Original Article

Pediatric Celiac Disease

Frequency of Atypical Manifestations of Pediatric Celiac Disease

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ABSTRACT

Objective: To determine Frequency of Atypical Manifestations of Celiac Disease in Pediatric age group.
Study Design: Descriptive / cross sectional study.
Place and Duration of Study: This study was conducted at two tertiary care hospitals of Sargodha, Pakistan between September 2014 and March 2019.
Materials and Methods: Total 72 biopsy proven patients of celiac disease were included in the study after informed consent from the parents. Their demographic details as well as clinical, serological and histopathological data was collected on proformas. These statistical variables were analyzed using SPSS 20.
Results: The male to female ratio in our study was 1:1.05, while the mean age of the patients at the time of diagnosis was 5.8 ± 3.12 years. The frequency of chronic diarrhea in these patients was 56.94 % as compared to 40.04% of non diarrheal presentations. The commonest atypical feature in the study was short stature (77. 78%). Other significant manifestations included anemia (51.38%), rickets (51.38%), malnutrition (70.8%), abdominal distension (38. 89%) and clubbing (12.5 %). Anti TTG was >300 IU in 80.55% patients. The commonest lesion reported on biopsy was Modified Marsh 3b in 39 patients (54.16%) followed by modified Marsh 3c in 21 patients (29.16%) and modified Marsh 3a in 12 patients (16.67%).
Conclusion: The non diarrheal presentations of pediatric celiac disease are increasingly being identified and it is prudent for all pediatricians to keep their threshold very low to screen Celiac disease when dealing patients with such clinical features.
Key Words: Celiac disease, Pakistan, Glutens, Biopsy

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INTRODUCTION

Celiac disease (CD) is a multi-factorial systemic immune dysregulation triggered by consumption of gluten in diet. It primarily affects small intestinal mucosa resulting in progressive villous atrophy.[1] Over the last few decades CD has been more frequently diagnosed all over the world with an estimated prevalence of about 3% in children.[2] This rising frequency of diagnosis is because of improved understanding of variety of presentations, optimal screening investigations as well as growing burden of the disease.[3]

Celiac disease has a wide range of clinical manifestations extending from completely asymptomatic forms to obviously symptomatic ones with severe malabsorption syndrome.[4]

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However, there has been a pronounced shift in the presenting complaints of pediatric celiac disease towards atypical symptoms during the recent years.[5] The present-day literature also strongly supports this growing trend of extra intestinal presentations, thus, emphasizing the heterogeneity in clinical spectrum.[6] This broad spectrum of presentations makes it indispensable for all pediatricians to have an adequate knowledge about the variability in manifestations for an early diagnosis and appropriate management of the disease.[7]

Pakistan is a country with wheat as the main course of weaning diet during early infancy, which makes genetically susceptible children more prone to develop CD. While prompt diagnosis and timely intervention of pediatric CD is critical to avert its complications, unfortunately, there is little local data available regarding the diverse non classical symptoms of CD leading to under diagnosis of the disease.[8, 9]

The rationale of our study is to determine the frequency of atypical manifestations of celiac disease among pediatric population in a low income country with high risk. This will add to the regional evidence regarding pediatric CD presentations and will help to sensitize health professionals for keeping a higher index of suspicion for CD when encountering non-classical symptoms.

MATERIALS AND METHODS

This was a multi-centered cross-sectional descriptive study carried out in District Head Quarters Hospital and Mubarak Hospital, Sargodha. The study was conducted from September 2014 to March 2019 after taking informed consent from institutional ethical committee. Total 72 children, 41 from District Head Quarters Hospital and 31 from Mubarak Hospital, Sargodha were included in the study after informed consent from their parents. Sample size was calculated by using online open Epi sample size calculator [10] by taking frequency of non diarrheal manifestations as 17.4 % [11], margin of error as 8.8 % and confidence level as 95%.

A total of 350 patients with clinical suspicion of celiac disease including diarrheal as well as non diarrheal presentations in the form of constipation, anemia, short stature, recurrent abdominal pain, delayed puberty, abdominal distension, rickets and malnutrition were subjected to screening through anti Tissue Transglutaminase IgA levels (TTG) and serum IgA levels. All those children with TTG IgA levels more than 12 IU with normal serum IgA levels for age were considered positive. These patients were total 167 in number. These patients were further evaluated by duodenal biopsies. These biopsies were conducted at Pediatric Gastroenterology department of Children hospital, Lahore. There were 72 such patients in which histopathology (Modified Marsh 3a or above) supported the diagnosis of celiac disease. All these recently labelled celiac patients whose parents gave consent were included in the study by non- random convenience sampling technique. The exclusion criteria of the study included all previously diagnosed cases of celiac disease, children with chronic diseases such as congenital heart disease, chronic kidney disease, tuberculosis, inflammatory bowel disease, endocrinopathies and all patients with dysmorphic features or neurodevelopmental problems.

The data was collected on specially designed proformas which included all the demographic details including age, sex, gender of the subjects, their symptoms, findings of the clinical examination and anthropometric measurements. These proformas were filled by consultant pediatricians and postgraduate residents of the pediatrics department. History was taken from the parents of the patients presenting to opd or admitted in indoor departments, while examination was done according to a set scheme. All examination findings were verified by a second consultant. All children with chronic diarrhea diagnosed as celiac disease according to the aforementioned criteria were categorized as patients with typical presentation of CD, whereas all other manifestations were described as atypical.

The Statistical analysis was done using SPSS version 20. All quantitative variables were represented as mean and their standard deviations (SD) while all categorical data was represented as frequencies as well as their percentages.

RESULTS

A total of 72 patients, who were finally diagnosed on serological and histopathological basis as having Celiac Disease, were included in the study. Out of these 72 patients 35 (48.6 %) were males while 37 (51.3 %) were females; with male to female ratio of 1:1.05. The mean age at diagnosis was 5.8± 3.12 years, with a range of 9 months to 17 years. Majority of the patients were in the age range of >2 to 5 years i.e. 31 patients (43.05%), 29 (40.3%) were >5to 12 years, 7 (9.7%) were under 2 years and 5 (6.94%) were > 12 to 17 years.

Most of the patients in our study group presented with chronic diarrhea. These were 41 (56.94%) in number .Another 13 patients (18.05%) presented with constipation whereas there were 2 patients (2.78%) who presented with delayed puberty. Short stature was present in 56 (77.78%), rickets (defined on the basis of clinical and radiological findings) in 37(51.38%), clubbing in 9 (12.5%) and abdominal distension in 28 (38.89%) patients (Table I). Anemia (haemoglobin below 5th centile for age and gender of the patients) was present in 37 patients (51.38%) and 16 out of these 37 patients (43.24%) required blood transfusion.

There were 60 patients (83.33%) in our study group who presented with multiple presentations while only 12 patients (16.67%) presented with a single clinical feature. Among those with sole clinical feature at presentation; 3 out of 12 patients had (25%) chronic diarrhea. Remaining 9 patients (75%) had atypical presentation; 1 patient out of 12 (8.33%) presented with constipation, 1 (8.33%) with delayed puberty and 1(8.33%) with anemia. However, there were 6 patients (50%) who had short stature as their sole presentation. The one patient who only had delayed puberty as the only presentation was a 17 years old boy and the one who had anemia as the single clinical finding was a 9 months old male.

Table No1: Frequency of Demographic Details and Clinical Manifestations

Variables	Number (%)
Age	5.8± 3.12 years
Gender	
Male	35 (48.62)
Female	37 (51.38)
Diarreha	41 (56.94)
Constipation	13 (18.05)
Abdominal distension	28 (38.89)
Anemia	37 (51.38)
Rickets	37 (51.38)
Short stature	56 (77.78)
Malnutrition	51 (70.8)
Delayed puberty	2 (2.78)

As regards to malnutrition; 51 (70.8%) were malnourished, with weight falling below 3rd centile when plotted on WHO centile chart for weight for age, 5(6.94%) patients had weight falling between 3rd and 10th centiles, 3 patients (4.16%) were between 10th and 25th centiles, 2 (2.77%) were between 25th and 50th centiles and 1 (1.38%) was above 50th centile. This 1 patient, above 50th centile, was a boy of 17 years who presented with delayed puberty. Among those presenting with a single presenting feature, 8 children (66.67%) were also malnourished with weights falling below 3rd centile.

Anti-TTG IgA was strongly positive in 69 patients (95.83%); 58 patients (80.55% of total) had anti-TTG IgA above 300iu/ml and remaining 11 patients (15.27%) had values in the range of 200 to 300 iu/ml. 3 patients (4.16%) had anti TTG IgA below 200iu/ml. These were diagnosed on the basis of small intestinal biopsy. All the 72 patients underwent small intestinal biopsy and were proven to be patients of celiac disease. The most common histopathological lesion found was Modified Marsh 3b in 39 patients (54.16%), modified Marsh 3c in 21 patients (29.16%) and modified Marsh 3a in 12 patients (16.67%).

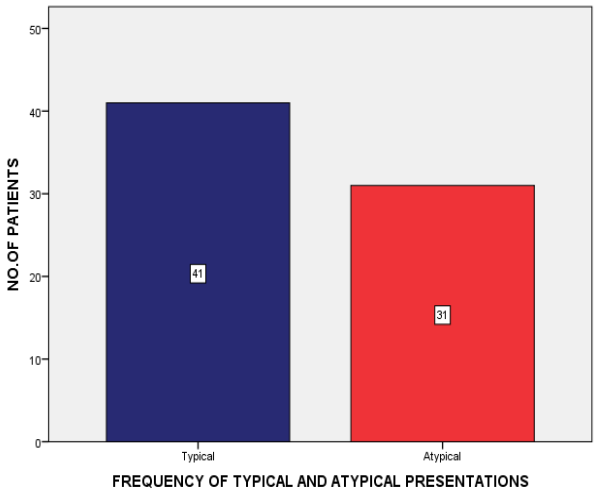

Figure No.1: Frequencey of Typical And Atypical Presentations

DISCUSSION

Celiac disease in pediatric age group in Pakistan is still diagnosed after a long delay due to inadequate awareness of various presentations among child health professionals. This delayed recognition of the disease poses a great risk of multiple celiac associated complications in these patients.[12] Our study has evaluated the demographics as well as clinical spectrum of the patients belonging to a peripheral area of Pakistan.

The male to female ratio in our study was 1: 1.05. Although we did not find a significant gender difference among the study subjects, this little female preponderance can be attributed to the autoimmune nature of the celiac disease. Similar female predominance has been observed in another local study.[8]

In the current study, the mean age of the patients was 5.8 ± 3.12 years which is comparable to another study carried out in Children Hospital Lahore in which the mean age was 6 years.[13] However, a study conducted in Arab population demonstrated a younger mean age (3.4 years)[14] of the celiac patients, while another Turkish literature reported 8.9 years as the mean age of the celiac patients.[15] These differences might owe to the underlying genetic and environmental factors of the disease.

In our study, the non-diarrheal presentation of the disease was found in a significant proportion of patients (43.06 %) which is in accordance with a study carried out in Agha Khan Hospital,Karachi.[16] Another study by Sharma et al also had 43% celiac patients with atypical presentations. Nevertheless, as discussed earlier there is a wide range of presentations of pediatric celiac disease, in a study by Alvi et al the non diarrheal presentations were only reported to be 17.4% .[11]

The commonest initial presentation in our subjects was chronic diarrhea which was consistent with the results of a study by cheema et al.[13] Among the atypical presentations short stature was the most common (77.8%) finding. This result of our study is comparable to the study by Hashmi et al in which there were 81% patients with short stature.[8] This is why literature now recommends screening for celiac disease in markedly stunted children. [18]

Anemia and rickets were the other two significantly reported non- classical manifestations with both reported to be 51.3%. This was concordant with the study by Aziz et al.[15] Similar results with a high percentage of 64% of iron deficiency anemia in another cohort were observed.[19] Anemia and rickets were more common among those who presented with chronic diarrhea than those who presented with atypical features. In our study group none of the patients with sole atypical presentation had rickets while only one had anemia.

In a study by Podder et al 48% patients presented with abdominal distension, which is concurrent with the findings of our study where 38.89% had this manifestation.[20] Constipation was another non-classical presentation of patients diagnosed as celiac in our cohort. It was in 18.05% patients which is comparable to 15% reported in a regional study.[13] There was a significant proportion of patients who were failure to thrive in our study (70.8%) which correlates with the result of another literature.[15] Clubbing was present in 12.5 % of our patients which is slightly lower than what was observed in a study by Ikram et al.[21]

The Modifid Marsh 3b was the most common histological finding in the current study (54.16%). Similarly, 55.3% children in a study conducted in

Bangladesh had biopsy with Modified Marsh grade 3b. However, in our study the second most common was grade 3a while in that study Modified Marsh grade 3c was more prevalent.

The limitation of our study includes small size of the study group. Therefore, larger multi-nation and multi-centre trials are needed to determine the clinical spectrum of CD in children.

CONCLUSION

The atypical presentations of pediatric celiac disease in Pakistan are not very uncommon and our study recommends that the pediatricians and physicians need to lower their threshold for screening CD in patients presenting with clinical manifestations that are recognized as non classical. This will result in early diagnosis and thus better outcomes in patients with CD.

Author's Contribution:

Concept & Design of Study:	Muhammad Arshad
Drafting:	Osama Anwar
Data Analysis:	Ahmad Hassan
Revisiting Critically:	Muhammad Arshad Osama Anwar
Final Approval of version:	Muhammad Arshad

Conflict of Interest: The study has no conflict of interest to declare by any author.

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