Diarrheal Versus Non-diarrheal Presentations of Paediatric Celiac Disease

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ABSTRACT

Objective: To compare the frequencies and clinical features of diarrheal versus non-diarrheal presentation of celiac disease (CD).

Study Design: Cross-sectional study.

Place and Duration of Study: Paediatric Department, Benazir Bhutto Hospital, Rawalpindi, from January to December 2013.

Methodology: Children with celiac disease, newly diagnosed on the basis of tissue transglutaminase (TTG) and intestinal histopathology, were included in the study by consecutive non-probability sampling. Patients were divided into diarrheal and non-diarrheal groups on the basis of presence or absence of chronic or recurrent diarrhea. Comparison between two groups was done and a p-value < 0.05 was considered significant.

Results: Total patients were 54 (26 males, 28 females) with mean age of 6.67 ±3.35 years. Chronic diarrhea was present in 31 (57.4%) and absent in 23 (42.6%). Patients in non-diarrheal group were diagnosed at a significantly later age (p=0.038) and had a greater frequency of severe malnutrition (p=0.02). Short stature, anemia, rickets, clubbing and abdominal distension were equally prevalent. There was no significant difference in TTG value and intestinal histopathology among two groups.

Conclusion: Children with atypical presentation of CD had significant severe malnutrition and higher age at diagnosis than at diarrheal presentation.


ORIGINAL ARTICLE

INTRODUCTION

Celiac disease (CD) is an immune mediated disorder expressed by dietary exposure to gluten containing grains such as wheat, rye and barley, in genetically predisposed individuals. Overall worldwide prevalence is 1%. Sero-prevalence in Asia is 1.6%, in Saudi Arabia 3%, while in India 0.1% to 1.23%. Data from Pakistan is lacking. Largest published data shows 2,861 patients have been diagnosed with CD over the last 7 years.

Classic presentation of CD is with malabsorptive diarrhea and small intestinal mucosal abnormality. Other features of CD include failure to thrive, anemia, abdominal distension, clubbing; and less common features include dermatitis herpetiformis and celiac crisis.

With improved serological markers including antitissue transglutaminase IgA, antiendomysial IgA, and antigliadin IgG antibodies, atypical cases are being frequently recognized reflecting remarkable change in the disease pattern over decades from diarrheal to non-diarrheal presentation. In a recent local study, 68.42% patients presented with atypical non-diarrheal presentation of CD. Similar trends have been identified around the globe. A Swedish study has identified a gradual change in the presentation of CD with a trend towards diagnosis of less severe, mono-symptomatic, and atypical presentation; and an increasing number of asymptomatic patients identified by screening. An Iranian study also showed that two-third of the patients presented with atypical non-gastrointestinal presentation.

It is clear that atypical presentation of CD is very frequent; and at times, the predominant mode of presentation. Besides, identification of less severe and asymptomatic patients is important and requires a high index of suspicion. Delayed diagnosis can result in irreversible short stature, delayed puberty, bone deformities, neurological disorders, and intestinal lymphoma. There is insufficient local data comparing the different presentations of CD. Moreover, diarrheal presentation has been found to be the predominant mode of presentation by some researchers, which is in contradiction with most of the recent contemporary literature. This is partly attributable to the selection bias.
The purpose of this study was to compare the relative frequency of diarrheal and non-diarrheal presentations of CD, and to compare relative frequencies of different clinical features with which they occur in each mode of presentation.

**METHODOLOGY**

This cross-sectional study was conducted at the Paediatric Department, Benazir Bhutto Hospital, Rawalpindi, from January to December 2013. Sample size was calculated for relative frequency of diarrheal and non-diarrheal presentations using WHO sample size calculator with frequency of non-diarrheal presentation in study population was 17.6%,15 desired precision of 10% and confidence interval of 95%, the sample size was 54.

After the hospital Ethical Committee approval of study and informed consent, patients suspected of CD on the basis of clinical features (3 or more of these features: chronic diarrhea, malnutrition, short stature, abdominal distension, clubbing, rickets and anemia) were screened for CD by TTG titre. Patients already diagnosed with CD and those with diagnosed conditions explaining the symptoms (hypothyroidism, abdominal tuberculosis and inflammatory bowel disease etc.) were excluded. Coagulated blood samples were taken by venous puncture and all samples were sent to same reference laboratory for analysis. As only the patients clinically suspected of CD were included, all patients underwent endoscopy at the endoscopy department and 04 mucosal biopsies were taken from second part of duodenum and beyond. Biopsies were subjected to histopathological analysis at pathology department and were reported by a consultant histopathologist. CD was diagnosed on the basis of raised TTG (more than 7 IU/ml) and small intestinal histopathology (Marsh 3a or higher lesion) or small intestinal histopathology alone in TTG negative patients.8 All patients newly diagnosed with celiac disease were entered into study by consecutive, non-probability sampling. Further data collected included history and examination, anthropometric measures and blood complete picture was recorded. Serum IgA level was done in TTG negative CD patients.

Patients were divided into diarrheal and non-diarrheal groups. Patients having history of diarrhea lasting more than 2 weeks at the time of presentation on any time within last 6 months were entered in the diarrheal group. Patients having no diarrhea were included in the non-diarrheal group. Comparison between the clinical and Lab features of the patients in each group was done.

Data was analyzed using SPSS version 20. Qualitative variables like gender, clubbing, abdominal distension, malnutrition and short stature were presented as frequencies and percentages. Chi-square test was used for comparing the frequencies of qualitative variables. Quantitative variables such as age, hemoglobin, and TTG were subjected to normality testing using Shapiro Wilk test. Variables having normal distribution were presented as mean and standard deviation while those having abnormal distribution were presented as median and interquartile range. Independent sample t-test was used for comparing the quantitative variables with normal distribution while Mann-Whitney U-test was used for comparing quantitative variables having abnormal distribution. A p-value of less than 0.05 was considered significant.

**RESULTS**

A total of 54 patients, 26 (48.1%) males and 28 (51.9%) females, newly-diagnosed with CD, were included in the study. The mean age at diagnosis was 6.67 ±3.35 SD years ranging from 2 to 13 years. History of chronic diarrhea was elicited in 31 patients (57.4%, 17 males, 14 females) which were included in diarrheal group, while 23 (42.6%, 14 females, 9 males) had no history of diarrhea and were placed in non-diarrheal group.

Malnutrition was present in 44 (81.5%), short stature in 47 (87.0%), clubbing in 19 (35.2%) and abdominal distension in 31 (57.4%) patients (Table I). Severe anemia (hemoglobin < 7 g/dL) was present in 44 (81.5%), short stature in 47 (87.0%), rickets in 28 (51.9%), clubbing in 19 (35.2%) and abdominal distension in 31 (57.4%) patients (Table I). Severe anemia (hemoglobin < 7 g/dL) was
found in 11 out of 31 (35.5%) with diarrheal presentation. The frequency was higher in the non-diarrheal group, where 10 out of 23 patients (43.5%) had severe anemia. Although the frequency of severe anemia was higher in non-diarrheal group, but there was no significant difference of mean hemoglobin among the two groups (p = 0.36).

TTG was positive in 27 (87.1%) patients with diarrheal presentation in 19 (82.6%) patients with non-diarrheal presentation. Value of TTG varied widely within the study population having a range of 0.27 to 1,139 IU/ml. The data did not follow normal distribution. Median TTG was 197.5 with a interquartile range of 176.88 IU/ml. TTG negative patients were diagnosed on the basis of small intestinal histopathology and clinical response to gluten-free diet. There was no significance difference of TTG value between the two groups (p = 0.17). Out of the 6 TTG negative patients with CD, one had IgA deficiency, while five had normal serum IgA level.

The most common histopathologic lesion was Marsh 3b seen in 24 (44.4%) patients followed by Marsh 3c in 13 (24.1%), 3a in 12 (22.2%). Marsh 2 was the least common seen in 5 (9.3%) cases. Histopathologic distribution of the two groups is described in Figure 1.

One patient was a known case of type 1 diabetes mellitus and workup for CD was done because of chronic diarrhea and failure to thrive. Vitamin D resistant (hypo-phosphatemic) rickets along with CD was present in one patient.

Two patients in diarrheal group presented with short history of worsening of diarrhea and inability to stand or sit. One patient in non-diarrheal group also presented with short history of explosive diarrhea, dehydration and loss of ambulation. All of these 3 (5.56%) patients were diagnosed as celiac crisis on the basis of typical history and biochemical abnormalities including hypokalemia, hyponatremia and hypocalcemia. They got well with meticulous intravenous rehydration and electrolyte replacement.

**DISCUSSION**

*Triticum aestivum* (wheat) is the most extensively grown grain and serves as a staple food for a large proportion of world’s population. It is also incriminated in etiology of many diseases; most notably CD. CD is very common in Pakistani population. However, it is important to note that these patients represent only the tip of iceberg with a large proportion of subclinical cases with subtle or no clinical features.

Mean age was 6.67 ±3.35 years in present study with male to female ratio of 1 : 1.08. Mean age and male to female ratio at diagnosis of present study closely correlates with the results reported by Cheema. In another study, the mean age was 8.9 ±3.7 years and male to female ratio 1.5 : 1, both being higher than the present study. In the study done by Tapsas, including patient data from the past four decades, there had been a change in age at presentation from a mean age of 2.2 years 3 decades ago to a mean age of 8.2 years in the recent years. The mean age of patients from recent years is only in slight discordance with the present study.

Chronic malabsorptive diarrhea was present in more than half (57.4%) patients, while remaining patients (42.6%) had no diarrhea at presentation. Mode of presentation varies widely in paediatric literature. Diarrhea at presentation is described in 51.9% patients by Cheema. In a meta-analysis by Ehsani-Ardakani, only 34.9% patients were reported to present with gastrointestinal symptoms. On the other side of spectrum, Noor reported frequency of diarrheal presentation of CD as high as 79.3%, while Alvi has reported a frequency of 82.6%. Even though these studies showed that the most common presentation of CD is diarrheal illness, but it is important to ensure that patients with subtle presentations without diarrhea have not been missed.

Comparison of clinical features of diarrheal and non-diarrheal presentation of CD has not been documented too often, which makes the present study unique. In the present study, mean age at presentation was 7.76 ±3.27 years in the non-diarrheal group, which was significantly higher than the mean age of diarrheal group i.e. 5.86 ±3.23 years. There was no significant variation in gender distribution among the two groups.

Severe malnutrition (weight < 5th percentile) was much more frequent in non-diarrheal presentation (95.6%) than in diarrheal presentation (70.9%). The difference was statistically significant. Severe anemia (hemoglobin < 7 g/dL) was also more frequent in non-diarrheal presentation (43.5% vs. 35.5%). However, the difference between mean hemoglobin was not significant. Clubbing was found much more frequently in patients with diarrheal presentation (43.3%) than those with non-diarrheal presentation (26.1%), but the difference was statistically insignificant. More than 85% patients had...
height less than 5th percentile for age in either group. Abdominal distension and rickets were present in nearly with no significant difference between the two groups. These findings are concordant with those of Ikram, who found diarrhea in only half of the patients with rest presenting with atypical non-diarrheal presentations including failure to thrive and anemia. Atypical presentation was also documented by Cheema, but only the main presenting feature was considered. In study done by Ikram in Faisalabad, Pakistan, abdominal distension and clubbing. TTG was positive in vast majority of patients in either group (87.1% in diarrheal; 82.6% in non-diarrheal presentation). TTG negative patients were diagnosed on the basis of small intestinal histopathology. TTG positive rate of present study correlates closely with existing literature. Most patients had histopathological features of Marsh 3b, followed by Marsh 3c and 3a, respectively; in either group. Few patients had Marsh 2 histopathology while none had Marsh 1. This observation is slightly discordant with the results of Brown who has reported a much higher proportion of Marsh 3c (56.6%), followed by Marsh 3b and 3a with very few patients having findings corresponding to Marsh 1 and Marsh 2.

Rare presentations of CD in present study were celiac crisis (3 patients) and hypo-phosphatemic rickets (one patient). Celiac crisis has been recognized among rare presentations of CD, but data is largely limited to case reports and case series. Presentation of celiac crisis in these patients with sudden onset (or exacerbation of existing) diarrhea, dehydration and loss of ambulation along with electrolyte abnormalities of hypokalemia, hyponatremia and hypocalcemia, is remarkably similar to other reported cases.

Bone disease is a well known feature of CD with significant osteopenia in more than half the patients at presentation. This bone disease responds well to treatment with gluten-free diet and vitamin D supplementation. However, association between hypophosphatemic rickets and CD has not been described in literature and it may represent a coincidental finding. No patient presented with dermatitis herpetiformis or overt neurological symptoms in present study. Large scale studies are mandated to determine the frequency of these rare presentations.

None of the patients had any high risk predisposing condition except one, who had pre-existing type 1 diabetes mellitus although it is a common association in literature. Prevalence of CD is particularly higher in certain high risk groups. These include patients with other autoimmune conditions like type 1 diabetes mellitus, Addison disease, autoimmune thyroiditis, autoimmune hepatitis, myasthenia gravis, primary biliary cirrhosis, primary sclerosing cholangitis and psoriasis. Other important high risk groups include chromosomal disorders, such as Down syndrome, Turner syndrome and William syndrome. Close relatives of patients with CD are also at a higher risk than general population, especially the siblings and twins. These high risk groups constitute a major target for the disease screening. This is especially pertinent with shifting impetus towards disease screening of asymptomatic high risk population.

CD is now known for ages, but the knowledge and understanding of the disease is being refined every day. Newer terms like “non-celiac wheat allergy” and “non-celiac gluten sensitivity” are being introduced with increasing evidence in their favour. Wheat allergy is an allergic reaction mediated by T-helper type 2 cells which can be IgE mediated or non-IgE mediated. IgE mediated response is brisk and can result in anaphylactic reaction. It is mediated either by ingestion, or inhalation of wheat. It can manifest as asthma or rhinitis. Non-IgE mediated allergy presents as chronic eosinophilic inflammation of esophagus, stomach or intestines. Non-celiac gluten sensitivity is less well understood entity with no clear biological markers available. It is considered to be an immune reaction mediated by the innate arm of the immune system having intestinal as well as extra-intestinal manifestations. Gluten-free diet has been shown to benefit in multiple conditions including CD, wheat allergy, non-celiac gluten sensitivity, and IBD; the debate is now turning towards general exclusion of wheat from diet. However, extensive research is still needed in the subject.

CONCLUSION

Atypical presentation of CD without diarrhea is quite common amounting to almost half of all cases. Non-diarrheal presentation has significant severe malnutrition and higher age at presentation than diarrheal presentation. TTG value and intestinal histopathology are comparable between the two groups.

REFERENCES


