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Original Research

The Frequency of Celiac Disease in Turkish Children with Cystic Fibrosis

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ABSTRACT

Objective: The aim of the present study was to investigate the frequency of celiac disease (CD) in children with cystic fibrosis (CF).

Methods: This prospective study was conducted from October 2015 to March 2017. A total of 71 patients with CF and 73 age- and sex-matched healthy children were included in the study. All groups were evaluated for CD with regard to clinical and laboratory findings. First, total IgA and tissue transglutaminase IgA (tTG IgA) levels were measured. Anti-endomysium IgA antibodies (EMAs) were analyzed for those patients with positive tTG IgA. Gastroduodenoscopy was performed to patients with both positive tTG and EMA IgA.

Results: Only 8 (11.2%) patients had tTG IgA positivity, whereas 4 (5.6%) patients had positive EMA. The pathological results were consistent with the Marsh 2 classification score in two patients. In addition to that, HLA-DQ2 is present in those two patients. Those patients were accepted as potential CD. Two patients who were thought to have potential CD were reassessed after 1 year, and celiac screening tests were detected as positive again.

Conclusion: Only 2 (2.8%) of 71 patients with CF were diagnosed with potential CD. Our study results showed that there might be an association between CD and CF.

Keywords: Celiac disease, cystic fibrosis, small intestine biopsy

INTRODUCTION

Cystic fibrosis (CF) is the most common autosomal recessive disorder associated with a deficit in the cystic fibrosis transmembrane regulator (CFTR) gene localized on chromosome 7 and is life-threatening among Caucasians (1). The global incidence of CF is 1 in 2500 newborns (2).

Celiac disease (CD) is an immune-mediated systemic disease characterized by intestinal villous damage at various levels, triggered by gluten intake in genetically susceptible individuals (3).

The prevalence of CD is estimated to be 0.5%-1% in different regions worldwide (4). CD has two peaks that are between 1 and 2 years old and 30 years old (5).

Cystic fibrosis was first described in 1938 and has been considered a separate disease from CD since then. A patient with CD and CF was reported for the first time in 1969, and after that, sporadic cases were reported (1).

Weight loss, steatorrhea, and diarrhea are associated with intestinal malabsorption in both diseases; thus, it is difficult to diagnose CD in patients with CF (6). It has been recommended that screening of CD should be performed in communities with a high prevalence of CD and those with CF particularly with malabsorption that does not respond to standard treatments, those with pausing in physical development, and those with CF with comorbidity of autoimmune disease (1, 6). There is no consensus on the screening of CD in children with CF.

There are very few studies investigating the prevalence of CD in patients with CF (6-9). To our knowledge, there is no study that investigates the frequency of CD in children with CF in our country. For this reason, the aim of the present study was to investigate the frequency of CD in children with CF.

METHODS

The study was conducted prospectively at the Outpatient Clinics of Pediatric Pulmonology and Gastroenterology between October 2015 and March 2017. A total of 71 patients were included

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in the study. Patients with incomplete information in their files at the time of diagnosis, patients with coincidental disease, and patients who refused to participate in the study were excluded from the study. Only three patients refused to participate in the study. Patients who were followed up with a diagnosis of CF, received gluten, and wanted to participate in the study voluntarily were included in the study. A total of 73 age- and sex-matched healthy children were included in the study as the control group.

The study protocol was approved by the local ethics committee (313608, October 6, 2015). Informed written consent was obtained from the patients, the healthy controls, and their parents before participation in the study. Those who refused to participate in the study and those who did not receive gluten were not included in the study.

Cystic fibrosis was diagnosed according to the generally accepted criteria (10). All groups were evaluated for clinical and laboratory findings with regard to CD. Venous blood samples were obtained from both groups. Each sample was divided into aliquots, and samples were stored at –80 °C until analysis.

Total IgA tests (Roche Diagnostics GmbH, Mannheim, Germany) by immunoturbidimetric method and tissue transglutaminase (tTG) IgA tests (catalog no. 3503; Aesku Diagnostics GmbH, Wendelsheim, Germany) by ELISA method were measured at the Central Biochemistry Laboratory of Cerrahpaia Medical Faculty. The tTG IgG test was planned for patients with IgA deficiency. The cut-off value of tTG antibody was 12 U/mL. Anti-endomysium IgA antibody (EMA IgA) test (Inova Diagnostics, Inc., Lübeck, Germany) by IFA method was analyzed in patients with positive tTG IgA in the Düzen Laboratories Group in İstanbul, Turkey. Gastroduodenoscopy was performed to the patients with both positive tTG and EMA IgA for definitive diagnosis.

Biopsy Procedures

Gastroduodenoscopy was performed to the patients with both tTG and EMA positivity. One biopsy from the duodenal bulb and four biopsies from the duodenum were obtained. Biopsies were evaluated by the same experienced pathologist according to the Marsh classification score (11).

Statistical Analysis

Statistical Package for the Social Sciences for Windows, version 17.0 software (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as frequency, percentage, mean ± standard deviation, and median (interquartile range). Independent samples t-test was used for nominal data with normal distribution. Mann-Whitney U test was used for patients with non-normally distributed variables, and chi-square test was used to compare the relationship between categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

Overall, 71 patients were included in the study. The mean age and weight of the patients were 9.94±5.55 years and 29.32±15.03 kg, respectively. Of 71 patients, 36 (50.7%) were female, and 35 (49.3%) were male. There were 37 (50.7%) girls and 36 (49.3%) boys in the control group. The mean age of the control group was 9.67±5.36 years. When the patient and control groups were compared with regard to age, sex, height, and weight, there was no significant difference between the groups (p>0.05) (Table 1).

Of 71 patients, 56 (78.9%) have gastrointestinal symptoms, such as chronic diarrhea, steatorrhea, and weight loss. In addition, 15 (21.1%) have anemia for extraintestinal symptoms.

tTG IgA positivity was detected in only 8 (11.2%) patients, then EMA was measured, and 4 (5.6%) patients had positive results (Table 2). Gastroduodenoscopy was performed to those patients.

Table 1. Demographic characteristics and laboratory findings of the patient and control groups

	Patient group (n=71)	Control group (n=73)	p
Age (years)*	10.75	10.00	0.873
Height (cm)*	134.00	137.00	0.440
Weight (kg)*	27.40	37.00	0.090
Hemoglobin (mg/dL)**	12.61±1.07	12.78±1.48	0.434
MCV**	80.95±5.04	79.39±4.87	0.060
Plt (/mm^3)*	319.00	287.00	0.066
tTG IgA (U/mL)*	1.70	0.90	0.001
Total IgA (mg/dL)*	141.00	133.00	0.414
Age at diagnosis (months)*	6.00	–	
Sweat chloride level (mEq/L)**	97.11±21.8	–	

Plt: thrombocytes; MCV: mean corpuscular volume; tTG: tissue transglutaminase
*Data are presented as median (interquartile range)
**Data are presented as mean±standard deviation

Table 2. Data of patients with positive tissue transglutaminase antibody

Patient no.	tTG IgA (U/mL)	Total IgA (mg/dL)	EMA IgA	Marsh classification score
1	300	84	+	2
2	47.1	147	+	2
3	72.9	241	+	0
4	15	69.3	+	0
5	31.4	184	–	–
6	32.6	92	–	–
7	26.5	187	–	–
8	33.8	210	–	–

tTG: tissue transglutaminase; EMA: anti-endomysium antibody

Table 3. Laboratory data of patients with potential celiac disease

Patient no.	tTG IgA (U/mL)	Total IgA (mg/dL)	EMA IgA	Marsh classification score
1	300	84	+	1
2*	32	147	+	–

tTG: tissue transglutaminase; EMA: anti–endomysium antibody
*Gastroduodenoscopy could not be performed due to chronic infection

One biopsy from the duodenal bulb and four biopsies from the duodenum were obtained. The endoscopic appearance of two patients has normal mucosal appearance of the bulbus and scalloping of the duodenum. The pathological results were consistent with the Marsh 2 classification score in those two patients, and HLA-DQ2 typing was also positive. Those patients were accepted as potential CD. In addition, they have typical gastrointestinal symptoms, such as chronic diarrhea and steatorrhea; thus, they are considered as typical CD.

The other two patients have normal mucosal appearance of the bulbus and duodenum, and their pathological results were compatible with the Marsh 0 classification score. Two patients who were thought to have potential CD were reassessed after 1 year, and celiac screening tests were detected as positive again. Gastroduodenoscopy could not be performed to one patient due to chronic pulmonary infection. In the other patient, the pathological result was consistent with the Marsh 1 classification score (Table 3).

In the control group, 3 (4.1%) children had tTG IgA positivity, but EMA positivity was not detected in any of them.

DISCUSSION

The CFTR gene associated with CF disease was identified in 1989. The most common CFTR defect is delta F508 mutation, which is present in approximately 70% of patients with CF (2). Currently, more than 1500 mutations have been identified (12). Different CFTR mutations result in different disease phenotypes. Some mutations may have less or no effect on the CFTR function or may cause mild forms of the disease (13).

The prevalence of CD has increased dramatically in the last 20 years due to the use of serological tests. Previous studies reported that its prevalence increased four times in the United States, whereas it increased two times in Finland (14, 15). Since only 10% of patients are symptomatic, the majority of asymptomatic patients remain undiagnosed despite screening of the high-risk populations (5, 16).

Celiac disease is a lifelong disorder and is associated with increased morbidity and mortality if left untreated (17). CD complications are predominantly in adults and include refractory CD, decreased fertility in women, cancers, and other autoimmune diseases. Compared with the general population, the risk of developing cancer is twice as high (18). With a gluten-free diet, the risk of developing complications is likely reduced (19). Therefore, it is very important to diagnose CD early and to start treatment.

Most of the symptoms of CD can be seen as gastrointestinal system findings of CF. Furthermore, it is difficult to distinguish between these two conditions in patients with CF, since clinical findings of iron deficiency anemia and lack of fat-soluble vitamins are equally seen among people with and without CD (6, 7). Mucosal changes in the small intestine and its associated malabsorption may worsen nutritional status and affect survival duration. Thus, diagnosing CD in coexisting patients with CF may play an important role in treatment efficacy (7).

Some hypotheses have been proposed to explain the coexistence of these two diseases. In patients with CF, the small bowel mucosa may have greater contact with the gluten protein due to incomplete digestion and pancreatic insufficiency. This can play an important role in comorbidity. However, malnutrition can also cause some additional mucosal damage. In patients with malabsorption, feeding with a high-energy diet results in more antigen burden, and gluten peptides may pass more easily to the epidermis and lead to the development of CD (7, 20).

Venuta et al. (21) reported a case report with an association of CD and CF, and they had opted for 15 cases of the coexistence of CD and CF as reported in the literature until 1999.

Previous studies have reported that the incidence of CD among children with CF is between 0.4% and 2.6% (6-9).

In a multicenter study, the prevalence of CD was found to be 1.2% (1/83) in 790 Scandinavian patients with CF (6). In this study, six patients were already diagnosed with CD, whereas four were recently diagnosed with CD. In addition, serological tests were positive in two patients, but normal histology of duodenal biopsy was detected. These patients were scheduled for follow-up because of suspected potential CD. Based on the prevalence studies conducted previously, it has been estimated that the prevalence of CD among Scandinavian patients with CF was 2-3 times higher than that of the general population. CD was diagnosed in three patients before the diagnosis of CF, whereas it was synchronously diagnosed with CF in two patients. According to clinical findings, it was difficult to distinguish between these two conditions, and iron deficiency and lack of fat-soluble vitamins were found to have equal prevalence in these patients. In this study, it has been recommended that screening should be performed for children >9 months with CF or those receiving gluten for >3 months in populations with a high prevalence of CF, such as Sweden (6).

In a study including 230 patients with CF in Poland, the prevalence of CD was found to be 2.6%. tTG IgA positivity was detected in 11 patients, and EMA IgA positivity was detected in six of those patients. Gastroduodenoscopy was performed to five of them, four were diagnosed with CD at that moment, and two were previously diagnosed. The incidence of CD was five times higher in patients with CF than in healthy populations. In addition, tTG positivity and EMA negativity were found in four patients, and gastroduodenoscopy was performed for those four patients, and the pathological results were detected as normal. Moreover, those patients were planned to be followed up for a long time, as

they might have latent CD (7). It has been suggested that CF as a risk factor should be examined as a consequence of this study, and it is thought that CF has a tendency to cause CD.

Abdominal pain was detected in 11% of the 500 patients with CF, and 2 (0.4%) patients were diagnosed with CD (8). It has been stated that the most common cause of admission to the hospital in older children with CF might be abdominal pain.

In the study conducted by Valleta and Mastella (9), the incidence of CD was found to be 0.4% in 1100 patients with CF and reported to have a higher incidence of CD in a population with CF than that in a healthy population.

The current approach to CD has changed with the development of highly sensitive and specific serological tests. Both EMA IgA and tTG IgA tests have been shown to be highly sensitive for CD (22). The European Association of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends total IgA and tTG IgA tests for initial screening of CD. It has been suggested that EMA IgA test should be performed in patients with tTG IgA positivity. If this test is found to be positive, small bowel biopsy should be performed (3). In patients with IgA deficiency, tTG IgG or EMA IgG may help in the decision for biopsy (16). EMA and tTG IgA tests have >95% sensitivity and specificity when used together (23).

Our study was based on the updated ESPGHAN guideline. tTG IgA positivity was detected in 8 (11.2%) patients, then the levels of EMA IgA were measured for these patients, and positive results were detected in 4 (5.6%) patients (Table 2). Gastroduodenoscopy was performed in those patients. The pathological results were compatible with the Marsh 2 classification score in two patients who had also positive HLA-DQ2 tests. Potential CD was thought in those two patients, and it was planned that those patients should be followed up serologically and clinically (24,25). In the other two patients, the pathological results were detected as normal. Two patients who were thought to have potential CD were reassessed after 1 year, and the celiac serological tests were found to be positive again. The first patient could not undergo endoscopy due to chronic infection. In the second patient who underwent endoscopy, the pathological result was compatible with the Marsh 1 classification score. In the latter patient, the patient did not have a gluten-free diet, and the pathological result of the second intestinal biopsy may be associated with the patchy distribution of villous atrophy of CD. In addition, the first patient who could not undergo endoscopy did not have a gluten-free diet. If we had performed gastroduodenoscopy to the first patient, we could detect the Marsh 2 classification score. Therefore, in the present study, the frequency of potential CD was 2/71.

As a limitation, the number of cases may be small due to the fact that our study was a single-center study, but only three follow-up patients did not accept to participate voluntarily. Therefore, the impact of our study may be weak, but we still consider that the present study is important for our country, as to the best of our knowledge, this is the first study on this issue.

In a study conducted in healthy Turkish children aged between 6 and 17 years in our country, the prevalence of CD was detected as 0.47% (26). According to our study results, the frequency of potential CD was found to be 2.8% in patients with CF. We detected that CD was seen approximately six times more in the CF population than in healthy children.

CONCLUSION

Despite the small number of cases, we suggest that all children with CF should be screened for CD. Multicenter studies with more children with CF are needed to provide more precise evaluation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (313608, October 6, 2015).

Informed Consent: Informed written consent was obtained from the patients, the healthy controls, and their parents before participation in the study.

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