Screening of celiac disease in children with growth failure

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Abstract

Celiac disease is a chronic enteropathy caused by intolerance to gluten. Its clinical spectrum is broad. Presentation of celiac disease varies from absence of symptoms to gastrointestinal (classic) and/or extraintestinal (non-classic) symptoms. Patients without symptoms may have latent or silent celiac disease. Because celiac disease can be atypical or even clinically silent, many patients remain undiagnosed and at risk for the long-term, sometimes serious complications of untreated celiac disease.

The aim of this study is to determine the prevalence of celiac disease (CD) in children with growth failure and the diagnostic value of tissue-transglutaminase (TTG) IgA antibodies and IgA antigliadin antibodies (AGA) for celiac disease.

Patients and Methods: A total of 104 children (43 male, 61 female) with growth failure without a specific etiology were studied. Extensive investigations had shown no abnormalities in any subject. Anthropometric parameters and IgA AGA and IgA TTG antibodies were evaluated in this study group. These antibodies were measured by enzyme-linked immunosorbent assay. All patients were referred for an endoscopic intestinal biopsy. The biopsy samples were classified according to revised Marsh criteria.

Results: the prevalence of properly diagnosed CD among patients with growth failure in this study was 25.9% (27 of 104 patients). Out of 104 patients 57 of them were positive upon screening with the serological tests. IgA -AGA, and IgA -TTG antibodies were found in 81.4% (n = 22 out of 27 with confirmed CD), and 88.8% (n = 24 out of 27 with confirmed CD) of patients with growth failure, respectively. Sensitivity, Specificity
the positive predictive value (PPV), negative predictive value (NPV) for TTG antibodies were found to be 88.8%, 94.2%, 85.7%, and 94.7% for CD in the group of patients with growth failure in this study and for IgA AGA: sensitivity 81.4%, specificity 88.4%, positive predictive value (PPV) 75.8%, negative predictive value (NPV) 90.6% were found in this study.

**Conclusion:** We conclude that the prevalence of celiac disease is high in patients with idiopathic growth failure and it is important to test all children with idiopathic growth failure for celiac disease by measuring serologic markers and performing an intestinal biopsy.

**Introduction**

Celiac disease is a chronic, immune-mediated enteropathy triggered by gluten proteins found in wheat, barley and rye. More than 95% of patients with celiac disease have the typical HLA-predisposing genotype (DQ2 or DQ8). Patients with confirmed celiac disease should be on a gluten-free diet for life to avoid the risks of untreated celiac disease [1]. Growth failure (short stature) is the term that describes a growth rate below the appropriate growth velocity for age. The frequency of celiac disease in children with short stature ranges from 2% to 8%. Short stature was found to be the leading extraintestinal symptom of celiac disease in 30% of 485 children in the study by Bottaro et al. Patients showed improved height velocity within 6 to 9 months of starting a gluten-free diet [2].

Diagnosis of celiac disease (CD) depends on the demonstration of a flat or almost flat jejunal mucosa in biopsy specimens from the small intestine and regeneration of the mucosa after a gluten-free diet [3]. It has been suggested that patients with untreated CD have circulating antibodies against gliadin, antiendomysium antibodies (anti-EMA), tissue transglutaminase and have proven to be a reliable screening test for CD, even in asymptomatic patients [2,4]. However, the anti-EMA IgA antibody test is an immunofluorescent technique and is relatively expensive and interpretation is operator dependent and prone to errors so that it has largely been replaced by anti-tissue transglutaminase [5]. In addition, esophageal tissue from monkeys is a common substrate, and the testing is time consuming. Transglutaminase (TTG) antibodies are also highly sensitive and specific and since IgA antibodies to TTG can be examined by enzyme-linked immunosorbent assay (ELISA), they are easier to use as screening antibodies compared with EMA testing [6]. Tissue transglutaminase (Ttg) is the major target antigen of EMA and it is an enzyme that upon wounding is released from cells where it is thought to aid in tissue repair [7]. The anti-tissue transglutaminase IgA antibody can be falsely negative with IgA deficiency which is associated with an increased incidence of celiac disease. Measurement of serum IgA concentration is mandatory to assure that false negative results in IgA–deficient individuals are excluded [7].

The aim of this study is to determine the prevalence of celiac disease (CD) in children with growth failure and the diagnostic value of tissue-transglutaminase (TTG) IgA antibodies and IgA antigliadin antibodies (AGA) for celiac disease.
Patients and Methods

A total of 104 children (43 female, 61 male) with growth failure (height and weight less than the 3rd percentile) adjusted for age and sex, but without specific etiology were enrolled in the study from November 1, 2009 to September 1, 2011 at AL-sadder general hospital in Amara -Iraq.

Ages ranged from 2 to 12 years. The height, weight and weight for height measurements had been recorded for all patients at presentation. All children were being followed and had undergone an extensive investigation which included: concentrations of serum electrolytes and glucose, total proteins and albumin, assessment of liver and renal function (determined by standard methods), and hormonal evaluation through the measurement of thyroid-stimulating hormone, free-thyroxin and growth hormone. When no cause of the growth failure was found, additional investigations were performed by measuring the serum levels of IgA antibody, IgA anti-TTG antibodies(IgA-TTG) and IgA antigliadin antibodies (IgA-AGA). Anti-AGA and anti –TTG were measured by a commercial ELISA assay(AESKULISA). A serum dilution of 1:100 was used and the results were reported in terms of arbitrary units (U/mL). An IgA AGA and IgA-TTG > 18 U/mL were considered positive. Intestinal biopsies were obtained from all 104 patients with endoscopic grasp forceps (who had negative or positive results for anti-TTG antibody). Four to six biopsy specimens were taken from the second and third parts of the duodenum. Formalin-fixed biopsy specimens stained with hematoxylin and eosin were studied with the use of light microscopy. Mucosal lesions were classified according to the criteria of Marsh[8] as: (1) type 0, normal mucosa, pre-infiltrative lesions; (2) type 1, normal mucosal architecture with epithelial lymphocyte infiltration, infiltrative lesions; (3) type 2, hypertrophic crypts with epithelial lymphocyte infiltration and hyperplastic lesions; and (4) type 3, typical flat mucosa and destructive lesions.

Results

The mean weight was 20.9±12.3 and the mean height was 110±30.4. Small intestine biopsies were performed in all 104 patients with growth failure. Duodenal mucosal histopathology was normal in 77 patients. Histopathologic analysis showed evidence of abnormalities compatible with celiac disease( CD) in 27 cases (25.9%).The following histological findings were obtained: (a) 8 of 27 patients had normal mucosal architecture with epithelial lymphocyte infiltration and (b) 14 cases had hypertrophic crypts with epithelial lymphocyte infiltration and partial villous atrophy and (c) 5 cases showed subtotal or total villous atrophy. Therefore, the prevalence of properly diagnosed CD among patients with growth failure in this study was 25.9% (27 of 104 patients).Out of 104 patients 57 of them were positive upon screening with the serological tests. IgA -AGA, and IgA -TTG antibodies were found in 81.4% (n = 22 out of 27 with confirmed CD), and 88.8% (n = 24 out of 27 with confirmed CD) of patients with growth failure, respectively. So only 11 patients were falsely positive with serologic screening. Sensitivity, Specificity ,the positive predictive value (PPV),negative predictive value(NPV) for TTG antibodies were found to be 88.8%, 93.5%, 85.7%, and 94.7% for CD in the group of patients with growth failure in this study and for IgA AGA: sensitivity
81.4%, specificity 88.3%, positive predictive value (PPV) 75.8%, negative predictive value (NPV) 90.6% were found in this study.

Table (1):

<table>
<thead>
<tr>
<th>Biopsy results</th>
<th>Serological tests results</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
</tr>
</tbody>
</table>

Table (2): Relationship between positive and negative IgA AGA, and IgA TTG Antibodies and histological evidence of celiac disease (n)

<table>
<thead>
<tr>
<th>Lab group</th>
<th>IgA AGA</th>
<th>IgA TTG antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Without CD</td>
<td>7</td>
<td>68</td>
</tr>
<tr>
<td>With CD</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>75</td>
</tr>
</tbody>
</table>

Discussion

Screening for CD in the general population indicates a prevalence of 1:300 to 1:100. About 50% of these children are completely symptomless but because of these figures some experts suggest CD screening for all adults [8] and children [9]. In a British population-based study on short stature, where CD was not specifically investigated, the prevalence of CD was 2:180. In children with short stature and no gastrointestinal symptoms who were investigated for CD, the prevalence increased to 2%-8%. When other (endocrine) causes for short stature are excluded, the prevalence might rise as high as 59% [10,11]. Despite the presence of clinical signs of CD during childhood in more than one-third of the patients, the disease remained undiagnosed for many years. This late diagnosis may lead to short stature and low female fertility. In the last 20 years the clinical picture of CD has changed considerably. The classic form of CD now accounts for a small and systematically shrinking percentage of cases, while atypical forms that present with few or no symptoms are the majority [12]. Short stature is a well-recognized complication of CD [13], although Cacciari et al [14] found that adult height is normal in patients who experienced their first symptoms of CD during adulthood. Adult height was shorter only in patients who had symptoms during childhood. This study demonstrated the prevalence of CD (n = 27) in a group of 104 patients with growth failure, similar to the results of the study by Mäki et al [15]. The age at onset of symptoms appeared to modify the clinical...
picture. Patients with an earlier onset of CD have a typical clinical picture, whereas patients with delayed onset have atypical presentation, such as short stature. According to our findings, the prevalence of biopsy-proven CD was 25.9% in the group of growth failure children, thereby justifying screening for this disease in all children with short stature. The proportion of CD in cases with short stature ranged from 18.6% to 59.1% in other studies [16,17]. The mechanism of growth retardation is not clearly understood in patients with CD; nutritional deficiencies especially zinc deficiency, low serum somatomedin activity and defects in growth hormone secretion have been proposed as underlying mechanisms [18, 19,20]. A jejunal biopsy remains the gold standard for the diagnosis of CD but both serologic and histopathologic parameters of CD were investigated in the patients in this study. The sensitivity and specificity of serologic tests were variable. The TTG antibody test has been shown to have a higher sensitivity and specificity for the diagnosis of CD in our patients. Our patients were also tested for IgA deficiency and all were found to have normal IgA values. However, negative results for these tests would not exclude CD. We found that seven cases with partial villous atrophy had normal AGA, and four of this subgroup had normal anti-TTG antibodies also. Anti-TTG antibodies seem to be more specific but both measurements had limitations in the diagnosis of CD. Our data support the view that there is no single test or measurement that can identify all subjects with CD and growth failure.

Conclusion

Symptoms of celiac disease are diverse and patients can frequently be asymptomatic. The leading extraintestinal symptoms of celiac disease in children are iron deficiency anemia, short stature and delayed onset of puberty. In evaluating patients who present with non-classic symptoms of celiac disease pediatricians should include screening for celiac disease with IgA tissue transglutaminase or anti gliadin-IgA antibody titers with quantitative IgA testing.

Referral to a pediatric gastroenterologist is recommended for patients who have positive serology screening in order to confirm the diagnosis of celiac disease. Patients who have histological identification of intestinal mucosal features compatible with celiac disease are placed on the only treatment available for celiac disease: gluten-free (<20 ppm or <20mg/kg) diet for life.

References

7. AESKULISA DIAGNOSTICS, INSTRUCTION MANUAL.