Original Article

Celiac disease in patient with short stature

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Summary:

Back ground: Celiac disease (CD) is an immune–mediated enteropathy induced by gluten with broad spectrum of presentation, many patients with atypical symptoms or clinically silent remain undiagnosed, and are at risk of long-term complications.

Objective: The aim of the present study is to determine the of prevalence celiac disease in children with short stature.

Patient and Methods: In this prospective study, 307 children 181(58.9%)males and 126(41.1%) females ,with ages ranging from 3 to 17.5years (mean 12.2 ±3.4) with short statures (height below 3rd percentile adjusted for age and sex) attending the consultation room of endocrinology/ Welfare Teaching Hospital/ medical city- Baghdad , were enrolled in this study from the first of Oct 2008 to the first of Aug 2010. Full history, thorough physical examination, immune-biochemical tests ; complete blood count ,renal function tests, serum electrolytes, thyroid function tests, immunoglobulin A and G, tissue transglutaminase (tTG) antibodies , and intestinal biopsy for those with positive celiac serological screens, growth hormone estimation, radiological assessment of bone age, genetic counseling for some females (when available) was done . Each celiac disease case once diagnosed was started on gluten free diet and followed up for one year for growth parameters.

Results: celiac disease (CD) was found as the second most common cause of short stature. Unfortunately there was delay in the diagnosis due to asymptomatic status of the disease. Complete catch up in growth had been found in 63.6% after one year of gluten free diet.

Conclusion: Celiac disease is an important cause of short stature in children, and should be an essential part of screening panel and workup of short children, irrespective to the presence or absence of gastrointestinal symptoms.

Key words: Celiac disease, short stature, anti tissue transglutaminase antibody, children, gluten free diet.

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Introduction:

The clinical concept of celiac disease (CD) has been expanded and it is now considered a multi- system autoimmune disorder. Celiac disease is characterized by permanent gluten intolerance in people who are genetically susceptible (1).

The disease has a varied spectrum of presentations, ranging from the classic form of celiac disease (chronic diarrhea, abdominal pain and distension, weight loss, failure to thrive and signs of malnutrition) to gastrointestinal symptoms free forms (2, 3, 4). Short stature is a well-known feature of pediatric CD, many of the patients with short stature have no identifiable medical abnormality and are classified as idiopathic short stature (ISS) (5, 6).

The pathogenesis of short stature as a monosymptomatic manifestation in children with CD is not known. A review of the literature showed that there are reasons to suggest that nutritional deficiencies can result in growth failure associated with changes in hormonal status, like low levels of insulin-like growth factor-1 (IGF-I), which occurs after prolonged exposure to gluten, and poor growth hormone release in stimulatory tests. (7, 8, 9).

The epidemiological pattern of CD has dramatically changed in the past few years as a result of the widespread use of highly sensitive and specific serological tests, especially the antiendomysial (EMA) and anti tissue transglutaminase (anti-tTG) antibodies (10). Still the gold standard for the diagnosis of CD is duodenal biopsy (4).

Prevalence of CD among children with short stature in Europe is approximately 0.05–0.2%. In Italy the prevalence is 59.1% (11) whereas in Spain it is 0.56% (12), and the prevalence of well-diagnosed CD among Saudi children with short stature was 10.9% (13) .

The aim of study is to assess the prevalence of CD among children with short stature.

Patients and methods:

In this prospective study, total of 307 children (181males, 126 females) with short statue were studied in the consultation room of endocrinology of the Children Welfare Teaching Hospital from the 1st Oct. 2008 to the 1st Aug. 2010. Children and adolescents were defined as with short stature cases if their

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heights were below the third percentile for their age and sex according to the height/age curves published by the National Center for Health Statistics (NCHS) 2003 (14) .

A Fully detailed history and complete physical examination were performed for all patients.

The study excluded Patients with chronic diseases like; chronic renal failure, congenital heart diseases, patients on chronic steroid therapy (asthmatic, nephrotic syndrome), patients on immunosuppressed chemotherapy with malignant disorder or rheumatologic diseases, and patients with skeletal deformities like; achondroplasia, pseudo achondroplasia , and others .

Laboratory investigations were done, including; complete blood count, biochemical renal and liver function tests, serum electrolytes, thyroid function tests. Anti tissue transglutaminase antibody (anti tTG) titers were estimated by ELISA (enzyme-linked immunosorbent assay) for all patients.

Duodenal biopsy was done for all patients with seropositive anti-tissue transglutaminase antibodies in order to document the characteristic histopathological morphologic features according to Marsh staging criteria (15).

Bone age was assessed for all patients, a radiograph of the left hand is used for the determination of bone age, standards of bone age determined by epiphysial appearance and fusion (16).

karyotyping had been evaluated in some patients having Turner`s syndrome phenotype. Growth hormone levels were estimated before and after stimulation test using clonidine, and glucagon (17) at the Teaching laboratories / medical city for all patients. Children with proven CD were evaluated for growth hormone and thyroid hormone as well.

Children diagnosed to have CD were kept on a gluten-free diet immediately once the diagnosis is established, and those with iron deficiency anemia were started on oral iron supplementation, megaloplastic anemia treated with folic acid supplementation. Patients were followed-up for one year for their growth parameters. The results of height were also expressed as Z-score.

Data analysis: The statistical analysis was done by using Excel application. Differences between groups were evaluated using ANOVA .The comparison of significance (P_ value) in any test:

S= significant difference ($P<0.05$), HS= highly significant difference ($P<0.01$), NS=no significant difference ($P > 0.05$).

Results:

Over a period of 2years , 307patients with various causes of short stature who attended the consultation room of endocrinology of the Children Welfare Teaching Hospital / Baghdad181(58.9%) males,126(41.1%) females , Their age range was (age 3–17.5 years) , with a mean (12.2 ±3.4).The etiological profile of these cases with short stature is shown in table 1.

Table 1. Etiological profile of patients with short stature.

Etiology	Number	Percentage %
Growth hormone deficiency	223	72
Celiac disease	22	7
Chronic disease	21	6.84
Hypothyroidism	17	5.53
Idiopathic SS	13	4.23
Physiological SS	8	2.60
Turner syndrome	3	0.97
100%	307	Total

Patients with chronic diseases were referred to special centers according to their illness type and those with celiac disease were followed up in collaboration with department of gastroenterology .

Celiac disease emerged as the second most common cause in the profile of short stature causes ,proved CD in 22 patients (7%) , 5 females (22.7%), and 17 males (77.3%), their age mean was (9.6 ± 4.8) . All those patients had positive t TG antibody (IgA) , and were confirmed histologically by the duodenal biopsies to have CD .

All children diagnosed with celiac disease had normal growth hormone and thyroid hormone secretion.

For those with CD apart from being Short, other accompanied clinical manifestations were shown in table 2. Those modes of presentations could overlap each other.

The most common presenting symptom was short stature 100% followed by weight loss (40.9%), anemia (13.6%), gastrointestinal disturbance (9%), asymptomatic cases, (patients presenting purely with SS with no other clinical manifestations were36%) .

Table 2: General manifestation (symptoms) of patients with CD at presentation (n =22).

Symptom	number	Percentage
Short stature	22	100%
Weight loss	9	40.9%
Anemia	3	13.6%
Gastrointestinal disturbance	2	9%
Pure short stature.*	8	36.3%

NB: there was an overlap of signs and symptoms in these patients.

* Pure short stature means patients presenting purely with SS with no other clinical manifestations.

All children diagnosed to have CD were kept on a gluten-free diet. Patients were followed-up for one year, Height and weight were estimated prior to and one year after starting gluten free diet as shown in table3.

Table3: Height, weight parameters pre and post treatment(gluten free diet) .

Parameters	No	Pretreatment mean	SD	Post treatment Mean	SD	P value
Height	22	122.14	16.691	126.00	16.116	.001
Weight	22	31	13.9	31.7	13.5	.008

All patients with CD showed improvement in growth parameters. Fourteen (63.6%) of them had complete catch-up in growth after one year on a gluten-free diet.

The Z score for height at time of diagnosis was -3.3± 1.8 while it was -2.9± 1.3 one year after starting the gluten free diet which were highly significant statistically ($P<0.01$) .

Discussion:

CD is a chronic inflammatory condition associated with small intestinal injury caused by intolerance to gluten in genetically susceptible individuals (18). Interestingly, in the last few years, the use of highly sensitive and specific serological tests, these are the antiendomysial and anti tissue transeglutaminase antibodies has led to the identification of atypical forms of CD, such as those in which SS may be the only clue for the disease (19,20) . Unfortunately, It was noticed that CD was missed as an important cause of SS as a reflection of several factors such as ,the low index of suspicion , asymptomatic presentation, reluctance of most of patients' parents to do duodenal biopsies considering it as an invasive procedure, low healthy conscious in community. Celiac disease formed 7%(22 patients) from the total 307 patients with short stature , with classic histopathological changes of CD ,coming next to growth hormone deficiency ,while in Saudi Arabia study where 91 Children were studied ,10(10.9%) of the children who were evaluated for SS were with classic CD(Asaad Mohamed et al 2010) (13) , While short stature was found to be the leading extra intestinal symptom of celiac disease in 30% in the study by Bottaro et al (20) .The lower incidence in our study than the other two studies can be explained by the public unawareness about the association between the short stature and celiac disease, as a consequence of the very few centers specialized in pediatric growth assessment and follow up. Weight loss and anemia were observed in more than 40%,13% of the cases respectively. Iron deficiency anemia can be the only abnormality in patients with celiac disease. Based on a study by Bottaro et al (20) , iron deficiency anemia was the most frequent extra intestinal marker of celiac disease; it was the leading symptom in 35% of the 485 children examined. In celiac disease patients, iron deficiency anemia is caused by decreased iron absorption due to chronic intestinal inflammation. Anemia is a frequent finding in patient with CD and may be the presenting feature, its prevalence varies greatly according to different reports and has been found in 12-69% of newly diagnosed cases with CD (21). Gastrointestinal disturbance (diarrhea) may be clearly steatorrhoeic owing to fat malabsorption. However gastrointestinal symptoms may be minimal, and bloating, discomfort may be misdiagnosed as irritable bowel syndrome (22). It is important to record the delay in diagnosis in most cases since the majority of the patients presented in the ages from 10 to 16 years. Fourteen (63.6%) of them had complete catch-up in growth after one year on a gluten-free diet ,this agrees with the Saudi study (13) , in which 40% of the affected children showed complete catch up of growth after one year of gluten free diet therapy but all of them showed some increment in their heights. While in Bottaro et al(20) patients showed improved height velocity within 6 to 9 months of starting a gluten-free diet, the study did not mention the exact number of patients.

Conclusions:

CD is an important cause of SS, and serological markers should be included in the diagnostic evaluation of SS children, irrespective of the presence or absence of general symptoms. After commencing Gluten free diets, all patients show marked improvement in their growth parameters specialy the height parameter.

Auther's contribution:

Study conception: Rawia M
Study design: hanaa A.Abduljabbar , Rawia M
Acquisition of data analysis: Rawia M
Interpretation of data: Dr safaa gafar(pediatrician / welfare teaching hospital) , Rabab F Thegeel
Drafting of manuscript: Rawia M
Critical revision: hanaa A.Abduljabbar, Rabab F Thegeel

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