ARC Journal of Pediatrics
Volume 4, Issue 2, 2018, PP 1-5
ISSN 2455-5711
http://dx.doi.org/10.20431/2455-5711.0402001
www.arcjournals.org

The Frequency of Celiac Disease in Children with Functional Abdominal Pain

Yasin Sahin[1*], Derya Aydin Sahin[2]

[1]*Clinics of Pediatric Gastroenterology, Mersin City Training and Research Hospital, Mersin, Turkey*

[2]*Clinics of Pediatric Cardiology, Mersin City Training and Research Hospital, Mersin, Turkey*

Corresponding Author:** ***Yasin Sahin, MD, *Clinics of Pediatric Gastroenterology, Mersin City Training and Research Hospital, Mersin, Turkey,* ***Email:*** *ysahin977@gmail.com*

Abstract

Backgrounds/Aim: *Chronic abdominal pain (CAP) is a common complaint in children, and there is no underlying organic cause in the majority of cases. It affects 8-17% of school-aged children. There is no specific diagnostic criteria to distinguish functional abdominal pain (FAP) from organic abdominal pain. Therefore, we aimed to evaluate the frequency of celiac disease (CD) in children with FAP.*

Materials and Methods: *This retrospective study was conducted between March 2017 and October 2018 and included 100 patients with functional abdominal pain. Total IgA and tissue transglutaminase antibody (tTG) IgA levels were analyzed. Gastroduodenoscopy was performed on patients with positive tTG.*

Results: *One hundred patients with FAP (58 female) with mean age of 8.6 ± 3.7 years were included. None of the patients had IgA deficiency. Only three of 100 patients (3%) was positive for tTG IgA. One of them did not accept the gastroduodenoscopy. Gastroduodenoscopy was performed on two patients positive for tTG IgA. According to the pathologic results, only one patient had Marsh 3b classification score compatible with CD.*

Conclusion: *One patient (1%) of 100 patients with FAP was found to have CD. According to our results, we suggest that children with FAP should be examined for CD. However, there is a need for multicentric studies that would support our findings.*

Keywords: *celiac disease, children, functional abdominal pain, intestinal biopsy*

Chronic abdominal pain (CAP) is a common complaint in children and adolescents, and there is no underlying organic cause in the majority of cases. It affects 8-17% of school-aged children (1).

The Rome III criteria is a symptom-based classification used for functional gastrointestinal diseases (FGIDs) in children aged 4 to 18 years. Functional abdominal pain (FAP) is classified as abdominal pain, which occurs at least once a week for at least two months in childhood and there is no organic cause to explain the patient's symptoms before the diagnosis according to Rome III criteria. It can be episodic or continuous (2). There is no specific diagnostic criteria to distinguish FAP from organic abdominal pain, and further investigations are generally not recommended in the absence of alarm symptoms and findings (1).

It has been shown that the Rome III criteria are insufficient to distinguish FAP from organic diseases (3,4). An organic disease was diagnosed in 21 (29%) of 73 patients who was diagnosed with FAP according to the Rome III criteria (3).

Celiac disease is an immune-mediated systemic disease characterized by variable combination of clinical manifestations and enteropathy triggered by gluten ingestion in genetically susceptible individuals (5). Celiac disease may present with malabsorbtion symptoms such as chronic diarrhea or may present with various extraintestinal symptoms such as increased liver enzymes, anemia and short stature. CD can also be diagnosed in children with vague symptoms such as chronic abdominal pain, abdominal distention or constipation. 90% of the affected individuals remains undiagnosed (5,6). The variable clinical findings of CD are both genetic and immunologically based, and also the onset age of the disease may affect the clinics (7).

The diagnosis of CD at the time can prevent the complications of chronic diseases such as osteoporosis, infertility and small bowel cancer in affected individuals (8).

Even though abdominal pain is one of the symptoms of CD, routinely serological screening tests for CD are not recommended in these children (9). However, it is recommended that serologic tests for celiac disease should be done in patients with persistent gastrointestinal symptoms such as recurrent abdominal pain, vomiting, constipation (10).

In this study we aimed to evaluate the frequency of CD in children with FAP.

1. Material and Methods

This study was retrospectively conducted between March 2017 and October 2018. This study protocol was approved by the Ethical Committee of Mersin University.

The children aged 4-18 years who were referred to pediatric gastroenterology outpatient clinics with chronic abdominal pain and diagnosed with functional abdominal pain according to the Roma III criteria were included in the study (11). According to Rome III criteria, patients with alarm symptoms such as abdominal pain in the right quadrant, dysphagia, vomiting, blood in stool, weight loss, growth retardation, fever, chronic diarrhea or positive family history of inflammatory bowel disease were excluded from the study (2). In addition, those who had previously diagnosed CD, positive family history for CD, and diseases associated with CD were not included in the study. All patients were initially evaluated with tissue transglutaminase (tTG) IgA antibody and total IgA test. The cut-off value of tTG IgA antibody was 20 U / ml.

Gastroduodenoscopy was performed on patients with tTG positivity. At least 4 biopsies from duodenum and 2 from bulbus were taken. The latest ESPGHAN and NASPGHAN guidelines recommend that at least 4 biopsies from the duodenum and one biopsy from bulbus should be taken endoscopically in case of suspectivity of CD because of the patchy involvement (5,12).

Biopsies were evaluated according to the Marsh classification criteria for the diagnosis of CD (13).

2. Statistical Analysis

Descriptive statistics were used for frequency, percentage, and mean ± standard deviation. Statistical Package for Social Sciences for Windows, version 22.0 software (SPSS Inc, Chicago IL, USA) was used for statistical analysis. P value <0.05 was considered as significant.

3. Results

Of the 100 patients included in the study, 58 of them (58%) was female. The mean age of patients was 8.6 ± 3.7 years. The mean tTG levels was 6.2 ± 11.3 U/ml (Table 1).

Table1. *The laboratory and demographic features of the patients*

The laboratory and demographic features of the patients	
	Patients (n=100)
Age (years)	8.6 ± 3.7
Sex (female/male)	58/42
tTG IgA (U/ml)	6.2 ± 11.3
Total IgA (mg/dl)	135.6 ± 64.1
Hemoglobin (g/dL)	12.7 ± 1.0
AST	28.0 ± 8.3
ALT	16.4 ± 5.4

IgA deficiency was not detected in any patients. Three patients (3%) had positive for tTG IgA. One of them did not accept the gastroduodenoscopy. Gastroduodenoscopy was performed on two patients with tTG IgA positivity. Four biopsies from duodenum and two biopsies from bulb was taken. Marsh 0 classification score was detected in one of them, and the other one had Marsh 3b classification score. According to Marsh classification score, the latter result of pathology was compatible with CD (Table 2). The frequency of biopsy-proven celiac disease was found to be 1%.

Table2. *The laboratory data of patients who had tissue transglutaminase antibody positivity*

Patient no	tTG IgA (U/ml)	Total IgA (mg/dl)	Pathology
1	110	143	Marsh 3b
2	37.1	201	Marsh 0
3*	20.7	115	-

tTG = tissue transglutaminase

**The patient did not accept the gastroduodenoscopy*

4. Discussion

Functional abdominal pain is one of the most common FGIDs of childhood. FAP is frequently localized in the periumblical region and is usually not associated with diarrhea, vomiting, weight loss, night symptoms or growth retardation. Inflammatory, anatomic and metabolic diseases should be ruled out before the diagnosis of FAP. Therefore, it is inevitable to conduct a diagnostic test. There is no

evidence-based guidelines regarding which tests are useful and which organic diseases must be rule out before diagnosis of FAP (14).

The pathogenesis of FGID-associated abdominal pain is not fully understood (15).

Celiac disease is the most common disease in Western Europe and North America, with a prevalence of approximately 1% (16). In the last few decades, the frequency of CD is increasing. The reasons for this are the widespread use of sensitive serologic tests, increasing awareness of CD among families and health personnels and screening of high-risk patients (17).

Celiac disease may present with a wide range of clinical manifestations. Classic symptoms include gastrointestinal system (GIS) symptoms such as chronic diarrhea, weight loss, and growth retardation (8). The atypical form is characterized by extraintestinal symtoms. These include iron deficiency anemia, abdominal distention, constipation, chronic fatigue, headache, abdominal pain and osteoporosis.

Although the last ESPGHAN guideline published in 2012 suggests CD screening tests for children with unexplained CAP, routine screening tests for CD are not widely accepted in practice because chronic abdominal pain is very common in childhood (5,18,19).

It is not clear that CAP is a marker of CD, because recurrent abdominal pain is more common in children. In children with CD there is a change from GIS symptoms to extraintestinal symptoms (5). Because of the increasing awareness of CD, it is unclear whether the chronic abdominal pain reflects a true clinical variation or better recognition of non-gastrointestinal forms of CD (5).

In celiac disease, abdominal pain is a common symptom (43-90%), it can be seen alone without any other symptoms, and rapidly grows with the gluten-free diet (5,7,20-22).

There is limited information about the potential association between FAP and CD in children. There is insufficient evidence to perform routine screening tests for CD in children with chronic abdominal pain in previous studies (18,23-26).

In some studies, the prevalence of CD in children with CAP was detected similar to the general population (9,23-26).

Conversely, there are also studies reporting that the prevalence of CD in children with CAP is higher than expected in the general population (1.3-3.9%) (18,27-30).

In a recent large population-based CD screening study, CD-associated symptoms including abdominal pain were interrogated prior to serological tests. There was no significant difference in CD prevalence between children with and without any celiac disease-associated symptoms (31).

In a single-center retrospective study, the incidence of CD was found to have higher incidence in children with chronic abdominal pain than in the general population (18). However, patients with comorbidities were not excluded from the study. The prevalence of CD was detected as 4.9% in 82 patients with CAP. In this study, authors suggested that children with CAP having additional GI symptoms should be careful in terms of screening for CD.

In an another study, serologic tests for CD were performed in 127 of 151 patients with recurrent abdominal pain. Gastroduodenoscopy was performed on 8 (6.2%) patients with tTG positivity, and 5 (3.9%) of these patients were diagnosed with CD. Three of those patients had no clinical signs other than abdominal pain (28).

With increasing awareness about various clinical findings of CD and availability of reliable serologic tests allows early diagnosis of atypical forms compared to previous studies (32).

The rate of patients with CD presenting with abdominal pain ranges from 19.4% to 90% (20,32-34).

1047 children (mean age 9.6±4.1 years) with CAP were evaluated in Turkey (9). Patients were assessed according to Roma III criteria. Those with alarm semptoms and those with CD were excluded from the study. All patients were assessed by rapid tTG test, positive patients were examined by tTG -ELISA and gastroduodenoscopy was performed on positive cases. Rapid tTG positivity was detected in 13 patients, tTG ELISA was positive in 10 of them, endoscopy was performed on 10 patients and CD was detected in all of them. The prevalence of CD in FAP was found a similar prevalence to that in the general population (9).

The main clinical manifestations of CD are diarrhea and abdominal bloating in younger children. Although abdominal pain is more common in older children with CD, there is no association between classic abdominal pain and CD (26).

Letizia et al. reported that recurrent abdominal pain is seen in 43% of patients with CD (35). Although recurrent abdominal pain is often reported in CD, celiac screening tests are not currently recommended in children with recurrent abdominal pain (19,26).

In a multicenter study from Turkey including healthy children between the ages of 6-17, the prevalence of CD was found to be 0.47% (36). According to our study results, the prevalence of CD in children with FAP was two times (1.0%) higher than in the general population of Turkey.

5. Limitations of the Study

The first limitation is that there was a small number of case. Second, since our study was retrospective, we don't know how many grams of gluten patients consume in a day. Third, one of the patients with tTG positivity did not accept gastroduodenoscopy. If this patient was diagnosed with celiac disease by biopsy, the frequency of biopsy-proven celiac disease would be 2%. Therefore, the effectiveness of the present study may be weak.

Celiac disease may commonly present with malabsorbtion symptoms. It is important that CD is diagnosed not only in children with significant gastrointestinal symptoms but also in children with vague clinical signs, as the disease may have negative effects on health. In the absence of typical diarrhea, many cases with CD may be skipped and non-classical CD may not be diagnosed (37).

As a result, the frequency of CD in children with FAP was found to be two times higher than in general population. We suggest that children with FAP should be examined for CD. However, multicentric studies with higher number of patients are needed in order to provide a more reliable data.

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Citation: *Yasin Sahin, Derya Aydin Sahin, The Frequency of Celiac Disease in Children with Functional Abdominal Pain. ARC Journal of Pediatrics. 2018; 4(2): 1-5. doi:dx.doi.org/10.20431/2455-5711.0402001.*