

The Prevalence of Celiac Disease in Children Suffering Chronic Constipation: A Study in the Western Region of Iran

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Abstract

Background: Although celiac disease is considered one of the preconditions and predisposing factors for chronic constipation in children, accurate statistics on the prevalence of the celiac disease among Iranian children with chronic functional constipation is not available. The present study aimed to determine the prevalence of celiac disease in children suffering from chronic constipation.

Methods: This cross-sectional study was conducted on 360 children over one year of age with chronic constipation. A sample of venous blood was extracted from all subjects and the serologic studies of total IgA, IgA TTG, and IgG TTG were performed using the ELISA technique. Upper gastrointestinal endoscopic biopsy was also scheduled for those children with the positive IgA TTG.

Results: Two patients with raised levels of both IgA and IgA TTG antibodies were assessed by endoscopy, and a definitive diagnosis of celiac disease was confirmed in one of them leading to the overall prevalence of 0.27% for celiac disease among children with chronic constipation.

Conclusion: In total, 0.27% of children with chronic constipation in the area under investigation suffer from celiac disease.

Key Words: Celiac Disease, Children, Constipation, Prevalence.

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1- INTRODUCTION

Constipation is one of the most common childhood problems that account for 3% of pediatric visits and 25% of pediatric gastroenterology consultations (1). The prevalence of childhood constipation is completely different in different societies due to a variety of genetic and environmental reasons including lifestyle, nutritional habits, genomic variants, and some clinical conditions such as anorectal abnormalities, Hirschsprung's disease, neuro ventricular disorders, spinal problems, pelvic floor muscle dysfunction, metabolic disorders, toxins, and allergies to cow's milk. (2,3). In this regard especially in some races such as Caucasians, chronic constipation can be found in a notable number of patients with gastrointestinal-related complications such as celiac disease; and according to recent reports, about 15% of celiac patients with gastrointestinal complaints experience constipation (4,5).

Celiac disease or enteropathy is a chronic gluten-sensitive nutritional disease associated with abnormal immune responses that ultimately cause malabsorption (6). The gluten in wheat, barley, and oats is closely associated with damage to the small intestine and in the end impedes the absorption of nutrients (7). The disease is the result of an interaction between gluten and the immune system, and genetic and environmental factors (8). Acquired immune response leads to a very specific interaction between selected gluten peptides and antigen-containing T class adaptation complex (II HLA-DQ2/8) that plays a pathogenic role in celiac disease (9). The most important genetic factor in the development of celiac disease is HLA DQ2/DQ8, which increases the chance of celiac disease by about 40%. Many environmental factors also contribute to the onset of celiac disease including viral infections such as rotavirus, which increase the risk of celiac

disease in children (10). Celiac disease is also associated with autoimmune diseases, especially type 1 diabetes, autoimmune thyroiditis, autoimmune hepatitis, Addison disease, and multiple sclerosis (11, 12). Some of these patients have a mild illness and may have no symptoms or only mild symptoms. Overall, celiac disease covers a wide range of clinical manifestations (severe to asymptomatic diarrhea); however, in children, clinical symptoms vary by age group. Malnutrition syndrome is predominant in infants. Diarrhea with abdominal pain, distension, vomiting, anorexia, and FTT are other symptoms of celiac disease in children (13, 14). In older children and young adults, the disease usually presents with milder symptoms such as constipation, anemia, osteopenia, and developmental limitations. The association of neurological diseases with celiac disease is also very common. At first, celiac disease was thought to present only with gastrointestinal symptoms, but over time, extraintestinal symptoms such as neurological manifestations were also observed in patients with celiac disease (15).

The prevalence of celiac disease in children is significant, but long delays between the onset of symptoms and diagnosis often occur, leading to undiagnosis in some cases, and some cases may not be detected until adulthood (16). Numerous studies show that children with celiac disease have gastrointestinal symptoms such as diarrhea with stunted growth, abdominal pain, vomiting, constipation, and bloating, but there is currently little information about the prevalence of celiac disease with these gastrointestinal symptoms in children (17). On the other hand, almost all outpatients in pediatric clinics and outpatient clinics of pediatric gastroenterology are due to constipation, which indicates the high prevalence of this disease in children. At present, no studies have been conducted on the prevalence of celiac disease in children

who have been referred for constipation in our area. The present study aimed to determine the prevalence of celiac disease in children suffering from chronic constipation.

2- MATERIALS AND METHODS

This cross-sectional study was conducted on 360 children over one year of age with chronic constipation that referred to two referral centers in Shahrekord city, Iran, in 2020 and 2021. The definitive diagnosis of functional constipation was based on the Rome III criteria. According to Rome III criteria, a diagnosis of functional constipation is determined when at least 2 of the following manifestations have been present for the last 3 months with the onset of clinical symptoms at least 6 months before diagnosis. The manifestations include: 1) hard or lumpy stools on more than 25 percent of defecations; 2) straining on more than 25 percent of defecations; 3) sensation of anorectal blockage/obstruction on more than 25 percent of defecations; 4) sensation of incomplete evacuation on more than 25 percent of defecations; 5) <3 defecations per week and 6) manual maneuvers on more than 25 percent of defecations (18). The checklist was completed and registered by a pediatric gastroenterologist. Reluctance to participate in the research process was the only exclusion criterion.

A sample of venous blood was extracted from all subjects and the serologic studies of total IgA and IgA TTG were performed using the ELISA technique. In cases where the reported values of total IgA were under the normal limit, serum IgG TTG was then measured. Normal range of Total IgA is 0.22 – 1.18 g/l and of IgA TTG is 0 -18 U/ml (18). The specificity for IgA and IgG, and TTG was 93.8 and 89.9%, and 96.0%, respectively, and 97-98.0%, specificity. Upper gastrointestinal endoscopic biopsy was also scheduled for those children with the positive IgA TTG.

During this procedure, multiple biopsy specimens from the duodenum and bulb were obtained for histological analysis. Using light microscopy and morphometric techniques, formalin-fixed biopsy specimens were examined by hematoxylin and eosin staining. Villous height and crypt depth were measured and the reduction in villous height/crypt depth ratio was considered as the diagnostic criteria for celiac diseases (19). Finally, the prevalence of celiac disease among children with functional constipation was estimated.

2-1. Data Analysis

As for the descriptive analysis, the results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. As for the inferential statistics, continuous variables were compared using a t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. P-values of ≤ 0.05 were considered statistically significant. The statistical software SPSS version 23.0 for Windows (IBM, Armonk, New York) was used for the analyses.

3- RESULTS

From among the 360 studied patients with chronic constipation, 160 (44.5%) were boys and 200 (55.5%) were girls with a mean age of 64.17 ± 37.55 months. Evaluation of serum level of total IgA antibody in children with chronic constipation showed that the mean level of this antibody was revealed to be 107.74 ± 69.2 ranged 10 to 411 (**Table 1**).

The mean level of total IgA antibody in girls was significantly higher than that in boys ($p = 0.002$). Moreover, the average level of IgA TTG antibody was 4.33 ± 2.40 ranging from 0 to 23.90, and was

significantly higher in boys than in girls (p=0.008) (**Table 2**).

Table-1: Age, Serum level Anti.TTG.IgA and total IgA in children with chronic constipation in the study population

Variables	Number	Min	Max	Mean \pm SD
Age (month)	360	11	180	64.17 \pm 37.55
Total IgA	360	10	411	106.74 \pm 69.25
Anti.TTG.IgA	360	0	23.90	4.33 \pm 2.40

Table-2: Serum level Anti.TTG. IgA. Total IgA in children with chronic constipation in terms of sex

Variables	Number	Mean \pm SD	p-value
Total IgA	Boy	160	110.84 \pm 5.58
	Girl	200	103.48 \pm 4.83
Anti.TTG.IgA	Boy	160	4.40 \pm 0.21
	Girl	200	4.28 \pm 0.15

In total, 357 children (99.2%) had abnormally high levels of total IgA antibody as well as low levels of IgA TTG antibody that thus were not candidates for endoscopic assessment. Out of the three residual cases, one of them had both a low level of biomarkers and a low level of IgG TTG antibody that was thus not planned for endoscopy. Therefore, only two of these patients with raised levels of both IgA and IgA TTG antibodies were assessed by endoscopy; and definitive diagnosis of celiac disease was confirmed in one of them leading to the overall prevalence of 0.27% for celiac disease among children with chronic constipation.

4- DISCUSSION

Constipation can be an early manifestation of celiac, as a chronic inflammatory disease. Although this complication may be an unusual manifestation of celiac disease, celiac disease should be considered as a possible diagnosis in children presented with chronic constipation, whose routine test results are normal. Failure to diagnose and treat it early can cause morbidity for the person and high costs for the health care

system. However, in recent years, more knowledge from physicians and the progress made in the field of diagnostic tests for this disease has led to the diagnosis of the disease in the early stages. Because research in Iranian children with celiac disease is limited and early diagnosis of this treatable disease can have significant effects in preventing its complications, this study was performed to evaluate the prevalence of celiac disease in a sample of Iranian children with chronic constipation.

For diagnosis of celiac disease, if the serological test is positive, endoscopy and biopsy are performed and histological changes are made for definitive diagnosis of celiac disease based on Marsh classification. In Marsh, I, the natural appearance of the esophagus is accompanied by an increase in lymphocytes inside the epithelium. In March II, the height of the villas is shortened, which is accompanied by hyperplastic crypts. Marsh III is also associated with hyperplastic crypts and a moderate to severe reduction of the willows. Most celiac patients are classified as Class III at the time of diagnosis (19).

In the present study, the results showed that out of 360 children with chronic constipation, 357 (99.16%) showed high IgA levels and low IgA TTG levels. Out of the remaining 3 cases (0.83%), an IgG TTG test was performed for the person who had both low total IgA and low TTG IgA levels. Finally, for the only 2 patients (0.55%) who had high total IgA levels and at the same time high TTG level IgA, the endoscopic assessment was scheduled. Histological results of endoscopic specimens of these two patients showed that only one of them (0.27%) with Marsh III was considered for a definitive diagnosis of celiac disease. The results of this study show that the prevalence of celiac disease in children with chronic constipation at our clinic was only 0.27%. Some studies have been performed on patients with functional constipation concerning the determination of the rate of celiac disease. The results of these studies have been different from that of the present study; due to the different dimensions of the subject. The prevalence of celiac disease has been reported to be 0.5-1% of the population in many countries (20, 21). The prevalence of celiac disease in the normal population in Shiraz, Iran is 0.6% (22). The prevalence of latent celiac disease has also been reported to be 0.5% in a study in Tehran (23). Pelleboer et al. (24) conducted a study on 370 children with functional constipation and found that out of 370 children with constipation, 7 (1.89%) had biopsy-proven celiac disease. In the study by Chogle and Saps (25), on 7472 children with functional constipation, 1731 patients were tested for celiac antibodies, among whom 55 (3.17%) had a high level of IgA TTG and 29 (1.67%) had positive celiac disease. Maki et al. (26) in a study, to investigate the prevalence of celiac disease among children in Finland, concluded that the prevalence of the celiac disease among Finnish students is at least 1 in 99 cases. The prevalence of celiac disease in various

Middle Eastern countries has been reported to be almost similar to that in the West (27). In another study in North America (28), the prevalence of celiac disease in children with diabetes was reported to be 1-1.4% and in Brazil (29) it was reported to be at least 4.8%. Differences in the prevalence of celiac disease in different countries can be due to several factors, including methodological causes, differences in the type of antibodies used for screening, and geographical differences, including environmental and genetic factors. Celiac disease may have different manifestations. Because limited studies have been done on the prevalence of celiac disease in children who have been referred with constipation; and determining the prevalence of celiac disease in patients with functional constipation is an important aspect of diagnosing the disease, all of which can be considered advantages of the present study. Nonetheless, the low sample size was a limitation of this study.

5- CONCLUSION

The results of the present study showed that out of a total of 360 children with chronic constipation, only one case was definitively diagnosed with celiac disease based on the results of Marsh III histopathology. Due to the low prevalence of celiac disease in children with chronic constipation referred to our clinics, it seems that celiac screening tests in children with chronic constipation are no longer required unless the patient has other clinical signs of celiac disease.

6- ETHICAL CONSIDERATIONS

This study protocol was approved by the ethics committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1398.163). Initially, the necessary explanations about the objectives of the study were given to the parents of the children, and written consent

was obtained from them before the start of the project.

7- ACKNOWLEDGMENTS

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8- CONFLICT OF INTEREST

None.

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