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An Observational Study of Serological and Histopathological Correlation of Celiac Disease in Pediatric Patients

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ABSTRACT

Celiac disease is an immune-mediated disorder caused by gluten intolerance, primarily affecting the gastrointestinal mucosa. Diagnosis involves serologic tests and biopsy, with a lifelong gluten-free diet as treatment. This study aimed to explore the correlation between histopathology and serology in pediatric celiac disease patients. The objectives were to study histopathology using Marsh criteria and to assess the correlation between tissue transglutaminase antibody (tTGA) levels and clinical presentation in pediatric patients. The study was a retro-prospective study of three years (January 2015- January 2016 and January 2021 -January 2023). Fifty cases were included, with biopsies graded according to the Oberhuber-modified Marsh criteria. Data on age, clinical features and tTGA levels were recorded and analyzed using SPSS software. The most common age group was 2.0-5.9 years, with a slight female preponderance (54%). Diarrhea was the most common clinical symptom. Serology showed that 78% of cases were tTGA-positive. Histopathologically, 42% had mild villous atrophy and 36% had moderate atrophy. tTGA levels significantly correlated with higher Marsh stages ($P<0.001$). TTGA levels showed a positive correlation with histopathological severity, aligning with Marsh-Oberhuber grading in pediatric celiac disease patients.

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Key Words
Celiac disease, pediatric age group, tissue transglutaminase antibody, villous atrophy, modified marsh staging

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INTRODUCTION

Celiac disease (CD) is an immunologically mediated inflammatory disease affecting gastrointestinal mucosa, attributed to intolerance to gliadin, a storage protein found incereals wheat, barley and rye, in genetically susceptible individuals. The other terms for the entity are beingceliac sprue, non tropical sprue, idiopathic sprue, idiopathic steatorrhoea or gluten sensitive enteropathy[1].

Genetic susceptibility to the cause is due to well-defined haplotypes in the human leukocyte antigen (HLA) class II region a complex interplay between genetic, environmental and immunological factors plays a crucial role in the pathogenesis of CD[1,2].

The autoimmunity involves plasma cells producing IgA and IgG., recent theories suggest that ingested a-gliadin (a component of the gluten protein) and related peptides bind with tissue transglutaminase (a ubiquitous intracellular enzyme) in enterocytes. The a-gliadin is rich in glutamine., transglutaminase deamidates glutamine residues, forming glutamic acid. Deamidation enhances the immunogenicity of a-gliadin by creating epitopes that are recognized as foreign by host cell-mediated immunity[3].

Celiac disease commonly presents in children, but in a minority of patients, it is first recognized in adolescents, adults or even in old age. It is presumed that these patients probably had the disorder from early life, but with minimal symptoms or silent disease., serologic tests for antibodies against endomysium, transglutaminase and gliadin identify most patients with the disease and must be considered in patients at increased genetic risk (with first degree relatives or with Type 1 Diabetes) along with classical symptoms[4]. The gold standard for diagnosis is duodenal biopsy to identify and stage enteropathy of CD and correlation of clinical, serologic and histological features is essential for a definitive diagnosis[5].

The anti-endomysial antibodies and anti-tissue transglutaminase antibodies have high sensitivity (85-100% and 95% respectively) and specificity (96-100% and 90% respectively)[6].

The histopathological features of celiac disease include or are as proximal small bowel involvement, decreasing distally, patchy distribution (in few cases), mucosal architectural changes(Villous atrophy, crypt hyperplasia, thickening of the basement membrane under the surface epithelium, reduced numbers of goblet cells, Mucosal inflammation, Increased intraepithelial lymphocytes Influx of immune cells in the lamina propria, Enterocyte changes(Cuboidal morphology, Loss of basal nuclear orientation, Cytoplasmic vacuoles)[7].

The diagnosis of celiac disease involves serologic testing (generally for IgA anti-tissue transglutaminase antibodies first) followed by upper endoscopy with biopsy for confirmation in most patients. Patients with celiac disease should follow a lifelong, strict gluten-free diet[8]. Because prevalence studies based only upon serology (tissue transglutaminase (TTG) and endomysial (EMA) antibodies) reported a higher prevalence than screening that requires confirmation through small intestinal biopsy[9].

Globally celiac diseases affect 1 in 100 to1 in 170 people and vary between different regions of the world from as few as 1 in 300 to as many as 1 in 40[8, 9] and it is believed that about 85% of people affected are undiagnosed[10,11].

A community-based study was done in Ludhiana, which estimated that the prevalence of Celiac disease in this city was at least 1 in 310 individuals[12]. There are regional variations in the prevalence of CD due to genetic and dietary factors, that is, the wheat-rice shift from the North to the South in India[13].

MATERIALS AND METHODS

The study was a retro-prospective study of three years (January 2015-January 2016 and January 2021 -January 2023), at KEM Hospital, Pune, after due approval from hospital ethics committee and included confirmed cases of celiac disease in children between 1-15 years of age who were further evaluated for correlation between histopathological findings (by modified Marsh criteria) and tissue transglutaminase level (Ttg).

Inclusion Criteria: New and old diagnosed cases of celiac disease, age between 1-15 years, children with known Ttg levels and clinical features are known, adequate well oriented duodenal biopsy.

Exclusion Criteria: Any patient with a history of bleeding diathesis or abnormal screening coagulogram, inadequate intestinal biopsy, patients whose tTG levels were not done and diagnosed cases of Celiac disease who were on gluten free diet. The sample size included 50 cases as per inclusion and exclusion criteria. Data was collected with respect to age, sex and site of biopsy along with histopathological report and matched with corresponding, registration number, histopathology lab number, date / month and year and sitewere collected from the Histopathology register and corresponding values of Serum tissue transglutaminase antibody (TtgA) levels were taken from reports outsourced to a NABL accredited laboratory. Blood samples in plain vials were used for estimation of Serumtissue transglutaminase antibody (TtgA) levels using enzyme linked immunosorbent assay (ELISA)and the results were evaluated as per following range in UNITS/ml: <20-negative, 20-30 weak positive and greater than 30-positive. Biopsy from duodenum was taken under general anaesthesia using

Table 1: The modified Marsh-Oberhuber classification[7]

	Marsh 0	Marsh 1	Marsh 2	Marsh 3a	Marsh 3b	Marsh 3c	Marsh 4
IEL count*	<30/100	>30/100	>30/100	>30/100	>30/100	>30/100	<30/100
Crypt Hyperplasia	-	-	+	+		+	+-
Villous atrophy	-	-		-	Mild	Moderate	TotalTotal
Type of lesion	Pre-infiltrative	infiltrative	Infiltrative-hyperplastic	Flat destructive	Flat destructive	Flat destructive	Atrophic-hypoplastic

IEL, intraepithelial lymphocytes.
*Number of intraepithelial lymphocytes per 100 enterocytes.
†This category is principally included for historical purposes.

fibreoptic endoscope and were routinely processed and stained with hematoxylin and eosin, for histopathological evaluation and were garded according to the modified Marsh-Oberhuber classification[7]. All data were analysed using software called PS: power and sample size calculation.

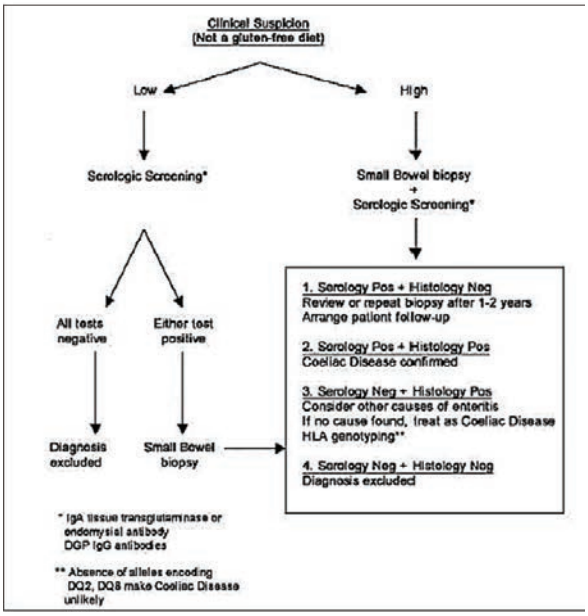

Fig. 1: The Following Algorithmwas used for Diagnoses of Celiac Disease

Observations: Themajority of cases had their age between 2.0-5.9 years (48.0%, 24 cases) followed by the age group 6.0-9.0 (22.0%,11 cases). Only 6 cases had their age below 2.0 year (12.0%) and 9 cases had their age between 10.0-13.09 years (18.0%). Sex wise there was only slight female preponderance (27 cases, 54%) over males. As per clinical sign and symptoms, of 50 cases studied, 40 cases (80.0%) had diarrhoea, 29 (58.0%) had chronic abdominal pain and 37 (74.0%) complained of failure to gain weight.

Of 50 cases studied, majority of cases studied (78.0%) had Positive tTGA, only 1 cases (2.0%) had weak positive tTGA and 10 cases (20.0%) had negative tTGA. Of 50 cases studied, 1 (2.0%) had Type 1 MARSH staging, 5 (10.0%) had Type 2 MARSH staging, the majority of cases i.e. 21 cases (42.0%) had Type 3a MARSH staging, 18 (36.0%) had Type 3b MARSH staging and 5 cases (10.0%) had Type 3c MARSH staging. (Figure 1, 2)

Table 2: Distribution of Average tTGA according to MARSH Staging among the Cases Studied with Celiac Disease (n=50)

	tTGA (U/mL)		
MARSH Staging	Median	Minimum-Maximum	p-value
Type 1 (n=1)	7.00	7.00-7.00	0.001***
Type 2 (n=5)	14.41	5.02-79.00	
Type 3a (n=21)	100.00	5.74-180.00	
Type 3b (n=18)	155.00	3.00-300.00	
Type 3c (n=5)	250.00	200.00-300.00	

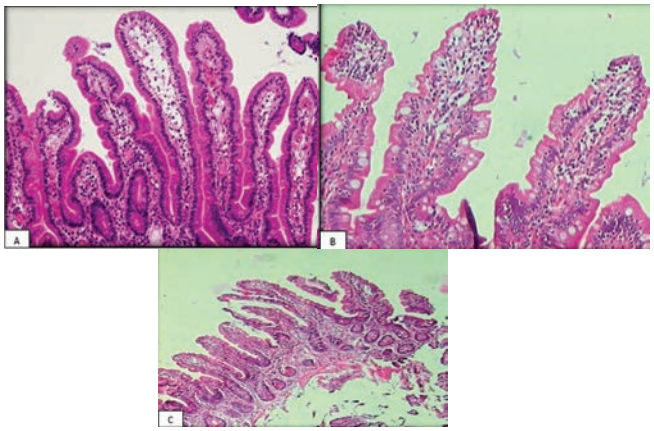

Fig 2: A) Normal duodenal mucosa. B) Grade 1, IEL >30(H and E 10X). C. Grade 2 IEL>30 with crypt hyperplasia (H and E 4X), Grade as per Marsh-Oberhuber classification, IEL: Intra-epithelial lymphocytes H and E: Hematoxylinand Eosin stain

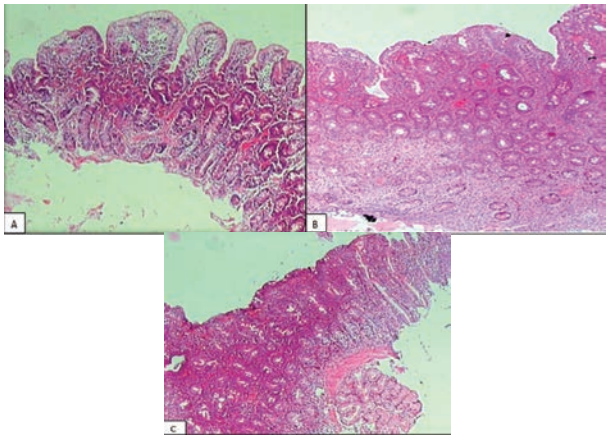

Fig 3: A) Grade 3a IEl>30, Crypt Hyperplasia, Mild Villous Atropy (H and E 4X). B) Grade 3b, crypt hyperplasia, moderate villous atrophy (H and E 4X) C) Grade 3c crypt hyperplasia, severe villous atrophy (H and E 4X), Grade as per Marsh-Oberhuber classification IEL: Intra-epithelial lymphocytes H and E: Hematoxylin and Eosin stain

Values are n (%of cases). Values are Median (Min-Max), P-value by Kruskal Wallis H test (Non-parametric analysis of variance test). P-value<0.05 is considered to be statistically significant. ***P-value<0.001. The average tTGA is significantly higher among the cases with higher MARSH staging than the cases with lower MARSH staging (P-value<0.001). The average tTGA significantly increases with the increase in MARSH staging (P-value<0.001).

RESULTS AND DISCUSSION

In our study majority patients belongs to age group 2-5.9yrs (48%), followed by age group 6-9yrs. (22%). Similar findings were seen in the study by Poddar *et al.,* in which the mean age at diagnosis was 2.6±6.3 years[2]. In another study it was found that celiac disease was more common in school going children, mean age being 9.5 years[14] where as Fasano *et al.* stated that CD can develop at any age, there is no predilection to specific age group[8]. The early presentation and diagnoses in our study could be attributed to introduction of gluten inclusive diet at or after the age of six months when infants are weaned from exclusive breast milk diet and increased awareness among paediatricians for possible celiac disease and along with availability of modern diagnostic techniques of endoscopy, serology and histopathology.

In our study we found cases of celiac disease more to be in females as compared to males (54Vs 46%) and this was in concordance with previous studies[15,16]. However, in the study of Poddar *et al.* male to female ratio was 3:2 whereas Hosein *et al.* stated that there was no significant correlationbetween celiac disease and sex ratio as it is a chronic and lifelong disease[2,17]. The preponderance of females in our study on pediatric population can be attributed to genetic makeup leading to increased susceptibility and symptoms ofceliac disease in females, an area requiring further studies.

In our study the most common clinical feature was diarrhoea (80%) followed by failure to gain weight (74%) and chronic abdominal pain (58%) and was similar to that documented in previous studies in paediatric population (children <3 years) and in older children[18,19].

Of 50 cases studied, the majority of cases studied (78.0%) had Positive tTGA, only 1 case (2.0%) had weak positive tTGA and 10 cases (20.0%) had negative Ttga. Previous studies on serological testing of tTGA have established the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of tTGA as 96.9, 91.0, 91.2, 96.8 and 97.7 respectively[20]. The positivity in our case was 79% which was lower than documented and thus it reiterated the fact that histopathology (Intestinal biopsy) remains the gold standard for diagnosis of celiac disease[21].

In our study, type 3a grading (42%) was the commonest followed by 3b(36%) and 3c(10%) as in concordance with findings of a previous studyby Wang et al. who also found grade 3 as the commonest histopathological grading as per MarshOberhuber classification. The most probable reason is avoidance of biopsy as it is an invasive and knowledge-intensive procedure, requiring specialized centersand by the time patient reported to such facilities the diseases had already progressed due to lack of therapeutic intervention[22].

Another significant finding was that as the severity of Marsh Oberhube grading increased, the average tTGA levels also increased. This was in concordance with previous studies which reported a positive correlation between measured levels of tTGA with severity of Celiac disease as per histopathology[23-25].

CONCLUSION

Celiac disease is quite common in pediatric population with slight predilection for females. The diagnoses include clinical sign and symptoms, serological tests and histopathological evaluation of intestinal biopsies, the last being the gold standard. Levels of tissue Transglutaminase antibody can be used as surrogate marker for severity of disease, in settings where histopathological evaluation is not possible.

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