Original Article

Beneficial effects of gluten free diet on IgA tissue transglutaminase levels and various growth parameters in celiac disease patients

Dayanand Hota[1], Kapil Bhalla[2], Sanjiv Nanda[2], Ashish Gupta[3], Shuchi Mehra[4]

[1]Department of Paediatrics, All India Institutes of Medical Sciences, Raipur, Chhattisgarh, Departments of [2]Paediatrics, [3]Trauma Centre and [4]Microbiology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

Abstract

Context: In the resource poor country like India it is difficult to get HLA screening and EMA testing in patients with celiac disease in small centres. **Aims:** To study the effect of gluten free diet on IgA tissue transglutaminase levels and various growth parameters in patients with celiac disease. **Settings and Design:** This was a prospective study conducted in the department of paediatrics of a tertiary referral hospital in north India in 3 stages viz. on presentation, after 3 months and 6 months of initial presentation. **Materials and Methods:** 392 patients with symptoms suggestive of celiac disease were screened for IgA tTG levels more than 10 folds of upper limit of normal. 50 cases (who followed up for 6 months regularly) were enrolled in the study. Spectrum of various growth and clinical parameters were also studied. Statistical analysis used: Statistical analysis was performed by the SPSS version 20.0. Data were checked for normality before statistical analysis. p value less than 0.05 was considered statistically significant. **Results:** 50 cases were enrolled in study. After initiation of gluten free diet, improvements were seen in various growth factors like height (12.71%) and weight (3.47 cm) after 6 months. Serum tTG(IgA) levels decreased to 94.88±55.35 U/mL from baseline level of 202±83.96 U/mL after 6 months. **Conclusions:** Gluten free diet has major role in improvement in growth parameters as well as anemia. So, early detection of celiac disease is an important step in prevention of morbidity associated with this chronic disease.

Keywords: Anemia, celiac disease, child, diet, gluten-free, growth, immunoglobin A

Introduction

Celiac disease (CD) is a chronic autoimmune disorder of small intestine in which ingestion of gluten leads to villous atrophy in genetically susceptible individuals.[1-3] CD is now considered as one of the most common genetic disorder in the West with male to female ratio of 1:2.8.[4,5] The prevalence of CD in India is nearly similar to Western Caucasian populations.[6] CD disease is characterized by the variable combination of CD-specific antibodies, HLA compatible haplotype, clinical manifestations, and enteropathy.[7] A combine genetic and immunological model has been well described.[8] The patient presents with features of malabsorption such as diarrhea, steatorrhea and weight loss or growth failure with serologic test results being abnormal and presence of varying degrees of villous atrophy. Iron deficiency anemia, megaloblastic anemia, anorexia, weight loss, abdominal distension/bloating, abdominal pain, vomiting, flatulence, diarrhea, short stature/growth failure, irritability, increased level of liver enzymes, chronic fatigue, failure to thrive, constipation, irregular bowel habits are some of the main symptoms. Associated conditions are down syndrome, turner syndrome, juvenile chronic arthritis, William's syndrome, diabetes mellitus type 1, IgA nephropathy, IgA deficiency, autoimmune thyroid disease and autoimmune liver disease.[9] The population with positive HLA DQ2/DQ8 typing for celiac have high chances of

Address for correspondence: Dr. Kapil Bhalla, Department of Paediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak - 124 001, Haryana, India.
E-mail: drkapilbhalla@gmail.com

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developing celiac symptoms when on high gluten consumption. However, the populations with diabetes, autoimmune disorder or relatives of CD individuals have even higher risk for the development of CD, since they share the same HLA typing. Assays for IgA anti-tissue transglutaminase (TGA) and IgA anti-endomysial (EMA) are regarded as being superior serological screening tools for diagnosis of CD. Initial CD evaluation is based on a combination of positive CD-specific serological tests, histological findings in the intestinal biopsy, CD-predisposing gene encoding HLA DQ2 or DQ8, family and medical history of CD, and clinical or histological response to GFD. Positive TGA or EMA at initial diagnosis of CD or at any time in the clinical course of the disease helps to confirm the diagnosis of CD because of their excellent specificities of over 99% when small bowel villous atrophy is present on biopsy.[10,11] A combination of biopsy and serological antibody can also be used to support diagnosis to reduce false positive results. CD patient can present with nonspecific signs and symptoms. Thus, it is essential to identify CD in patients with less clear clinical symptoms. The diagnosis is supported by serological tests and other diagnostic tests with high specificity. "The interpretation and consequences of the test results differ between symptomatic and asymptomatic patients in at-risk groups".[12] The mainstay of treatment for CD is a Gluten Free Diet (GFD) i.e., avoidance of the gluten-containing grains wheat, rye, and barley. Newer therapies such as intraluminal agents, immunomodulators, and vaccination have been used in some trials. In the resource poor country like India it is difficult to get HLA screening and EMA testing in patients with celiac disease in small centers. This study was undertaken assuming high prevalence of celiac disease among north Indian population with symptoms of celiac disease and IgA tissue transglutaminase (tTG) level >10 times of upper normal limit. We also studied the clinical spectrum and investigation profile of this suspected celiac disease children.

Subjects and Methods

This prospective study was conducted in the department of pediatrics of a tertiary referral hospital in north India in 3 stages viz. on presentation, after 3 months and 6 months of initial presentation. Total of 392 patients with clinical symptoms suggestive of celiac disease were screened for IgA tTG levels more than 10 folds of upper limit of normal. Seventy-seven cases fulfilled the inclusion criteria, out of which 50 cases (who followed up for 6 months regularly) were enrolled in the study.

Case definition

A child between 1 and 14 year of age presented to OPD or admitted in ward with symptoms which are highly suggestive of celiac disease such as chronic diarrhea, abdominal distension, constipation, failure to thrive or growth retardation, features of malabsorption, refractory anemia, micronutrient deficiency and other extra intestinal sign and symptoms with IgA tTG level 10-folds of normal level was taken as a case. Children with IgA deficiency were excluded from the study.

Inclusion criteria included children more than 1 year and less than 14 years of age with positive IgA tissue transglutaminase more than 10 folds of normal level for celiac disease with commitment for adherence to a gluten-free diet. Exclusion criteria included children already receiving gluten-free treatment, children with chronic active gastrointestinal disease such as irritable bowel syndrome, inflammatory bowel disease, intestinal malignancies etc., and children with any uncontrolled systemic/chronic disease. Total of 392 patients with clinical symptoms suggestive of celiac disease were screened by IgA tTG level more than 10-folds of upper limit of normal and enrolled in study. Demographic details like name, age, sex, address, contact number with hospital enrolment number was taken. Chief complaints of patients were noted in chronological order, systemic and general examination findings, anthropometric data which included weight for age, height for age, weight for height, and physical examination done. All the patients were subjected to routine investigation test like complete hemogram, serum electrolytes (Na^+, K^+), blood sugar, thyroid function test and other celiac disease-related serological test. After taking consent regarding study, child was kept on gluten free diet which includes product made from wheat, rye, and barley (i.e. roti, chapatti, bhature, biscuits, daliya, some wheat-based sweets, bread, sandwitch, burgers, etc.) and after 3 months and 6 months, same detailed clinical examination, anthropometric assessment and some investigations were done. Laboratory values were assessed with standard parameters for age and sex. An enzyme linked immunosorbant assay (ELISA) for the semi-quantitative detection of IgA antibodies to tissue transglutaminase (endomysium) in human serum was done. Statistical analysis was performed by the SPSS version 20.0. Continuous variables were presented as mean ± SD, and categorical variables as absolute numbers and percentage. Data were checked for normality before statistical analysis. For all statistical tests, *P* value less than 0.05 was considered to indicate a significant difference.

Results

Seventy-seven cases fulfilled the inclusion criteria and of which 50 cases (who followed up for 6 months regularly) were enrolled in study. Distribution according to age and sex of enrolled cases are shown in Tables 1 and 2, respectively.

Among 50 cases of suspected celiac disease, mean age of presentation was 7.14 ± 3.22 years. Majority of children belonged to 5–9 year age group (48%) followed by less than 5 years (30%)

Table 1: Distribution according to different age groups of enrolled cases

Age (years)	Frequency (*n*)	Percentage (%)
<5	15	30
5-9	24	48
10-14	11	22
Total	50	100

and 10–14 year age group (22%). 60% were female and 40% male with ratio of 1.5:1.

Seventy percent of cases (35) presented with complaints mostly related with non-gastrointestinal symptoms. Rest 15 cases presented with gastrointestinal symptoms. Most of the patients presented with short stature (46%), 40% had abdominal distension, 28% had diarrhea, 24% had constipation, 24% had vomiting, and 22% patients complained with pain abdomen. Other features included 20% patients having oral ulcers, 16% having joint, and skeletal abnormality. Herpatitis dermatiformis was found in 16% cases while neuropsychiatric features in 6% and coagulopathy in 10% of patients. Among neuropsychiatric features, 2 were cases of epilepsy and other one was a case of ataxia. One patient with vitiligo and one with vision problem secondary to vitamin A deficiency were also there [Figure 1].

In 20 male patients, 7 children (35%) had short stature (height less then 3rd centile) according to WHO growth charts. Out of 30 female patients, 16 (53.3%) were short stature. Thus overall 23 patients of both sexes were short statured which is 46% of total. Among 50 cases, 62% ($n = 31$) were having weight less than 3rd centile and 38% were between 3rd to 97th centile. No case was above 97th centile in study population. Among 50 cases, 46% ($n = 23$) were having height less than 3rd centile and 54% were having height between 3rd to 97th centile.

Anemia was seen in 82% of patients. All patients had high ESR with mean of 27.4 2 ± 10.94. Mean sodium level was 136.94 ± 6.42 mEq/l, 13 patients (26%) had hypokalemia, 20% had elevated AST and 16% had elevated ALT levels. 24% were hypocalcaemic and 18% had elevated urea level. Hypoproteinemia was seen in 18% patients. 50% children were vitamin D deficient.

In our study group mean weight for age was 16.814 ± 6.35 kg (Mean ± SD) at the time of diagnosis. Considering it as baseline weight we started gluten-free diet and at 3 months and 6 months of age we followed up them. After 3 months of starting GFD, the mean weight of population was 17.74 ± 6.63 kg and at 6 months 18.81 ± 6.96 kg. This increase in weight was 6.08% and 12.71% from baseline at 3 months and 6 months. Similarly baseline height was

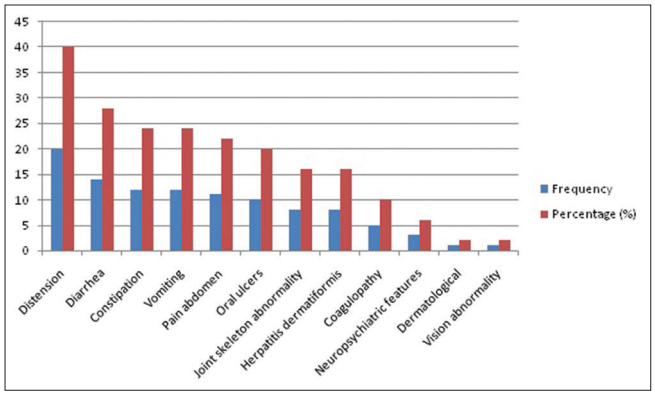

Figure 1: Bar diagram depicting frequency and percentage of various signs and symptoms observed in celiac disease patients

107.23 ± 17.72 cm (Mean ± SD), 108.43 ± 17.75 cm at 3 months, and 110.70 ± 18.16 cm at 6 months observed. Total mean growth was seen 1.208 cm and 3.47 cm at 3 and 6 months respectively after initiation of gluten free diet. Mean BMI 14.116 ± 2.16 (mean ± SD) increased to 14.58 ± 2.07 and 14.87 ± 2.36 at 3 and 6 months, respectively. BMI z score improved from –2.3904 to –1.6568 in 6 months after gluten free diet ($P = 0.805$). After initiation of gluten-free diet mean hemoglobin also increased in study population. From baseline hemoglobin of 8.886 ± 2.92 gm% (Mean ± SD) it increased to 9.36 ± 2.29 gm% and 9.79 ± 1.96 gm% at 3 and 6 months, respectively. Increment was 10.48% and 17.89% from baseline hemoglobin at 3 and 6 months. Serum tTG (IgA) levels decreased to 142.5 ± 74.70 U/mL (Mean ± SD) and 94.88 ± 55.35 U/mL at 3 and 6 months respectively from baseline mean level of 202 ± 83.96 U/mL [Table 3].

Discussion

Celiac disease is characterized by classic gastrointestinal manifestations such as diarrhea, weight loss, failure to thrive, vomiting, and constipation, or by non-gastrointestinal manifestations such as short stature, iron-deficiency anemia, hypertransaminasemia, delayed puberty, dermatitis herpetiformis, and others. It may be associated with other autoimmune

Table 2: Distribution according to sex of enrolled cases

Age (years)	Male (%)	Female (%)
<5	3	12
5-9	12	12
10-14	5	6
Total	20 (40)	30 (60)

Table 3: Effect of gluten free diet on various clinical and growth parameters

Parameter	Mean±SD (kg)	Change from baseline	*P*
Weight			
At presentation	16.814±6.35		
After 3 months	17.744±6.63	+ 6.08%	0.475
After 6 months	18.812±6.96	+12.71%	0.1369
Height			
At presentation	107.23±17.72		
After 3 months	108.43±17.75	+1.208 cm	0.73
After 6 months	110.70±18.16	+3.47 cm	0.336
BMI			
At presentation	14.116±2.16779		
After 3 months	14.5793±2.07239		0.277
After 6 months	14.876±2.35931		0.096
Hemoglobin			
At presentation	8.886±2.92		
After 3 months	9.36±2.29	+ 10.48%	0.369
After 6 months	9.79±1.96	+ 17.89%	0.0722
IgA tTG level			
At presentation	202±83.96		
After 3 months	142.5±74.70	-28.15	0.0003
After 6 months	94.88±55.35	-50.72	0.001

disorders. We studied clinical spectrum and investigation profile of 50 children in our center that presented with typical and/or atypical manifestations of celiac disease. These children were also followed up at interval of 3 and 6 month after starting of Gluten free diet. Their growth parameters such as height for age, weight for age and BMI were plotted. Certain hematological parameters and IgA TTG level were also monitored during these intervals. The mean age of cases was 7.14 ± 3.22 years which are in concordance with a study by Bhattacharya M, *et al.*[12] The sex distribution of current study comprised 20 (40%) male and 30 (60%) female with ratio of 1:1.5, similar to a study by Nadia Waheed *et al.*[13] Most of the cases belonged to middle class (60%) according to modified kuppuswamy scale, followed by lower class (34%) and 6% of cases belonging to upper class. Oza SS *et al.* also found higher symptoms in lower socioeconomic status in a study population.[14]

Among 50 cases, 62% (n = 31) were having weight less than 3rd centile and 38% were between 3rd to 97th centile. No cases were above 97th centile in study population. In total 50 cases 23 were below 3rd centile in height for age and sex reference which is 46% of total thus qualifying as short stature. Similar findings were reported by Bhattacharya M *et al.*, Saeed A *et al.*, and Işikay S *et al.*[12,15,16]

Presenting complaints were mostly related to non-gastrointestinal symptoms [total 35 cases (70%) were presented to us with non-gastrointestinal symptoms], similar to those observed by Saeed A *et al.*[15] The occurrence of extra-intestinal symptoms was similar to studies by Bhattacharya *et al.*, and Khatib *et al.*[12,17]

Anemia was the most common hematological manifestation seen in patients with celiac disease. Total 41 (82%) patients were anemic, out of which 39% were normocytic normochromic, 37% microcytic hypochromic, and 24% were macrocytic in nature. Studies from Turkey reported that as much as 48.2-80.1% of children with CD had IDA.[18,19] Vitamin B_{12} deficiency in untreated CD-patients has been confirmed in several previously conducted European studies, ranging from 12% up to 41%.[20] Dahele *et al.* found 41% patients were vitamin B12 deficient (<220 ng/L) and 41% patients were anemic. Bhadada *et al.* had seen anemia in 80.9% of celiac disease patients. In another study by north Indian teaching hospital, anemia was seen in 90.7% cases (48.1% severe anemia). Iron deficiency anemia was seen in 77.8% children.[21,22] These studies have similar prevalence of anemia as our study population.

Elevated levels of ESR, hypernatremia, hypokalemia, hypocalcaemia, elevated urea level, hypoproteinemia, vitamin D deficiency in patients with celiac disease were also observed by Nadia Waheed *et al.*, Castillo *et al.*, and Erdem T *et al.*[13,23,24]

The treatment of Celiac Disease is still based on the GFD, as originally proposed by the Dutch Pediatrician, Doctor Willem-Karel Dicke, which requires the complete elimination from the diet of all types of foods containing or prepared with wheat, rye, barley grains, and their derivatives. Although this treatment guarantees the recovery from both clinical symptoms and intestinal damage in almost all cases, it seriously affects the patient's quality of life, since its stringency and lifelong duration cause chronic distress and it Segregates patients in a sort of "social apartheid". This is the reason why compliance is very often suboptimal, ranging from 52% to 95% in the pediatric population, with adolescents having serious difficulties with permanent adherence to the GFD. In general, factors that improve chances of compliance are early age diagnosis, the presence of symptoms after gluten ingestion, a good awareness in the family, and frequent follow-ups by both a physician and a meticulous nutritionist. Similarly, in adults the adherence to a GFD improves by having regular follow-ups, even by telephone, within the setting of a dedicated adult celiac Unit. Therefore, patients' education, close supervision with scheduled nutritional counseling, and maintenance of dietary adherence when traveling or dining out, are all crucial factors needed to achieve full compliance.

The improvement in mean height for age after initiation of GFD was also reported by Patwari *et al.*,[25] Virginia A. Keane.[26] Agardh D *et al.* had studied Tissue transglutaminase (tTG) autoantibodies decline after gluten-free diet in patients with celiac disease, as seen in present study also.

There are concerns regarding the concept of using the same threshold (10 × ULN) of non-standardized tests with recognized inter- and intra-test variability as criterion to omit biopsies for CD diagnosis. As this approach gives quantification of TGA concentrations a large weight, type, and quality of serology tests are crucial and calibration curves allowing linear calculation of results are obligatory. The ESPGHAN criteria also request the presence of symptoms for the non-biopsy approach.[27]

Symptoms of malabsorption increase the pre-test probability for CD compared to less-specific complains such as abdominal pain and thereof the post-test probability of a given serological result.

Transient TGA-IgA positivity occurs in persons at genetic risk for CD, particularly those with type 1diabetes mellitus, although TGA-IgA levels are mostly low. A recent population-based screening study in Swedish school children suggested that the non-biopsy approach is also safe to diagnose CD in the absence of symptoms There is some concern that the non-biopsy approach may result in clinically relevant missed co-morbidities such as gastroesophageal reflux disease, eosinophilic esophagitis or *Helicobacter pylori* infection-related complications.[27]

Hence for family physicians it is very important to diagnose celiac disease as soon as possible because the introduction of gluten-free diet prevents the nutritional anemia and physical retardation of children.

The ESPGHAN non-biopsy approach also allows a correct diagnosis of celiac disease. It will reduce burden and risk of endoscopy and anesthesia while saving costs for better care system.

Conclusion

In our study it is found that majority of patients presented with non-gastrointestinal symptoms with significant growth failure, also having severe anemia. Thus, celiac disease should be screened in patients of severe anemia with growth failure. Gluten free diet has major role in improvement in growth parameters as well as anemia. So, early detection of celiac disease is an important step in prevention of morbidity associated with this chronic disease.

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Conflicts of interest

There are no conflicts of interest.

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