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Celiac disease in children with chronic constipation

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Background/aim: Chronic constipation (CC) and celiac disease (CD) are the most common conditions encountered in pediatric gastroenterology. The association of these two disorders has not been evaluated properly. We analyzed the prevalence and outcome of CD in children with CC.

Materials and methods: The study included children with CC (n = 313) and healthy children (n = 990). Serum IgA and IgA antitissue transglutaminase antibodies (IgA-tTG) were studied in all subjects. Intestinal biopsy and HLA-DQ2/DQ8 typing was performed in subjects with elevated IgA-tTG.

Results: Serology was positive in 8 children (2.5%) with CC and 6 children (0.6%) from the control group ($P < 0.05$). Histopathological examination revealed total villous atrophy in two subjects in the control group. Other subjects had Marsh 0–1 lesions. All patients with CC and 4 children from the control group were classified as having potential CD. Two children in the control group had silent CD. Spontaneous loss of serum tTG-IgA occured in 75% of the subjects with potential CD at the end of the 1st year.

Conclusion: Our study revealed that serological evaluation CD may be omitted in children with CC at initial examination. It may be perform in selected patients such as those associated with prolonged symptoms or malnutrition.

Key words: Chronic constipation, celiac disease, potential

1. Introduction

Celiac disease (CD) is an immune-mediated systemic disorder triggered by gluten-containing grains in genetically suspected individuals. It is one of the most common lifelong disorders and affects approximately 1% of the general population (1–3). It is characterized by a wide range of clinical presentations, ranging from typical malabsorptive symptoms including chronic diarrhea, abdominal distention, and failure to thrive, to extraintestinal manifestations such as osteopenia, isolated short stature, and elevated liver enzymes (1,2).

Chronic constipation (CC) is one of the most common conditions encountered in general pediatric and pediatric gastroenterology offices (4). It is defined as decrease in defecation frequency or painful defecation, and is sometimes associated with involuntary loss of stool. It is mainly functional and there is no identifiable organic lesion or disorder in most cases. Most of the cases respond to toilet training, diet, and medical treatment. However, a minority of children with CC does not respond to medical treatment and may present an inextricable condition for the physician and parents (5). Although it is not recommended to perform routine screening tests for organic causes such as CD, hypercalcemia, and hypothyroidism in the absence of alarm symptoms according to a recent guideline by ESPGHAN and NASPGHAN, most physicians perform these tests in order to rule out organic causes at initial admission (5).

Peptide YY is a novel neuroendocrine peptide that localizes endocrine cells in the colon. It plays an important role in regulating gastrointestinal motility and absorption of water and electrolytes. Increased levels of peptide YY were shown in children with slow transit constipation (6,7). Elevated levels of peptide YY were also reported in patients with newly diagnosed CD (7). Therefore, the coexistence of CD and CC may be seen more commonly and patients with CD may present with CC. However, the prevalence of CD in children admitted only with the compliant of CC has not been properly evaluated previously. Therefore, we aimed to analyze the prevalence

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of CD in children admitted with CC and the outcome of these patients.

2. Materials and methods

The study included children (>1 and <17 years old) who were admitted to the pediatric gastroenterology unit with the complaint of CC during a 1-year period (n = 360). Patients with definite organic problems (n = 40, 11.1%) such as spinal cord problems and intestinal pseudoobstruction (n = 16), drug- or toxin-related problems (n = 10), anatomic problems (n = 5), endocrinological problem (n = 4), Down syndrome (n = 2), Hirschsprung disease (n = 2), and pelvic mass (n = 1), and patients with previous diagnosis of CD (n = 4, 1.1%) and family history of CD (n = 3, 0.8%) were excluded from the study. Demographic features, clinical findings, accompanying symptoms, and anthropometric measurements of the patients were recorded (n = 313, 86.9%). All the children fulfilled the Rome III criteria at the time of initial examination (8,9). The control group included healthy children without known chronic diseases and CC (> 1 and < 17 years old). The number of children in the control group was calculated according to previous population studies on CD prevalence in Turkey. With the assumption that CD is expected to occur in 1% of the population, we calculated that a sample of 1510 healthy children has 95% confidence interval, but due to limited financial resources 1000 healthy children were included to the study. Due to a technical problem (inadequate material), 10 children were excluded during the laboratory examinations (n = 990).

Between 5 and 10 mL of peripheral venous serum samples were obtained from all patients with CC and all children in the control group in order to study serum IgA and IgA antitissue transglutaminase antibodies (IgA-tTG). IgA levels were measured on a Dade Behring nephelometer using Dade Behring reagents. Patients with IgA deficiency according to their age were further tested for IgG-tTG. Antibodies against human IgA and IgG-tTG were tested with an enzyme-linked immunosorbent assay (Euroimmune, GmbH) kit. The cutoff level for IgA and IgG-tTG defining a positive result was set at 20 RU/mL (the maximum calibrator was 200 RU/mL). All sera positive for IgA-tTG and IgG-tTG were further tested for IgA antiendomysial antibodies (IgA-EMAs) using an indirect immunofluorescence method. The EMA determination was conducted with a commercial kit (EUROPLUS Primate Liver and Gliadin (GAF - 3X) BIOCHIPs, GmbH) following the manufacturer's instructions. Sera were considered positive in a 1:10 dilution. Additionally, all sera positive for IgA-tTG or IgG-tTG were further tested for HLA-DQ2 and HLA-DQ8 typing. Genomic DNA of subjects in the study were isolated from 200 mL aliquots of peripheral venous blood samples by using the Bio-robot EZ1 magnetic bead-based workstation (Qiagen). Genotyping of HLA-DQ2 and HLA-DQ8 alleles were performed in all subjects by polymerase chain reaction with sequence specific oligonucleotide probes (PCR-SSOP) hybridization method using Luminex technology (Gen-probe Lifecodes).

A small-intestinal biopsy was offered to all subjects with IgA and IgG-tTG positivity. Three biopsy specimens were taken from the bulbus and the second part of the duodenum and carefully oriented on filter paper before submersion in 10% neutral buffered formalin. The biopsies were evaluated by the same expert histopathologist. The Marsh classification was used for the histopathological classification. Normal mucosa with >30 intraepithelial lymphocytes per 100 epithelial cells was defined as Marsh type 1, infiltrative/hyperplastic lesions were defined as Marsh type 2, and villous atrophy was defined as type 3 (10).

Patients with positive serology were classified as: 1) overt CD (silent or symptomatic): positive serology together with the features of mucosal changes on intestinal biopsy (Marsh stage 2–3) (these patients were initiated on a strict gluten-free diet); and 2) potential CD: positive serology with normal or slightly infiltrated bowel mucosa (Marsh stage 0–1) (patients with potential CD were suggested to continue their unrestricted gluten-containing diet). After diagnosis, serology and clinical symptoms were determined with 6-month intervals for 1 year.

Informed consent for participating in the study was obtained from the parents of all participants and the ethics committee of the Karadeniz Technical University Faculty of Medicine approved this study.

Data were analyzed using SPSS 16.0. Differences between groups were calculated using an independent samples t-test for the normally distributed data and the Mann–Whitney test for data not normally distributed. Chi-square test was used for the comparisons of qualitative data. Values of $P < 0.05$ were considered significant.

3. Results

Demographic and clinical features of the patient and control groups are shown in Table 1. There was no significant difference between the groups in terms of sex (female sex: 56.2% vs. 51.3%, $P > 0.05$) and age (5.8 ± 3.7 vs. 5.1 ± 2.6 years of age, $P > 0.05$). Underweight (weight for age) and obesity were more common in children with CC (12.1% vs. 7.5%, $P < 0.05$, and 10.2% vs. 2.4%, $P < 0.05$, respectively).

Duration of constipation (mean ± SD) was 2.6 ± 1.1 years and 103 patients (32.9%) had family history of CC. Clinical features of the patients with CC are shown in Table 2. The most common symptoms were painful or hard bowel symptoms (96.4%), followed by ≤2 defecations

Table 1. Demographic characteristics of the patients with CC and the healthy controls.

	Patients with CC (n = 313)	Healthy children (n = 990)
Sex: female, n (%)	176 (56.2)	508 (51.3)
Age; mean ± SD, years	5.8 ± 3.7	5.1 ± 2.6
Age group; n (%)		
>1– ≤5 years	134 (42.8)	591 (59.7)
>5– ≤10 years	127 (40.5)	347 (35.1)
>10 years	52 (16.7)	52 (5.2)
Underweight, n (%)	38 (12.1)	75 (7.5)
Obesity, n (%)	32 (10.2)	24 (2.4)

Table 2. Clinical findings of the patients with CC (n = 313).

Parameters	Number of cases (%)
Rome III diagnostic criteria	
≤2 defecations per week	202 (67.7)
Fecal incontinence	67 (21.4)
Retentive posturing	199 (63.5)
Painful or hard bowel movements	302 (96.4)
Large fecal mass in the rectum	188 (60)
Large-diameter stools	35 (11.1)
Accompanying symptoms	
Rectal bleeding	113 (36.1)
Vomiting	50 (15.9)
Abdominal pain	224 (71.5)
Decreased appetite	24 (7.6)
Ribbon-like stools	274 (87.5)
Urinary tract infection	57 (18.2)

per week (67.7%). Ribbon-like stools and abdominal pain were seen in 87.5% and 71.5% of the patients, respectively.

Serology positivity (tTG-IgA>20 RU/ml) was found in 8 children (2.5%, 95% CI: 0.77–4.23) with CC and in 6 children (0.6%, 95% CI: 0.12–1.08) from the control group ($P < 0.05$, OR: 4.3, 95% CI: 1.48–12.4). tTG-IgA levels were <100 RU/mL in all children with CC. In the control group, tTG-IgA levels were >200 RU/mL in two children and <100 RU/mL in the others. IgA deficiency was found in 4 children (1.2%) with CC and in 7 children (0.7%) from the control group, and none had tTG-IgG positivity. Endoscopy was performed in all subjects with positive serology (n = 14). Histopathological examination revealed total villous atrophy (Marsh 3) in two subjects who had tTG-IgA > 200 RU/mL in the control group. Other subjects had Marsh 0–1 lesions. At the end of the serologic and histopathological examinations all patients with CC (8/313, 2.5%) and 4 children (4/990, 0.4%) from the control group were classified as having potential CD. Two children in the control group had silent CD (2/990, 0.2%) (Figure 1). Demographic, laboratory, and histopathological findings of the subjects with positive

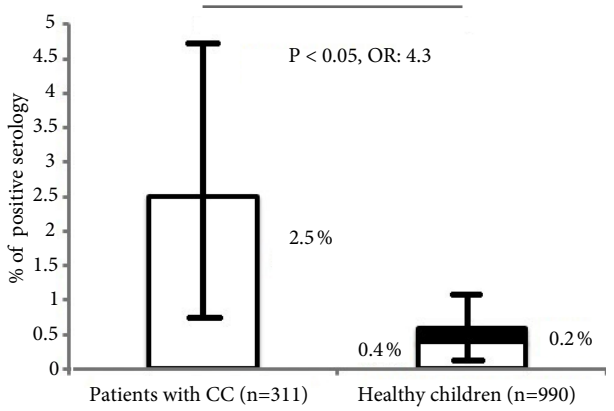

Figure 1. Prevalence of CD in children with CC and healthy children. Note that the prevalence of potential CD is more common in children with CC than in the healthy children (white boxes indicate potential CD and black boxes indicate silent CD; black lines indicated 95% confidence interval).

serology are shown in Table 3. Of the 8 patients with positive serology in CC group, 5 (62.5%) had constipation over 3 years, and 3 children had malnutrition (37.5% in serology positive vs. 11.4% in serology negative, P = 0.02).

Patients with CC were followed with gluten containing diet. tTG-IgA levels were negative in 5 of the 8 patients in the 6th month. tTG-IgA levels increased in one patient, and decreased in 2 patients, but remained above the 20 RU/mL. Only one patient with increased tTG-IgA levels had constipation despite medical treatment at the 6th month. In the 1st year tTG-IgA levels became negative in one patient (a total of 6 patients were negative in the 1st year). One patient had decreased tTG-IgA levels, but the value remained above 20 RU/mL (case 7 in the patient group) . tTG-IgA levels continued to increase in the last patient who had increased tTG-IgA levels in the 6th month. The patient had unresponsive constipation and second endoscopy was performed. Histopathological examination revealed Marsh 1 lesion, and he was started on gluten-free diet due to positive serology and intractable constipation (case 5 in the patient group). The subjects in the healthy group with silent CD were initiated on strict gluten-free diet. tTG-IgA levels decreased in the 6th month and became negative in the 1st year in these subjects. tTG-IgA levels increased in 2 of the other 4 subjects in the 6th month, but they did not have gluten-related symptoms. The other two subjects became negative in the 6th month. Only 1 subject had elavated tTG-IgA levels (98 RU/mL) in the 1st year, but the

Table 3. Clinical and laboratory findings of the subjects with positive serology.

	Age*/S	W/Hp	DC (year)	Ferritine& (ng/mL)	tTG-IgA (RU/mL)	HLA DQ2/DQ8	EMA	Marsh	FD
Patients with CC									
Case 1	3/M	50–75/50–75	1	28.7	37	+ / –	–	0	P
Case 2	2/F	<3/<3	1	34.1	28.5	+ / –	–	0	P
Case 3	7.5/F	75–90/50–75	7	64.2	43.3	+ / –	+	0	P
Case 4	3.5/M	10/25	3	26	78.8	– / +	–	1	P
Case 5	11/M	50–75/50–75	10	14.4	77.3	+ / –	++	1	P
Case 6	4/F	<3/<3	3	36.4	50.9	– / +	–	1	P
Case 7	3.5/F	50–75/75	1.5	21.9	62	+ / +	–	1	P
Case 8	9/M	<3/3–10	8	20	93	– / –	+	1	P
Control group									
Case 1	4/F	50–75/3–10	-	29.3	25.3	+ / –	–	1	P
Case 2	1.5/F	50–75/50–75	-	78	78.4	+ / –	+	1	P
Case 3	2.5/F	10/10–25	-	8.6	>200	+ / –	+++	3	S
Case 4	2/F	50–75/50	-	20	>200	+ / –	+++	3	S
Case 5	2/M	90–97/90–97	-	93	87	+ / –	+	1	P
Case 6	2/F	25–50/25–50	-	57	58	+ / –	–	1	P

*: age in years, DC: duration of constipation, FD: final diagnosis, S: sex, W/Hp: weight/height percentile, P: potential CD, S: silent CD, &: normal values > 12 ng/mL.

parents did not consent to endoscopy (case 2 in the control group) (Figure 2). Overall, spontanous loss of serum tTG-IgA occured in 9 of the 12 (75%) subjects (patients with CC and healthy children).

4. Discussion

In this study we analyzed the association between CC and CD. Motility problems such as increased frequency of gastroesophageal reflux disease, prolonged gastric emptying, decreased postprandial antral motility, and prolonged orocecal transit time have been reported in patients with active CD (11–13). The association of CC with CD was first reported by Egan-Mitchell and McNicholl in 1972 (14). They reported that 12 of 112 infants or children (10.7%) had constipation before the diagnosis of CD. They suggested that constipation is related with decreased intestinal motility due to mucosal inflammation. In a recent report from Turkey, CC was found in 6.8% of patients at the time of initial admission (15). However, reports about the frequency of CD in patients admitted with CC are rare. Pelleboer et al. (16) studied the prevalence of CD in patients with CC, referred by their general practitioner to a pediatrician because of failure of laxative treatment, and they found increased prevalence of CD in these children (7 in 370 patients, 1.9%); they recommend screening for CD in patients with CC who do not respond to medical treatment. On the other hand, Chogle and Saps (17) analyzed the prevalence of CD in patients with CC (n = 1731) and they found similar prevalence of CD in children with CC (n = 33, 1.9%) and in the healthy population (only 3 patients had the sole symptom of constipation as a presenting symptom); they do not recommend routine screening for CD in patients with CC. Similar to this report, we found that overt CD prevalence did not increase in children with CC; however, our study revealed that CC is a risk factor for potential CD.

Potential CD is defined as positive celiac serology with normal villous morphology. Approximately 20% of the patients with positive serology had normal villous morphology at the time of initial admission. It was shown that potential CD is more common in patients with autoimmune diseases, such as type 1 diabetes mellitus and autoimmune thyroiditis, and in the first degree relatives of patients with CD. Additionally, potential CD was also more common in children who had gluten avoidance, and in patients who had tTG-IgA positivity, but <100 RU/mL. The cause of potential CD is unclear, but the lack of innate immune response or a lower level of proinflammatory adaptive antigluten immunity may be responsible for the lack of villous atrophy. Patients with potential CD were advised to continue their gluten containing diet. In the follow-up, serology became negative in most of the patients, but high levels of tTG-IgA may persist in some patients and villous atrophy and overt CD may develop. Risk factors for the development of villous atrophy are male sex, slight mucosal inflammation, presence or absence of some polymorphisms (AA genotype of IL12A, AA genotype of RGS1), and presence of intestinal anti-TG2 IgA deposits (18–20). In our study 75% of the subjects with potential CD became serologically negative at the 1 year follow-up under gluten containing diet. Only 25% (3 of the 12 patients) of the patients had persistent elevated tTG-IgA levels, all had HLA-DQ2 positivity, and 2 had EMA positivity.

Due to the small number of patients with positive serology, we were not able to analyze the risk factors

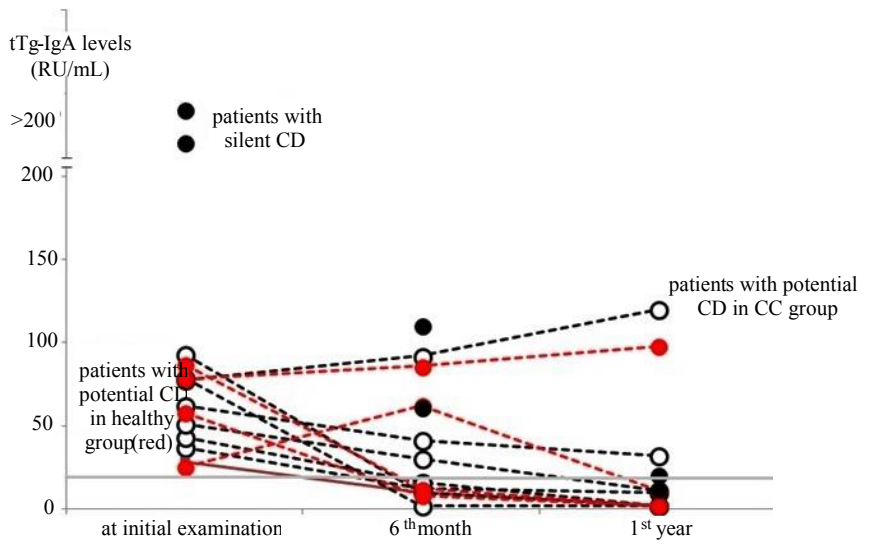

Figure 2. Serological outcome of the subjects with CD (the grey line indicates the normal upper limit of tTG-IgA).

for potential CD in children with CC. However, the presence of malnutrition increases the risk of potential CD. Additionally, the majority of patients with positive serology had constipation over 3 years. Although we did not analyze the quantity of gluten consumption or gluten avoidance in our study groups, the increased frequency of potential CD may be associated with gluten avoidance or low levels of gluten consumption, especially in patients with CC. It was shown that gluten avoidance is common in children who had nonspecific gastrointestinal symptoms (21). Therefore, serum tTG-IgA levels may not increase to 10 times the normal upper limit and total or partial villous atrophy may not be more prominent. One limitation of our study is that the dietary gluten consumption of the participants was not studied with questionnaire forms.

In conclusion, our study revealed that serological evaluation of CD may be omitted in children with CC at initial examination. It may be performed in selected cases, such as in patients with CC associated with prolonged duration of symptoms or associated with malnutrition. CC is a risk factor for potential CD, but the majority of patients became serologically negative on long-term follow-up.

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