

# The Presentation Pattern of Celiac Disease in Central India – A Prospective Study in Children

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## ABSTRACT

**Introduction:** Celiac disease is a common immune-mediated enteropathy characterised by villous atrophy. It has clinical phenotypes of classic, non-gastrointestinal and silent / subclinical or potential depending on the clinical phenotype. We intended to assess the clinical features and laboratory findings of patients with celiac disease and compare the classical celiac disease with non-gastrointestinal celiac disease.

**Methods:** This is a two-year cross-sectional study conducted at our institute. Children from one year to 18 years diagnosed as celiac disease based on the revised ESPGHAN criteria were enrolled. They were categorised into classical celiac disease and non-gastrointestinal celiac disease (atypical) and their clinical features and laboratory findings were documented.

**Results:** Forty patients had confirmed celiac disease. The mean age of the subjects was  $6.84 \pm 4.41$  years, with male : female ratio of 1.85. The commonest presentations were failure to thrive (75%), anaemia (70%), associated rickets (67.5%) and 32% diarrhoea. Patients with classical features were identified at an earlier age than those with non-gastrointestinal celiac disease. Marsh grade 3a and above were more commonly seen in classical celiac disease. The most common symptom among the classical group was abdominal distension. Among the non-gastrointestinal group, the most common symptom was anaemia. Vitamin D deficiency was almost equally present in both groups.

**Conclusions:** Non-gastrointestinal celiac disease is not uncommon among our population. Patients with clinical features of recurrent abdominal pain, vomiting, failure to thrive, or merely short stature and refractory anaemia should be worked up for celiac disease.

**Keywords:** Biopsy; Celiac disease; Diarrhoea; Serum tissue Transglutaminase antibodies



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## INTRODUCTION

Celiac disease (CD) is a common genetically related food intolerance to dietary gluten and other related proteins, which are a component of wheat, rye, and barley. It is an immune-mediated enteropathy characterised by a variable degree of damage to small intestinal mucosa leading to villous atrophy and flattening in genetically susceptible individuals.<sup>1</sup> The current prevalence of paediatric celiac disease is estimated to be around 1% in the general population worldwide.<sup>2</sup> However, there has been great variability in its prevalence according to the geographic area. In a study conducted in the year 2018 by Singh P et al., it has been suggested that the pooled global seroprevalence of CD was 1.4% whereas biopsy-confirmed CD was 0.7%.<sup>3</sup> Celiac disease has a broad clinical spectrum categorised as classic, non-gastrointestinal, silent / subclinical or potential depending on the clinical phenotype. In classical CD, the patient presents with features of malabsorption such as diarrhoea, abdominal distension, steatorrhea, weight loss, or growth failure. In non-gastrointestinal CD, patients have few or no gastrointestinal symptoms. They have predominantly extra-intestinal symptoms such as anaemia, short stature, rickets, failure to thrive, and recurrent oral ulcers.<sup>4-6</sup> In subclinical CD, the disease is below the threshold of clinical detection without symptoms or signs. In potential CD, the patient has an abnormal antibody test but normal intestinal histology.

It has been observed that many cases of CD remain undiagnosed until they present with severe complications in adulthood.<sup>7</sup> Typically, the inflammation in CD includes an increased intraepithelial lymphocyte (IEL) count, most often > 25/100 cells. Another feature of CD is that it incorporates an adaptive T-cell-mediated response (to gluten) and it occurs in people who are DQ2 and DQ8 positive.<sup>8</sup> Increasingly, the presence of specific endomysial antibodies (EMA), anti-tissue transglutaminase antibodies (TGA), and / or deamidated antigliadin antibodies (DGP) plays an important role in the serological work-up for CD. These antibodies strongly support the diagnosis of CD. For initial testing, the combination of total IgA and TGA-IgA antibodies is recommended. With

high TGA-IgA values > 10 times, the upper limit of normal and a positive EMA-IgA in a second serum sample a confirmatory diagnosis of CD can be made. However low titers (< 10 times upper limit of normal) of TGA-IgA antibodies should undergo biopsies for diagnosis according to revised ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) criteria.<sup>9</sup> The study aimed to assess the clinical spectrum and laboratory findings in paediatric patients with biopsy-proven celiac disease. We compared these features among classical celiac disease and the non-gastrointestinal celiac disease in our population.

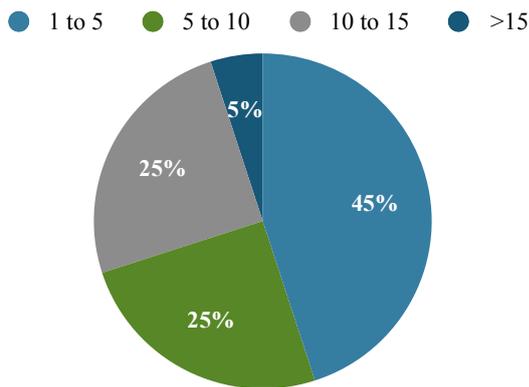
## METHODS

This is a two-year cross-sectional study conducted at SGT Medical College, Haryana, India from July 2017 to June 2019. Children of age from one year to 18 years of either gender diagnosed as celiac disease were enrolled into the study. All children with TGA-IgA levels > 10 U/ml with a normal total IgA levels underwent upper GI endoscopy with four biopsies from distal duodenum and one from the bulb during a gluten-containing diet. The information recorded for analysis included age, gender, clinical presentation, serological marker (IgA-TTG) levels, small intestinal mucosal biopsy interpretation using Marsh grading, haemoglobin, serum vitamin D levels, and radiological evaluation of wrist for features of rickets.

The data was compiled, entered, and analysed using Epi info version 7.2. The qualitative variables were expressed in terms of proportions and to test the difference between two proportions, chi-square or Fisher exact test was used. The quantitative variables were expressed in terms of mean and standard deviation. To test the difference between the two means, student t-test was used. All analysis was two-tailed and the significance level was set at 0.05. All patients were enrolled in the study after taking informed consent from parents / guardians. Approval was taken from the Institutional Ethical Committee before initiation of the study.

## RESULTS

A total of 40 patients had confirmed celiac disease according to the inclusion criteria. The mean age of



**Figure 1.** Pie chart showing the distribution of the study subjects based on age group (years)

the subjects was  $6.84 \pm 4.41$  years with an age range of a minimum of one year and maximum of 16 years. Most common age group was between one to five years followed by five to 10 years (Figure 1).

Male to female ratio was 1.85. The most common chief complaint was failure to thrive (75%) whereas around 32% of patients had diarrhoea at the time of presentation (Figure 2). It was also seen that patients with classical features were identified at an earlier age. The non-gastrointestinal celiac disease had an extended duration of symptoms prior to diagnosis as shown in Table 1.

Abdominal distension, failure to thrive, oral ulcers, short stature, and vomiting were significantly

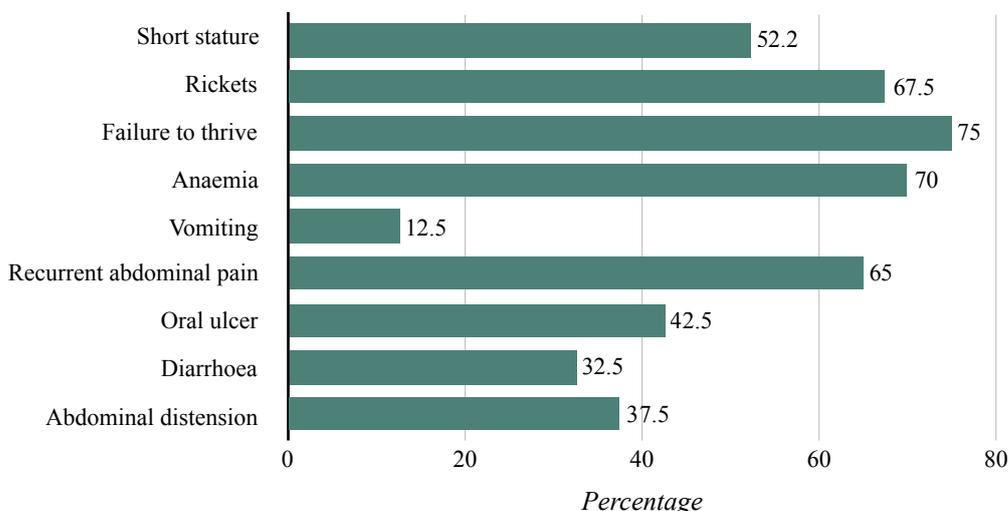
higher among the classical group when compared with the non-gastrointestinal group as shown in Table 2. Short stature can be the only presentation of celiac disease.

Marsh grade 3a and above were more commonly seen in classical celiac disease. The most common grading noticed among the study subjects was 3c grade (47.50%). As the grade increased, the proportion of classical celiac disease increased significantly ( $p < 0.05$ ) as shown in Table 3.

The laboratory parameters suggested that vitamin D deficiency and low haemoglobin was almost equally present in both the groups as there was no significant difference in their levels in both the groups.

### DISCUSSION

Celiac disease, a common disorder in children traditionally presents between the age of six months and 24 months with classical symptoms.<sup>10</sup> However as our study demonstrates, it is not limited to that particular age group. The mean age group was  $6.84 \pm 4.41$  years. It is evident in many series that patients with classical presentation were identified at an earlier age. This was corroborated in our study too. Similarly, the age of appearance of symptoms and diagnosis was significantly higher in non-gastrointestinal celiac disease. A similar study conducted by Mohindra et al. also suggested delayed recognition of disease.<sup>11</sup> The sex ratio in



**Figure 2.** Distribution of the study subjects based on chief complaints and other associated diseases (n=40)

**Table 1.** Comparison between the classical and non-gastrointestinal type of celiac disease based on demographic factors

Factors	Classical (n = 13)		Non gastrointestinal (n = 27)		p-value
	Mean	SD	Mean	SD	
Age	3.39	1.74	8.50	4.37	0.0002

between male to female in our study was 1.8, which was in line with previous studies stating higher prevalence among males than females as suggested by Altwaty and Elbargathy et al. and Sharma et al.<sup>12,13</sup> Surprisingly, many studies conducted in other countries have shown to have female preponderance more than males.

Children with CD can present with a wide spectrum of manifestations. Our study has also demonstrated the same. Beside common GI symptoms like diarrhoea, pain abdomen, abdominal bloating etc this study has shown that even short stature, rickets or anaemia may be the presentation of celiac disease. We have found that both classical and non-gastrointestinal types are seen, the latter being more common among our population. According to Ludvigsson et al, the main clinical presentation of celiac disease in the paediatric population included persistent diarrhoea.<sup>14</sup> Mohindra et al. also observed that diarrhoea, abdominal distension, and abdominal pain are the main clinical manifestations of celiac disease in their study.<sup>11</sup> On the contrary, a higher proportion of cases (20 - 40%) did not have diarrhoea in CD among western studies.

The most common symptoms among the classical group were abdominal distension, failure to thrive, oral ulcers, and anaemia. Danish Abdul et al. and Dinler et al. also reported abdominal distension as a predominant feature in patients with classical celiac disease.<sup>15,16</sup> A study conducted by Letizia et al. showed that 43% of patients experienced only recurrent abdominal pain.<sup>17</sup> In our study, 63% of patients had recurrent abdominal pain as the manifestation of CD in non-gastrointestinal celiac disease and 69% of patients in the classical group. In our experience, all patients in the classical group had failure to thrive whereas only 63% of patients in the non-gastrointestinal group had failure to

**Table 2.** Comparison between the classical and non-gastrointestinal type of celiac disease based on signs and symptoms

Factors	Classical (n = 13)		Non gastrointestinal (n = 27)		p-value
	Value	%	Value	%	
Abdominal distension	13	100.00	2	7.41	<0.001
Anemia	10	76.92	18	66.67	0.5073
Failure to thrive	13	100.00	17	62.96	0.0163
Oral ulcer	12	92.31	5	18.52	<0.001
Recurrent abdominal pain	9	69.23	17	62.96	0.6790
Rickets	9	69.23	18	66.67	0.8771
Short stature	3	23.08	18	66.67	0.0097
Vomiting	5	38.46	0	0	0.0005

thrive. This is quite similar to Aziz S et al. where around 61% of patients had failure to thrive.<sup>18</sup>

Among the non-gastrointestinal group the most common symptoms of CD were anaemia, short stature, and rickets (67%). It is seen that short stature can be the only presentation of CD. Hence many studies recommend screening for CD among children with short stature, especially in severely stunted children. Sherwani RK et al. also observed pallor in all of the study subjects while Misha Khalid et al. showed 67% of patients with non-gastrointestinal celiac disease presented with anaemia.<sup>15,19</sup> Most of the patients in our study had Marsh grade 3 lesion, the most common being 3c (total villous atrophy). This was similar to a study done by Saeed et al. Topal et al. found that 52% of patients with celiac disease had vitamin D deficiency at the time of presentation.<sup>20</sup> In our study serum vitamin D and haemoglobin levels were deficient equally in both the groups. Hence an initial screening is required in all patients with CD.

Our study has tried to highlight that the general prevalence of CD might be more, even in our population. The varied presentation of CD should always be kept in mind while evaluating children. Although it is a gastrointestinal disease, the presentation might involve other systems besides

**Table 3.** Comparison between the classical and non-gastrointestinal type of celiac disease based on Marsh grading

Marsh Grading	Classical (n = 13)		Non gastrointestinal (n = 27)		P-value
	Value	%	Value	%	
2	0	0	7	25.93	0.0421
3a	2	15.38	5	18.52	
3b	2	15.38	5	18.52	
3c	9	69.23	10	37.04	

gastrointestinal. Our study is a limited study conducted in a single centre with relatively lesser number of study subjects. Thus, it is difficult to extrapolate our findings to the general population of our country. Hence, our findings should be further analysed with larger multi-centric studies.

## CONCLUSIONS

Children with CD can present with a wide spectrum of manifestations. Both classical and non-

gastrointestinal types are seen, the latter being more common among our population. Around 70% of patients did not have diarrhoea at the time of the presentation. It was also seen that patients with classical symptoms were diagnosed earlier in the course of the disease. Hence patients presenting with features of recurrent abdominal pain, vomiting, failure to thrive, or merely short stature and refractory anaemia should prompt physicians to think and investigate for celiac disease to avoid complications associated with untreated cases.

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