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Prevalence of celiac disease in Brazilian children of short stature

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Abstract

The aim of the present study was to determine the prevalence of celiac disease in children of short stature and to assess whether some of the routine laboratory examinations performed to determine the cause of short stature could suggest the presence of celiac disease. A total of 106 children of short stature and no gastrointestinal symptoms were studied. An extensive endocrine work-up had been negative for all of them and an additional investigation was performed by measuring the concentration of antiendomysial antibody. Patients who were positive for antiendomysial antibody (≥1:10) or who exhibited IgA deficiency (less than 5 mg/dl) were referred for an endoscopic intestinal biopsy. We detected a pathological titer of antiendomysial IgA in six of these patients. Five of them showed histological abnormalities compatible with celiac disease and one had normal histology and was considered to have potential celiac disease. The prevalence of celiac disease in the population studied was 4.7% (with another 0.9% of the subjects being considered to have potential celiac disease). The children with celiac disease did not differ in any of the parameters tested when compared to those without celiac disease, though they showed an improvement in growth velocity after treatment with a gluten-free diet. We conclude that it is important to test all children with short stature for celiac disease by measuring antiendomysial IgA.

Key words
• Celiac disease
• Short stature
• Antiendomysial antibody
• Growth failure
• Celiac sprue

Introduction

Celiac disease is characterized by malabsorption resulting from inflammatory injury of the mucosa of the small intestine after ingestion of wheat gluten or related rye and barley proteins. The highest reported prevalence has been observed among western Europeans and in countries to which Europeans emigrated, notably North America and Australia. It is rare among people of purely African-Caribbean, Chinese, or Japanese background (1). Until recently, celiac disease was considered uncommon in Brazil and no studies were conducted to assess its prevalence; however, the availability of new accurate serologic tests has led to the realization that celiac disease could be relatively common. A recent study (2) pointed out a prevalence of undiagnosed disease of 1:681 among ap-

parently healthy blood donors, while another study (3) carried out on patients diagnosed as having celiac disease described a spectrum of presentation similar to that observed in other developing countries.

Celiac disease has a wide spectrum of gastrointestinal and extraintestinal manifestations, with many patients showing atypical symptoms or none at all. Classically, infants with celiac disease present impaired growth, diarrhea and abdominal distention between the ages of 4 and 24 months. Atypical disease is usually seen in older children or adolescents, who often have no overt features of malabsorption. In addition to recurrent abdominal pain, aphthous stomatitis, arthralgia, defects in dental enamel, short stature, and delayed puberty, affected children may show behavioral disturbances such as depression and irritability, and may perform poorly in school (4).

Although celiac disease is a known cause of short stature in children, its diagnosis is often difficult because of the presence of few symptoms and of biochemical parameters that fall within the normal range. Sometimes short stature could be the principal or only finding (5) and the rate of diagnosis depends on the level of suspicion for the disease. The diagnosis is based on clinical symptoms, positive antibodies, and an intestinal biopsy, which is considered to be the Gold Standard (6,7). Histological evidence of celiac disease among patients consuming a regular (gluten-containing) diet includes small-bowel mucosal villous atrophy, crypt hyperplasia and increased numbers of intraepithelial lymphocytes, with clinical improvement and complete remission of symptoms occurring after the introduction of a gluten-free diet. Furthermore, the presence of specific antibodies at the time of diagnosis and their disappearance after treatment with a gluten-free diet has been considered to be a helpful diagnostic criterion.

Serum IgA-class antireticulin, antigliadin, and antiendomysial antibodies are widely used for the screening for celiac disease. However, and as recommended by the European Society of Paediatric Gastroenterology and Nutrition and by the American Gastroenterological Association, the diagnosis requires histological evidence through a small bowel biopsy (6,7). Prospective studies (8-13) in patients with positive autoantibodies and no abnormalities in the intestinal biopsy have revealed that 28 to 100% of these patients show histological evidence of celiac disease within 4 months to 5 years. These findings suggest that positive antibodies could be a marker for gluten sensitivity even in the absence of typical histological abnormalities.

The purpose of the present study was to determine the prevalence of celiac disease among Brazilian children with short stature who have no gastrointestinal symptoms, and to assess whether some of the routine laboratory examinations performed during investigation of the cause of short stature could suggest the diagnosis of celiac disease.

Patients and Methods

A total of 106 children, 34 girls and 72 boys with height less than the 3rd percentile adjusted for age and sex (14), were enrolled in the study. Age ranged from 1.3 to 16.4 years (mean = 9.6 years, SD = 3.6 years). The patients and their parents answered a structured questionnaire, and gastrointestinal symptoms were not a major complaint for these patients. The research protocol was reviewed and approved by the Medical Ethics Committee of the University Hospital, Faculty of Medicine, University of São Paulo, where the laboratory investigation was performed, and of the Brigadeiro Hospital, where the patients enrolled in this study were under endocrinological investigation. Written informed consent was obtained from the children's parents.

All children were being followed at the Department of Endocrinology of Brigadeiro Hospital and had undergone an extensive negative endocrine work-up which included: concentration of serum electrolytes, glucose,

total proteins and albumin, determination of immunoglobulin A (IgA), assessment of liver and renal function (determined by standard methods), and hormonal evolution through the measurement of thyroid-stimulating hormone, free-thyroxin, growth hormone (GH) (Immulite Diagnostic Products Corporation, Los Angeles, CA, USA), and concentrations of IGF1 and IGF-binding protein-3 (IRMA, Diagnostic Systems Lab. Inc., Webster, CA, USA). Routine GH stimulation testing using either clonidine or insulin-induced hypoglycemia as secretagogues was performed (oral clonidine, 150 μg/m^2; insulin, 0.1 U/kg of weight, *iv*). Patients were considered not to be GH deficient when the peak GH value during the stimulation test was equal to or higher than 5 ng/ml. All etiologic factors known to produce growth failure had also been excluded, e.g., diabetes mellitus, hematological and liver disease, renal failure, fetal growth failure, disease of bone metabolism, and chromosomal abnormalities.

When no cause of the short stature was found, additional investigation was performed by measuring the concentrations of antiendomysial antibody (immunofluorescence in umbilical cord). Patients who either had positive results for antiendomysial antibody (titer ≥1:10) or exhibited IgA deficiency (IgA less than 5 mg/dl) were referred for an endoscopic intestinal biopsy and four to seven biopsy specimens were taken from the distal part of the duodenum. The slides were examined by the routine anatomy and pathology service of the Hospital, and the results were confirmed by a pathologist experienced in celiac disease. The histological results were scored according to Marsh criteria (15). Bone age was determined using the Greulich and Pyle atlas (16). Pubertal stages were evaluated according to Tanner (17).

The results are reported as means ± SD. Statistical analysis was performed by the unpaired Student *t*-test (GraphPad Prism Software Incorporated), with the level of significance set at $P < 0.05$.

Results

Six of the 106 patients had positive serology for antiendomysial antibody, and underwent an endoscopic intestinal biopsy (group 1, N = 6). Children with a negative antiendomysial antibody were included in group 2 (N = 100).

The following histological results were obtained: a) three of six patients (patients 2, 4 and 6) had complete mucosal villous atrophy with a villus:crypt ratio of 1:1; b) two patients (patients 3 and 5) had subtotal mucosal villous atrophy with a villus:crypt ratio of 3:1 associated with a dense inflammatory infiltrate in the lamina propria and an intraepithelial lymphocyte infiltrate; c) one patient (patient 1) had a normal mucosa. Therefore, the prevalence of well-diagnosed celiac disease among children with short stature in this study was 4.7% (5 of 106 patients) and one patient (0.9%) was diagnosed as having potential celiac disease.

The mean values (and the range) for chronological age, Z score for height and weight, as well as bone age, puberty stage, growth rate and target height were not significantly different between patients with celiac disease and patients with short stature of undetermined cause ($P > 0.05$, Table 1). The

Table 1. Clinical data of patients with short stature with active or potential celiac disease (group 1) and patients with short stature of undetermined cause (group 2).

	Group 1	Group 2
Chronological age (years)	7.7 ± 4.1 [1.9-13.3]	9.7 ± 3.6 [1.2-16.4]
Height Z score	(2.8) ± 0.8 [(4.3)-(2.0)]	(2.8) ± 0.6 [(4.6)-(2.0)]
Weight Z score	(1.7) ± 0.6 [(2.8)-(1.0)]	(1.6) ± 0.7 [(3.5)-0.9]
Bone age (years)	5.5 ± 4.3 [1.3-13]	7.2 ± 3.4 [1.0-14.0]
Pubertal stage	[1.0-2.0]	[1.0-5.0]
Height velocity (cm/years)	3.8 ± 0.8 [2.9-5.2]	5.3 ± 2.1 [1.2-10.8]
Target height Z score	(1.8) ± 0.7 [(2.9)-(1.0)]	(1.7) ± 0.7 [(2.9)-0.7]

The results are reported as means ± SD. The numbers in brackets are range values and the numbers in parentheses are negative values. Height Z score was calculated as patient height minus average height of the population of the same age and sex/average SD of height for age and sex. Weight Z score was calculated as patient weight minus average weight of the population of the same age and sex/average SD of weight for age and sex. Target height Z score was calculated as patient height minus final height of population of the same sex/average SD of final height of the population of the same sex. $P > 0.05$ for all parameters (unpaired Student *t*-test).

results of laboratory (data not shown) and hormonal assessment were also not significantly different (P > 0.05, Table 2). None of the patients had cutaneous lesions or dental anomalies that could be associated with a diagnosis of celiac disease.

Table 3 shows the relationship between positive antiendomysial antibody and histological evidence of celiac disease.

Five children diagnosed as having celiac disease received a gluten-free diet. The children under treatment were followed up for 3 months (patient 5), 6 months (patient 6), and 1.5 year (patients 2, 3 and 4); unfortunately patient 1 was lost to follow-up. We observed improvement of growth rate in all patients and patient 4 had complete catch-up of growth after one year on a gluten-free diet (Table 4).

Table 2. Hormonal measurements of patients with short stature and active or potential celiac disease (group 1) and patients with short stature of undetermined cause (group 2).

	Group 1	Group 2
T_{4F} (ng/dl)	1.4 ± 0.3 [1.0-1.8]	1.5 ± 0.4 [0.6-2.4]
TSH (µIU/ml)	2.2 ± 1.2 [0.6-4.7]	2.2 ± 1.3 [0.2-5.0]
GH peak in the stimulatory test (ng/ml)	11.8 ± 4.8 [7-19.2]	17.1 ± 12.6 [5.5-77.3]
IGF1 Z score	(1.2) ± 0.4 [(1.7)-(0.7)]	(0.7) ± 0.9 [(2.4)-1.4]
IGFBP3 Z score	(0.1) ± 0.7 [(0.8)-0.9]	(0.3) ± 0.8 [(1.8)-1.4]

The results are reported as means ± SD. The numbers in brackets are range values and the numbers in parentheses are negative values. GH = growth hormone; T_{4F} = free thyroxin; TSH = thyroid-stimulating hormone. IGF1 Z score was calculated as patient IGF1 value minus average IGF1 value for the population of the same puberty stage/average SD of the IGF1 value for puberty stage. IGFBP3 Z score was calculated as patient IGFBP3 value minus average IGFBP3 value for the population of same puberty stage/average SD of the IGFBP3 value for puberty stage. P > 0.05 for all parameters (unpaired Student *t*-test).

Table 3. Correlation between histological results and measurements of plasma antiendomysial antibody titer among group 1 patients.

Patient	EmA titer (IgA)	Histological results
Patient 1	1/320	Without abnormalities
Patient 2	1/10	Complete mucosal villous atrophy in areas of variable atrophy; villus:crypt ratio, 1:1 to 3:1
Patient 3	1/40	Subtotal mucosal villous atrophy with hypercellular mucosa; villus:crypt ratio, 3:1
Patient 4	1/320	Complete mucosal villous atrophy; villus:crypt ratio, 1:1
Patient 5	1/10	Subtotal mucosal villous atrophy with heavy lymphoplasmocyte infiltrate in the lamina propria; villus:crypt ratio, 3:1
Patient 6	1/320	Complete mucosal villous atrophy; villus:crypt ratio, 1:1

EmA = antiendomysial antibody.

Discussion

The present data show an expressive number of celiac disease (4.7%) children in a group of short stature, thereby justifying the search for this disease in all children with short stature. Previous studies on children with growth failure but without gastrointestinal symptoms have shown a variable incidence of celiac disease (0 to 59.0%) depending on the region where the study was performed (18-25). All patients with a diagnosis of celiac disease showed an improvement in growth velocity after the introduction of a gluten-free diet, indicating that this parameter would be useful to confirm the correct diagnosis, as also reported by others (19, 23,26). Unfortunately, the patient diagnosed as having potential celiac disease (13,27) because of a positive result in the antiendomysial antibody test and no histological abnormalities was lost to follow-up. These findings might be explained by patched alteration of celiac disease (28), or by silent/subclinical disease (15,26).

Antiendomysial antibody has been shown to have a high sensitivity and specificity for the diagnosis of celiac disease and correlates well with villous atrophy in untreated patients, but false-negative results have been obtained for patients with IgA deficiency, justifying its measurement (29-32). However, an intestinal biopsy continues to be the Gold Standard for the diagnosis of celiac disease (6,7). Our children were also tested for IgA deficiency and all were found to have normal IgA values. Hence, the negative result of the antiendomysial antibody test cannot be attributed to IgA deficiency.

A review of the literature (5,18,19,21,33-36) led us to conclude that there is no single parameter suggesting the presence of celiac disease in children of short stature. Our data support the view that there is no single test or measurement that can identify all subjects with celiac disease, with the occurrence of even a few false-positive results. None of measurements (clinical, laboratory and hormonal) were positive in all of our patients with documented duodenal villous atrophy, nor did they differ significantly between patients diagnosed as having celiac disease and others of short stature of unknown etiology.

Currently, very little is known about the pathogenesis of growth failure in children with celiac disease. There are reasons to believe that nutritional deficiencies can result in growth failure associated with changes in hormonal status such as poor GH release in a stimulatory test (18,19) and low levels of IGF1 (5). Eichler et al. (37) found a strong relationship between the duration of gluten exposure and reduced IGF1 levels and concluded that reduction in IGF1 levels occurs only after prolonged exposure to gluten. The children enrolled in the present study had no gastrointestinal symptoms or significant malnutrition (Z score for weight = -1.6 ± 0.7, and Z score for height = -2.8 ± 0.6) or abnormal GH secretion and a reduction in IGF1 levels (Z indices for IGF1 = -0.8 ± 0.9) that could explain the delayed growth.

The prevalence of celiac disease amongst children of short stature was 4.7% (with another 0.9% with potential celiac disease). The children affected by celiac disease did not differ from those without celiac disease in any of the parameters tested. Hence, it is important to search for celiac disease in all children with short stature.

Table 4. Clinical data before and after the introduction of a gluten-free diet for subjects with duodenal abnormalities (group 1).

	Patient					
	1	2	3	4	5	6
Before the diet						
CA (years)	8.66	9.83	5.91	1.91	13.3	5.41
Height Z score	(2.0)	(3.2)	(3.1)	(2.4)	(4.3)	(2.9)
GV (cm/years)	5.1	2.9	3.7	3.6	5.2	3.3
Weight Z score	(1.5)	(1.3)	(1.7)	(1.8)	(2.5)	(2.5)
After the diet						
Height Z score	–	(3.2)	(3.2)	(1.2)	(4.2)	(1.5)
GV (cm/years)	–	5.9	5.2	10.0	6.5	15.3
Weight Z score	–	(2.2)	(1.7)	0	(2.2)	(1.2)

The results are reported as means ± SD. The numbers in brackets are range values and the numbers in parentheses are negative values. CA = chronological age; GV = growth velocity. Height Z score was calculated as patient height minus average height of the population of the same age and sex/average SD of height for age and sex. Weight Z score was calculated as patient weight minus average weight of the population of the same age and sex/average SD of weight for age and sex. Patient 1 was lost to follow-up.

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