Is celiac disease misdiagnosed in children with functional constipation?

Sezin Akman[1], Özlem Şahaloğlu[2], Ceyhun Dalkan[2], Nerin Nadir Bahçeciler[2], Çiğdem Arıkan[2]

[1]Department of Pediatrics, Balıkesir University School of Medicine, Balıkesir, Turkey
[2]Department of Pediatrics, Near East University School of Medicine, Cyprus

Cite this article as: Akman S, Şahaloğlu O, Dalkan C, Bahçeciler NN, Arıkan C. Is celiac disease misdiagnosed in children with functional constipation? Turk J Gastroenterol 2018; 29: 210-4.

ABSTRACT

Background/Aims: Functional constipation is one of the common problems in childhood, and it comprises approximately 5% of the pediatric outpatient clinical applications. On the other hand, celiac disease (CD) is an immune enteropathy with the prevalence between 1/150 and 1/200. In addition to the classical symptoms of the disease such as diarrhea and weight loss, the incidence of atypical symptoms is increasing. This study aims to determine the prevalence of CD in patients with chronic constipation.

Materials and Methods: The study was conducted between 2010 and 2012 and included 1046 children (range, 2-18 y; median, 11.4 y) diagnosed with chronic constipation according to the Rome III criteria. Serum immunoglobulin A, tissue transglutaminase, and/or anti-endomysial antibodies were examined. The patients with serological positive results were subjected to upper gastrointestinal system endoscopy and duodenal biopsy to confirm the diagnosis of CD.

Results: Blood tests were positive in 36 patients (3.25%). One of the patients had Hashimoto's thyroiditis, and 4 patients had short stature. Endoscopic findings included nodularity in bulbus and duodenal mucosa (n=16), scalloping fold (n=13), and normal mucosa (n=5). Histopathologic findings revealed that 10 patients had total villous atrophy, 24 patients had subtotal and partial villous atrophy, and 34 patients had intraepithelial lymphocyte infiltration. All patients followed a gluten-free diet, resulting in a resolution of symptoms.

Conclusion: In the present study, a CD ratio of 1:28 was diagnosed in chronically constipated children. The use of screening tests for CD should be considered in children with conventional treatment-resistant constipation.

Keywords: Celiac disease, children, constipation, misdiagnosis

INTRODUCTION

Chronic constipation is a common problem during childhood. The definition of chronic constipation has changed over the years and has been standardized according to the Rome criteria, which defines it as a decrease in the frequency of defecation or painful defecation for at least 2 months. The prevalence of chronic constipation is reported to be 0.3%-8% in the general population. Most cases involve abdominal pain, rectal pain, soiling, and poor appetite, which can be a sign of other organic diseases such as celiac disease (CD) (1-5).

Celiac disease is an immune-mediated, gliadin-triggered intestinal inflammation in genetically susceptible individuals. The prevalence of CD is approximately 1/150-200 in most countries and 0.45%-1.15% in healthy Turkish school children (6-9). The manifestation of CD has also changed over the years; instead of classical symptoms such as diarrhea, growth retardation, and abdominal distention, atypical symptoms such as chronic constipation may be the only signs of CD. Abdominal pain, constipation, and meteorism are very common complaints during admission in pediatric gastroenterology clinics and are generally accepted as functional gastrointestinal disease (FGID) if there is a lack of alarm symptoms such as abdominal distention, bilious vomiting, bloody stools in the absence of anal fissures, sacral dimple, perianal fistula, and abnormal position of anus; these symptoms are also shared by CD (10-12). Despite the definition of functional diseases, CD is not routinely excluded in patients with chronic constipation, and there is no general recommendation to routinely test them (13,14).

This study aims to determine the frequency of CD in children with chronic functional constipation unresponsive to conventional treatment.

ORCID IDs of the authors: S.A. 0000-0002-6515-8066; Ö.Ş. 0000-0003-4915-0571; C.D. 0000-0003-4156-9706; N.N.B. 0000-0003-1337-2041.

Address for Correspondence: **Sezin Akman** E-mail: **aa.sezin@gmail.com**
Received: **July 20, 2017** Accepted: **October 18, 2017**

DOI: **10.5152/tjg.2018.17369**

MATERIALS AND METHODS

The study was conducted between 2010 and 2012 and included 1046 children (range, 2-18 y; median, 11.4 y) with diagnosed chronic constipation according to the Rome III criteria and who were resistant to conventional treatment. The constipated children whose symptoms had not been resolved after ≥6 weeks of the conventional treatment (i.e., high-fiber diet and osmotic agents) were considered as resistant patients. The children who were previously diagnosed with CD or immuno deficiency or who had exhibited chronic gastrointestinal or endocrinological disorders were excluded from the study. A blood sample was obtained from each child, and serum immunoglobulin A (IgA), immunoglobulin G (IgG), anti-tissue transglutaminase (anti-tTG), and/or anti-endomysial antibodies (EMA) were used for CD diagnosis. Serologic tests were performed using an available enzyme-linked immunosorbent assay (AESKU Diagnostics 7503, Düsseldorf Germany). The patients with higher-than-normal anti-tTG and EMA levels and a normal serum IgA were subjected to upper gastrointestinal endoscopy and gastrointestinal biopsy under sedation to confirm the diagnosis of CD. The gastrointestinal endoscopy was performed with pediatric upper gastrointestinal endoscope (Fujinon EG530N flexible video gastroscope, Fujinon Inc. NJ 07470 USA) after obtaining informed consent from parents. A minimum of five intestinal biopsy specimens were obtained from different sites of the first, second, and third part of the duodenum, and a routine biopsy was performed at the stomach and esophagus. The endoscopic findings were reported. All endoscopic samples underwent standard histological processing that was previously defined. The biopsy specimens were evaluated according to the Marsh criteria by two expert pathologists (15). Patients with Marsh 3 and 4 were recommended gluten-free diet. All the patients with CD were re-evaluated for constipation during each periodic examination. In the CD patients, dietary compliance was evaluated according to the interview with patients and improvement in serological parameters. The study was approved by the Medical School Ethics Comittee. Informed consent forms were provided by all parents after provision of written and verbal information by physicians.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22 for Windows (IBM Corp.; Armonk, NY, USA) was used for data analysis. Statistical differences were determined using chi-squared and Student's *t*-tests. A p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 1046 children diagnosed with chronic constipation were included in the current study (550 female and 496 male). The median age was 11.4 y (range 2-18 y). The clinical findings of the patients were in accordance with the Rome III criteria. Antibodies were found to be positive in 36 patients (3.25%). Anti t-TG was positive in those 36 patients, and 34 of them underwent upper gastrointestinal endoscopy, wherein duodenal biopsy specimens were obtained. The endoscopic findings of patients are summarized in Table 1. Histopathologic findings revealed that 10 patients had total villous atrophy, 24 had subtotal and partial villous atrophy, and 34 had intraepithelial lymphocyte infiltration. All CD patients had both intraepithelial lymphocyte infiltration and villous atrophy at different rates (Table 1). One of the patients had Hashimoto's thyroiditis, and 4 patients had short stature. The dietary compliance was found to be sufficient in all CD patients. All the patients followed a gluten-free diet with complete resolution of constipation in 26 patients within the first 6 months. Eight patients required constipation medication such as osmotic laxatives, despite strict adherence to the diet.

DISCUSSION

Constipation is one of the important motility disorders during childhood. Most cases do not have any detectable organic pathology and are accepted as functional disorders, such as irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain. In many FGIDs, it is still difficult to decide the further steps when the etiology remains uncertain. Although CD should be included in the differential diagnosis of FGID, there is no general recommendation regarding screening for these children. Instead, there are studies that advise

Table 1. Endoscopic and histopathologic findings of CD patients

Endoscopic findings	n*
Nodularity in bulbus and duodenal mucosa	16
Scalloping fold	13
Normal mucosa	5
Histopathologic findings	n*
Total villous atrophy	10
Subtotal + partial villous atrophy	24
Intraepithelial lymphocyte infiltration	34

n*: number of cases

testing for CD in some FGID patients (2,11,13,16,17). In the current study, biopsy-proven CD was detected in 3.25% of children with functional constipation, which is common in childhood, particularly among toddlers and school children. The diagnosis is based on the Rome III criteria, which depend on a symptomatic questionnaire. One important resource is the Rome criteria and classification system to diagnose symptoms and to manage children with suspected functional constipation. There is no specific diagnostic marker for this disorder. The need for knowledge on association between CD and functional constipation has been increasing since several years. Pelleboer et al. (14) performed a study on 370 children exhibiting functional constipation. The study found that 1.89% of cases had biopsy-proven CD. They concluded that CD is significantly higher in patients with constipation who did not respond to laxative treatment.

Chogle et al. (18) included 1731 children in their study, and all of them were screened for celiac antibodies; 55 (3.2%) had elevated anti t-TG levels and 29 (1.7%) had biopsy-positive CD. Only 0.2% (n: 2) of the patients were diagnosed with CD had constipation as their sole presenting symptom. Other patients had additional complaints such as abdominal pain, vomiting, abdominal distension, growth abnormalities, diarrhea, or a combination of the above symptoms. They did not recommend CD screening in patients who had only constipation due to high costs of screening tests for CD. In Dehghani's study, the frequency of CD in 101 constipated children aged 2-18 years was not significantly higher than the general population (0.99%) that was similar to the results by Chogle, and screening for CD was not recommended for this population (13). Cakir et al. (19) reported that celiac serology was positive in 8 out of 313 (2.5%) children with chronic constipation, and these cases were evaluated as potential CD after histopathological examination.

Short stature is frequently detected as atypical feature at presentation. Additionally, other atypical presentation findings such as anemia, osteoporosis, abnormal liver enzymes, arthralgia, neuropathy, and delayed puberty are observed in CD patients (20). Off all the patients, 4 patients had short stature and 1 patient had autoimmune thyroiditis that was diagnosed after CD. None of the patients had gastrointestinal symptoms other than constipation. On the other hand, constipation that is resistant to conventional treatment, particularly among young age is frequently misdiagnosed as functional constipation or other gastrointestinal disease. Resolution of all symptoms was expected following dietary restriction. But in these series, 8 out of 34 patients with CD partially responded to dietary therapy while continuing intermittent intake of laxative drugs. This may be explained by multifactorial etiology of functional constipation, such as genetic tendency, neuronal abnormality, and visceral hyperalgesia. However, we could not explain the reasons for the children developing constipation instead of diarrhea or whether it was another group of motility disorders related to gliadin peptid. Bowel motility could be impaired by the gliadin peptide based on inflammation or directly by the peptide. Furthermore, despite dietary therapy, some CD patients required medication to treat constipation; diet is not enough for the relief of constipation in some patients (21). Thus, coexistence due to the high frequency of both conditions in the general population may be an explanation. In summary, we need to perform a long-term follow up with these patients to answer the remaining questions. Furthermore, motility studies should be performed before and after dietary therapy, which may help to exclude the role of gliadin in the development of constipation.

Motility abnormalities are also a hallmark of functional bowel disorders such as IBS, where it has been proposed as an underlying mechanism for symptom generation (diarrhea, constipation, and bloating) (22). Substantial overlap of symptoms and comorbidities may occur between IBS, constipation, and other FGIDs. In these patients, the CD prevalence rates are reported to be between 2% and 19%. All of these studies consisted of adult patients (10, 23-30). Fasano et al. (10) conducted a large, comprehensive study on patients with IBS symptoms and reported that within a subgroup of patients who had constipation-dominant IBS, the prevalence of CD was 2.6%. Some investigators reported that the IBS symptoms were relieved with a gluten-free diet, and this condition was accepted as gluten intolerance. But these patients had normal duodenal mucosa and negative serologic tests. Considering the current reports, CD must be separately considered from the diagnosis of IBS (23,25-27).

The limitation of this study is the lack of a control group consisting of asymptomatic healthy children. This may help to provide further recommendations. The other limitation is a lack of genetic testing for HLA- DQ status of patients. This is largely due to the fact that a person who has DQ2 and/or DQ8 is susceptible to the development

of CD at any time during their lives. We were unable to predict whether CD serology negative children with constipation are not diagnosed with CD. A long-term follow-up may be necessary for this reason. In our study, CD prevalence was not compared among constipated children resistant and responsive to treatment; this can be regarded as another limitation.

Overall, a ratio of 1:28 of CD was diagnosed in chronically constipated children in this trial study. To the best of our knowledge, this is the most comprehensive study evaluating the prevalence of CD among children with functional constipation resistant to treatment in our country, demonstrating a prevalence of 1:28 that is relatively high. Additionally, typical clinical findings of CD were absent in most cases. Therefore, we believe that the use of screening tests for CD should be considered in children with functional conventional treatment-resistant constipation. This strategy assists in an early diagnosis and prevents unnecessary time and money consumption and prolonged laxative treatments.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Near East University (Decision Date: 14.01.2010; Decision No: 2010-22).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.A., C.A.; Design - S.A., C.A., N.B.; Supervision - O.Ş., C.D.; Resource - S.A., C.A.; Materials - S.A., O.Ş.; Data Collection and/or Processing - C.D., O.Ş.; Analysis and/ or Interpretation - S.A., C.A., N.B.; Literature Search - S.A., C.A.; Writing - S.A., C.A.; Critical Reviews - S.A., C.A., N.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by Near East University School of Medicine.

REFERENCES

1. Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. Nat Rev Gastroenterol Hepatol. 2011; 8: 502-11. [CrossRef]
2. Gfroerer S, Rolle U. Pediatric intestinal motility disorders. World J Gastroenterol 2015; 21: 9683-7. [CrossRef]
3. Motta ME, Silva GA. [Signs and symptoms associated with chronic constipation] J Pediatr (Rio J) 2000; 76: 222-6. [CrossRef]
4. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006; 130: 1377-90. [CrossRef]
5. Silverman AH, Berlin KS, Di Lorenzo C, et al. Measuring Health-Related Quality of Life With the Parental Opinions of Pediatric Constipation Questionnaire. J Pediatr Psychol 2015; 40: 814-24. [CrossRef]
6. Hill ID, Dirks MH, Liptak GS, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40: 1-19. [CrossRef]
7. Egritas O, Dalgic B. Celiac disease in children. Journal of Pediatric Sciences 2011; 3: 99.
8. Dalgic B, Sari S, Basturk B, et al; Turkish Celiac Study Group. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol 2011; 106: 1512-7. [CrossRef]
9. Ertekin V, Selimoğlu MA, Kardaş F, Aktaş E. Prevalence of celiac disease in Turkish children. J Clin Gastroenterol 2005; 39: 689-91. [CrossRef]
10. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163: 286–92. [CrossRef]
11. Shannahan S, Leffler DA. Diagnosis and updates in celiac disease. Gastrointest Endosc Clin N Am 2017; 27: 79-92. [CrossRef]
12. Shalaby SA, Sayed MM, Ibrahim WA, Abdelhakam SM, Rushdy M. The prevalence of coeliac disease in patients fulfilling Rome III criteria for irritable bowel syndrome. Arab J Gastroenterol 2016; 17: 73-7. [CrossRef]
13. Dehghani SM, Ehsaei Z, Honar N, Javaherizadeh H. Frequency of Celiac Disease in children with chronic functional constipation in Shiraz-Iran. Middle East J Dig Dis 2015; 7: 166-9.
14. Pelleboer RA, Janssen RL, Deckers-Kocken JM, et al. Celiac disease is overrepresented in patients with constipation. J Pediatr (Rio J) 2012; 88: 173-6. [CrossRef]
15. Marsh MN, Johnson MW, Rostami K. Mucosal histopathology in celiac disease: a rebuttal of Oberhuber's sub-division of Marsh III. Gastroenterol Hepatol Bed Bench 2015; 8: 99-109.
16. Choung RS, Rubio-Tapia A, Lahr BD, et al. Evidence against routine testing of patients with functional gastrointestinal disorders for celiac disease: a population-based study. Clin Gastroenterol Hepatol 2015; 13: 1937-43. [CrossRef]
17. Squires JE, Fei L, Cohen MB. Role of celiac disease screening for children with functional gastrointestinal disorders. JAMA Pediatr 2014; 168: 514-5. [CrossRef]
18. Chogle A, Saps M. Yield and cost of performing screening tests for constipation in children. Can J Gastroenterol 2013; 27: e35-8. [CrossRef]
19. Cakir M, Cezaroglu S, Cobanoglu Ü. Celiac disease in children with chronic constipation. Turk J Med Sci 2016; 46:651-6. [CrossRef]
20. Jericho H, Sansotta N, Guandalini S. Extraintestinal manifestations of Celiac Disease: Effectiveness of the gluten-free diet. J Pediatr Gastroenterol Nutr 2017; 65: 75-9. [CrossRef]
21. Wald A. Chronic constipation: advances in management. Neurogastroenterol Motil 2007; 19: 4-10. [CrossRef]
22. Pinto-Sanchez MI, Bercik P, Verdu EF. Motility alterations in celiac disease and non-celiac gluten sensitivity. Dig Dis 2015; 33: 200-7. [CrossRef]
23. Korkut E, Bektas M, Oztas E, Kurt M, Cetinkaya H, Ozden A. The prevalence of celiac disease in patients fulfilling Rome III criteria for irritable bowel syndrome. European Journal of Internal Medicine 2010; 21: 389-92. [CrossRef]
24. Locke GR, Murray JA, Zinsmeister AR, Melton LJ, Talley NJ. Celiac disease serology in irritable bowel syndrome and dyspepsia: a popu-

lation-based case-control study. Mayo Clin Proc 2004; 79: 476-82. **[CrossRef]**
25. Ozdil K, Sokmen M, Ersoy O, et al. Association of gluten enteropathy and irritable bowel syndrome in adult Turkish population. Dig Dis Sci 2008; 53: 1852-5. **[CrossRef]**
26. Bakhshipour A, Nezam SK, Zakeri Z, Gharibi R, Bahari A, Kaykhaei MA. Coeliac disease in irritable bowel syndrome (Rome III) in Southeast Iran. Arab J Gastroenterol 2012; 13: 24-7. **[CrossRef]**
27. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastroenterol Hepatol 2003; 15: 407-13. **[CrossRef]**
28. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001; 358: 1504-8. **[CrossRef]**
29. Jadallah KA, Khader YS. Celiac disease in patients with presumed irritable bowel syndrome: a case-finding study. World J Gastroenterol 2009; 15: 5321-5. **[CrossRef]**
30. Van derWouden EJ, Nelis GF, Vecht J. Screening for coeliac disease in patients fulfilling the Rome II criteria for irritable bowel syndrome in a secondary care hospital in The Netherlands: a prospective observational study. Gut 2007; 56: 444-5. **[CrossRef]**