The presentation of celiac disease in 220 Turkish children

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The aim of this study was to investigate the presentation pattern of newly diagnosed celiac disease (CD) in Turkish children in the last eight years.

Two hundred twenty patients with newly diagnosed CD were included. The medical records of all the patients between January 2000 and October 2008 were reviewed. The clinical spectrum was divided into three categories according to the main symptoms that led to the diagnosis: gastrointestinal presentation, non-gastrointestinal presentation, and silent cases.

The mean age of the patients was 7.2±4.3 years at diagnosis. According to the presenting signs, the patients were defined as gastrointestinal presentation (129 patients, 58.6%), non-gastrointestinal presentation (76 patients, 34.6%) and silent cases (15 patients, 6.8%).

This study showed that the number/percentage of CD cases who presented with non-gastrointestinal symptoms/conditions, so-called "non-gastrointestinal presentation", have been increasing in the last eight years.

Key words: celiac disease, presentation pattern, Turkish children.

Celiac disease (CD) is an immune-mediated inflammatory condition of the small bowel mucosa caused by intolerance to gluten-derived peptides of wheat, rye and barley. The recent epidemiological studies in Europe and United States show a marked increase in CD prevalence, reported to range between 1:300-1:80[1,2]. CD might present with either gastrointestinal or non-gastrointestinal symptoms. The patients who are asymptomatic but have a positive serologic test and villous atrophy on biopsy are referred to as silent CD. These patients are usually diagnosed during screening of individuals who have associated conditions such as diabetes mellitus type 1, thyroiditis, Down syndrome, immunoglobulin A (IgA) deficiency, or family history of CD[3,4]. There is little knowledge available about the presentation patterns of CD in Turkish children[5,6].

The aim of this study was to describe the presentation pattern of newly diagnosed Turkish children with CD in the last eight years in our institution.

Material and Methods

Patients

The medical records of all patients with newly diagnosed CD at Hacettepe University, İhsan Doğramacı Children's Hospital (a tertiary center) between January 2000 and December 2008 were reviewed. Data extracted from the medical records included year of diagnosis, demographic features, growth parameters, sign and symptoms, complete blood count, liver function tests, serum levels of IgA, serum levels of IgA endomysial antibodies (EMA), serum levels of IgA anti-tissue transglutaminase antibodies (TGA), indication for biopsy, and degree of histopathological injury on samples obtained by upper gastrointestinal endoscopy. The degree of histopathological injury was classified according to modified Marsh classification[7]. CD was diagnosed according to the revised criteria of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition[8].

The patients were divided into four groups according to their ages as: 6 months to 2 years (Group 1), 2-6 years (Group 2), 6-12 years (Group 3), and >12 years (Group 4).

The clinical spectrum was divided into three categories according to the presenting symptoms that led to the diagnosis as: gastrointestinal, non-gastrointestinal presentation and silent presentation.

Gastrointestinal Presentation

Chronic diarrhea, abdominal pain, bloating, constipation, and any other gastrointestinal symptoms were accepted as gastrointestinal presentation. If a patient had one or more gastrointestinal symptoms, the condition was accepted as "gastrointestinal presentation" whether or not he/she had any non-gastrointestinal symptoms or associated conditions.

Non-Gastrointestinal Presentation

Patients presenting with growth failure, short stature, iron-unresponsive anemia, alopecia, hypertransaminasemia, cryptogenic cirrhosis, recurrent aphthous stomatitis, dermatitis herpetiformis, or any other non-gastrointestinal symptoms and conditions were accepted as non-gastrointestinal presentation. Growth failure was defined as weight for age <3rd percentile and/or weight for height <3rd percentile. Short stature was defined as a height for age <3rd percentile.

Silent Cases

The patients with CD-associated conditions such as diabetes mellitus type 1, thyroiditis, Down syndrome, and family history of CD but without symptoms related to CD were accepted as "silent cases".

Serologic Features

The presence of IgA EMA was analyzed by indirect immunofluorescence using a section of monkey esophagus (Euroimmune GmbH, Lübeck, Germany), and serum levels of IgA TGA were measured by commercial enzyme-linked immunosorbent assay (ELISA).

Histopathologic Features

The histopathologic injury was divided into two categories based upon Marsh–Oberhuber classification system as 1-mild (Marsh 1, 2 and 3a) and 2-severe (Marsh 3b, 3c).

Others

Iron deficiency anemia was defined based upon the World Health Organization (WHO) criteria as ferritin levels lower than 12 μg/L and hemoglobin concentration <11 g/dl in children <5 years old or <12 g/dl in children >5 years old[9].

Informed Consent

Written informed consent was obtained from parents or legal guardians before endoscopy in each case.

Statistical Analysis

Data were analyzed by descriptive analysis using SPSS v11.0. Chi-square test was used to compare categorical data. T-test was used to compare means between groups.

Results

The study population consisted of 220 patients [134 female (60.9%), 86 male (39.1%)] with newly diagnosed CD. Demographic data, presentation and symptoms/associated conditions are presented in Table I. Mean age at presentation was 7.2±4.3 years. One hundred twenty-nine (58.6%) patients presented with gastrointestinal symptoms, 76 patients (34.6%) with non-gastrointestinal symptoms/conditions and 15 patients (6.8%) as silent cases. Among silent cases, there were 5 with diabetes mellitus, 2 with thyroiditis, 1 with Down syndrome, 1 with Down syndrome and family history, and 2 with diabetes mellitus and thyroiditis, and 4 cases were diagnosed during family screening. The patients presenting with gastrointestinal symptoms were significantly younger than the other two groups ($p<0.001$).

Gender was not related to the presentation type. Gastrointestinal presentation was present in 57.5% of girls and 60.5% of boys. Non-gastrointestinal presentation was present in 36.6% of girls and 31.4% of boys, and silent cases were seen in 5.9% of girls and 8.1% of boys.

Distribution of the presentation type according to age groups was also significantly different when groups were compared ($p<0.05$) (Table II).

Table I. Features of the Patients

Parameters	All patients	Gastrointestinal presentation	Non-gastrointestinal presentation	Silent cases
Number	220	129 (58.6%)	76 (34.6%)	15 (6.8%)
Age (yr) mean±SD	7.16±4.29	5.13±3.61	9.87±3.52	10.86±3.10
Female (%)	134 (60.9%)	77 (59.7%)	49 (64.5%)	8 (53.3%)
Diarrhea	94 (42.7%)	94 (72.9%)	-	-
Bloating	58 (26.4%)	58 (45.0%)	-	-
Abdominal pain	34 (15.5%)	34 (26.4%)	-	-
Constipation	15 (6.8%)	15 (11.6%)	-	-
Growth failure (>2 years old)	95 (53.1%)	68 (52.7%)	44 (57.9%)	3 (20%)
Iron deficiency anemia	106 (48.2%)	68 (52.7%)	35 (46.1%)	3 (20%)
Refractory iron deficiency anemia	19 (8.6%)	-	19 (25.0%)	-
Short stature	18 (8.2%)	-	18 (23.7%)	-
Hypertransaminasemia	14 (6.4%)	7 (5.4%)	7 (9.2%)	-
Alopecia	3 (1.4%)	-	3 (3.9%)	-
Stomatitis	3 (1.4%)	2 (1.6%)	1 (1.3%)	-
Obesity	1 (0.5%)	1 (0.8%)	-	-
Arthritis	1 (0.5%)	1 (0.8%)	-	-
Dermatitis herpetiformis	1 (0.5%)	-	1 (1.3%)	-
Cirrhosis	1 (0.5%)	-	1 (1.3%)	-
Family history of CD	14 (6.4%)	7 (5.4%)	2 (2.6%)	5 (33.3%)
Type-1 diabetes mellitus	9 (4.1%)	1 (0.8%)	1 (1.3%)	7 (46.7%)
Thyroiditis	7 (3.2%)	2 (1.6%)	1 (1.3%)	4 (26.7%)
Down syndrome	2 (0.9%)	-	-	2 (13.3%)
Turner syndrome	2 (0.9%)	1 (0.8%)	1 (1.3%)	-
IgA deficiency	9 (4.1%)	6 (4.7%)	3 (3.9%)	-

CD: Celiac disease

Among the total group, weight for age was below the 3rd centile in 115 patients (52.3%), and height for age was below the 3rd centile in 84 of the patients (38.2%). Short stature was the sole presenting symptom in 18 (8.2%) of them. Comparison of weight and height at the time of diagnosis according to presentation type showed no significant differences between the patients. The incidence of growth failure in terms of weight and/or height was significantly lower in silent cases compared to gastrointestinal and non-gastrointestinal cases (Table III). Only 3 of the silent cases had growth failure (2 had thyroiditis and 1 had type 1 diabetes). There was no gender difference regarding growth failure.

Severity of the mucosal lesion was related to the type of presentation (Table IV). Severe injury was significantly lower in silent cases (p=0.007). Mild injury was present in 58.1%, 72.4%, and 93.3% of the gastrointestinal, non-gastrointestinal and silent cases, respectively.

Serum levels of IgA EMA were studied in 219 patients (99.5%), and it was found positive in 200 (91.3%). Nine of the 19 EMA IgA-negative patients also had IgA deficiency. Serum levels of IgA TGA were obtained from 170 patients (77.2%), and it was negative in 14 patients (8.2%), 8 of whom had selective IgA deficiency. The remaining 156 were found positive (91.8%).

Anemia was observed in 106 (48.2%) patients. Anemia was not related to gender, histopathological activity or age group. The prevalence of anemia was significantly lower in silent cases compared to typical and atypical cases (p=0.05). Only 3 of the silent cases (2 type 1 diabetes, 1 Down syndrome) had anemia, which was detected during screening. Although 48.2% of the study population had

Table II. Presentation Type According to Age Groups

Age groups	Gastrointestinal presentation	Non-gastrointestinal presentation	Silent cases
<2 years	39 (95.2%)	1 (2.4%)	1 (2.4%)
2-7 years	52 (77.6%)	15 (22.4%)	0 (0.0%)
7-12 years	31 (38.8%)	40 (50.0%)	9 (11.2%)
>12 years	7 (21.9%)	20 (62.5%)	5 (15.6%)

Table III. Incidence of Low Weight and Short Stature According to the Presentation Type

Presentation type	Low weight N (%)	Short stature N (%)
All cases	115 (52.3)	84 (38.2)
Gastrointestinal presentation	68 (52.7)	42 (32.6)
Non-gastrointestinal presentation	44 (57.9)	40 (52.6)
Silent	2 (13.3)	2 (13.3)
p value	0.027	0.002

anemia at the time of diagnosis, only 8.6% of the patients had refractory iron deficiency as the sole complaint.

Discussion

In recent years, CD has appeared to be more common than was previously thought. This condition is related to the advances in understanding the CD pathogenesis, increased awareness of CD (particularly the atypical forms) and widespread use of specific and sensitive serological tests such as EMA and TGA (11,12). The prevalence of CD in Turkish children is similar to that seen in western European countries, and has been reported to be 1:111[10,13].

Although CD is common in our country, data about its presentation patterns are scarce[6]. A previous study about the presentation of CD was carried out in our department during the period 1995-1999[5]. In this study, we tried to document and assess the changes in the presentation pattern of CD in Turkish children diagnosed between 2000 and 2008.

The mean age of the patients at diagnosis was 7.2±4.3 years in this study. The mean age at diagnosis has increased from 5.7 years to 7.2 years since 2000, when compared to results of our previous study[5]. The reason for this difference is that almost half of the patients diagnosed during the last eight years were silent cases and the cases with non-gastrointestinal presentation, which are diagnosed at older ages. Similar trends have been observed in recent studies[12,14].

The proportion of the classical form of CD, commonly seen in children less than two years of age with diarrhea, failure to thrive and abdominal distention, has decreased in the last eight years. In the present study, 18.6% of children were under two years of age, while this proportion was 56.7% in the study including the patients diagnosed between 1995 and 1999[5]. Stone et al.[14] investigated the presentation patterns of children with CD between 1997 and 2002, and found that among 69 celiac patients, infants less than two years of age represented only 12% of the study population. In the present study, the ratio of non-gastrointestinal presentation and silent cases increased as the age of the patients increased, and two-thirds of the patients older than seven years presented with non-gastrointestinal symptoms/conditions or were silent cases. That ratio was similar to the studies performed in developed countries[12,15] and higher than that in our previous study[5].

Growth failure is prevalent in patients with CD irrespective of presentation type. Weight and height were below the 3rd percentile in 52.3% and 38.2% of the patients, respectively. These percentages were almost the same in our previous study (51.9% and 45.2%, respectively)[5]. Short stature may be the only presenting symptom in children with CD. It has been shown that 8% to 10% of children with short stature had CD[3]. In this study, although 38.2% of the study population had short stature at the time of diagnosis, only 8.2% of the patients had short stature as

Table IV. Histopathologic Correlation of the Presentation Type

	Gastrointestinal presentation N (%)	Non-gastrointestinal presentation N (%)	Silent cases N (%)	P value
Mild injury	75 (58.1)	55 (72.4)	14 (93.3)	0.007
Severe injury	54 (41.9)	21 (27.6)	1 (6.7)	

the sole presenting symptom. Short stature is less common in patients presenting with gastrointestinal symptoms probably because of the relatively short duration of symptoms before diagnosis, allowing failure to thrive to develop but not to short stature.

Persistent and refractory iron deficiency anemia appeared to be the most frequent non-gastrointestinal finding, and this may be the only primary symptom of CD in reported cases[3,16]. In this study, 19 patients (8.6%) were diagnosed as CD with the complaint of refractory iron deficiency anemia. Alopecia areata (AA), presumed to be a result of autoimmune reaction, is a common, unpredictable, non-scarring form of hair loss. This disorder affects all age groups, with a higher prevalence in children and adolescents. Recently, an association of CD with AA has been reported[17]. In this study, three patients (1.4%) presented with AA and CD. Liver disease is more common in individuals with CD compared with the general population both at diagnosis and follow-up. The liver involvement in CD includes a wide spectrum that may change from asymptomatic hypertransaminasemia to cirrhosis[18,19]. Although the cause of liver involvement in CD is not known exactly, autoimmune mechanisms might play a role. Hypertransaminasemia may be present at diagnosis[18]. In this study, raised serum levels of transaminases at diagnosis were detected in 14 patients (6.4%), and one patient presented with cirrhosis.

The concordance rate for CD in close relatives ranges from 8% to 18% and reaches 70% in monozygotic twins[20]. In this study, 14 patients (6.4%) were identified via the screening of first-degree relatives.

Autoimmune diseases are common in patients with CD and their relatives with respect to the general population. Neuhausen et al.[21] reported that in the setting of CD, 13.2% of patients and 4.6% of their first-degree relatives had at least one autoimmune disease. Sari et al.[22] reported that the prevalence of biopsy-proven CD in patients with autoimmune thyroiditis was 4.9% in Turkish children. In our study, seven patients had type-1 diabetes mellitus and five patients had thyroiditis, and two patients had both diseases. Autoimmune diseases showed an increase in this study compared to our previous study[5].

Strong evidence exists for an association between selective IgA deficiency and CD. The risk of CD is 10-20-fold higher in patients with selective IgA deficiency compared to healthy individuals. For this reason, patients with selective IgA deficiency should be screened for CD. These patients represent a special challenge since the specific IgA class antibodies against gliadin (AGA), EMA, and TGA are not produced in patients with CD[23]. Based on retrospective studies, 1.7% to 7.7% of individuals of European origin with selective IgA deficiency also have CD[3]. In this study, selective IgA deficiency prevalence was 9/220 patients (4.1%), similar to the results of the study by Demir et al.[5,19] (4.1% vs. 4.6%, respectively).

Currently, measurement of serum IgA TGA and EMA are recommended for initial testing for CD. Both these tests are highly sensitive and specific for CD, with values of 90-100% in children[3,24]. In this study, TGA was positive in 96.7% and EMA was positive in 96.4% of the patients when the patients with selective IgA deficiency were excluded. As previously reported by van Heel et al.[11], we did not observe a relationship between serological test positivity and presentation types. The relationship between EMA negativity and mild histopathological injury was reported by Rostami et al.[25] In this study, we found mild mucosal injury in small bowel biopsies in 8 of the 10 EMA-negative patients.

As reported by Telega et al.[12], histopathological damage was more pronounced in patients presenting with gastrointestinal symptoms. In this study, we also observed more severe mucosal injury in patients presenting with gastrointestinal symptoms. In addition, mucosal injury was mild in the silent cases.

In conclusion, this study showed that important changes have been observed in the presentation pattern of newly diagnosed CD in Turkish children. The number/percentage of the patients presenting with non-gastrointestinal symptoms/conditions have been increasing over the last eight years. According to the results of this study, pediatricians must consider CD in school-aged Turkish children with growth failure, short stature and refractory iron deficiency anemia.

REFERENCES

1. Maki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. N Engl J Med 2003; 348: 2517-2524.
2. Hoffenberg EJ, MacKenzie T, Barriga KJ, et al. A prospective study of the incidence of childhood celiac disease. J Pediatr 2003; 143: 308-314.
3. Hill ID, Dirks MH, Liptak GS, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for 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.
4. NIH consensus statement on celiac disease. NIH Consens State Sci Statements 2004; 21: 1-23.
5. Demir H, Yüce A, Koçak N, Ozen H, Gurakan F. Celiac disease in Turkish children: presentation of 104 cases. Pediatr Int 2000; 42: 483-487.
6. Dinler G, Atalay E, Kalaycı A. Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey. World J Pediatr 2009; 5: 282-286.
7. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for standardized report schema for pathologists. Eur J Gastroenterol Hepatol 1999; 11: 1185-1194.
8. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990; 65: 909-911.
9. Nutritional anemias. Report of a WHO Scientific Group, Geneva, World Health Organization, 1968 (WHO Technical Report Series. No. 405).
10. Demirceken FG, Kansu A, Kuloglu Z, Girgin N, Guriz H, Ensari A. Human tissue transglutaminase antibody screening by immunochromatographic line immunoassay for early diagnosis of celiac disease in Turkish children. Turk J Gastroenterol 2008; 19: 14-21.
11. Van Heel DA, West J. Recent advances in coeliac disease. Gut 2006; 55: 1036-1046.
12. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in presentation of celiac disease. Arch Pediatr Adolesc Med 2008; 162: 164-168.
13. Ertekin V, Selimoglu MA, Kardas F, Aktas E. Prevalence of celiac disease in Turkish children. J Clin Gastroenterol 2005; 39: 689-691.
14. Stone ML, Bohane TD, Whitten KE, Tobias VH, Day AS. Age related clinical features of childhood coeliac disease in Australia. BMC Pediatr 2005; 5: 11.
15. Lopez-Rodriguez MJ, Canal Macias ML, Lavado Garcia JM, Sanchez Belda MS, Andres PR, Zamorano JD. Epidemiological changes in diagnosed coeliac disease in a population of Spanish children. Acta Paediatr 2003; 92: 165-169.
16. Di Sabatino A, Corazza G. Coeliac disease. Lancet 2009; 373: 1480-1493.
17. Fessatou S, Kostaki M, Karpathios T. Coeliac disease and alopecia areata in childhood. J Paediatr Child Health 2003; 39: 152-154.
18. Volta U. Pathogenesis and clinical significance of liver injury in celiac disease. Clinic Rev Allerg Immunol 2009; 36: 62-70.
19. Demir H, Yüce A, Caglar M, et al. Cirrhosis in children with celiac disease. J Clin Gastroenterol 2005; 39: 630-633.
20. Schuppman D. Current concepts of celiac disease pathogenesis. Gastroenterology 2000; 119: 234-242.
21. Neuhausen SL, Steele L, Ryan S, et al. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. J Autoimmun 2008; 31: 160-165.
22. Sari S, Yesilkaya E, Egritas O, Bideci A, Dalgic B. Prevalence of celiac disease in Turkish children with autoimmune thyroiditis. Dig Dis Sci 2009; 54: 830-832.
23. Villalta D, Alessio MG, Tampoia M, et al. Diagnostic accuracy of IgA anti-tissue transglutaminase antibody assays in celiac disease patients with selective IgA deficiency. Ann N Y Acad Sci 2007; 1109: 212-220.
24. Rodrigues AF, Jenkins HR. Investigation and management of coeliac disease. Arch Dis Child 2008; 93: 251-254.
25. Rostami K, Kerchkhaert JP, Tiemessen R, Meijer JW, Mulder CJ. The relationship between anti-endomysium antibodies and villous atrophy in celiac disease using both monkey and human substrate. Eur J Gastroenterol Hepatol 1999; 11: 439-442.