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Assessment of the Initial Clinical Presentations of Patients with Celiac Disease

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Abstract

Background: The prevalence of celiac disease, which is gastrointestinal enteropathy, is increasing. This study aimed to assess the clinical presentations of celiac disease in children.

Methods: The current research is a descriptive-cross-sectional study conducted on 200 children with celiac disease who presented to the gastroenterology clinic of Ghaem Hospital. All patients with celiac disease, presented between 2016 and 2021 were included. For all patients, a checklist including demographic information such as age, sex, weight, weight Z score, height, height Z score, the initial clinical presentations leading to the diagnosis, laboratory examinations including CBC, Anti-TTG IgA, as well as pathological findings including biopsy, and Marsh score were recorded. Subsequently, the findings were described using the frequency table.

Results: Out of 200 children examined, 65.5% were girls, and 34.5% were boys. The average age of the patients was 7.70±3.71 years. The most common clinical presentations were: growth failure (38.5%), diabetes (21%), and abdominal pain (15.5%). The average Anti TTG (IgA) level of the patients in the study was 202.03, with a standard deviation of 146.05. Also, the weight z score for the age of the studied subjects varied between 64 and 147, and its average was 2.06 with a standard deviation of 10.85. The height Z score for age ranged between 6 and 6.7, with the average was 0.87, and a standard deviation of 1.63.

Conclusion: In the current study, growth failure was the most common clinical presentation. As children with celiac disease do not always have the typical presentations such as diarrhea, abdominal pain, steatorrhea, and bloating, it is recommended that the atypical presentations be also noted, particularly growth failure.

Key Words: Celiac disease, Children, Clinical Presentations, Growth failure.

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1- INTRODUCTION

Celiac disease or gluten-sensitive enteropathy (GSE) is an immune system-related enteropathy. In this disease, persistent sensitivity to wheat gliadin or other prolamins in barley is seen in genetically predisposed people. The impact of both genetic and environmental factors on the pathology of this disease has been described in detail (1).

The key features of celiac disease, which is an autoimmune disease, are genetic genotypes HLA-DQ2 and HLA-DQ8, environmental factors (gluten intake), and autoantigen against tissue transglutaminase tTG, which play an important role in the pathogenesis of the disease. More than 99% of celiac patients have HLA-DQ2 or HLA-DQ8, while this figure is 40% in the general population (2).

Celiac disease is one of the most common genetic diseases, which is strongly related to genetic predisposition; and several people from the same family may be affected by this disease. The prevalence of celiac disease in the world is reported to be 1% (3) and the prevalence of celiac disease among first-degree relatives varies between 2.8 and 17.2% (5, 4). The evaluation of the antibody profiles, such as anti-gliadin antibodies (both IgG and IgA), endomysial antibodies, and tissue transglutaminase, can be of great value for screening and early diagnosis of celiac disease (6).

A systematic review article on the comparison of diagnostic tests for celiac disease demonstrated that anti-endomysial tests using animal or human kits in both children and adults have a very high specificity (almost 100%) for diagnosis of the disease (7, 8).

Celiac is a multi-organ systemic disease, and its presentations can be very diverse. The common presentations of the disease include gastrointestinal symptoms, which are very common in children, and present during the first two years of life. These symptoms include delayed growth, chronic diarrhea, delayed puberty, vomiting, abdominal distension and pain, muscle wasting, anorexia, and irritability (2, 9).

With advancing child age, the presentations of the disease become extra-intestinal without any gastrointestinal symptoms, which can inflict all body organs. Therefore, short stature and small body structure can appear as the first extraintestinal presentations of celiac disease (9).

Extraintestinal presentations are detected in 60% of children with celiac disease (10). Iron deficiency anemia is diagnosed in 40% of children with celiac disease (11). It should be noted that in both children and adults, the most common extraintestinal manifestation of celiac disease is iron deficiency anemia. The prevalence of celiac disease among adult patients with microcytic anemia caused by iron deficiency which does not respond to oral iron treatment is reported as 8.5%. (12). It should be emphasized, however, that many patients without specific manifestations of the disease are identified only through screening tests of high-risk groups (12).

Generally, the administration of a gluten-free diet early after the diagnosis in children and adults is the mainstay of the treatment. In a celiac disease crisis, which is characterized by severe malabsorption, dehydration, and electrolyte disturbances, liquid therapy and electrolyte correction should be considered along with the administration of a gluten-free diet (13).

In developing countries, patients with celiac disease may become severely malnourished and can present the symptoms of a celiac crisis. Typically, these patients experience an exacerbation of symptoms by following the above diet and develop electrolyte disturbances, especially hypophosphatemia (14, 15).

During the first weeks and months after the diagnosis of the disease, nutritional support is vital for children with celiac disease. Therefore, these children and their parents should be visited every 3 to 6 months during the first year of diagnosis. They should be warned that even the consumption of small amounts of gluten can lead to tissue damage and long-term complications, even without any specific symptoms (16).

Celiac disease is a very common genetic disease in Iran and the world. Several studies have demonstrated that celiac disease is not only limited to the digestive system, and the disease can present a wide range of gastrointestinal and non-gastrointestinal manifestations. Celiac disease is not rare, as it was believed in the past, and its prevalence in Iran is approximately 1% of the general population (17).

Therefore, considering the high prevalence of this disease, we aimed to conduct a comprehensive study to investigate the initial clinical manifestations of this disease in children, which has a definitive cure and 100% recovery rate. This study is designed to spotlight the common manifestation of this disease. Since there have been limited studies in this regard hitherto, the results of this study can pave the way for further studies aimed at the early identification of patients with celiac disease in order to facilitate the commencement of treatment, as soon as possible, and prevent complications of gluten malabsorption.

2- METHODS

This is a descriptive cross-sectional study conducted on 200 children with celiac disease who presented to the gastroenterology clinic of Ghaem Hospital between 2016 and 2021.

All patients diagnosed with the celiac disease within the past 5 years were included in the study, and for all patients, a checklist including demographic information such as age, sex, weight, weight Z score, height, height Z score, the initial clinical presentation that led to the diagnosis, laboratory findings including CBC, Anti-TTG, IgA, as well as the pathological findings including biopsy and Marsh score were recorded. The data were analyzed by SPSS version 20 software, and the findings were described using a frequency table.

3- RESULTS

In this study, among 200 children with celiac disease, 131 (65.5%) were female, and 69 (34.5%) were male. The average age of the patients was 7.65 ± 3.59 years, with a minimum age of 1 year and a maximum age of 14 years. The mean and standard deviation of weight and height Z score was calculated. As can be seen in **Table 1**, the Z score of the weight for the age of the subjects varied between 147 and 64, and its mean was 2.06 with a standard deviation of 10.85. Height-for-age Z score also varied between 6.6 and 6.7, and its mean was 0.87 with a standard deviation of 1.63.

Table-1: Mean and standard deviation of Z score, weight, and height of the patients

Variable	Mean	SD	Minimum	Maximum
Weight-for-age Z Score	-1.23	1.35	-6.54	2.48
Height-for-age Z Score	-0.88	1.49	-4.3	4.7

The initial clinical manifestations of the patients were investigated and demonstrated in **Table 2** and **Fig. 1**. As can be seen, the initial clinical presentation among the patients included growth failure in 81 patients (40.5%), asymptomatic in 49

patients (24.5 %), abdominal pain in 31 (15.5 %), and chronic diarrhea in 16 (8%), anemia in 10 (5%), abdominal distension in 4 (2%), vomiting 3 (1.5%), constipation 3 (1.5%), and weakness in 3 patients (1.5%). Among asymptomatic patients in screening, 21% had diabetes, and 7% had a positive family history. The frequency of primary clinical presentation of patients is shown in **Fig. 1**.

Table-2: Frequency and frequency percentage of primary clinical manifestations of patients

Clinical manifestation	Frequency	Frequency (%)
Growth failure	81	40.5
Asymptomatic (screening)	49	24.5
Abdominal pain	31	15.5
Chronic diarrhea	16	8
Anemia	10	5
Abdominal distention	4	2
Constipation	3	1.5
Weakness	3	1.5
Vomiting	3	1.5
Total	200	100

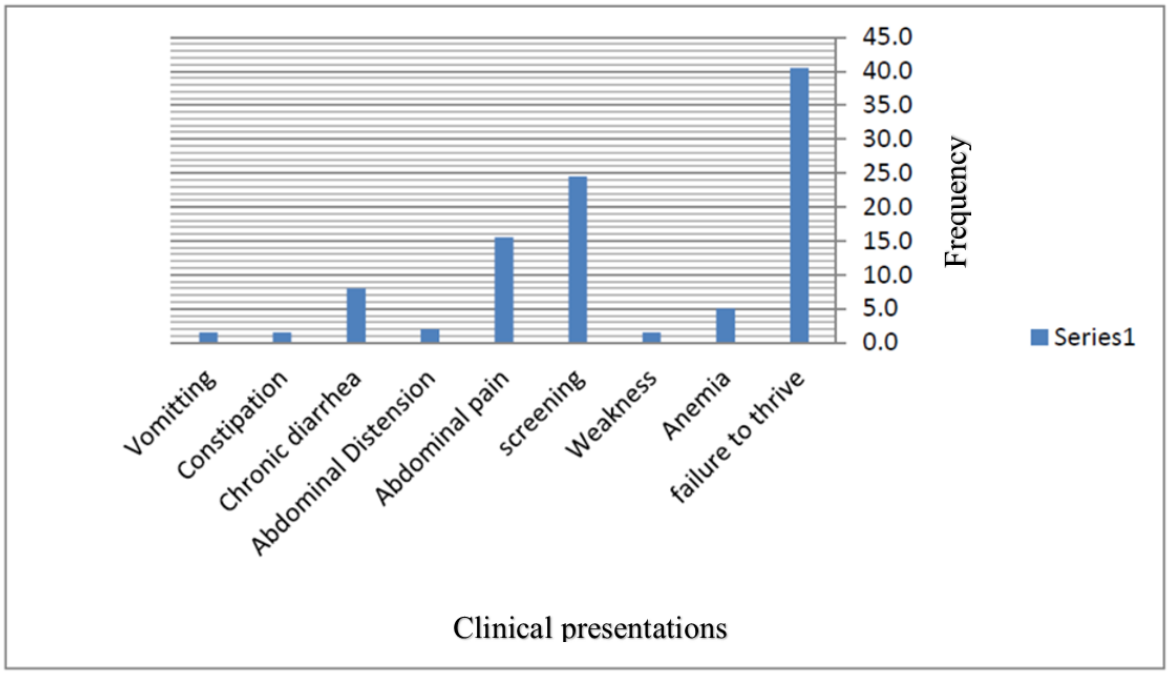

Fig. 1: Frequency of initial clinical presentations

The laboratory findings of the patients were also recorded. Changes in hemoglobin and Anti TTG (IgA) can be seen in **Table 3**. The mean hemoglobin of the patients was 11.87, with a standard deviation of 2.14. The minimum hemoglobin was 2.5 g/dl, and the maximum 15.5 g/dl. The mean Anti TTG (IgA) of the patients was 203.6 ±145.43, with a minimum of 4.7 mg/dL, and maximum of 799 mg/dL.

Table-3: Alternations in hemoglobin and Anti TTG (IgA) in patients

Variable	Mean	SD	Minimum	Maximum
Hemoglobin	11.87	2.14	2.5	15.5
Anti TTG(IgA)	203.63	145.43	4.7	799

Table 4 demonstrates the level of (IgA) in two groups of female and male patients in three sub-groups of less than 10 mg/dL, between 10 and 100 mg/dL, and higher than 100 mg/dL, As demonstrated in the table, Anti TTG level, in all subgroups, was significantly different between males and females (P Value = 0.012).

Table-4: Anti TTG (IgA) difference between the male and female patients

Anti TTG (IgA)	Female number (%)	Male number (%)	Total	P Value
<10	0 (0%)	2 (100%)	2 (100%)	0.012
100-10	30 (55.6%)	24 (44.4%)	54 (100%)	
>100	92 (72.4%)	35 (27.6%)	127 (100%)	
Total	122 (66.6%)	61 (33.3%)	183 (100%)	

Based on the results of this table, out of all 200 patients, only 2 patients had negative Anti-TTG (IgA). The mean Anti TTG (IgA) level in the patients was 144.7 mg/dL ± 104.63, with a minimum of 1.8 mg/dL, and maximum of 550 mg/dL.

The endoscopic findings were evaluated based on the severity of the mucosal damage of the small intestine according to the Marsh criteria. In endoscopy, 9 patients (5.92%) had a Marsh score of 1, 4 (2.63%) had a Marsh score of 2, and 139 cases (91.44%) had a Marsh score of 3. **Fig. 2** demonstrates the changes in the small intestine mucosa based on the Marsh scoring system.

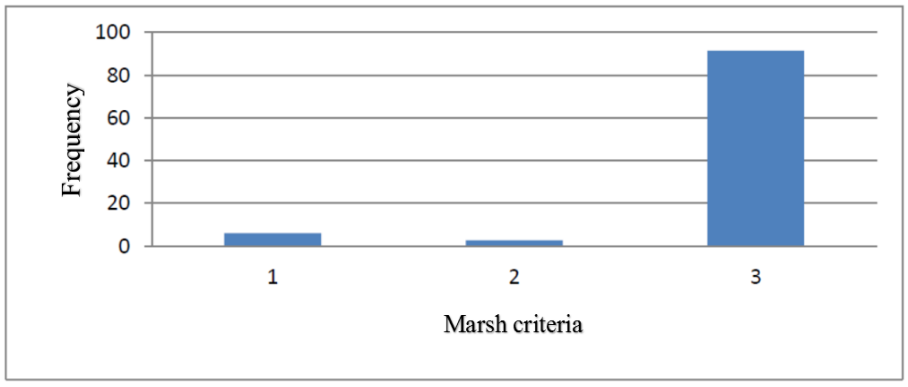

Fig. 2: Small intestine mucosal damage according to Marsh criteria

The difference in Marsh scores between boys and girls is tabulated in **Table 5**. As presented in **Table 5**, there was no significant difference between girls and boys in terms of Marsh score (P Value: 0.253). In this study, the inferential findings were also investigated. The relationship between the clinical presentation and the Marsh score can be seen in **Table 6**. Based on these results, the majority of the clinical presentations were recorded in patients with a Marsh score of 3.

Table-5: Marsh score difference between boys and girls

Variable	Marsh 1	Marsh 2	Marsh 3	Total	P Value
Female	8 (8.2 %)	3 (3.1%)	87 (88.8%)	98 (100%)	0.253
Male	1 (1.9%)	1 (1.9%)	52 (96.3%)	54 (100%)	

Table-6: The relationship between clinical manifestations and Marsh score

Clinical presentation\Marsh score	Marsh 1	Marsh 2	Marsh 3	Total
Growth failure	4 (44.4%)	2 (50%)	56 (41.2%)	62 (41.6%)
Asymptomatic (screening)	2 (22.2%)	1 (25%)	34 (25%)	37 (24.8%)
Abdominal pain	1 (11.1%)	1 (25%)	23 (16.9%)	25 (16.8%)
Chronic diarrhea	1 (11.1%)	0 (0%)	10 (7.4%)	11 (7.4 %)
Anemia	1 (11.1%)	0 (0%)	6 (4.4%)	7 (4.7%)
Abdominal distention	0 (0%)	0 (0%)	3 (2.2%)	3 (2%)
Constipation	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)
Weakness	1 (11%)	0 (0%)	6 (4.4%)	7 (4.7%)
Vomiting	0 (0%)	0 (0%)	3 (2.2%)	3 (2.2%)

4- DISCUSSION

Celiac disease (CD) or gluten-sensitive enteropathy (GSE) is an immune system-related enteropathy that develops as a result of malabsorption caused by mucosal damage to the small intestine. This malabsorption is caused by persistent sensitivity to wheat gliadin or other dietary prolamins in genetically predisposed patients (19, 18). Serological screening of healthy individuals in different parts of the world demonstrated that the incidence of this disease is between 0.5% and 1% (20-20). Similar incidence rates are reported in Iran (23).

This study aimed to investigate the initial clinical presentations of patients with celiac disease. Out of 200 children with celiac disease, 131 (65.5%) were female, and 69 (34.5%) were male. The average age of the patients was 7.65 ± 3.59 years, with a minimum age of 1 year and a maximum age of 14 years. The higher proportion of female patients with celiac disease in this study is consistent with the findings of other similar studies. For example, in the study of Alvi et al., conducted on 46 children with an average age of 6.7 years, it was demonstrated that 54% of the patients were female (24).

The main clinical presentations among the patients included growth disorder in 81 patients (40.5%), asymptomatic in 49 (24.5%), abdominal pain in 31 (15.5%), chronic diarrhea in 16 (8%), anemia in 10 (5%), abdominal distension in 4 (2%), vomiting in 3 (1.5%), constipation in 3 (1.5%), and weakness in 3 patients (1.5%). Among asymptomatic patients, 21% had diabetes in screening, and 7% had a positive family history.

The results of the current study demonstrated that the most common clinical presentation of the disease was the failure to thrive, and children with this presentation are considered at high-risk for celiac disease. Consistent with our results, Alvi's retrospective study in 2010 reported growth failure in 41 people (98.1) as the most common clinical presentation among the participating childrenS (24). Other clinical presentations were chronic diarrhea in 38 patients (82.6%), pallor in 44 (80%), irritability in 33 (71.7%), abdominal distention in 30 (65.5%),

clubbing in 8 (17.4%), rickets in 4 (8.7%) and edema in 3 patients (6.5%) (24).

Moreover, in the study by Poddar et al., in 2006, growth failure (91%) was reported as the most common clinical presentation. Other clinical presentations were weight loss (87%), chronic diarrhea and anemia, each in 84%, and short stature in 60% of the patients (25).

Another case-control study by Hoffenberg et al. in America included 118 children with celiac disease (26). These patients were divided into two anti-TTG negative and anti-TTG positive groups. 100 children were anti-TTG negative, and 18 children were anti-TTG positive. The most common clinical presentations in the Anti-TTG positive group included abdominal pain (39%), restlessness/drowsiness (34%), constipation (33%), abnormal weight gain (28%), abdominal distension, diarrhea and asymptomatic (22% each) and Short stature (11%) was reported. In the Anti TTG-negative group, the most common presentations were asymptomatic (87%), constipation (7%), abdominal pain, abnormal weight gain, and short stature (3% each) (26).

Khuhro, 2005, in Pakistan, followed up approximately 100 children with celiac disease for a period of 6 months to investigate the frequency of common presentations of celiac disease (27). The ratio of boys to girls was 1 to 1.2. The most common clinical presentation among girls was diarrhea (75.9%). Other clinical manifestations among girls were growth failure (74%), edema (42.5%), and clubbing (27.8%). Among boys, the most common clinical presentation was diarrhea (87%), followed by growth failure (85%), edema (32.6%), and clubbing (34.4%) (27).

In another study by Kuloglu et al., 109 children with celiac disease were included. 66 of them had typical presentations of celiac disease, 41 had atypical presentations, and 2 were asymptomatic. Diarrhea (53.2%) was the most common clinical presentation, followed by growth failure (45.9%), short stature (42.2%), and abdominal pain (40.4%) (28).

As elaborated in our study, growth failure was the most common clinical presentation of children with celiac disease. In some of the mentioned studies, it was also the first or the second of the common presentations. Therefore, it can be concluded that a child with celiac disease does not always present with diarrhea or other digestive presentations. In fact, according to our findings, after growth failure, asymptomatic clinical presentation is most common, and diagnosis is based on screening. Therefore, screening for celiac disease should be conducted if there are any indications for screening (such as celiac disease in first-degree relatives, autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, autoimmune liver disease, Down syndrome, Turner and Williams syndromes, and selective IgA deficiency). In this manner, the potential cases of the disease should be identified in the early stages of disease, and a gluten-free diet should be prescribed to prevent complications.

The results of the present study can pave the way for further studies to be conducted with the aim of timely identification of patients with celiac disease and the initiation of treatment for the prevention of gluten malabsorption complications.

5- CONCLUSION

Results of the study revealed a higher prevalence of celiac disease in girls. It was also found that the most common clinical presentation among the patients was growth failure in 40.5%. Therefore, children with this clinical presentation are considered a high-risk group for the disease. Also, the other clinical manifestations of the children in the study

were: being asymptomatic in 49 patients (24.5%), abdominal pain in 31 (15.5%), and chronic diarrhea in 16 cases (8%); the rest of the symptoms were also discussed in detail. Among the asymptomatic patients, 21% had diabetes in the screening and 7% had a positive family history. Therefore, it should be emphasized that a child with celiac disease does not always have the typical presentations of the disease. Therefore, screening is of vital importance in high-risk groups.

6- ETHICAL CONSIDERATIONS

In this research, the principles of respecting the rights of the patients and establishing trust were observed. The names and surnames of the patients were not recorded in the checklist; and the patients and their families were ensured about the confidentiality of all information. This research was approved by the ethics committee of Mashhad University of Medical Sciences with the code of IR.MUMS.fm.REC.1395.274.

7- CONFLICT OF INTERESTS

None.

8- ACKNOWLEDGMENT

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