Original Article

Diagnostic usefulness of Anti-Tissue Transglutaminase in Celiac Disease: Correlation with Intestinal Mucosal Biopsy

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ABSTRACT

Objective: To describe the clinical value of Anti-tTG (IgA, IgG) in the diagnostic work-up of celiac disease patients.

Methodology: Children with clinical suspicion of celiac disease, presenting in Gastroenterology and Hepatology out patient department, Children's Hospital & The Institute of Child Health, Multan were recruited. It was a descriptive case series, study was conducted from Jan 2007 to Jan 2009, blood samples for Anti-tTGs (IgG, IgA) & duodenal biopsies for histological analysis were taken. Data was analyzed for descriptive analysis.

Results: **Sixty** patients with symptoms suggestive of celiac disease were submitted *for Anti-tTGs (IgG, IgA) &* duodenal biopsy, 46 patients had histological changes according to the Marsh criteria and 49 had raised *Anti-tTGs*. A total of 54 patients who had one or both the tests positive, were considered for final analysis. 41 patients showed histological changes of celiac disease on duodenal biopsy and raised Anti-tTGs, 5 patients with histological changes of celiac disease had Anti-tTGs levels within normal limits. Five patients with raised Anti-tTGs levels had nonspecific inflammatory changes (not consistent with celiac disease) and 3 patients with raised Anti-tTGs levels had normal histology of intestinal mucosa.

Conclusion: Anti-tTGs (IgA, IgG) is very valuable screening marker in the diagnostic work-up of celiac disease, specially in selecting the patients for duodenal biopsies.

KEY WORDS: Celiac disease, Anti-tTG, Duodenal biopsy.

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INTRODUCTION

Celiac Disease, is a common cause of chronic malabsorption in children.[1] It is characterized by mucosal damage of the small intestine induced by gluten containing foods, may present with wide spectrum, ranging from silent asymptomatic form to chronic diarrhea, abdominal pain, failure to thrive, dermatitis herpetiformis, dental enemal defects, osteoporosis, short stature, delayed puberty and persistent iron deficiency anemia.[2] It is more prevalent among individuals with type-1 diabetes, Down syndrome, Turner syndrome, and first degree relatives of the individuals with celiac disease.[3]

The diagnosis of celiac disease is based on the presence of symptoms, demonstration of abnormal

small bowel histology and clinical response to gluten-free diet.[4] Positive serology, according to the European Society for Pediatric Gastroenterology and Nutrition criteria, makes the diagnosis more certain.[5-6] Tissue transglutaminase (tTG) has been claimed to play a fundamental role in the pathogenesis of celiac disease, when gluten derived peptides are subjected to tTG action, their complexes originate. These complexes are thought to behave as autoantigens determining the formation of antibodies elicited against gliadin peptides and tTG.[7] Several studies suggest that tTG auto-antibodies themselves are pathogenic, they induce epithelial cell proliferation[8], increase epithelial permeability and activate monocytes[9] and disturb angiogenesis.[10] Screening tests (Anti-tTGs) can be utilized to identify individuals at risk for celiac disease, but the small bowel biopsy remains the gold standard.[11]

In this case series we have tried to see the usefulness of (Anti- tTGs) in the diagnostic work-up of celiac disease and its relationship with small intestinal biopsy findings.

METHODOLOGY

The study was performed in Pediatric Gastroenterology Department Children Hospital, Multan from January 2007 to January 2009. A detailed history and physical examination, including anthropometric measurement (height, weight) were taken for all the children.

The subjects (2-14 years of age) with strong suspicion of celiac disease during the out patient evaluation were recruited. The presence of one or more of the following clinical findings were used to identify suspected cases for further evaluation: (i) chronic or recurrent diarrhea. (ii) short stature (i.e. linear height below 5th percentile for the age in the absence of any other specific identifiable cause); (iii) failure to thrive / gain weight (i.e. a weight for age below the 5th percentile or a weight for height ratio below the 10th percentile); (iv) unexplained pallor (v) abdominal symptoms (vomiting, abdominal bloating / discomfort),(vi) autoimmune disease such as (type I diabetes mellitus) autoimmune thyroiditis and (vii) being a sibling or descendent of celiac patients.

Table-I: Results of Anti-tTGs of 54 patients.

Patients positive for Anti tTGs	49 (90.74%)
Patients negative for Anti tTGs	5 (9.25%)

Total 60 cases suspected of celiac disease according to the above mentioned criteria, agreed for admission and evaluation. Parents / guardians were explained about risks / benefits of the study and informed consent was taken. They were also explained about duodenal biopsy for the final diagnosis and blood test for (Anti- tTGs IgA, IgG). The study protocol was approved by the Institutional Ethical Committee.

After admission in the ward, their hemoglobin, platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), hepatitis B surface antigen and anti HCV were sent to the Children Hospital laboratory. If any derangement was found in these tests, it was corrected by packed cells, platelets, fresh frozen plasma (FFP) transfusions, which ever was needed. Blood samples of the patients were sent to the Aga Khan Laboratory, Karachi for anti-tTGs (IgA and IgG) to be measured by the ELISA procedure, (Normal cut off value for IgA is 0-7U/ml and of IgG is 0-17U/ml). At the same time these prepared patients underwent upper gastrointestinal endoscopy under local / general anesthesia (Olympus GIF 160 end-viewing gastroscope, Tokyo, Japan) for small bowel biopsy taken from the second part of the duodenum (Biopsy forceps, Olympus FB-25K, Tokyo). At least two biopsy samples were obtained for each subject. The biopsies were preserved in formalin and sent for histopathological examination to Shaukat Khanam Hospital, laboratory Lahore. Histopathology was expressed according to the Marsh Criteria. The final analysis was done on fifty four (54) patients, who had one or both the tests positive.

RESULTS

Fifty four patients (2 to 14 years of age), who had one or both the tests (Anti-tTG, duodenal biopsy) positive, were included for final analysis. There were 28 (52%) males and 26 (48%) females. In small bowel biopsy, 46 patients had histological changes of celiac

Table-II: Histological changes of duodenal mucosal biopsy of 54 patients.

Patients having histological changes consistent with celiac disease	46(85.2%)
Patients having non-specific histological changes (not consistent with celiac disease)	5 (9.59%)
Patients having normal duodenal mucosa	3 (5.5%)

Table-III: Co-relation of anti-tTGs with duodenal mucosal damage.

Total patients having histological changes of celiac disease = 46	Positive anti-tTGs = 41 (89.13%)
	Negative anti-tTGs =05 (10.86%)
Total patients having positive anti-tTGs = 49	Histological changes of celiac disease = 41 (83.67%)
	Non-specific chronic inflammation but not consistent with celiac disease = 05 (10.20%)
	Normal histology = 03 (6.12%)

disease according to the marsh criteria, five had non-specific chronic inflammatory changes (not consistent with celiac disease) and three with normal histology were noted. Anti tTGs were found raised in 49(90.74%) patients and within normal range in 5(9.25%). The correlation of anti tTGs with duodenal mucosal damage is given in Table-III. It was seen that among 46 biopsy proven cases, 41 (89.13%) were having raised anti-tTGs, 5 with raised Anti-tTGs had nonspecific inflammatory changes and three with raised Anti-tTGs had normal histology of intestinal mucosa. It was also noted that five patients who had high levels of anti-tTGs (IgG and/or IgA >100 units/ml) were also having severe mucosal damage according to the Marsh criteria.

DISCUSSION

Small intestinal biopsy is the gold standard for the diagnosis of celiac disease but anti-tTGs(IgG, IgA) is a valuable screening test with high sensitivity and specificity, moreover, it may be used in monitoring the success of therapy with gluten free diet.[12] . In our study a total of 54 patients who had one or both the tests positive, were considered for the final analysis, 46 patients had histological changes according to the Marsh criteria and 49 had raised Anti-tTGs , raised antibodies assay have been observed in about 90% of the cases where histological evidence of celiac disease is present, which is comparable with the study done by Biagi F and colleagues.[13] There is a strong correlation between disease specific autoantibodies (Anti tTG's) level and severity of duodenal mucosal lesions in celiac disease, this correlation demonstrated in this study, suggests that antibodies may have a role in immunologic injury which has also been observed in another international study done by Pena AS, et al.[14]

In present study we noted 5 biopsy proven celiac disease cases, who were negative for anti tTG's, it is important to remember that a child in high risk group, whose serology is negative at initial screening may develop a positive serology subsequently if not treated . Similarly 03 of our patients with normal histology and 05 with non specific inflammatory changes (not consistent with celiac disease) were positive for anti tTG's (IgA, IgG). This finding may be explained on the basis of false positive results of anti-tTG's, insufficient biopsy bites / inappropriate site or latent / potential forms of celiac disease.[15,16]

In the clinical setting of celiac disease, presence of these antibodies (Anti tTG's, IgA, IgG) along with typical intestinal mucosal changes almost confirms the diagnosis of celiac disease, even before response to gluten free diet is available.[17] It is crucial that the diagnosis is made correctly, and a trial of gluten exclusion in suspected celiac disease patients, is not recommended without confirmation. We believe that Anti tTG's,(IgG & IgA) is a useful screening test in the diagnostic work-up of celiac disease and may be used in selecting the patients for duodenal biopsies.

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Authors Contribution:

Rabbani MW: Conceived, designed, did statistical analysis and editing of manuscript.
Aziz MT, Ali I, Khan WI: Did data collection, manuscript writing.
Ali Z, Aslam M: Review of manuscript.