ORIGINAL ARTICLE

Coeliac disease — clinical presentation and diagnosis by anti tissue transglutaminase antibodies titre in children

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Abstract

Objective: To study the spectrum of clinical presentation of coeliac disease and the role of IgA anti-tissue transglutaminase antibodies titer in the diagnosis and effect of gluten-free diet on such titers in children.

Methods: The prospective study was conducted in the paediatric department of Combined Military Hospital, Kharian from Sep 2011 to Sep 2012. Children of 1-12 years of age presenting with chronic diarrhoea, malnutrition and failure to thrive were included regardless of gender, socioeconomic status, ethnicity and geographical distribution. Anti-tissue transglutaminase angibodies titers were done on enrolment. Patients with levels more than 30u/ml were enrolled. They were advised strict gluten-free diet for six months. These titers were repeated after six months to document the effect of gluten-free diet on these titers. Paediatric endoscopy and duodenal biopsy facilities were not available at the study site, so the response was monitored through titers. Data was analysed using SPSS-20.

Results: Out of 61 patients with IgA levels more than 10 u/ml, 52(85.24%) were found to have a positive (>30u/ml) anti-tissue transglutaminase antibodies titers with a mean value of 42.67±7.60U/ml. These 52 patients were then put on a trial of gluten-free diet for six months after which significant reduction in titer was noticed, with a mean value of 13.25±2.59U/ml. This reduction in titer was associated with marked clinical improvement and regression of symptoms. Frequency of different clinical features in descending order revealed that chronic diarrhoea, abdominal distension, iron deficiency anaemia, failure to thrive, pallor and rickets were present in 38 (73.1%), 30 (57.7%), 29 (55.8%), 29 (53.8%), 28 (53.8%) patients respectively.

Conclusion: Chronic diarrhoea, failure to thrive, pallor, abdominal distention and iron deficiency anaemia were common modes of presentation. The antibodies were strongly positive in most of the cases. All children showed significant improvement in clinical features and reduction in antibody titers after six-month trial of gluten free diet.

Keywords: Celiac disease, Anti-tissue Transglutaminase antibody, Diagnosis, Clinical presentation. (JPMA 64: 437; 2014)

Introduction

Coeliac disease (CD) is an immune-mediated enteropathy caused by permanent intolerance to gliadin and related proteins present in gluten part of diet in genetically susceptible individuals.[1,2] In history, first of all Aretaeus and Galen gave a brief description of this disease in 2nd century AD. Later on in 1888 AD Samuel Gee described the classical features of CD. Initially in 20th century, CD was considered a disease of western society but now prevalence data from India, Middle East and North Africa show that its prevalence ranges from 0.14% to 1.17% in low-risk and 2.4% to 4.4% in high-risk groups.[3] In some studies reported prevalence is 0.5 to 1% of the general population.[4] However incidence varies in different ethnic, racial and geographical parts of the world. Indian Punjabis in England have a 2.9 times more incidence of CD than the native English.[1] Genetic susceptibility is now proven beyond any doubt.[2] It has been documented that ratio of diagnosed to undiagnosed cases is 1:53, that indicates poor recognition of clinical spectrum of the disease.[2] Prevalence is 2-10% in patients with Type-1 diabetes mellitus (IDDM), Downs syndrome, Turner syndrome, Thyroiditis, other autoimmune diseases and family history of CD.[5,6] In Pakistan there are no specific documented figures regarding its prevalence, but is thought to affect both paediatric and adult population in our country.[4,7]

Typically, CD is classified into classic, silent/subclinical, latent and potential CD.[2,8] Clinically it presents with both gastrointestinal and non-gastrointestinal symptoms. Gastrointestinal (GIT) symptoms include classical triad of chronic diarrhoea, failure to thrive (FTT) and abdominal distention. Less frequently occurring GIT symptoms are vomiting, anorexia, recurrent abdominal pain,

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constipation. Non-gastrointestinal or atypical features include short stature, rickets, oedema weight loss, iron deficiency anaemia (IDA), raised alanine aminotransferase (ALT), non-hereditary cerebellar ataxia, dental enamel hypoplasia and idiopathic peripheral neuropathy. It is utmost important to rule out CD in all patients presenting with typical, atypical features , first degree relatives of CD and those with auto immune disorders to avoid disastrous sequel.

Duodenal biopsy and evidence of histological changes in intestinal mucosa are confirmatory of CD. However, amongst the various serologic markers used for the diagnosis of CD, IgA-specific anti-tissue Transglutaninase (tTG) antibodies are 90-98% specific and 95-97% sensitive.[9] It has been further improved by the use of human tTG in place of non-human tTG preparations used earlier in immunoassay kits.[10] Serologic markers like anti tTG antibodies and anti-endomyseal antibodies if used for screening can significantly increase the diagnostic rate of this disease.[11] A decrease in the antibody titer or eventual disappearance after introduction of gluten-free diet (GFD) is a supportive indicator of recovery and adherence to dietary regimen by the patient. GFD is the only treatment of CD but this diet is quite complex, not easily available, costly and socially off-putting.[7] Managing patients with CD is a challenging task. GFD is not readily available in the market. Those brands available in the form of gluten free flour are very expensive for daily use. Need of the hour is provision of GFD at a cheaper cost in the market, initiation of support groups (www.celiac.com.pk) and enforcement of consumer laws where GFD is labelled accurately and made easily available.

We conducted this study to look at the pattern of clinical presentation of CD in our children, screen suspected cases of CD by IgA anti-tTG antibodies, place patients with titers >30u/ml on GFD and observe the effect of GFD on anti-tTG titers in our setup.

Patients and Methods

The prospective study was conducted in the Department of Paediatrics, Combined Military Hospital, Kharian, from September 2011 to September 2012. It is a tertiary care and referral hospital for nearby districts of upper Northern Punjab. Children from 1 to 12 years of age presenting with chronic diarrhoea and malnutrition/FTT, which are clinical suspicions of CD, were included in the study. Inclusion was regardless of gender, ethnicity, socioeconomic and geographical background. Verbal and written consent was obtained from the parents. Detailed history and clinical examination including anthropometric measurements was done and recorded. Variables like gender, age of onset, family history, consanguinity, clinical features and laboratory parametres were recorded on predesigned proforma.

Children with diseases like Giardiasis, Abdominal tuberculosis, Inflammatory bowel disease, Immunodeficiency, Cystic fibrosis, and other established causes of FTT and short stature were excluded from the study.

Serum IgA specific anti-tTG antibodies were done in clinically suspected CD patients. About 4ml of venous blood was collected and analysed by chemiluminescence immunoassay technique for IgA specific anti-tTG antibodies. Manufacturer reference range for positive Anti-tTG was >10 U/ml. A cutoff level >30 U/ml of anti-tTG antibody was considered strongly positive. Children having raised antibody titers (>30 U/ml) were placed on a GFD for six months. Gluten is present in grains such as wheat, barley, rye and triticale. Products which contain gluten are easily available at any market shelve and include gram flour, semolina, spelt, farina, beers, breads, cakes, pastries, pies, pizzas, pastas, cereals, vermicelli, cookies, candies, chocolates, jellies, croutons, sauces and home/market made sweets. Diet products which are gluten-free and can be used include rice, beans, seeds, nuts, eggs, fish, meat, poultry (not breaded, battered or marinated), fruits, vegetables, dairy products. Grains which do not contain gluten include amaranth, buckwheat, corn, millet, soya and gluten-free flours like soya, corn, potato, bean and rice. These diets were translated into Urdu language and parents were counselled in detail regarding their use and restrain. After six months of GFD the antibody titers were measured again and compared with previous value. Data was collected and analysed using SPSS version-20. Mean ± standard deviation was calculated for IgA anti-tTG antibodies titers at the time of diagnosis and after 6 months of GFD. Paired sample t-test was applied to see the mean difference in IgA, anti-tTG antibodies titers at time of diagnosis and after 6 months of gluten, absence from diet. P value <0.05 was considered significant. Unfortunately paediatric endoscopic biopsy facility was not available at our setup, so we could not document histopathological evidence or improvement of CD.

Results

Of the 61 patients who were initially diagnosed to have CD on the basis of raised (>10u/ml) anti-tTG IgA levels, 52 (85.24%) were found to have >30u/ml IgA anti-tTG

antibody titers and these patients comprised the study population. The mean age of onset of symptoms was 3.25±2.28 years; 15(28.8%) patients had started having complaints from age of 2.5 years.

Table-1: Parameters of coeliac disease.

Parameter	Variable	Number	Percentage
Parental consanguinity	Yes	16	30.8%
	No	36	69.2%
Family history	Yes	7	13.5%
	No	45	86.5%
Weight and height	<0.4th centile	17	32.7%
	0.4th-5th centile	18	53.8%
	>5th centile	7	13.5%
Autoimmune disorders	Yes	1	1.9%
	No	51	98.1%
Clinical presentation	Chronic diarrhoea	38	73.1%
	Failure to Thrive	28	53.8%
	Abdominal distention	30	57.7%
	Pallor	15	28.8%
	Iron deficiency anaemia	29	55.8%
	Rickets	1	1.9%
	Oedema	1	1.9%
SEX			
I)	Male	29	55.80%
II)	Female	23	44.20%
III)	Total	52	100%
Age of Onset of Symptoms			
Number 52	Mean	Std. deviation	Std. Error
	3.25years	2.28	mean 0.316

Table-2: Comparision of clinical features in different studies.

Parameter study	Poddar et al[17] (%)	Cheema et al[15] (%)	Alvi et al[1] (%)	Our study
Chronic diarrhoea	84	52	82.6	73.1
Failure to Thrive	84	54	89.1	53.8
Abdominal distension	48	83	65.2	57.7
Anaemia/pallor	84	82	95.6	85.6
Rickets	--	45	8.7	1.9
Oedema	6	3	6.5	1.9

In table-2, sub heading clinical presentation, number is more than 52 and percentage sum more than 100. Reason for this is that some patients were having more than one clinical feature at presentation.

Table-3: Effect of gluten free diet on IgA-Anti-tTG level.

	N	Mean	Std. Deviation	Std. Error Mean
On diagnosis	52	42.67	7.60	1.06
After gluten with drawl	52	13.25	2.59	0.36

p-value: 0.000 highly significant.

Out of 52 patients, 29 (55.8%) were male and 23(44.2%) female. Consanguinity was present in 16 (30.8%) cases, whereas family history was positive in only 7(13.5%) patients. Regarding weight and height parametre, 35(86.5%) patients were <5th percentile and only 7(13.5%) cases above the 5th percentile.
Mode of presentation was with chronic diarrhoea 38(73.1%) cases, abdominal distension 30(57.7%), IDA 29(55.5%), FTT 28(53.8%), pallor 15 (28.8%), rickets 1(1.9%) and oedema 1(1.9%). Only 1(1.9%) patient was suffering from other associated autoimmune diseases i.e. Type 1 DM (Table-1). Comparison of clinical features with other local and international studies was also done (Table-2).

At the time of diagnosis, IgA anti-tTG antibodies titers were at a mean value of 42.67±7.60 U/ml. After GFD for 6 month, mean values dropped to 13.25±2.59 U/ml (Table-3). The mean IgA anti-tTG antibodies titers improved significantly with decrease of 29.42±5.90u/ml (p=0.001).

Discussion

In different studies conducted in Pakistan, spectrum of clinical presentation of CD in children includes chronic diarrhoea, abdominal distention, FTT, rickets, IDA, short stature, oedema, clubbing and delayed bone age.[12,13]

Mean age of onset of symptoms in our study was 3.5±2.28 years (SE: 0.316). It is consistent with that reported by Alvi (3.4 years)[1] and a Jordanian study (3.4 years).[14] But Cheema et al had reported a mean age of 6 years in their study and in western countries it is 9-18 months.[15]

After gender analysis, there was a male preponderance. Our reported male preponderance is in contrast with female preponderance as documented by Alvi et al.[1] Babar et al have also shown female preponderance, 60% females versus 40% males, in his study.[16] Consanguinity reported in our patients is less when compared to 43.9% reported by Butt et al among their patients.[13]

A large proportion of our patients presented with chronic diarrhoea and it is comparable to those reported in India and 70% as shown by Butt et al.[13,17] Frequency of patients reporting with IDA is in comparison with 64% documented by Siyal et al.[18] However, it is in contrast with 15% demonstrated by Iqbal et al.[12] Plausible explanation for these differences may be sample nature, size and methodology used to diagnose CD. Mode of presentation of a minute proportion of patients was rickets and oedema. It is comparable to 2.5% incidence of rickets reported by Iqbal et al.[12] Again, nature of sample, methodology for

diagnosis and age at time of diagnosis may be the underlying factors for this difference. In contrast to all our Pakistani studies, a study from Jordan[14] showed prevalence of rickets at 26%. It may be due to late diagnosis, ethnic and geographical differences. Weight and height of majority of patients were below 5th percentile in our study. As narrated by Cheema et al 82% patients were below the 3rd percentile for weight and height parameter.[15] Alvi et al had also reported nearly similar results for growth parametres. Only one patient was having associated autoimmune disorder in the form of IDDM and nearly double the frequency for this parameter was reported by Alvi et al.[1]

Gold standard for diagnosis of CD is duodenal biopsy, but serological markers are gaining importance for screening. In recent years, role of serological assay solely for diagnosis of CD has been proposed. There are different serological markers like anti-reticulin, anti-gliadin, anti-endomyseal and anti-tissue transglutaminase antibodies for diagnosis of CD. Anti-endomyseal antibodies have high sensitivity and specificity, but costly and not easily available everywhere. IgA anti-tTG level >100u/ml showed a high specificity for Marsh type 3a or greater changes.[19] Guidelines issued by North American Society for Paediatric Gastroenterology, Hepatology and Nutrition, and European Society for Paediatric Gastroenterology, Hepatology and Nutrition state that Marsh type 1 or 2 changes are less specific or perhaps unlikely to be included in CD.[20] Based upon these results it has been proposed to start GFD for those patients with high Anti-tTG levels and to perform duodenal biopsy only if clinical features of patients do not improve after GFD for a certain period. It further highlights the role of Anti-tTG in diagnosis of CD. Now it is argued that duodenal biopsy can be avoided when significantly high titer of transglutaminase antibodies are present.[21,22] We did not perform duodenal biopsy because our patients improved a lot clinically and, secondly, facility for paediatric endoscopy was not available at our setup. Moreover in a study conducted by Vivas et al,[21] it has been shown that duodenal biopsy can be avoided in children if IgA anti-tTG antibodies levels are more than 30u/ml (three times the upper limit of normal) and there is a positive response to GFD. We have followed these criteria in our study. In the same study Vivas et al[21] has shown that IgA anti-tTG >30u/ml has both specificity and positive predictive value of 98% for Marsh type 3 lesions in children. High predictive value of IgA anti-tTG antibody for villous atrophy also rules out duodenal biopsy as prerequisite for diagnosis and initiation of GFD.

To the best of our knowledge this study is the first in Pakistan regarding CD diagnosis by solely IgA anti-tTG serology. But it does not apply to adults.

In terms of our study's limitations, the Combined Military Hospital, Kharian, is a referral hospital for the surrounding hospitals so our study is not a community reflection of CD presentation. Besides, we could not perform anti-endomyseal antibodies and human leukocyte antigen (HLA) typing due to financial constraints. Finally, we were unable to perform duodenal biopsy.

Conclusion

Coeliac disease is not a rare entity in paediatric population of our country. It has wide spectrum of clinical presentation and facilities for duodenal biopsy diagnosis do not exist everywhere. We recommend that strongly positive IgA anti-tTG titer can be used for diagnosis and prognostic follow up in clinically suspected CD cases where facilities for intestinal biopsy are not available.

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