3.9
Undefined	14	7.9

CDGP, constitutional delay in growth and puberty; FSS, familial short stature.

phosphorus and alkaline phosphatase and urinary pH), X-ray skull lateral view of the pituitary fossa, serum thyroid-stimulating hormone and T4 assay.

The following additional tests were performed if the screening tests did not reveal a cause of short stature. To assess growth hormone (GH) deficiency, patients were subjected to a clonidine (4 µg/kg) stimulation test¹⁷ and/or insulin tolerance test, depending on the number of pituitary hormone deficiency. If patients had more than one pituitary hormone deficiency, in addition to GH, only insulin hypoglycemia was carried out. In girls with stigma of Turner's syndrome, serum follicle stimulating hormone (FSH) and karyotype were done. If no endocrine cause was forthcoming or if diarrhea for more than 3 months was present, IgA anti-tissue transglutaminase antibody (anti tTG) titers were estimated and an endoscopic biopsy was taken from the second part of the duodenum. Hormone levels were measured by standard radioimmunoassay method. Anti tTG antibody was estimated by enzyme-linked immunosorbent assay (Blue Well; D-Tek, Mons, Belgium). CD was diagnosed as per revised ESPGHAN criteria.¹⁸ CD was treated with a gluten-free diet, calcium (500 mg/day), vitamin D (300 000 U cholecalciferol once/3 months), iron and multivitamin supplementation including folic acid and vitamin B₁₂.¹⁹

Results

Over a period of 2 years, 5650 patients with various endocrine disorders were registered at the Endocrine Clinic of our hospital. Of these, 176 (3.1%) patients (97 boys, 79 girls) were found to have short stature. The majority of the patients presented in the age group of 10 to 15 years. Overall, CD emerged as the single most common cause of short stature in 27 (15.3%) patients followed by sellar/suprasellar disorders in 25 (14.2%), hypothyroidism in 24 (13.6%) and physiological short stature in 18 (10.6%) (constitutional delay in growth and puberty [CDGP] and familial short stature [FSS]), metabolic bone disease in 16 (9.1%), and Turner syndrome in 10 (5.7%). In 14 (7.9%) patients, the cause of short stature could not be defined (Table 1). The most common causes of short stature in boys ($n = 97$) were pituitary disorders 18.5% (18/97), followed by CD 14.4% (14/97) and constitutional delay in

Table 2 Clinical manifestations of patients with CD at presentation ($n = 27$)

Symptom	Percentage
Short stature	100.0
Anemia	88.0
Weight loss	80.3
Diarrhea	69.2
Delayed puberty	53.8
Goiter	32.0
Rickets	12.0
Hypothyroidism	3.8
Hypoadrenalism	3.8
Constipation	3.8
Diabetes mellitus	3.8

CD, celiac disease.

Table 3 Hemogram, biochemistry and hormonal profile in patients with CD ($n = 27$)

Parameter	Mean (\pm SD)
Hemoglobin (g/dL) (reference range 11–19)	7.6 \pm 2.4
Serum calcium (mg/dL) (reference range 8.5–11)	9.1 \pm 2.4
Serum phosphate (mg/dL) (reference range 3.5–5)	4.4 \pm 0.7
Alkaline phosphatase (KAU) (reference range 3–13)	20 \pm 9.5
SGOT (IU/L) (reference range 2–20)	24.4 \pm 7.9
SGPT (IU/L) (reference range 2–20)	26.4 \pm 8.5
Serum TSH (mIU/mL) (reference range 0.17–4.05)	12 \pm 36.5
Cortisol (nmol/L) (300–540)	342 \pm 31.1
Anti-tissue transglutaminase (reference range U/mL 5–50)	136 \pm 131

CD, celiac disease; SGOT, serum glutamate oxalate transferase; SGPT, serum glutamate pyruvate transferase; TSH, thyroid stimulating hormone.

growth and puberty 13.4% (13/97). Juvenile hypothyroidism 20.2% (16/79), CD 16.4% (13/79) and Turner syndrome 5.6% (10/176) and pituitary disorders were common causes of short stature in girls.

All patients with CD were symptomatic at presentation. The most common presenting symptom was growth retardation (96.2%) followed by anemia (88%), weight loss (80%), diarrhea (69.2%) and rickets (12%). Endocrine involvement observed in these patients was delayed puberty, goiter, hypothyroidism and hypoadrenalism (Table 2). The mean (\pm SD) age at presentation and lag time from symptoms to diagnosis of the patients with CD was 14.5 \pm 2.0 years and 5.5 \pm 3.0 years, respectively. Male to female ratio was 1:1. Mean (\pm SD) follow up of CD patients was 8.3 \pm 7.7 months. Details of biochemistry and hemogram are given in Table 3. All (100%) patients had tTG antibody (IgA) positivity and duodenal biopsy which was suggestive of CD (partial or total villous atrophy, increased intra-epithelial lymphocytes and crypt hyperplasia). All patients showed good response to a gluten-free diet. Pretreatment growth rate velocity was 2.9 \pm 0.49 cm/year, which increased to 8.9 \pm 2.2 cm/year after starting a gluten-free diet during a follow-up period of 6–9 months.

Table 4 Comparison of etiology of short stature in various Indian studies

Etiology	Present study (%) (n = 176)	Zargar <i>et al.</i> ¹⁰ (%) (n = 193)	Colaco & Desai ⁹ (%) (n = 200)	Bhadada <i>et al.</i> ¹¹ (n = 352)
Celiac disease	15.3	—	—	—
Normal variant constitutional growth delay and familial short stature	10.6	—	20.5	36.1
Endocrine disorders				
Hypothyroidism	13.6	7.8	10.0	14.2
Hypothalamo-pituitary diseases	14.2	34.7	19.5	8.5
Turner syndrome	5.7	—	7.5	7.4
Diabetes mellitus	3.9	—	—	—
Malnutrition and chronic diseases	3.4	7.8	8.5	12.4
IUGR and dysmorphic syndromes	5.1	—	9.5	8.5
Rickets	9.1	10.4	6.5	5.7
Miscellaneous and undiagnosed	19.1	39.3	17.0	7.2

IUGR, intrauterine growth retardation.

Discussion

In the present study comprising patients from north India, CD emerged as the single most common cause (15.3%) of short stature, which is in striking contrast to existing reports from India (Table 4), although endocrine disorders (hypopituitarism, hypothyroidism, metabolic bone diseases, Turner syndrome, adrenal disorders and diabetes mellitus) as a group remained the single largest etiological group causing short stature. Colaco and Desai,⁹ and Zargar *et al.*,¹⁰ in their retrospective studies from referral centers in India, also reported endocrine disorders to account for nearly one-third of all cases of SS. In our previous study, physiological short stature (CDGP and FSS) was the most common cause of short stature.¹¹

It is interesting to note that among the reported Indian series on short stature, none had reported CD as a cause of short stature.^{9–11} In all of these, malnutrition was a common non-endocrine cause of short stature. We believe that CD was missed as a cause of short stature in these reports because of a number of factors: (i) mono-symptomatic presentation; (ii) low index of suspicion; (iii) lack of widespread availability of sensitive and specific serological tests, such as endomysial antibody (IgA) and tTG IgA; and (iv) duodenal biopsy was rarely performed. The present prospective study took into account all of these factors and yielded CD as the single most common cause of short stature.

The common presenting manifestations of childhood CD are growth retardation, anemia, abdominal pain, chronic diarrhea and weight loss.^{5–7,19,20} In our patients, the common manifestations were short stature, anemia and weight loss. We must emphasize that these patients were referred to an endocrine clinic for work-up of short stature. The prevalence of CD in Western populations is in the range of 0.3% to 2%²¹ with the highest prevalence being in type 1 diabetes mellitus (T1DM).²² Until recently, epidemiological studies on CD from the Indian subcontinent were lacking. A school survey from North India reported a frequency of CD to be one in 310 children.²⁰ The same authors⁵ have reported an exponential increase in the number of patients

with CD in north India similar to the observations from the West.¹⁹ The rise in number was attributed to the advent of new and better serological testing and by targeted screening.²⁰ While SS has been reported as a manifestation of CD from Indian studies on pediatric CD,^{6,7} this association has not gained the attention it deserves.

Diagnosis of CD was based on elevated tTG antibody and complemented by duodenal biopsy. Anti-tTG antibody has been reported to have a sensitivity close to 100% in diagnosing CD.²³ It is important to exclude IgA deficiency as a cause of false-negative serology. In such children, IgG tTG antibody levels should be measured. Earlier, the jejunum was considered an ideal site for intestinal biopsy, although, later, duodenal biopsy has made the diagnosis simpler and easier. Duodenal biopsy in all of our patients showed features suggestive of celiac disease.

Celiac disease causes short stature by multiple mechanisms. First, malabsorption not only leads to protein calorie malnutrition but also leads to defective absorption of calcium and vitamin D.^{24,25} Second, there is growth hormone resistance characterized by elevated growth hormone and low circulating insulin like growth factor-1 (IGF1), which attenuates the growth from early childhood to puberty.²⁵ Third, there is hypogonadism with low gonadotropins and low testosterone, which further attenuates the achievement of peak bone mass and inhibits the pubertal growth spurt.²⁵ Finally, hypothyroidism is commonly associated with CD due to a similar autoimmune predisposition.^{25,26} If hypothyroidism remains undiagnosed, it can also cause short stature. In the present study, anemia and weight loss were observed in more than 80%, delayed puberty in 53%, goiter in 32%, rickets in 12%, hypothyroidism and hypoadrenalism in 4% of patients with CD.

Treatment of CD includes a gluten-free diet, and calcium, vitamin D₃ and multi-vitamin supplements. The majority of patients show a good response to this treatment. Within 6–9 months of starting a gluten-free diet all of our patients showed a remarkable improvement in anemia and growth rate velocity, which increased from 2.9 cm to 8.9 cm per year.

Conclusion

Celiac disease is an important cause of short stature in north India. We propose tTG antibody should be a part of the screening tests for short stature, irrespective of the presence or absence of gastrointestinal symptoms.

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