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CELIAC DISEASE;

HISTOPATHOLOGICAL EVALUATION OF ENDOSCOPIC DUODENAL (D2) BIOPSIES IN PATIENTS

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ABSTRACT… Objective: To find out the Modified Marsh type of celiac disease (CD) patients on histopathological examination of duodenal (D2) biopsies and to correlate it with tissue transglutaminase IgA levels. **Study Design:** Cross sectional study. **Place of Study:** Histopathology laboratory (Department of Pathology), Isra University Hospital and Asian Institute of Medical Sciences (AIMS), Hyderabad. **Duration of Study:** July 2013 to December 2013. **Materials and Methods:** 96 patients with a history of malabsorption or atypical symptoms with clinical suspicion of CD were subjected to endoscopy. Endoscopic duodenal (D2) biopsies were taken regardless of age and gender. D2 biopsies were processed for histopathological examination under light microscopy. **Results:** Out of 96 patients, 45 (46.9%) patients had moderate type of lamina propria inflammation along with highly significant p-value (0.0001).CD type 3a was observed in 34 patients (35.4%). In this study the comparison of serological level of tissue Transglutaminase IgA (tTGA) and histological severity revealed significant correlation. All Modified Marsh types of CD with tTGA level seen in our study were highly significant (p-value 0.001). **Conclusion:** In this study strong correlation was observed between the serological tTGA level and histological findings by Modified Marsh classification along with lamina propria inflammation of duodenal mucosa in CD patients.

Key words: Celiac disease, Endoscopy, Modified Marsh Classification.

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INTRODUCTION

Celiac disease (CD) is one of the most common causes of intestinal malabsorption in childhood[1]. It is an immune-mediated enteropathy that develops after exposure to the dietary gluten[2]. This immune reaction is completely reversible upon gluten withdrawal[3]. Breast feeding reduces the risk of CD in early childhood and probably also during the subsequent childhood period[4].

The morphological features of CD (mucosal inflammation, crypt hyperplasia and atrophy of villi) manifest due to exposure to storage protein of wheat, rye and barley known as gluten, combination of gliadin and prolamine[5,6]. Complete avoiding of gluten from diet sets back the immune mediated inflammation[3].

First step in diagnosis of CD is serological testing based upon detection of highly specific and sensitive auto-antibodies, especially Immunoglobulin A (IgA) anti-endomysium antibodies (EMA) and IgA anti-tissue-transglutaminase antibodies (tTGA)[7]. Quantification of tTGA is a sensitive test for CD, however, CD can be confirmed by observation of biopsies taken from second part of duodenum (D2) through endoscope[8].

Finding of a raised Intestinal intraepithelial lymphocyte (IEL) count even with normal villous architecture is of great significance in routine D2 biopsy examination. Presence of 25 or more IELs/100ECs is sufficient for confirmation of CD, however increased IEL with villous atrophy and crypt hyperplasia is an established classical feature of CD[9]. CD is classified in various types (type 1 to type 3) based on histopathological findings on D2 biopsies examination. Presently the Marsh classification of CD is further modified by Oberhuber *et al (1999)[10] which is now widely used worldwide*[11].

Thus present study was designed to find out the patterns according to Modified Marsh

classification in patients presenting with features of CD and correlate it with the sensitive serum marker i-e: tissue transglutaminase IgA level.

MATERIALS AND METHODS

This is a cross sectional study conducted in the Histopathology laboratory (Department of Pathology), Isra University Hyderabad and Asian Institute of Medical Sciences (AIMS), Hyderabad from July 2013 to December 2013. Total of 96 duodenal biopsy samples with informed consents were obtained and study was approved by the Ethical Committee at Isra University, Hyderabad. Patients who had history of malabsorption and atypical symptoms with clinical suspicion of CD were selected regardless of age and gender.

Biopsy specimens from the distal duodenum (D2) with a minimum of three conventional forceps samples per patient were obtained by upper duodenoscopy. The histopathology slides were examined and results of villous atrophy were categorized according to the modified Marsh criteria. Briefly, Marsh 0 represents normal mucosa, Marsh 1 represents normal mucosa architecture with increased intraepithelial lymphocytes (30 intraepithelial lymphocytes/100 enterocytes), Marsh 2 represents additional crypt hyperplasia, Marsh 3a represents partial villous atrophy, Marsh 3b represents subtotal villous atrophy, and Marsh 3c represents total villous atrophy. Additionally slides were examined for lamina propria mononuclear inflammatory cell infiltrates such as; lymphocytes, mast cells, plasma cells, and eosinophils that grade as mild, moderate and severe inflammation.

Whole blood (03 ml) was collected in gel tube, after centrifugation (1500 rotation per minute) serum was separated and collected in separate aseptic tube for the measurement of tTGA level. The tTGA level was performed using the BioSystems Reagents and Instruments commercial kits.

All the data obtained was analyzed statistically by SPSS version 21. The frequencies of the variables were seen, Chi-square was applied to analyze the significance of the results. P-value of <0.05 was considered to be significant.

RESULTS

All types of Modified Marsh Classification (histological features) were seen in our patients. In this maximum number of patients, 34 (35.4%) had developed Type3a CD followed by type 3b CD in 28 (29.1%), type 3c CD in 14 (14.6%), type 2 CD in 9 (9.4%), type 1 CD in 6 (6.3%) and type 0 in 5 (5.2%) patients (Figure 1).

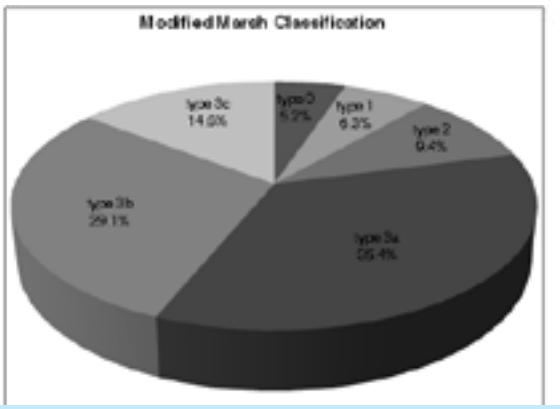

Figure-1. Frequency of celiac disease patients according to Modified Marsh classification

In duodenal (D2) biopsies we found the lamina propria inflammation in duodenal mucosa along with Modified Marsh classification. Out of 96 patients, 45 (46.9%) patients had moderate type of lamina propria inflammation and mean ± S.D of tTGA level of 63.66 ± 30.78 U/ml with lesser extent of mild lamina propria inflammation in 30 (31.3%) patients and severe inflammation of lamina propria in 21 (21.9%) patients. There was highly significant difference seen in this finding with p-value of 0.0001 ($p<0.05$). This correlates well with the increasing level of tTGA (Table I). Mean and standard deviation (Mean±S.D) of tTGA of the CD patients was 56.87 ± 38.66 U/ml with range between 2.0-186.94 U/ml (Table II).

In this study the comparison of serological level of tissue transglutaminase IgA and histological severity by Modified Marsh types revealed significant correlation with p-value of 0.001 (Table III). There is stipulation between the serological tTGA level and histological findings by Modified Marsh types along with lamina propria inflammation of duodenal mucosa in CD patients.

Lamina Propria Inflammation	Frequency (%)	tTGA (Mean ± S.D)	p-value
Moderate	45 (46.9)	63.66 ± 30.78	0.0001
Mild	30 (31.3)	24.51 ± 17.55	
Severe	21 (21.9)	112.76 ± 137.39	
Total	96 (100)	-----	

Table-I. Lamina propria inflammation of duodenal mucosa in Celiac Disease patients and correlation with tTGA level

tTGA IgA	
Mean ± S.D	56.87 ± 38.66
Range	2.0 - 186.94

Table-II. Descriptive statistics of tTGA in celiac disease patients

Lamina Propria Inflammation	Frequency (%)	tTGA (Mean ± S.D)	p-value
Type 0	5 (5.2)	4.58 ± 3.51	0.0001
Type 1	6 (6.3)	24.61 ± 19.68	
Type 2	9 (9.4)	14.26 ± 5.73	
Type 3a	34 (35.4)	57.78 ± 37.50	
Type 3b	28 (29.1)	91.87 ± 117.28	
Type 3c	14 (14.6)	80.88 ± 46.82	
Total	96 (100)	-----	

Table-III. Frequency of Modified Marsh classification and its correlation with tTGA level

DISCUSSION

Celiac disease is an immune-mediated enteropathy that develops after exposure to the dietary gluten[2]. This immune reaction is completely reversible upon gluten withdrawal[3]. The diagnosis of CD is based on Serologic analysis but histopathological evaluation is considered to be most reliable[8].

In this study correlation of all types of Modified Marsh classification of CD with tTGA levels was highly significant with p-value of 0.001. CD type 3a was observed in 35.4% patients followed by 29.1%, 14.6%, 9.4%, 6.3% and 5.2% cases showed type 3b, 3c, 2, 1 and 0 respectively. In contrast to our findings study by Dahele A et al 2001[12] showed less numbers of cases of CD type 3a. Brar P et al (2007) showed[13] that in duodenal biopsies the degree of villous atrophy did not show a relationship with the features of presentation.

Parizade M et al (2009)[14] found that Modified Marsh type 3a, 3b and 3c CD in 90.5% of cases in pediatric age group and also indicated association between Modified Marsh classification and anti-tTGA levels. The tTGA level was found to be most reliable test (91.4%) and cutoff point for tTGA level was 10 U/ml almost same as this results.

Study by Liu E et al (2003)[15] found correlation between TG antibody levels and results of the small intestinal biopsy and are consistent with results of this study. In this study mean and standard deviation (Mean±S.D) of tTGA of the CD patients was 56.87 ± 38.66 U/ml with range between 2.0-186.94 U/ml and the significant association is seen between the tTG-IgA with modified Marsh classification.

CONCLUSIONS

Serological level of tissue transglutaminase IgA and histological severity of CD type revealed significant correlation. In this study there is strong correlation between the serological tTGA level and histological findings by Modified Marsh classification along with lamina propria inflammation of duodenal mucosa in CD patients. This study also concludes that Modified Marsh type 3a of CD is the commonest type of CD in our population.

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