Celiac Disease in children and the impact of late diagnosis

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ABSTRACT

Objective: To compare the typical and atypical celiac patients in terms of different clinical parameters and the impact of late diagnosis.
Study Design: A retrospective descriptive comparative study.
Place and Duration: Pediatric Outpatient of Federal General Hospital (FGH), Chak Shahzad, Islamabad from 1st January 2018 to 31st December 2019.
Methodology: Diagnosed patients with celiac disease were divided into two groups according to typical or atypical symptoms and evaluated for the clinical and biochemical markers and the long term effects of late diagnosis were determined, especially in atypical celiac disease.
Results: A total of 50 patients were studied. Mean age at diagnosis was 7.1 years. The younger age was associated with typical symptoms. Most common extra-intestinal manifestations were anemia and short stature, combined or alone. The mean length of late diagnosis was 3.8 years. Urban areas had a high rate of late diagnosis despite having more facilities. The study shows unnecessary investigations and treatment interventions were done especially in atypical celiac disease patients' further delaying diagnosis.
Conclusion: Atypical celiac disease is quite common in children and they showed more different aspects of late diagnosis negatively affecting them than the typical ones especially in terms of anemia and short stature.
Keywords: Celiac disease, Children, Diagnosis, Atypical presentation, Late diagnosis, Anemia

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INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy triggered by gluten present in wheat, barley and rye, in susceptible persons causing inflammation of small intestine[1]. CD individuals present with gastrointestinal symptoms, extra-intestinal symptoms or no signs or symptoms. The classical symptoms include gastrointestinal symptoms such as diarrhea, malabsorption etc., while extra-intestinal or atypical symptoms are anemia, osteoporosis, dermatitis, short stature etc[2]. The classic form typically presents in infancy while atypical form presents late[3,4]. In CD, serological markers are widely used in laboratory testing[,5] followed by small-bowel biopsy. The atypical form is becoming more common and might reach about 50% of all diagnosed patients[6]. The undiagnosed CD or late diagnosis leaves individuals exposed to the risk of long-term complications[7,8]. It also leads to unnecessary investigations and multiple different OPD visits, causing burden on parents and healthcare system. The estimated ratio of diagnosed to undiagnosed individuals varies between 1:5 to 1:8[9,10].

Literature review has revealed that although atypical form is becoming common, with short stature and anemia exhibiting as the manifestation of atypical celiac disease, the diagnosis is still overlooked[10,11]. The late diagnosis in this case has a deleterious effect on patients. This leads to stunting and severe anemia when finally diagnosed. It results in a remarkable loss of height years which is not completely recovered even when put on gluten free diet. Similarly, undiagnosed anemia results in prolonged ill health and multiple unnecessary investigations and burden on parents. All these findings formed the basis of this study.

This highlights the importance of spreading awareness and sensitizing physicians about its atypical forms. Therefore, the primary aim of this study was to compare the typical and atypical celiac patients in terms of different clinical parameters and the

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impact of late diagnosis, thereby emphasizing low threshold of celiac testing and thus, to improve outcome. So this study was conducted with an objective to compare the typical and atypical celiac patients in terms of different clinical parameters and the impact of late diagnosis.

METHODOLOGY

This retrospective descriptive comparative study was conducted at Pediatric Outpatient of Federal General Hospital (FGH), Chak Shahzad, Islamabad from 1st January 2018 to 31st December 2019.

As our hospital is in vicinity of The National Institute of Health Islamabad which offers allergy testing and immunotherapy, a large number of celiac disease patients visit with the hope of immunotherapy as a cure and are then referred to our OPD. The referred diagnosed celiac disease patients, who had a well-maintained record of illness, presenting to the out-patient were included. All cases of chronic diarrhea, anemia, short stature who did not test positive for celiac disease, or those celiac patients who did not have a well-maintained record or lacked recall of information were excluded from the study. Non-probability consecutive sampling was done. Sample size was calculated using WHO sample size calculator with prevalence of 1%[12] keeping 95% confidence interval. Diagnosis of celiac disease was based on serological markers (Anti-Tissue Transglutaminase IgA >10 times normal, with or without positive anti-endomysial antibody), with or without small bowel biopsy confirmed cases.

Typical celiac disease patients were defined as those presenting with chronic diarrhea along with failure to thrive. Atypical celiac disease patients were those who presented with extra-intestinal manifestations like anemia, short stature, headache, atopy etc. 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 Hemoglobin (Hb) less than 10g/dl and severe anemia was defined as Hb less than 7g/dl.

Based on the operational definitions, participants were divided into 2 groups: 22 patients had typical celiac disease & 28 had atypical celiac disease. Patient data including demographic features, clinical presentation, laboratory findings at the time of diagnosis, different aspects of impact of late diagnosis were obtained on a proforma. The weight and height were measured in kilograms (kg) and centimeters (cm) respectively and were plotted on CDC growth charts. Z score for weight and height were calculated by CDC Z score calculator. Z score of -1.8 or less corresponds with 3rd centile.

Data Analysis: Data was entered and analyzed in SPSS version 26. The mean and SD were calculated for quantitative variables and frequencies were calculated for qualitative variables. Data was divided into two groups, typical and atypical CD. Frequencies and means for each group were calculated separately. Mean values were compared between the two groups by applying independent t test. The qualitative variables in both groups were compared using Pearson's Chi-square test. A t value of>1.96 or χ^2>3.84 or a p value≤ 0.05 were considered statistically significant.

RESULTS

A total of 50 diagnosed cases of celiac disease on basis of TTG with or without bowel biopsy were included. The patients' ages ranged from 3 years to 13 years with a mean of 7.1 years. 22 (44%) of our patients suffered from typical celiac disease & 28(56%) suffered from atypical celiac disease. In all, 48% (n=24) of the participants were male and 52% (n=26) were female.

Table-I: Comparison of parameters of typical and atypical celiac patients (N=50)

	PARAMETERS	TYPICAL CELIAC DISEASE		ATYPICAL CELIAC DISEASE		p-VALUE
PARTICIPANTS	Male	8	16%	16	32%	
	Female	14	28%	12	24%	
	Urban residence	19	38%	10	20%	0.000
	Mean age (years)	4.76		8.95		0.000
CLINICAL PRESENTATION	Chronic diarrhea + anemia + failure to thrive	22 (44%)		0		
	Anemia + short stature	0		15 (30%)		
	Anemia only	0		7 (14%)		
	Short stature only	0		6 (12%)		
	Recurrent aphthous ulcer	0		1 (12%)		
	Abdominal pain	2 (4%)		7 (14%)		
	Vomiting	0		5 (10%)		
	Alopecia	0		1 (2%)		
	Allergic conjunctivitis + asthma	0		1(2%)		
	Headache	0		1 (2%)		
	Generalized edema	0		1 (2%)		
	Epilepsy	0		1 (2%)		
ANTHROPOMETRY	Mean z-score height	-1.95		-2.52		0.001
	Mean z-score weight	-2.84		-2.08		0.001
INVESTIGATIONS	Mean Hemoglobin (g/dl)	7.92		7.52		0.045
	ANTI-TTG IGA (U/ml)	272		236		0.097
	Mean time from presentation to diagnosis (years)	1.9		3.75		0.000

The mean age of patients with typical celiac disease was 4.7 years as compared to 8.9 years in patients with atypical celiac disease. This difference was found to be statistically significant (p=0.000). Almost 36% (n=12) of patients with typical celiac disease were male, compared to 57% (n=16) in patients with atypical celiac disease. Gender variation between the two groups was statistically insignificant (p>0.05). Comparison of the area of residents of the both groups revealed that 86% (n=19) of the patients with typical celiac disease belonged to urban areas compared to 35% (n=10) of those with atypical celiac disease. The most frequent presentation of atypical celiac disease was

found to be anemia with short stature (53%, n=15), followed by abdominal pain (25%, n=7) and anemia alone (25%, n= 7). The mean Z-score weight was -2.8 in typical celiac patients as opposed to -2.0 in atypical celiac, with a p-value of 0.001. On the other hand, the mean Z-score height was -1.95 in typical celiac disease in contrast to 2.52 in atypical celiac patients, with a p-value of 0.001. (Table-I).

The mean time from presentation to diagnosis was double (3.8 years) in patients with atypical celiac disease compared to those with typical celiac disease (1.9 years). This delay is statistically significant with a p-value of 0.000

Table-II: Comparison of total investigations conducted in both groups (N=50)

INVESTIGATION	TYPICAL CELIAC	ATYPICAL CELIAC
CBC	22	28
RFT	19	27
ELECTROLYTES	20	8
FERRITIN	0	17
HB ELECTROPHORESIS	0	7
STOOL R/E & C/S	21	1
USG ABD	13	10
X-RAY ABDOMEN	4	0
TB WORK UP	5	2
LFT	18	18
HEPATITIS B & C SEROLOGY	13	13
TSH	1	13
MRI BRAIN	0	1
CALCIUM PROFILE	0	11
URINE R/E	1	9
SERUM IgE	0	4

Patients with atypical celiac disease were also subjected to more investigations compared to those with typical celiac disease. (Table-II). None of patients with typical disease were assessed for serum ferritin or Hb electrophoresis, however, in the atypical celiac patients, 61% (n=17) were investigated for ferritin levels and 25% (n=7) for Hb electrophoresis. About 32% (n=9) of patients with atypical celiac disease had urine routine examination done compared to 5% (n=1) in patients with typical disease, although urine routine examination is unnecessary in this disease. Also 39% (n=11) of atypical disease patients were investigated for calcium levels and 14% (n=4) for IgE, whereas none of the patients with typical celiac disease were investigated for calcium level or IgE levels. TSH was performed in 5% (n=1) of patients with typical disease, whereas 46% (n=13) of patients with atypical disease underwent TSH investigations. MRI was also performed in one patient (3.6%) who presented with an unusual complaint of headache.

Hemoglobin levels were performed in all patients. There is a significant difference (p=0.045) between mean hemoglobin levels in typical celiac patients (7.9 g/dl) and atypical celiac disease (7.5 g/dl). Anti-tissue transglutaminase IgA levels had been done in all patients. The average value was found to be 272 U/ml in typical celiac disease compared to 236 U/ml in atypical celiac disease. This difference was not statistically significant (p>0.05).

Our study also showed that patients with typical celiac disease received much more medication than those with atypical celiac disease. All the patients with typical disease received antibiotics and anti-protozoals and 95% (n=21) received probiotics. 11 (50%) patients with typical disease were prescribed lactose free milk and 4 (18%) were prescribed anti- tuberculous (ATT) drugs. (Figure-1) Hakeem medicine was used by 5% (n=1) of patients with typical disease and 36% (n=10) of patients with atypical disease. This difference is statistically significant (p=0.008). Similarly, 19 (68 %) patients with atypical disease used homeopathic medication, in contrast to only 2 (9%) patients in the other group, which was also statistically significant (p=0.000). Repeated blood transfusion was given to 18% (n=5) patients with atypical disease compared to only one (5%) patient with typical celiac disease, however, this is statistically insignificant (p>0.05). Likewise, a greater number of hematinic per year were used in atypical celiac than typical ones.

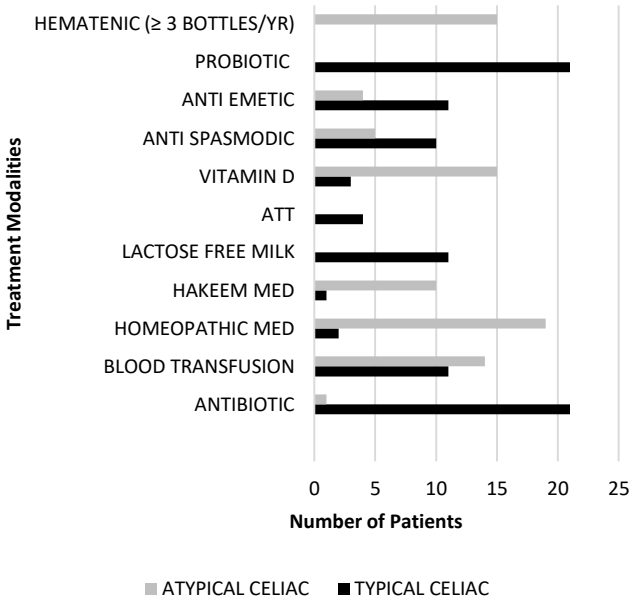

Figure-1: Comparison of treatment modalities used in typical and atypical celiac disease (N=50)
(ATT: Anti tuberculous therapy)

DISCUSSION

The present study was done to look into clinical, biochemical parameters and different aspects of implications of late diagnosis of celiac disease and to compare typical and atypical celiac disease. In this study, 50 children with CD were analyzed. Mean age at diagnosis was 7.1 years, with later age associated with atypical celiac disease. It is comparable to that described in the literature. The age pattern remains the same in Pakistan as shown by Javed et al[13]. In our study, females were more (58%) than males (42%). It is in accordance to the accepted finding that celiac disease and other autoimmune disorders are more common in females as shown by Saeed et al[14].

Celiac disease has been considered mainly a gastrointestinal disease; however, with increasing incidence, more awareness and frequent testing, the disease is emerging as a multisystem disease and thus the non-classical disease is being recognized more than before. In our study, 56% patients had no gastrointestinal symptoms at presentation. This is higher than the data from other studies. Almallouhi et al reported 43% frequency of non-classical CD[15], while Aziz et al reported that 40.91% patients diagnosed as celiac disease in Pakistan had atypical presentation[16] but it is consistent with the fact of increasing incidence of atypical celiac disease. In our study, atypical celiac patients presented at a later age (8.9 years vs 4.7 years, p value < 0.05). Villanueva et al[17] also identified the same pattern of the non-classic CD presentation being common with increasing age. Diarrhea with failure to thrive was the most frequent symptom in typical celiac disease patients, while most common presentation in non-classical CD was anemia with short stature (53%) or sole anemia (25%). Albrady et al[18] showed 48.4% participants in their study had anemia. Anemia in our study was almost 100% .There is a significant difference (p=0.045) between mean hemoglobin levels in typical celiac patients (7.9 g/dl) and atypical celiac disease (7.5 g/dl). However, severe anemia (<7g/dl) was present in 18% of patients among which 77% were atypical celiac disease patients. Refractory and severe anemia was found in 66% of children with CD in a local study by Javed et al.[13] In our study, 50% children required a blood transfusion and more atypical celiac's had repeated blood transfusions compared to typical celiac's (18% vs 1%). This may be due to late presentation and delay in diagnosis particularly in patients with atypical CD. Among 28 atypical celiac's, 35% were from urban area. It shows a high number is missed in urban areas too despite more facilities. Short stature remains the most common extra-intestinal symptom in children affecting 10-40% pediatric patients at the time of diagnosis[19]. In the present study, 82% patients had height below 3rd centile for age, this frequency is remarkably high. Though the sample size is small, this result is very close to the 83 % of patients having short stature below 3rd centile by Javed et al[13]. Similarly, atypical celiac disease patients were shorter than typical celiac disease patients. (p= 0.001). This finding has also been described in a previous study[20].

Our study also analyzed the effects of late diagnosis of celiac disease in terms of unnecessary usage of antibiotics, hakeem and homeopathic medications and unrelated investigations. Patients with typical celiac disease took much more medication than those with atypical celiac disease with over 90% patients with typical disease used antibiotics, probiotics , anti-protozoals and many others were advised lactose free milk. Hakeem medicine was used by 5% of patients with typical disease and 45% of patients with atypical disease. Similarly, 68% of patients with atypical disease used homeopathic medication. Likewise, a lot of unnecessary investigations were carried out especially in atypical celiac patients causing further delay in diagnosis and a burden on patients and healthcare system. Serum ferritin, Hb electrophoresis, serum IgE levels, renal function tests , serum calcium, TSH levels were done in many patients with atypical celiac disease in lieu of anemia and short stature as celiac disease wasn't considered early in the diagnosis. Also occipital headache is an atypical manifestation of celiac disease[21], still an MRI was conducted in one of the patients as celiac wasn't kept in diagnosis and his accompanying short stature was missed too. To our knowledge, no such associations have been studied previously. It is important to note that short stature and anemia are important presenting feature of CD in children without gastrointestinal symptoms. Therefore, CD should be considered early in the diagnosis of these symptoms so as to avoid long term complications and minimize unnecessary OPD visits, investigations and unrelated medicine use. Early diagnosis in atypical celiac disease may reduce different aspects of late diagnosis and can result in better growth centiles and less anemia.

CONCLUSION

- Atypical presentation of celiac disease is becoming increasingly common. A lot of unnecessary investigations and medications are in common practice thus the diagnosis is significantly delayed especially in patients with atypical features resulting in significantly more short stature and refractory anemia at the time of diagnosis.

AUTHOR'S CONTRIBUTION

Ammara F: Conceived idea, Designed research methodology, Data collection, Data analysis, Manuscript writing.
Taimur K: Manuscript writing, Data collection, Data analysis.
Huma B: Literature search, Literature review.
Sadaf H: Manuscript final reading and approval

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