Original Article

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Clinical Spectrum of Celiac Disease in Children: Experience from A Public Hospital in Pakistan

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ABSTRACT

Objective: To evaluate the clinical and laboratory parameters of celiac disease (CD) in children and perform a comparison between classical and non-classical presentation. **Study Design:** A prospective observational study. **Settings:** DHQ hospital Toba Tek Singh Pakistan. **Duration:** From January 2005 to December 2018. **Methodology:** Children between 1 and 16 years of age, diagnosed with CD during this period were included in the study. Clinical features and relevant laboratory findings were documented at the time of presentation. Data was divided into classical and non-classical CD groups according to clinical presentation. Overall disease features were studied and necessary comparisons were made between classical and non-classical disease groups. **Results:** A total number of 323 patients with celiac disease were included in study. 195(60.03%) Patients had a classical presentation and 128 (39.97%) patients had a non-classical presentation. 292(90.4%) children had anemia, out of which n=84 (26%) required blood transfusion. Failure to thrive/under-weight n=293(90.7%), Short stature n=271(83.9%), Isolated short stature was the presenting complaint in 121 (37.4%) patients. Chronic diarrhea n=195(60.37%) abdominal distension n=187(57.9%), repeated vomiting n=130(40.4%), recurrent abdominal pain n=116(35.9%), constipation n=84 (26%), hypokalemic paralysis n=12 (3.71%), family history was positive in 29(9%), consanguineous marriage of parents was found in 196 (60.7%). Mean age at presentation for non-classical CD group (7.28±3.33) was significantly higher than classical CD group (4.98±2.91). Mean centiles for height in non-classical CD (4.39±7.43) were significantly lower as compared to classical CD (7.67±12.28). There was no significant difference in mean centiles for weight, mean hemoglobin and mean Anti-TTGs levels between two groups. **Conclusion:** The non-classical presentation of celiac disease is not uncommon. The diagnosis is significantly delayed in patients with non-classical features resulting in significantly compromised height at the time of diagnosis. Early diagnosis in patients with non-classical feature may ensure better growth centiles.

Keywords: Celiac Disease, Pediatric, Chronic diarrhea, Short stature, Anemia

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INTRODUCTION

Celiac disease is an autoimmune enteropathy that occurs in genetically predisposed individuals in response to ingestion of gluten containing food.[1] Celiac disease is a fairly common disease with a worldwide prevalence of biopsy proven cases estimated to be 1% of general population.[2] However, The disease shows remarkable geographical variation with very high prevalence in Europe and North America and almost rare in Africa and East Asia.[3] This variation is due to genetic and environmental factors. The prevalence of celiac related HLA DQ2 and DQ8 gene expression in Indian population was around 35%, with higher disease prevalence in Punjab population.[4] Krigel et al. did a cross sectional study on duodenal biopsy sample submitted between January 2008 and 2015 and found prevalence of villous atrophy to be highest in Indian Punjab ethnic population.[5] Although no large epidemiological studies has been done on disease burden in Pakistan, however, we can presume prevalence of in Punjab, Pakistan to be similar due to ethnic predisposition and very high per capita wheat consumption.[6]

The Celiac Disease has a wide clinical spectrum. Oslo classification divides celiac disease into 2 main groups, Asymptomatic and Symptomatic. The Asymptomatic group comprises of silent celiac disease and potential celiac disease. The symptomatic celiac disease group is further divided into classical (gastrointestinal symptoms) and non-classical (extra intestinal symptoms).[7] With the increasing incidence of celiac disease, a lot of patients are being identified with atypical manifestations as short stature, iron deficiency anemia,[8] altered bone metabolism and elevated liver enzymes.[9] Short staure is the most common extra-intestinal presentation of celiac disease and can sometime be the only sign.[10]

In some cases, short stature was the only presenting complaint.[11] Iron deficiency anemia is the commonest extra-intestinal presentation in adults but less frequently reported in pediatric population.[10] In a study conducted at Agha Khan hospital Karachi, frequency of anemic Pakistani children with CD was found to be remarkably higher than reported in international studies.[12] Celiac crisis is rare but can be presenting feature in about 25% of patients in Pakistan.

Celiac disease is fairly common in Pakistan, but little is known about its characteristics in our population. Available data about the disease is mostly from the European population. Results from local studies have indicated some variations in the clinical pattern of the disease as compared to other populations reportedly due to poor socioeconomic status, nutritional deficiencies and delay diagnosis.[14] The purpose of this study was to determine the characteristics of CD in our population on

a larger cohort, with a particular focus on its non-classical manifestations. This may help in better understanding and early identification of disease in future.

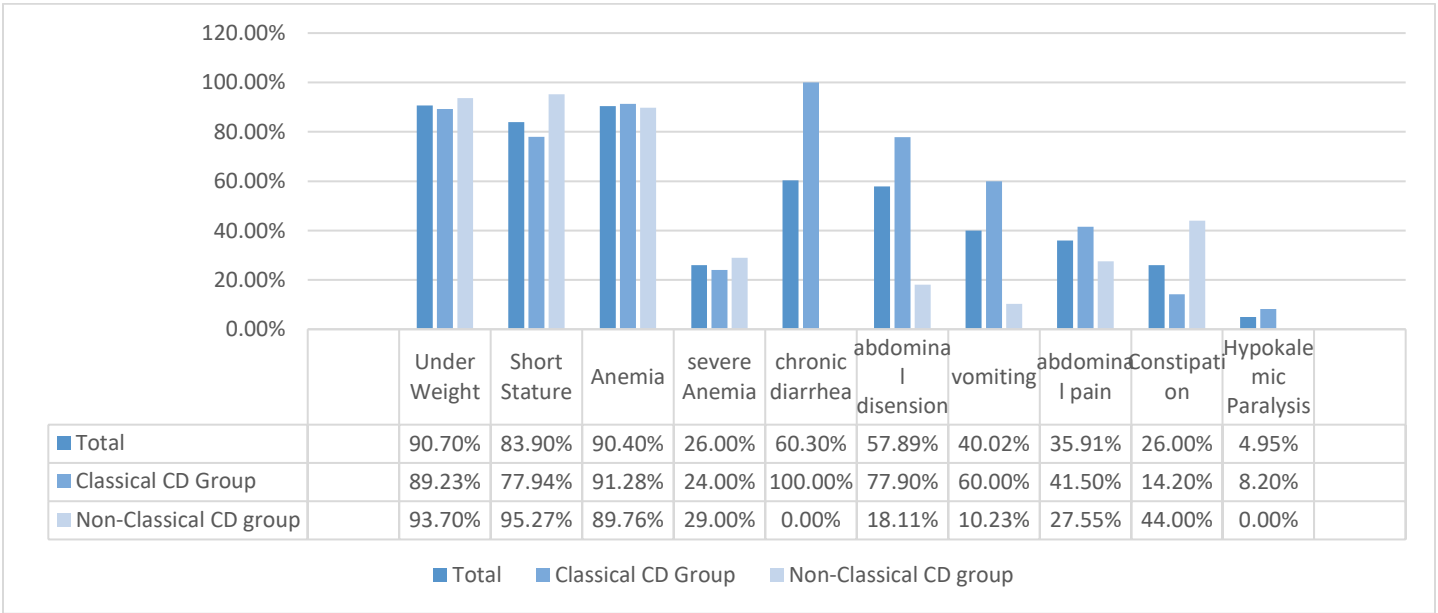
METHODOLOGY

Study Design: Prospective observational study.
Settings: DHQ hospital Toba Tek Singh Pakistan.
Duration: 14 years January 2005 to December 2018.
Sample Technique: Non-probability consecutive sampling.
Study Population: 323 (calculated with WHO calculator 1.1 keeping 95% confidence interval and margin of error 0.05 with the minimum prevalence of outcome 9%).
Inclusion Criteria: Children of both sexes between 1 and 16 years of age, who received the diagnosis of CD.
Exclusion Criteria: Patients diagnosed at other Centers and those with other co-morbid conditions were excluded.
Method: Diagnosis of celiac disease was made by modification of American Academy of Gastroenterology (ACG) clinical guidelines of celiac disease diagnosis.[16] Anti-Tissue Transglutaminase IgA level was obtained for all patients suspected of celiac disease. Those with strong clinical suspicion and Anti TTG IgA level more than 10 times normal were labelled as confirmed cases. The genetic testing for these patients was not carried out due to resource limitations. Those with borderline elevation of antibodies were referred to pediatric Gastroenterology department of children hospital Lahore for duodenal biopsy and their diagnosis was confirmed after positive histopathology report. Patient data including demographic features, clinical presentation and laboratory findings at the time of diagnosis was obtained on a Proforma. The weight and height were measured in kilograms (Kg) and centimeters (CM) respectively and were plotted on CDC growth charts. Failure to thrive was defined as weight for age below 3rd centile. Short stature was defined as length or height for age below 3rd centile. Anemia was defined as Hb less than 10g/dl and severe anemia was defined as Hb less than 7g/d. Data was entered and analyzed in SPSS version 16. The Mean and SD were calculated for quantitative variables and frequencies were calculated for qualitative variables. Data was divided in into two groups, classical and non-classical CD. Frequencies and means for each group were calculated separately. Mean values were compared between the two groups by applying independent sample T-test.

RESULTS

A total number of 323 diagnosed patients of celiac disease at this Centre were included in the study. In 251 patients, diagnosis of celiac disease was made on the basis of more than 10 times raised Anti-tissue transglutaminase IgA levels while 72 patients who had inadequate serological evidence were confirmed as CD after a positive duodenal biopsy. The mean age at diagnosis was 5.93±3.28 years (range 1 to 16 years), 153 (47.3%) were male and 170 (52.9%) were females. Female to male ratio was of 1.1:1. Twenty-three patients (11.5%) were younger than 2 years of age. Family history was positive for CD in n=29(9%) patients. Consanguineous marriage of parents was found in 196 (60.7%) of patients. Two patients were IgA deficient. Type 1 IDDM was found in 2 patients, hypothyroidism was diagnosed in 1 patient.

At the time of presentation, 195 (60.03%) patients had gastrointestinal symptoms while 128 (39.97%) patients had a non-classical presentation. Overall, the most frequent findings were failure to thrive/under-weight n=293(90.7%), anemia n=292(90.4%), short stature n=271 (83.9%), chronic diarrhea n=195(60.3%), abdominal distension n=187(57.9%), repeated vomiting n=130 (40.4%), recurrent abdominal pain n=116 (35.9%), severe anemia requiring blood transfusion n=84 (26%), constipation n=84 (26%). Comparative frequencies of these parameters in Classical Vs Non-classical CD groups are given in Figure-I



	Under Weight	Short Stature	Anemia	severe Anemia	chronic diarrhea	abdominal disension	vomiting	abdominal pain	Constipation	Hypokalemic Paralysis
Total	90.70%	83.90%	90.40%	26.00%	60.30%	57.89%	40.02%	35.91%	26.00%	4.95%
Classical CD Group	89.23%	77.94%	91.28%	24.00%	100.00%	77.90%	60.00%	41.50%	14.20%	8.20%
Non-Classical CD group	93.70%	95.27%	89.76%	29.00%	0.00%	18.11%	10.23%	27.55%	44.00%	0.00%

Figure-1: Clinical Parameters of CD: Frequencies in Classical vs Non-Classical CD Group

In classical CD, mean age at diagnosis was 4.98 ±2.91 years and in non-classical CD mean age was 7.28 ±3.33 years. Mean height and weight were lower in classical CD, however, mean centiles for height were significantly lower in non-classical CD. There was no significant difference in centiles for weight, mean hemoglobin level and mean anti-TTGs level between two groups. The Comparative values of different clinical and laboratory parameters between classical and non-classical disease groups are given in Table-I.

Table 1: Comparison of clinical and lab parameters between classical and non-classical CD

	Classical Celiac Disease			Non-Classical Celiac Disease			Comparison of means
	Min.	Max.	Mean (SD)	Min.	Max.	Mean (SD)	p-value
Age (years)	1.3	16	4.98±2.91	1.5	15	7.28±3.33	0.0001
Height (cm)	67	146	94.86±16.0	75	145	108.95±17.9	0.0001
Weight (kg)	5.6	30	12.67±4.77	7	35	17.16±6.1	0.0001
Height Centiles	<3	75	7.67±12.28	3	50	4.39±7.43	0.003
Weight Centiles	<3	25	4.34±4.61	3	97	4.48±8.99	0.855
Anti TTG IgA	1	728	208.89±125.6	1	393.87	213.4±117.1	0.7489
Anti TTG IgG	2.8	357.60	98.92±75.43	0.78	408.40	92.73±86.35	0.924
Hemoglobin (g/dl)	4.2	12.7	7.92±1.46	4.4	11.6	8.0±1.57	0.478

DISCUSSION

In this study, 323 children with CD were analyzed. Mean age at diagnosis was comparable to that described in the literature. In this study 60.7% of patients had consanguinity related parents. Ouda S et al. described 96% of patients having parents with consanguinity in their celiac cohort.[16] Consanguinity was reported in 40-96% of Pakistani children with celiac disease in previous studies.[12-14] We can conclude that consanguinity is a major risk factor for CD, however, family history was positive in only 9% patients.

The celiac disease is classically considered a gastrointestinal disease mainly, however, with increasing incidence & awarenes, the disease pattern is changing and more cases of the non-classical disease are being recognized. In this study, 39.97% patients had no gastrointestinal symptom at presentation. This is consistent with data from other recent studies. Almallouhi et Al. reported 43% frequency of non-classical CD.[17] Aziz et Al. reported that 40.91% patients diagnosed as celiac disease in Pakistan had atypical presentation.[12] Bardella et al (year??) identified that the prevalence of the non-classic CD presentation increased with age,[18] this finding was also observed in this study as there was significant difference in mean age at diagnosis between classical and non-classical disease groups (p-value >0.001), mean age being significantly higher in patients with non-classical presentation in the classical CD group. Among the gastrointestinal symptoms, diarrhea was the most frequent symptom followed by abdominal distension, repeated vomiting and recurrent abdominal pain. Twelve patients with classical CD presented with hypokalemic paralysis, all of them had a prolonged history of diarrhea.

Most common presentation in non-classical CD was the failure to gain weight, short stature and anemia. The frequency of anemia in this cohort was 90.4% with mean hemoglobin level 7.96±1.51 /dl. Reported frequency of anemia in literature is (9-23%).[19,20] However, refractory anemia was found in 66% of children with CD in a local study.[12] As this study was conducted in a public hospital and most of the patients belonged to low socioeconomic class, primary nutritional deficiencies may be the contributing factor in higher frequency of anemia. In this cohort, 84(26%) children had severe anemia and required a blood transfusion. This high frequency of severe anemia may be due to late presentation and delay in diagnosis particularly in patients with non-classical CD.

The Short stature remains the most common extra-intestinal symptom in children effecting 10-40% pediatric patients at the time of diagnosis.[21] In this study 83.9% patients had height below 3rd centile for age, this frequency is remarkably higher than the previous studies. Short stature was the isolated manifestation at presentation in 121 (37.4%) patients, this finding was similar to that observed by Aziz et al.[12] It is observed that patients who received the diagnosis of CD after the age of 6 years had a significantly lower z-score for height and weight centiles as compared to the children diagnosed at a younger age as shown in Figure-2, this finding has also been described in previous studies.[22] Our study concluded that short stature is an important presenting feature of CD in children who lack gastrointestinal symptom, so short stature in children should be identified early and CD must be suspected all children who lag

behind their ideal centiles for age. Final height may be less compromised if CD is diagnosed early in these children.

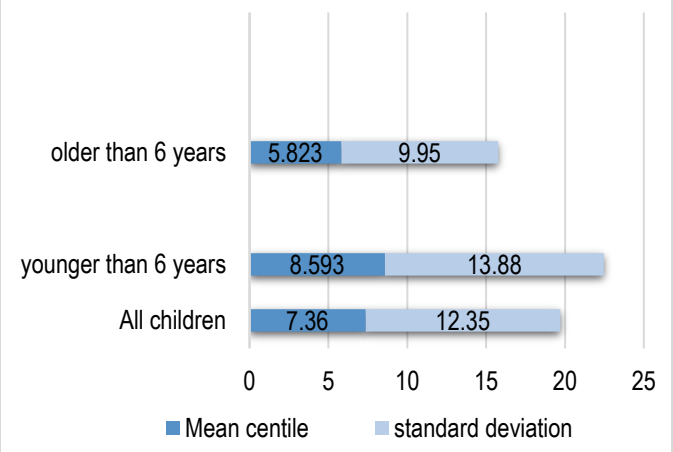


Figure 2: Mean height for age centiles according to age of presentation

This study was conducted over a longer period of time, sample size was larger than similar studies done in the past, however, this was a single centered study and most of the patients in this study belonged to low socioeconomic class. It is difficult to rule out primary nutritional deficiencies as a contributing factor for their growth failure and anemia. By taking the growth parameters of siblings and levels of iron, vitamin B12 and folic acid in cases as well as in their healthy siblings, primary nutritional deficiencies could be ruled out. In future, better results can be obtained from similar studies by including nutritional and family data in the questionnaire. Moreover, this study can further be extended to include the follow up data of compliance, catch-up growth and outcome.

CONCLUSION

Non-classical presentation of celiac disease is not uncommon. The diagnosis is significantly delayed in patients with non-classical features resulting in significantly compromised height at the time of diagnosis. Early diagnosis in patients with the non-classical feature may ensure better growth centiles.

STUDY LIMITATIONS

Due to resource limitation, HLA typing could not be performed, so a modification of diagnostic criteria was utilized in this study.

SUGGESTIONS

In future this study may be extended by including the follow up growth parameters of patients already on gluten free diet, so that, the effect of early diagnosis and early initiation of gluten free diet on catch up growth may better be defined.

CONFLICT OF INTREST

There is no conflict of interest in this study.

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