

Prevalence of Celiac Disease and Role of Anti-Tissue Transglutaminase Antibodies in Different Types of Intestinal Damage in Celiac Disease According to Marsh Classification

TAHREEM KASHIF¹; AYESHA KASHIF², ZERTAJ KASHIF³, ANEELA AROOJ⁴

ABSTRACT

Aim: To study the prevalence of celiac disease in different age groups ranging from 7 months-22 years in Multan and its periphery and the role of anti-tissue transglutaminase antibodies in the diagnosis of celiac disease (CD).

Methods: This cross-sectional study of all duodenal biopsy cases, in whom anti-tissue transglutaminase antibody test was conducted prior to duodenal biopsy, referred to Zartaj Laboratory and FNA Clinic Multan from the year 2013-2016 were reviewed. This comprised 178 patients, both male and females, from the age group 7 months to 22 years with the suspicion of CD. Anti-tissue transglutaminase antibody titers were done in all patients by ELISA. Upper gastrointestinal endoscopies were performed and multiple duodenal biopsies from distal part of duodenum were taken for confirmation of CD in all the cases reviewed. Histopathology results were expressed according to Marsh Classification criteria of CD. A trial of gluten free diet was given in all suspected CD patients with villous atrophy and a follow up was made to confirm the diagnosis of CD.

Results: Out of 178 cases that had been reviewed, 96 (53.93%) cases fulfilled the diagnostic criteria of celiac disease, 76(42.69%) patients had nonspecific enteritis and duodenitis and 6 (3.37%) patients were suggested a repeat biopsy as celiac disease could not be ruled out. Out of these 96 cases, 35 (36.45%) had infiltrative hyperplastic stage marsh type 2 on histopathology, 34(35.41%) had 3a type and 27 (28.12%) had 3b type according to Marsh criteria. Out of these 96 patients, 49 (51%) had positive anti-tissue transglutaminase IgA antibodies. 24(48.97%) patients who had high titers ranging from >60->800 fell under 3b Marsh Type, 16(32.65%) patients had titers ranging from >25-300 had Marsh Type 3a, 9(18.36%) patients had titers ranging from >10-40 had Type 2 on histopathology.

Conclusion: Celiac disease may present at any age but predominantly in young age groups. Celiac disease is not a rare disease in Multan and its periphery. Duodenal biopsies play a significant role in diagnosis of CD as compared to serological tests. Anti TTG IgA is more sensitive and shows high titer only in severe cases of CD with Type 2 and above Marsh classification. However, Anti tissue transglutaminase IgG antibodies as compared to transglutaminase IgA didn't show any significant prevalence pattern.

Keywords: Celiac disease (CD), anti-tissue transglutaminase (anti TTG), gastroenterology

INTRODUCTION

Celiac disease (HLA-DQ2 and HLA-DQ8 associated Gluten sensitivity enteropathy) is a lifelong autoimmune chronic gastrointestinal disorder in which ingestion of Gliadin portion of Gluten present in wheat, rye and barley causes the damage to mucosa of the small intestine in genetically susceptible individuals¹. Typically, CD is classified into classic, silent/subclinical, latent and potential CD². It presents with both gastrointestinal and non-gastrointestinal symptoms. Gastrointestinal symptoms include chronic diarrhea, malabsorption, failure to thrive, pallor, abdominal distention and iron deficiency

Anemia³. Upon exposure to gluten, an abnormal immune response that leads to production of anti-tissue transglutaminase antibodies to the enzyme tissue transglutaminase occurs in majority of people with CD⁴.

Duodenal biopsy and evidence of histological changes in intestinal mucosa are helpful in diagnosing CD. However, amongst the various serologic markers used for the diagnosis of CD, anti-tissue Transglutaminase (TTG) antibodies are found to be the most sensitive^{5,6,7}. We conducted this study to look at the prevalence of CD in different age groups by performing duodenal biopsy and by screening suspected cases of CD by IgA & IgG Anti-TTG antibodies.

^{1,2,4}Medical Officers, Zartaj Laboratory and FNA Clinic Multan,
³Assistant Professor of Histopathology, Bakhtawar Amin Medical & Dental College, Multan Email: zertajkashif@yahoo.com

PATIENTS AND METHODS

We conducted a cross sectional study of 178 duodenal biopsy cases, received at Zartaj Laboratory and FNA Clinic Multan, of those individuals in whom anti tissue transglutaminase antibody test was performed. Anti-tissue transglutaminase antibody test was performed by ELISA method and samples were collected before performing duodenal biopsies. Anti-tissue transglutaminase antibody results were expressed in terms of titers by calculating observed values with cut off values. Cut of value was 10. All cases with results less than 10 were considered negative. And those with results more than 10 were considered positive. Upper gastrointestinal endoscopies were performed and multiple duodenal biopsies from distal part of duodenum were taken for confirmation of CD in all the cases reviewed. Histopathology results were expressed according to Marsh Classification criteria of CD.⁸

RESULTS

In our study, among the 178 cases, 96 (53.93%) were found to have celiac disease, 76 (42.69%) had nonspecific enteritis and duodenitis, while there were 6 patients who had mild focal increase in lymphocytes in subepithelial region of their mucosa and increase anti-tissue transglutaminase IgG level on ELISA who were suggested a repeat biopsy as CD could not be ruled out in those patients (Fig. 1). Among the 96 cases who were found to have celiac disease, 57 (59.3%) were male patients and 39 (40.6%) were female patients. Among different age groups ranging from 07 months to 22 years, children upto the age of 15 years were seemed to be more affected with CD. The mean age was found to be 5.5±2.8 years (Fig. 2).

Out of these 96 CD cases, 35 (36.45%) had infiltrative hyperplastic stage Marsh Type2 on histopathology, 34 (35.41%) had Marsh 3a Type and 27 (28.12%) had 3b Type according to Marsh criteria. Out of these 96 patients, 49 (51%) had positive anti-tissue transglutaminase IgA antibodies, 24 (48.97%) patients who had high titers ranging from >60->800 fell under 3b Marsh Type, 16(32.65%) patients had titers ranging from >25-300 had Marsh Type 3a, 09(18.36%) patients had titers ranging from >10-40 had Type 2 on histopathology (Fig. 3).

Out of the 178 patients who had anti TTG antibody ELISA test, 49 patients had positive anti-tissue transglutaminase IgA level and these 49 were diagnosed as CD on duodenal biopsy and by giving a trial of gluten free diet ,all these patients showed a reverse of their symptoms. 49(51%) out of 96 diagnosed cases of CD had positive anti-TTG IgA

levels, while 57 patients showed a positive anti-tissue transglutaminase IgG level, out of these 57 cases, 39(68.43%) patients had villous atrophy on histopathology and they responded to a gluten free diet, while 16(28.07%) patients had nonspecific enteritis/duodenitis on histopathology and didn't show any improvement to gluten free diet and 02(3.5%) patients were suggested a repeat biopsy (Table 1).

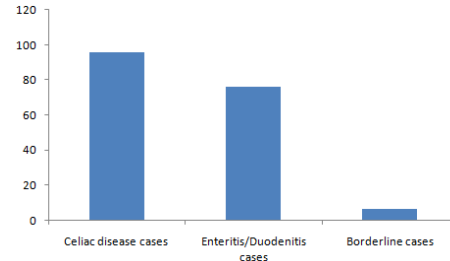


Fig. 1: Prevalence of celiac disease (n=178)

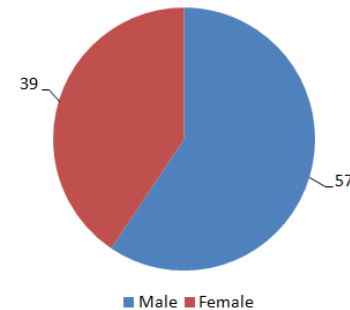


Fig. 2: Frequency of gender in celiac disease

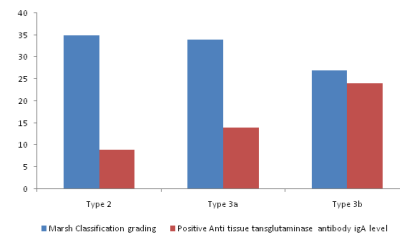


Fig. 3: Frequency of Celiac disease according to types

Table 1: Frequency of anti-TTG antibody ELISA test

TEST NAME	Anti TTG IgA ELISA	Anti TTG IgG ELISA
Total cases	178	178
Positive titers Value >10	46	57
Negative titers Value < 10	132	121
CD Cases with positive titers	46(100%)	39(68.43%)
Other cases with positive titers	0	18(31.57%)

DISCUSSION

Current study suggested that celiac disease, which is characterized by small intestinal damage with loss of absorptive villi and hyperplasia of the crypts typically leading to malabsorption and production of anti-tissue transglutaminase IgA & IgG antibodies on exposure to

gluten diet, is prevalent in our community. This study showed that almost 53.93% cases are suffering from celiac disease, with males more prone to the disease. In addition, CD may present at any age but predominantly in young age groups with children aged up to 15 years, with the mean age of 5.5 ± 2.8 years, were seemed to be more affected with the diseases, we reviewed data at Zartaj Laboratory and FNA Clinic which is mainly referred by Children Hospital Multan so it largely consists of young age groups. In many western studies, the disease mainly affects children but in recent studies the true prevalence of celiac disease increases over time⁹. However, in our study we conclude that celiac disease is not a rare disease in Multan and its periphery among children.

Duodenal biopsies play a significant role in the diagnosis of CD as compared to serological tests^{5,6,7}. Histopathology is the gold standard in the confirmation of diagnosis along with a trial of gluten free diet^{10,11}. Our data showed that Anti TTG IgA antibody level is more sensitive than anti tissue transglutaminase IgG antibody test,^{12,13} as it shows a 100% correlation with the disease but only in severe cases of CD with >2 Type Marsh classification on histopathology. With the intake of gluten as the severity of villous atrophy increases, likewise the anti-TTG IgA level increases in the serum of the affected individual.

It is therefore suggested that screening strategies to detect the level of anti-tissue transglutaminase IgA & IgG antibody should be addressed before duodenal biopsy in suspected cases but mucosal biopsies should be performed in all cases with low anti TTG antibody titers for confirmation as many patients with CD has low titers. However, Anti tissue transglutaminase IgG antibodies against transglutaminase IgA didn't show any significant prevalence pattern^{12,13}. As out the 57 patients with positive titers, 39(68.43%) had villous atrophy on histopathology and showed response to gluten free diet while the remaining 18(31.57%) were not found to have CD. The level of the anti TTG IgG antibody are less specific to CD, however people who are IgA antibody deficient, their IgG levels could be a helpful tool for diagnosis^{14,15,16}.

CONCLUSION

The celiac disease is prevalent in our surroundings but we recommend further studies with large data to find out the true prevalence of this disease. All those patients with malabsorption and gastrointestinal abnormalities should go for anti-tissue transglutaminase IgA level detection tests for the correct diagnosis before invasive procedures unless

the patient is IgA deficient. Though duodenal biopsy and evidence of histological changes in intestinal mucosa along with a strict trial of gluten free diet are the basic diagnostic criteria's of CD and should be performed in all suspected cases to detect all the undiagnosed cases.

REFERENCES

1. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992;102:330-54.
2. Green PH. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. *Gastroenterology* 2005;128:S74-8.
3. Green PH, Cellier C. Celiac disease. *N Engl J Med* 2007;357:1731-43.
4. American Gastroenterological Association medical position statement: Celiac Sprue. *Gastroenterology* 2001;120:1522-5.
5. Abdulkarim AS, Murray JA. Review article: The diagnosis of coeliac disease. *Aliment Pharmacol Ther* 2003;17:987-95.
6. Rashtak S, Murray JA. Tailored testing for celiac disease. *Ann Intern Med* 2007;147:339-41.
7. van der Windt DA, Jellema P, Mulder CJ, et al. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA* 2010;303:1738-46.
8. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;11(10):1185-94.
9. American Gastroenterological Association medical position statement: Celiac Sprue. *Gastroenterology* 2001;120:1522-5.
10. Hill ID, Dirks MH, Liptak GS, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005;40(1):1-19
11. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology*. 2001;120(3):636-51.
12. Giersiepen K, Leigemann M, Stuhldreher N, et al. ESPGHAN Working Group on Celiac Disease Diagnosis. Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. *J Pediatr Gastroenterol Nutr* 2012;54(2):229-41.
13. Husby S, Koletzko S, Korponay-Szabó IR, et al. ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54(1):136-60
14. Mäki M, Hällström O, Vesikari T, Visakorpi JK. Evaluation of a serum IgA-class reticulon antibody test for the detection of childhood celiac disease. *J Pediatr* 1984;105: 901-5.
15. Korponay-Szabó IR, Halttunen T, Szalai Z, Laurila K, Kiraly R, Kovacs JB, et al. Evaluation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease. *Gut* 2003;52: 1567-71.
16. Collin P, Mäki M, Keyriläinen O, Hällström O, Reunala T, Pasternack A. Selective IgA deficiency and coeliac disease. *Scand J Gastroenterol* 1992;27: 367-71.