# Correlation between Clinical Symptoms of Coeliac Disease, Serum IgA Anti TTG and Biopsy in Pediatric Population of Northern India

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## Abstract

**Background:** Celiac disease is basically an immune-mediated enteropathic condition produced by permanent sensitivity to gluten in genetically susceptible subjects. There is paucity of data in north India regarding clinical symptoms of coeliac disease, Serum IgA Anti TTG and Biopsy in pediatric population. The present study was conducted with the aim to determine the correlation between clinical symptoms of coeliac disease, Serum IgA Anti TTG and Biopsy in pediatric population of northern India. **Materials and Methods:** The present study was conducted in prospective including 73 pediatric patients at Department of Pediatric Gastroenterology, Institute of Child Health, Sir Gangaram Hospital, New Delhi, India. Esophagogastroduodenoendoscopy and serum anti Ig A tissue transglutaminase were performed. The characteristic scalloping of the folds were looked for in endoscopy followed by four duodenal biopsies performed from second part of duodenum and histological grading was performed as per modified marsh system. Patients with Serum IgA anti tTG>20 U/ml were confirmed to be at risk. Complete histological work up was done including hemoglobin, RBC indices and peripheral blood smear examination. The association of clinical manifestations with disease grade was also established with correlation coefficient. All the data thus obtained was arranged in a tabulated form and analyzed using SPSS software. Probability value of less than 0.05 was regarded as significant. **Results:** There were 4 males and 16 females with marsh grade 1 and 2 and mean age of $7.3\pm1.9$ years. There were 5 males and 8 females with marsh grade 3a and mean age of $6.8\pm2.3$ years. The mean weight of $18.11\pm3.89$, height of $103.17\pm8.73$ and BMI of $16.26\pm3.78$ was observed amongst subjects with Marsh grade 1 and 2. The mean weight of $15.12\pm3.17$, height of $99.28\pm9.19$ and BMI of $15.02\pm3.20$was observed amongst subjects with Marsh grade 3a. Diarrhoea was maximum amongst subjects with grade 3c and 4(70%) and minimum amongst Grade 1 and 2 (40%). There was a significant difference between the frequency of anemia amongst different grades as the p value was less than 0.05. **Conclusion:** The most common presenting signs and symptoms were diarrhea and abdominal pain. The study also concluded that the incidence of anemia increases with higher marsh grades.

**Keywords:** Anemia, Celiac, Prospective, Marsh.

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## Introduction

Celiac disease is basically an immune-mediated enteropathic condition produced by permanent sensitivity to gluten in genetically susceptible subjects.[1] Initially it was regarded as malabsorption syndrome of younger ages but is now identified as a common disease that can be seen at any age group. The overall incidence of celiac disease in North India is approximately 1.04%.[2] Clinical signs and symptoms vary vividly, classical celiac disease presents with diarrhea, steatorrhoea, loss of weight, while non-classical celiac disease presents with anemia, osteoporosis, osteopenia, steatosis, increased liver enzymes and aphthous stomatitis.[3] Recent indications have debated on the practice of performing duodenal biopsies amongst all subjects testing positive for anti-tissue trans glutaminase antibodies and a hypothesis was advised that biopsy could be avoided amongst patients with increased titers of serum antibody levels.[4-7] As per European Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines published in 2019 have recommended that The no-biopsy approach for CD diagnosis is safe in children with high TGA-IgA values ($\geq$10 times the upper limit of normal) with appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample. Children with positive TGA-IgA but lower titers (<10 times upper limit of normal) should undergo biopsies to decrease the risk of false positive diagnosis. HLA testing and presence of symptoms are not obligatory criteria for a serology based diagnosis without biopsies. There is paucity of data in north India regarding clinical symptoms of coeliac disease, Serum IgA Anti TTG and Biopsy in pediatric population. The present study was conducted with the aim to determine the correlation between clinical symptoms of coeliac disease, Serum IgA Anti TTG and Biopsy in pediatric population of northern India.

## Subjects and Methods

The present study was conducted in prospective including 73 pediatric patients at Department of Pediatric Gastroenterology, Institute of Child Health, Sir Gangaram Hospital, New Delhi, India. The study was approved by the institutional ethical board and all the subjects were informed about the study and a written consent was obtained form them in their vernacular language. A total of 73 subjects with suspected malabsorption syndrome were examined in this study. Pediatric patients (age-1-15 years) with following symptom groups: gastrointestinal symptoms ( diarrhea, Constipation, vomiting, pain abdomen and abdominal distention) and extra intestinal manifestations ( anemia, short stature and type I diabetes mellitus) were enrolled. Three siblings of confirmed patients were also enrolled. Complete history and clinical examination were done. Esophagogastroduodenoendoscopy and serum anti Ig A tissue transglutaminase were performed. The characteristic scalloping of the folds were looked for in endoscopy followed by four duodenal biopsies performed from second part of duodenum and histological grading was performed as per modified marsh system (Table 1A). Serum IgA Anti tTG

levels were performed by enzyme linked immunosorbent assay (ELISA).Patients with Serum IgA anti tTG>20 U/ml were confirmed to be at risk. Complete histological work up was done including hemoglobin, RBC indices and peripheral blood smear examination. The association of clinical manifestations with disease grade was also established with correlation coefficient. All the data thus obtained was arranged in a tabulated form and analyzed using SPSS software. Probability value of less than 0.05 was regarded as significant.

## Results

The The study enrolled a total of 73 patients. Table 1 shows the gender and age distribution according to Marsh grade. There were 4 males and 16 females with marsh grade 1 and 2 and mean age of 7.3±1.9 years. There were 5 males and 8 females with marsh grade 3a and mean age of 6.8±2.3 years. There were 12 males and 8 females with marsh grade 3b and mean age of 7.1±1.7 years. There were 9 males and 11 females with marsh grade 3c and 4 and mean age of 6.9±2.2 years. There was no significant difference between the gender distribution and marsh scale.

**Table 1a: Marsh Grading**

| Marsh grade | Histological features |
|---|---|
| 0 | Normal mucosa |
| 1 | Increased number of intraepithelial lymphocytes, usually exceeding 30 per 100 enterocytes |
| 2 | Perforation of cysts of liberkuhn |
| 3 | Variable villous atrophy |
| 3a | Partial villous atrophy |
| 3b | Subtotal villous atrophy |
| 3c | Total villous atrophy |
| 4 | Hypoplasia of small bowel architecture |

**Table 1: Gender and age distribution according to Marsh grade**

| Parameters | Marsh Grade | | | | p value |
|---|---|---|---|---|---|
| | 1+2 (N=20) | 3a (N=13) | 3b (N=20) | 3c+4 (N=20) | |
| Male (N, %) | 4 (20) | 5 (38.46) | 12 (60) | 9 (45) | 0.23 |
| Female (N, %) | 16 (80) | 8 (61.54) | 8 (40) | 11 (55) | |
| Age in years (Mean±SD) | 7.3±1.9 | 6.8±2.3 | 7.1±1.7 | 6.9±2.2 | 0.67 |

**Table 2: Weight, height and BMI according to Marsh grade**

| Parameters | Marsh Grade | | | | p value |
|---|---|---|---|---|---|
| | 1+2 (N=20) | 3a (N=13) | 3b (N=20) | 3c+4 (N=20) | |
| Weight (Mean ± SD) | 18.11±3.89 | 15.12±3.17 | 14.67±3.40 | 14.08±2.9 | 0.03* |
| Height (Mean ± SD) | 103.17±8.73 | 99.28±9.19 | 97.09±10.12 | 95.29±10.58 | 0.04* |
| BMI (Mean ± SD) | 16.26±3.78 | 15.02±3.20 | 14.71±2.97 | 14.08±3.14 | 0.02* |

*: statistically significant

**Table 3: Abdominal and other symptoms according to Marsh grade**

| Parameters | Marsh Grade | | | | p value |
|---|---|---|---|---|---|
| | 1+2 (N=20) | 3a (N=13) | 3b (N=20) | 3c+4 (N=20) | |
| Diarrohea (N, %) | 8 (40) | 7 (53.85) | 12 (60) | 14 (70) | 0.04* |
| Vomiting (N, %) | 7 (35) | 5 (38.46) | 9 (45) | 10 (50) | 0.07 |
| Pain Abdomen (N, %) | 7 (35) | 6 (46.15) | 11 (55) | 13 (65) | 0.06 |
| Abdominal Distension (N, %) | 2 (10) | 5 (38.46) | 8 (40) | 9 (45) | 0.04* |
| Constipation (N, %) | 2 (10) | 4 (30.77) | 6 (30) | 9 (45) | 0.08 |
| Not gaining weight (N, %) | 13 (65) | 10 (76.92) | 18 (90) | 20 (100) | 0.03* |

*: statistically significant

**Table 4: Anorexia and anemia according to Marsh grade**

| Parameters | Marsh Grade | | | | p value |
|---|---|---|---|---|---|
| | 1+2 (N=20) | 3a (N=13) | 3b (N=20) | 3c+4 (N=20) | |
| Anorexia (N, %) | 2 (10) | 4 (30.77) | 6 (30) | 9 (45) | 0.08 |
| Anemia (N, %) | 5 (25) | 4 (30.77) | 13 (65) | 14 (70) | 0.01* |

*: statistically significant

**Table 5: Mean serum IgA anti TTG levels according to Modified Marsh Grade**

| Modified Marsh Grade | N | Mean | SD |
|---|---|---|---|
| 1+2 | 20 | 28.55 | 7.13 |
| 3a | 13 | 39.00 | 11.51 |
| 3b | 20 | 53.80 | 15.50 |
| 3c+4 | 20 | 84.00 | 8.49 |
| ANOVA test | | 47.35 | |
| p value | | <0.01* | |

*: statistically significant

[Table 2] illustrates the weight, height and BMI according to Marsh grade. The mean weight of 18.11±3.89, height of 103.17±8.73 and BMI of 16.26±3.78 was observed amongst subjects with Marsh grade 1 and 2. The mean weight of 15.12±3.17, height of 99.28±9.19 and BMI of 15.02±3.20was observed amongst subjects with Marsh grade 3a. The mean weight of 14.67±3.40, height of 97.09±10.12 and BMI of 14.71±2.97 was observed amongst subjects with Marsh grade 3b. The mean weight of 14.08±2.9, height of 95.29±10.58 and BMI of 14.08±3.14 was observed amongst subjects with Marsh grade 3c and 4. There was a statistically significant difference in weight, height and BMI amongst different Marsh grades.

Table 3 shows the Abdominal and other symptoms according to Marsh grade. Diarrhoea was maximum amongst subjects with grade 3c and 4(70%) and minimum amongst Grade 1 and 2 (40%). There was a significant difference in the incidence of diarrhea amongst different grades. No significant difference was observed in vomiting and abdominal pain amongst all the grades. There were 45% subjects with grade 3c and 4 and 40% with grade 3b and 10% with grade 1 and 2 having abdominal distention, indicating significant difference between the grades.

Table 4 shows the incidence of Anorexia and anemia according to Marsh grade. Anorexia was observed amongst 10% patients with grade 1 and 2, 30.77% patients with grade 3a, 30% patients with grade 3b and 45% patients with grade 3c and 4. There was no significant difference between the frequency of anorexia amongst different grades as the p value was more than 0.05. Anemia was observed amongst 25% patients with grade 1 and 2, 30.77% patients with grade 3a, 65% patients with grade 3b and 70% patients with grade 3c and 4. There was a significant difference between the frequency of anemia amongst different grades as the p value was less than 0.05. Table 5 shows Mean serum IgA anti TTG levels according to Modified Marsh Grade.

## Discussion

Malabsorption is a disorder that is considered by defective absorption of fats, carbohydrates, proteins, and vitamins, electrolytes and minerals. Celiac disorder is regarded as one of the most frequent reasons of malabsorption.[8] In 2013, Oslo told that Celiac diseases are a chronic small intestinal immunologically-mediated enteropathy that is initiated in genetically predisposed patients due to exposure to dietary gluten.[9] Celiac disease, also known as gluten-sensitive enteropathy, non-tropical sprue and endemic sprue. It is basically a autoimmune condition that is triggered by the ingesting wheat gluten and associated proteins of barley and rye amongst genetically susceptible populace.[10] Well-identified prototypes amongst human leukocyte antigen class II region such as HLA-DQ8 and HLA-DQ2 produce this genetic susceptibility.[11] The incidence of having Celiac disorder is more amongst first-degree relatives (10%) and is 5% amongst second-degree relatives, also amongst people with autoimmune conditions, diabetes, Down's syndrome and several other related conditions.[12] A certain diagnosis of Celiac condition is dependent on histological alterations, like intraepithelial lymphocytosis, hyperplasia, and varying frequency of villous atrophy, that are graded as per a classification system given by Marsh in 1992 and now extensively used as a modification of Marsh grading.[13-16] Duodenal biopsy is the gold standard for detecting Celiac disease, even with the presence of very specific serologic tests Such as anti-gluten and anti-tissue transglutaminase antibodies. Association of clinical, serologic, and histological outcomes are crucial for the definitive diagnosis of this disease.[17] As per the present study, there were 4 males and 16 females with marsh grade 1 and 2 and mean age of 7.3±1.9 years. There were 5 males and 8 females with marsh grade 3a and mean age of 6.8±2.3 years. There were 12 males and 8 females with marsh grade 3b and mean age of 7.1±1.7 years. There were 9 males and 11 females with marsh grade 3c and 4 and mean age of 6.9±2.2 years. There was no significant difference between the gender distribution and marsh scale. The mean weight of 18.11±3.89, height of 103.17±8.73 and BMI of 16.26±3.78 was observed amongst subjects with Marsh grade 1 and 2. The mean weight of 15.12±3.17, height of 99.28±9.19 and BMI of 15.02±3.20was observed amongst subjects with Marsh grade 3a. The mean weight of 14.67±3.40, height of

97.09±10.12 and BMI of 14.71±2.97 was observed amongst subjects with Marsh grade 3b. The mean weight of 14.08±2.9, height of 95.29±10.58 and BMI of 14.08±3.14 was observed amongst subjects with Marsh grade 3c and 4. There was a statistically significant difference in weight, height and BMI amongst different Marsh grades. Diarrhoea was maximum amongst subjects with grade 3c and 4(70%) and minimum amongst Grade 1 and 2 (40%). There was a significant difference in the incidence of diarrhea amongst different grades. No significant difference was observed in vomiting and abdominal pain amongst all the grades. There were 45% subjects with grade 3c and 4 and 40% with grade 3b and 10% with grade 1 and 2 having abdominal distention, indicating significant difference between the grades. Anorexia was observed amongst 10% patients with grade 1 and 2, 30.77% patients with grade 3a, 30% patients with grade 3b and 45% patients with grade 3c and 4. There was no significant difference between the frequency of anorexia amongst different grades as the p value was more than 0.05. Anemia was observed amongst 25% patients with grade 1 and 2, 30.77% patients with grade 3a, 65% patients with grade 3b and 70% patients with grade 3c and 4. There was a significant difference between the frequency of anemia amongst different grades as the p value was less than 0.05. Past studies have also demonstrated female predominance.[18-20] Anti-tTG levels in grades 3c+4 were maximum in all grades.[19] As per Rahmati A et al, who examined 159 subjects also demonstrated an elevated trend in mean tTG antibody levels from normal.[18] As per the study by Vivas S et al, amongst 97 children and 227 adults also observed that the mean tTG antibody titer showed a progressive elevation with increasing Marsh grades amongst both pediatric and adults. The level of tTG antibody was also correlating significantly with different Marsh types in the complete population.[21]

## Conclusion

The incidence of celiac disease was more amongst females than males. The most common presenting signs and symptoms were diarrhea and abdominal pain. The study also concluded that the incidence of anemia increases with higher marsh grades.

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