

Celiac Disease Screening in Short Stature Children Using Antigliadin IgA and IgG

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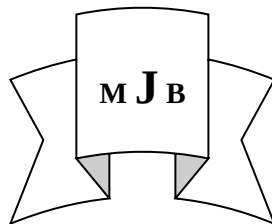
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Abstract

Objective: To assess the possibility of celiac disease in short stature children by estimating serum level of antigliadin IgA and IgG.

Method: Forty short stature children (height below 3rd centile) were screened, 18 (45%) were males and 22 (55%) were females with male/female ratio; 1:1.2. Antigliadin IgA and IgG levels were assessed by ELISA, and considered to be positive if the level of antibody ≥ 18 IU/dL. All patients had been already sent for X ray for bone age, thyroid function test, and growth hormone assessment (both basal and after stimulation). No patient on gluten-free diet.

Results: Of the 40 patients, 12 patients (30%) had positive antigliadin antibody test, 3 of them (25%) had no underlying cause for short stature, while 9 (75%) had already diagnosed cause.

Conclusion: Screening for celiac disease is mandatory in all short stature children.

الخلاصة

اجري هذا البحث في مستشفى بابل للنسائية والاطفال خلال الفترة بين ٢٦ شباط و ٨ نيسان للكشف عن وجود الداء الزلاقي (سيلياك) عند قصار القامة من الاطفال الذين يزورون وحدة الغدد الصماء في هذه المستشفى باستخدام اختبار الاجسام المضادة للجلادينينوع IgA و IgG، وقد بينت نتائج البحث ان هذه الاجسام المضادة موجودة في ٣٠% من هؤلاء الاطفال (أي من الممكن ان يكونوا مصابين بالداء الزلاقي).

Introduction

Growth retardation in childhood may be one of the earliest signs of an underlying disease, such as celiac disease (CD)[1]. CD is an immune-mediated disorder elicited by the ingestion of gluten in genetically susceptible persons and characterized by chronic inflammation of the small intestine[2]. The mode of presentation of CD is variable[3,4]. In fact, many patients have no gastrointestinal symptoms or signs of malabsorption [4]. Perhaps as many as 10% of children referred to endocrinologists for growth retardation

without an endocrine or gastrointestinal disorder have gluten sensitivity[3]. CD can lead to short stature by causing autoimmune-hypothyroidism, resistance to growth hormones, and malabsorption of protein, calcium and vitamin D, additionally; CD can lead to hypogonadism which inhibits the pubertal growth spurt[5].

Currently, the criteria for the diagnosis of CD require the demonstration of typical changes in the small intestinal (jejunal) biopsy followed by clinical improvement on a gluten-free diet. This invasive procedure requires

trained personnel and is unpleasant for patients. Moreover, the total period of time for the diagnostic investigation is more than two years[6]. Valuable experience has been obtained with the quantitation of anti gliadin antibodies as an additional diagnostic method in several developed countries[7,14]. This method helps to prevent the lack of detection of cases of CD and also to avoid many unnecessary jejunal biopsies [6].

The anti gliadin antibodies IgG and IgA recognize a small piece of the gluten protein called gliadin[15]. Anti gliadin IgG has good sensitivity, while anti gliadin IgA has good specificity[15,16] and therefore their combined use provided the first reliable screening test for CD[15]. In clinical trials, the IgA antibodies have a specificity of 97% but the sensitivity is only 71%. On the other hand, the IgG anti-gliadin antibodies are 91% specific and have an 87% sensitivity, and the combined IgA and IgG anti-gliadin antibody assay has an overall sensitivity of 95% with a specificity of 90%[16].

A strength of the anti gliadin antibodies is that they are ELISA tests¹⁵. ELISA is an abbreviation for "enzyme-linked immunosorbent assay"[15,16], and it is not a test in itself, rather it is a method of testing[16]. The importance of an ELISA test is that it is rapid and run by a machine. Thus the results are independent of observer variability[15].

A problem with serology is represented by the association of CD with IgA deficiency; 10-fold increase compared to the general population (2-3% of CD patients are IgA deficient). However, negative serology should not preclude a biopsy examination when the clinical suspicion is strong².

Other screening tests for CD are anti-endomysial and anti-tissue transglutaminase antibodies, and each

antibody test varies widely in its sensitivity and specificity for predicting whether the disease is present in any individual.[15]

Until the 1990s, the prevalence of CD in Middle East and North Africa countries was considered low, However, with the introduction of anti-endomysial antibodies and anti gliadin antibodies testing, CD has been more readily reported from developing countries[17], and its prevalence seems to that of Western countries[17,20]. In recent studies, CD was considered to be a more common cause of short stature in otherwise healthy children than growth hormone deficiency (GHD)[21,22].

Objective

To assess the possibility of CD in short stature children by estimating serum level of anti gliadin IgA and IgG.

Patients and Method

This study was conducted at endocrine clinic in Babylon Maternity and Children Hospital during the period 26/2-8/4, 2012.

Patients:

A cross-sectional study was done to patients who attended the endocrine clinic during the studying period. All these patients were short statured (height below 3rd centile) and had regular endocrine clinic visits (every month). Any patient who had one of the followings was excluded from this study:

1. Patient or family refuse blood sampling (5 patients).
2. Patient on gluten free diet.
3. Patient previously screened for CD by any serologic markers and had positive result (any patient with positive screening test for celiac disease was kept on gluten free diet in our province without confirming the diagnosis by intestinal biopsy). Thus

these patients met the second criteria for exclusion.

So, the net number of studied patients were 40, aged between 2-17 years with mean age 9 years, 18 (45%) were males and 22 (55%) were females with male/female ratio; 1:1.2. All these patients had been already sent for X ray for bone age, thyroid function test, and growth hormone assessment (both basal and after stimulation), and according to these tests some patients had no underlying cause for short stature while others had specific diagnosis as hypothyroidism or GHD and so kept on specific therapy.

Method:

Same questioner was applied for all patients and this including age, sex, GIT symptom, and if there is any diagnosed cause for short stature. Three mL of blood was aspirated from each patient and sent to the lab for assessing antigliadin IgA and IgG level by ELISA. Result considered to be

positive if the level of antibody was ≥ 18 IU/dL.

Statistical analysis

Chi-square and Fisher-exact test were used to determine the significance relationship between seropositivity and the different studied factors. P value >0.05 was considered insignificant.

Results

Total number of patients included initially was 45, 5 of them refuse blood sampling; the response rate was 89%. Serological results were negative in 28 patients (70%), considered to be negative cases, while 12 patients (30%) had positive results (either antigliadin IgA or IgG or both) and considered as positive cases.

Table (1) shows that 50% of positive cases and 43% of negative cases are males. There is no relationship between sex and seropositivity in this study (P value >0.05).

Table 1 Distribution of cases according to the sex between positive and negative cases.

	No. of males	%	No. of females	%	Total	P value
Positive cases	6	50	6	50	12	>0.05
Negative cases	12	43	16	57	28	

Table (2) shows that GIT symptoms are absent in 58.3% and 50% of positive and negative cases respectively, and these show that there

is no relation between presence of symptoms and the presence of antibodies (p value >0.05).

Table 2 Distribution of cases according to the presence of GIT symptoms between positive and negative cases.

	No. of cases with GIT symptoms	%	No. of cases without GIT symptoms	%	Total	P value
Positive cases	5	41.7	7	58.3	12	>0.05
Negative cases	14	50	14	50	28	

Table (3) show that 91.7% of positive serologic group have delayed bone age, while 100% of those negative

group have delayed bone age and there is no relation between bone age and serologic results (P value >0.05).

Table 3 Distribution of cases according to the bone age between positive and negative cases.

	No. of cases with delayed bone age	%	No. of cases with normal bone age	%	Total	P value
Positive cases	11*	91.7	1	8.3	12	>0.05
negative cases	28	100	0	0	28	

*9 of them had already diagnosed endocrinological cause for short stature.

Table (4) shows that 75% of positive serologic cases and 96.4% of negative cases had already diagnosed cause for

short stature and there is no relation between serologic results and presence of a cause (P value >0.05).

Table 4 Distribution of cases according to the presence of already diagnosed cause of short stature between positive and negative cases.

	No. of cases without underlying cause	%	No. of cases with other causes	%	Total	P value
Positive cases	3	25	9	75	12	>0.05
negative cases	1	3.6	27	96.4	28	

The already diagnosed causes for short stature in those 9 seropositive patients were; hypothyroidism in one patient and GHD in 8.

Discussion

Screening patients with short stature for CD is not a part of the medical routine in Babylon province, since these tests are expensive.

The response rate for blood sampling in our patients was high (89%) which facilitate the performance of the research in a short period and indicate the cooperation and education of our patients and their parents.

The ages of short stature patients involved in this study were ranged between 2-17 years. All these children might have CD as the disease can develop at any age after the introductions of grains contain gluten[23]. So, antigliadin antibody had been tested in all those children, screening for possible CD.

As reported by researchers from Brazil and Italy, 1-5% of short stature children had CD, while other researchers from India reported that CD was found in 15.3% of the short stature patients, making it the single most common

cause of short stature⁵. In this study, 30% of short stature children might have CD as indicated by positive antigliadin antibody test. This high figure (30%) as compared with the previous one (15.3%) might be explained by the fact that, there are other causes for raising antigliadin antibody such as cows milk protein enteropathy, Crohn's disease, IgA nephropathy, eosinophilic enteritis, tropical sprue, and dermatitis herpetiformis³, and this proportionally high figure might decreased after performing intestinal biopsy as the ultimate diagnosis of CD relies on it[2,7,14].

Most studies indicate that CD is more prevalent in females with female: male ratio 1.8:1 to 2:1[24]. Others mentioned equal sex distribution during childhood²⁵. Our study show no sex predilection among positive cases which is consistent with the second statement and at the same time not reversed the first one. So, sex distribution according to our screening test is consistent with that of CD.

Atypical CD which is characterized by few or no gastrointestinal symptoms is responsible for 50% of pediatric celiac

patients[26,27]. In this study, among positively screened short stature children, 58.3% had no gastrointestinal symptoms, making CD screening mandatory in all short stature patients regardless the presence of gastrointestinal manifestations[26], as the absence of intestinal symptoms does not preclude the diagnosis of CD[28].

By affecting the absorption of nutrients, CD greatly affects a child's bone age[29], and it has been reported that 60% of celiac patients had delayed bone age[30]. According to our study, from the 12 positive cases, 11 patients (91.3%) show delayed bone age. The higher percentage in our study can be attributed to the presence of already diagnosed endocrinologic disease such as hypothyroidism or GHD in 9 of our positive patients, and it is well known that endocrinologic short stature is also associated with delayed bone age[31], while the first result (60%) was associated with celiac disease alone.

It is well known that there is an association between CD and hypothyroidism through an autoimmune process[2,3,5,32], and hypothyroidism is more likely in celiac patients than in healthy individuals[2]. Gluten-free diet, not only improve celiac-related antibody levels, but thyroid antibody levels also decrease[32]. One study revealed that 10.3% of the celiac patients had hypothyroidism[33]. In this study 8.3% of positively screened patients had hypothyroidism, 25% had no diagnosed cause for short stature, and the surprising result is that 66.7% had GHD. This unpredicted value (66.7%) is considered high when compared with what mentioned by researchers that 25-36.7% of short stature celiac patients had GHD[34,35], but we know the fact that, the diagnosis of CD is depend on intestinal biopsy[2,7,32],

and a number of our patients may not have CD when biopsy is performed.

Conclusion

All short stature children should be screened for CD whether:

- They are males or females.
- Had GIT symptoms or no.
- Had delayed or normal bone age.
- Had already diagnosed cause for short stature or no.

Recommendation

1. Serologic tests for CD should be included in the routine investigations of short stature children.
2. Make serologic tests for CD available at Endocrine Clinic at Babylon Maternity and Children Hospital.
3. Jejunal biopsy should be done for every patient with positive screening test and for those with negative results in whom clinical suspicion is high.

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