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ARCHIVES OF Clinical Gastroenterology

ISSN: 2455-2283 DOI: https://dx.doi.org/10.17352/acg

Research Article

Clinical evaluation of children with celiac disease: A single-center experience

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Received: 28 April, 2020
Accepted: 06 May, 2020
Published: 12 May, 2020

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Keywords: Celiac disease; Children; Intestinal biopsy

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Abstract

Background and objectives: The clinical findings of Celiac Disease (CD) change over time. Instead of classical symptoms such as diarrhea, growth retardation, abdominal bloating, atypical symptoms such as chronic constipation and abdominal pain may be the only sign of CD. In this study, we aimed to evaluate the clinical features of our patients with CD.

Material and methods: This retrospective study was conducted between March 2017 and January 2019. 61 children with CD were included in the study. Local Ethics Committee approval was received. As an initial diagnostic test, tissue transglutaminase antibody (tTG) IgA test and total IgA test were analysed in all patients. Endomysial antibody (EMA) IgA test was analysed in patients with positive tTG IgA. If both celiac tests are detected as positive, gastroduodenoscopy was performed for definitive diagnosis of CD.

Results: Of the 61 patients, 37 (60.6%) was female. The mean age of patients was 8.28±4.28 years. Tissue transglutaminase antibody (tTG) IgA test was positive in all patients, then endomysial antibody (EMA) IgA test was analysed in those patients. Endomysial antibody IgA test was also positive in all patients except three. The pathological results of our patients were Marsh 3a in 30 patients, Marsh 3b in 19 patients, and Marsh 3c in 12 patients. The positive family history of CD was found in the first degree relatives of 6 asymptomatic patients. Those patients were diagnosed with CD after celiac screening tests and endoscopic biopsy. Most of our patients had more than one symptom; 33 patients (54.1%) had classical symptoms such as failure to thrive and diarrhea, and 25 patients (40.9%) had non-classical symptoms.

Conclusion: The first degree relatives of celiac patients even if asymptomatic, and all patients with uncertain complaints and abnormal laboratory findings associated with CD should be evaluated for CD.

Introduction

Celiac Disease (CD) is an immune-mediated systemic disease triggered by gluten intake in genetically susceptible individuals and characterised by the combination of various degree of the intestinal damage and the presence of celiac antibodies [1]. Its prevalence is reported to be approximately 1% [1]. The frequency of CD varies according to the geographic region and genetic factors [1]. In a study conducted in healthy school children in our country, the prevalence of CD was reported to be 0.47% [2].

The clinical findings of CD change over time. Instead of classical symptoms such as diarrhea, growth retardation, abdominal swelling, atypical symptoms such as chronic constipation and abdominal pain may be the only sign of celiac disease [1].

The risk of developing CD is higher in type 1 Diabetes Mellitus (DM), Down syndrome, Turner syndrome, autoimmune disorders, and relatives of celiac patients sharing the same type of HLA [3-6].

The prevalence of CD has increased dramatically over the past 20-30 years due to the use of sensitive and specific celiac serological tests and better recognition of CD by physicians. Even if celiac screening tests are recommended in risk groups, the majority of asymptomatic patients are still undiagnosed [7-10].

Citation: Sahin Y (2020) Clinical evaluation of children with celiac disease: A single-center experience. Arch Clin Gastroenterol 6(2): 026-030.
DOI: https://dx.doi.org/10.17352/2455-2283.000074

In this study, we aimed to evaluate the clinical features of our patients with CD.

Material and methods

This retrospective study was conducted between March 2017 and January 2019. 61 children with CD were included in the study. This study was conducted in accordance with the Helsinki Declaration Principles revised in 2013. Also, Local Ethics Committee approval was received (09.01.2019-E.942120).

The files, complaints, demographic features, clinical, and laboratory features of patients were examined retrospectively. As an initial diagnostic test, tissue transglutaminase antibody (tTG) IgA and total IgA tests were analysed in all patients [1]. It is planned to perform tTG IgG in patients with IgA deficiency [11]. Endomysial Antibody (EMA) IgA test was performed on patients with positive tTG IgA [1]. When used in combination with EMA and tTG IgA tests, the sensitivity and specificity is close to 95% or more [12].

Gastroduodenoscopy was performed on patients with both positive celiac antibodies to diagnose CD, and at least 4 biopsies from duodenum and 2 biopsies from the bulb were obtained. The endoscopic biopsies were evaluated according to the Marsh Classification [13].

Statistical analysis

Descriptive statistics were used for frequency, percentage and mean ± standard deviation which are descriptive parameters. Independent-Samples t test was used to compare numerical variables. Mann Whitney U test was used for parameters with non-normal distribution. Statistical Package for Social Sciences for Windows, version 13.0 software (SPSS Inc, Chicago IL, USA) was used for statistical analysis.

Results

Of the 61 patients, 37 (60.6%) was female. The mean age of the patients was 8.28±4.28 years (Table 1). Tissue transglutaminase antibody IgA test was positive in all patients, then EMA IgA test was analysed in those patients. EMA IgA test was detected as positive in all patients except three. As CD was strongly considered, gastroduodenoscopy was also performed on those three patients. Gastroduodenoscopy was performed in all patients, at least 4 biopsies from the duodenum and 2 biopsies from the bulb were obtained. IgA deficiency was not detected in any of our patients.

The pathological results of our patients were detected as Marsh 3a in 30 patients, Marsh 3b in 19 patients, and Marsh 3c in 12 patients.

Only one of the 61 patients had chronic nausea. Both tTG IgA test and EMA antibody IgA test were detected as positive. The histopathological changes of Marsh 0 was detected in the first endoscopic biopsy. In the follow-up of outpatient clinic, both celiac antibodies were found as positive again. In the second endoscopic biopsy, the histopathological changes of Marsh 2 and moderate Helicobacter Pylori (HP) infection were detected. The control endoscopic biopsy was performed 3 months after the eradication therapy of HP, the changes of Marsh 3a were detected in the duodenum, and then CD was diagnosed.

Most of our patients had more than one symptom; 33 patients (54.1%) had classical symptoms such as failure to thrive and diarrhea, and 25 patients (40.9%) had non-classical symptoms (Table 2). Growth retardation was detected in 28 patients (45.9%), constipation in 10 patients (16.4%), and anorexia in 4 patients (6.5%).

The positive family history of CD was found in the first degree relatives of 6 asymptomatic patients. Those patients without any symptoms were diagnosed with CD after celiac screening tests and gastroduodenoscopy.

One of our patients, who has positive family history of CD, presented with growth retardation. Both tTG and EMA antibodies IgA tests were found as positive. Gastroduodenoscopy was performed on this patient, multiple millimetric ulcers were detected in the corpus, and Marsh 0 classification score was detected in the duodenum and bulbus. After six months,

Table 1: The demographic and laboratory features of patients.

	Patients (n= 61)
Age (years)	8.28±4.28
Sex (female/male)	37/24
Height (cm)	120.40±22.28
Weight (kg)	23.98±12.12
Hemoglobin (g/dL)	11.68±1.45
MCV	74.42±8.09
Ferritin	12.04±14.05
Folate	8.44±3.47
Vitamin B12	353.67±129.99
Vitamin D	18.83±7.29
tTG IgA (U/ml)	132.79±50.37
EMA IgA (U/ml)	124.78±55.34
Total IgA (mg/dl)	133.65±82.93

MCV: Mean Corpuscular Volume; tTG: tissue Transglutaminase antibody; EMA: Endomysial Antibody

Table 2: The presenting complaints of patients.

	Patients no.(%)
Growth retardation	29(47.5%)
Abdominal pain	9(14.7%)
Comstipation	9(14.7%)
Anorexia	4(6.5%)
Diarrhea and constipation episodes	2(3.2%)
Diarrhea	2(3.2%)
Abdominal bloating	2(3.2%)
Nausea	1(1.6%)
Inability to lose weight	1(1.6%)
Underweight	1(1.6%)

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both celiac antibodies were found as positive again. The histopathological changes of Marsh 3c was detected in the bulb, and then CD was diagnosed.

One of our patients with type 1 DM diagnosed 11 years ago underwent gastroduodenoscopy because of both positive celiac antibodies. The pathological result was compatible with Marsh 2 classification score. Also, the patient had growth retardation and constipation. It was learned that she had a gluten-free diet for 20 days before endoscopy. After 2 months with normal diet including gluten, both of the celiac antibodies were detected as positive. The second endoscopic biopsy was performed, and the changes of Marsh 3a compatible with CD was detected.

Multiple millimetric ulcers were detected in the bulb of an another patient with growth retardation, a clear assessment for CD could not be made because of the ulcerative lesions. Also, we found a high degree of helicobacter pylori infection in the biopsy of antrum. Gastroduodenoscopy was performed 3 months after the eradication of HP infection, the changes of Marsh 3a was detected, and then the patient was diagnosed with CD.

A 17-year-old patient with constipation and unable to lose weight despite a gluten-free diet was admitted. She had learned a gluten-free diet through social media. She had gained 5 kg in 2 months after a gluten-free diet. Both celiac antibodies were found as positive, and gastroduodenoscopy was performed. The endoscopic biopsy revealed Marsh 3a compatible with CD, and then she was diagnosed with CD.

Of the 61 patients, 7 (11.4%) diagnosed with CD had type 1 DM; 3 had hypothyroidism, 1 had Down syndrome; 1 had both Turner syndrome and Hashimoto thyroiditis (Table 3).

Table 3: The conditions, which are associated with high risk of celiac disease, accompanying celiac disease.

	Patients no.(%)
Type 1 diabetes mellitus	7(11.4%)
Hypothyroidism	2(3.2%)
Down syndrome	1(1.6%)
Turner syndrome and Hashimoto thyroiditis	1(1.6%)
Positive celiac history in siblings	5(8.1%)
Positive celiac history in father	1(1.6%)
Positive celiac history in second degree relatives	3(4.9%)

Discussion

In a systematic review and meta-analysis, the prevalence of biopsy-proven CD was reported to be 0.7% and its seroprevalence 1.4% [14].

Celiac patients can also present with gastrointestinal symptoms, extraintestinal symptoms or without any symptoms. The classical findings of CD related to the gastrointestinal system are weight loss, steatorrhea and diarrhea due to malabsorption [1]. Approximately 50% of celiac patients presented with extraintestinal or atypical findings such as anemia, osteoporosis, dermatitis herpetiformis, neurological problems, and dental enamel hypoplasia [15]. As compatible with literature, classical symptoms were present in 54.1% of our pateints and non-classical symptoms in 40.9%.

The presenting findings of patients diagnosed with CD change over time, especially in older children. The milder findings of CD are present in those patients [16,17]. Therefore, the diagnosis of CD may be overlooked and it may be difficult to diagnose CD in those patients. In parallel with the literature, a patient with a height of 177 cm (75^{th} percentile) and a weight of 55kg (10^{th} percentile) presented with the complaint of low weight. Iron deficiency anemia and positive celiac antibodies were detected in the laboratory examinations. Gastroduodenoscopy was performed and the histopathological changes of Marsh 3a compatible with CD was detected in the duodenum. With a gluten-free diet, the patient has gained 5kg in a three months.

A 17-year-old patient with constipation and unable to lose weight despite a gluten-free diet was admitted. She gained 5 kg in 2 months after a gluten-free diet. Both tTG and EMA IgA antibody tests were found as positive, and gastroduodenoscopy was performed on this patient. The endoscopic biopsy revealed Marsh 3a compatible with CD. Then, the patient who applied with atypical symptoms, was also diagnosed with CD in accordance with literature [16,17].

Approximately 10% of the positive family history of CD was reported in the first degree relatives of celiac patients [18,19]. In parallel with these studies, 6 of our patients (9.83%) had a positive family history of CD in their first degree relatives.

Of the patients, 39.7% had growth retardation, 18.9% had anemia, and 12.1% had constipation in a recent study [20]. In consistent with this study, 28 of our patients (45.9%) had growth retardation, 9 of our patient (14.7%) had anemia and 9 of our patients (14.7%) had constipation.

Most of our patients had more than one symptom in consistent with literature (1,18,19); the classical symptoms such as failure to thrive and diarrhea in 33 patients (54.1%), and non-classical symptoms in 25 patients (40.9%) was detected. Also, growth retardation in 28 patients (45.9%), constipation in 9 patients (14.7%), chronic abdominal pain in 9 patients (14.7%), and anorexia in 4 patients (6.5%) was detected.

It has been reported to be 10.8-62.0% of newly diagnosed celiac patients have vitamin D deficiency (18,21,22). In the current study, vitamin D deficiency was found in 38 of our patients (62.2%). The reason for high rate of vitamin D deficiency detected in our patients may be due to insufficient use of sunlight, the high number of our patients with low socio-economic level, and related to malnutrition.

In a study, type 1 Diabetes Mellitus (DM) was detected in 9.4% of celiac patients, hypothyroidism in 4.4% and Down syndrome in 0.6% [18]. In accordance with this study, 7 patients (11.4%) had type 1 DM, 2 patients (3.2%) had hypothyroidism, 1

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patient (1.6%) had Down syndrome, 1 patient had both Turner syndrome and Hashimoto thyroiditis.

Iron deficiency anemia is a typical complication of malabsorption in CD [23]. As compatible with literature, 8 of our patients (13.1%) had refractory iron deficiency anemia at the time of diagnosis.

The intensity of the pathological lesion is from proximal to distal in CD. Sometimes, villous atrophy is seen only in the bulbus mucosa [24-26]. In accordance with the literature, the pathological findings compatible with CD were detected only in the bulbus mucosa of 8 patients (13.1%) in the current study. Therefore, at least 4 biopsies from the duodenum and 2 biopsies from the bulb should be obtained from patients who are considered to have CD, while considering that pathological findings of CD may be seen only in the bulb.

As celiac patients can present with gastrointestinal system symptoms, extraintestinal symptoms, atypical findings or without symptoms, the majority of celiac patients are still not diagnosed [14,27-29].

In our study, 20 patients (32.7%) in the CD risk group were either asymptomatic or presented with atypical findings, and then diagnosed with CD as a result of careful assessment. As compatible with literature, approximately 1/4 of our patients presented with atypical symptoms such as chronic abdominal pain and constipation, and those symptoms were mostly present in older children [1,16,17].

Conclusion

The majority of celiac patients are still undiagnosed, patients diagnosed with CD constitute only the tip of the iceberg. Those patients have the risk of developing long-term complications of CD such as growth retardation, infertility, osteoporosis, and malignancies. To prevent these long-term complications, early diagnosis of CD is crucial. In the current study, approximately 1/3 of our patients diagnosed with CD were either asymptomatic or presented with atypical findings. All patients with atypical symptoms or vague symptoms, with abnormal laboratory findings associated with CD, and those who are in the risk group for CD even if asymptomatic, should be carefully evaluated for CD.

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