Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey

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Background: **Celiac disease presents with a spectrum of clinical disorders. The variety of clinical presentations largely depends on age and extraintestinal findings. This study aimed to determine typical and atypical cases according to presenting symptoms and to evaluate their biochemical and pathological parameters.**

Methods: **Eighty-seven patients with celiac disease in our unit between 2000 and 2007 were reviewed. Their diagnosis was made by serological and histological examination. The patients were divided into two groups according to their typical or atypical symptoms.**

Results: **The mean age of the patients at diagnosis was 8.2 years (range, 1-18 years), but patients presenting with typical symptoms were younger than those presenting with atypical symptoms. The patients in the two groups did not differ significantly in sex, weight and height Z scores except age. Diarrhea (96.3%), abdominal distention (65.4%) and failure to thrive (60%) were the most common clinical presentations in the typical group, and short stature (62.5%) and anemia (31.2%) were the most common in the atypical group. Total/subtotal villous atrophy was significantly higher in the typical group than in the atypical group.**

Conclusions: **Many children with celiac disease show an atypical form. The understanding of presentations of celiac disease may prevent delayed diagnosis. Celiac disease should be specially investigated in patients with recurrent iron deficiency anemia, short stature and autoimmune disorders.**

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Key words: **atypical presentation;**
celiac disease;
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Introduction

Celiac disease (CD) is a permanent inflammatory disease of the small intestine, induced by the intake of gluten proteins present in wheat, barley and rye. It was first described by Samuel Gee and believed to be a chronic enteropathy affecting the people of European descent until the last decade. Today it is known to be distributed all over the world with a mean prevalence rate of 1%-2%.[1]

Celiac disease is characterized by chronic diarrhea, failure to thrive and abdominal distention usually observed within the first 1-2 years of life. At the older age, atypical features such as anemia, short stature, bone disease and liver failure may occur.[2] Since the symptoms of the disease are diverse, pediatricians must be able to recognize its varied clinical presentations.

This study was to describe the variable clinical features of children with celiac disease and to determine if the presenting symptoms in typical and atypical cases vary with age, sex and to correlate the laboratory results and the intensity of mucosal damage in both forms.

Methods

In this retrospective study, the medical records of 87 children with CD treated at the Pediatric Gastroenterology Hepatology and Nutrition Department between 2000 and 2007 were reviewed. Of the 87 patients, 54 (62.1%) were female and 33 (37.9%) were male. The mean age at diagnosis was 8.2 years (range: 1-18 years). The mode of presentation, clinical features, any associated disorders, the results of biochemical and serological studies, and the histological features of duodenal biopsy specimens from all patients were recorded. The patients were classified according to their main symptoms. The typical group (55 patients, 63.2%) included CD patients with typical symptoms such as chronic diarrhea, abdominal distension

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and failure to thrive. The atypical group (32 patients, 36.8%) comprised patients with atypical symptoms such as anemia, short stature, abdominal pain, constipation, recurrent aphthous stomatitis. The atypical group had never suffered from neither diarrhea nor abdominal distension.

The patients who had typical or atypical symptoms were investigated for CD by anti-endomysial antibodies (EMA) and antigliadin antibodies (AGA). In addition, patients with insulin dependent diabetes mellitus (IDDM) attending the Pediatric Endocrinology Department of our hospital have been screened for CD by serological tests since 2005, and the patients presenting positive serologic results were referred to our department. Thus the study also included three patients without symptoms.

Height and weight for age had been recorded for all patients at presentation. Complete blood cell count, liver function tests, serum protein, albumin, vitamin B12, folic acid, ferritin and immunoglobulin A levels, and serum transferrin saturation were evaluated by standard methods. Direct smears of stools were examined to exclude any parasitic infection, especially giardiasis.

Serum levels of EMA IgA were analyzed by indirect immunofluorescence using a section from specimens of monkey esophagus (In the first four years of the study period, Euroimmun, Lübeck, Germany; later, IMMCO Diagnostics, Buffalo, USA). Values with an antibody titer ≤1/10 were regarded as positive. AGA (IgA and IgG) were measured by a commercial enzyme-linked immunosorbent assay (ELISA). In the first four years of the study period, the cut-off values used for children were IgA>12 and IgG>12 (Orgentec Diagnostika, Mainz, Germany). Whereas in the later stages of the study period, the cut-off values used for children were IgA>23 and IgG>28 (IMMCO Diagnostics, Buffalo, USA).

Endoscopic duodenal biopsy was performed if EMA or AGA or both were positive. Three pieces of mucosa were obtained from the second part of the duodenum. The intensity of intestinal damage was graded according to the criteria of Marsh and Oberhuber.[3] Partial villous atrophy (VA) was defined as shortened villi with a villous/crypt ratio <1:1. If villi were atrophic but still separated and recognizable, it was described as subtotal VA. Finally total VA was defined as villi rudimentary or absent. Patients with normal villous architecture were excluded. CD was diagnosed by compatible serologic tests, small bowel biopsy mentioned above and response to a gluten free diet according to the ESPGAN criteria.[4] If relevant serologic tests or small bowel biopsy was not performed at the time of diagnosis, this case was not included in the study. In this period, 87 patients fulfilled the criteria and their medical records were reviewed.

Statistical analysis was performed using SPSS 13.0. Data were presented as the mean ± SD. The Chi-square test and Mann-Whitney U test were used to compare the results of the two groups. A *P* value less than 0.05 was considered statistically significant.

Results

Demographic features and anthropometric parameters of the two groups are shown in Table 1. Fifty-five patients with typical CD were younger than 32 patients with atypical CD ($P<0.001$). Although Z score for weight less than -2 ($P<0.05$) was found in 36 (65.5%) children of the typical group and 12 (37.5%) children of the atypical group, the difference in age at diagnosis, sex, and the height and weight Z score was not statistically significant between the two groups.

Most of the patients presented with two or more symptoms in each group, while 20 patients in the atypical group had only one symptom such as short stature ($n=13$), anemia ($n=6$), and chronic urticaria ($n=1$). In the atypical group, 8 (25%) patients had IDDM, 2 (6.2%) had only short stature, 1 (3.1%) had both short stature and anemia, 2 (6.2%) had both

Table 1. The patient profile in typical and atypical celiac disease (CD)

	Typical CD (n=55)	Atypical CD (n=32)	*P* value
Mean age at diagnosis (y)	6.2±4.4	11.5±3.4	<0.001
Male/female ratio	19/36	14/18	NS
Height (cm) Z score (mean)	-1.8±1.7	-1.7±1.7	NS
Number of below -2 SD, *n* (%)	41/54 (75.9%)	19/32 (59.3%)	NS
Weight (kg) Z score (mean)	-1.7±1.1	-2.0±1.2	NS
Number of below -2 SD, *n* (%)	36/55 (65.5%)	12/32 (37.5%)	<0.05

NS: not significant.

Table 2. Symptoms and signs of the patients in the typical and atypical celiac disease (CD) groups

Symptoms and signs	Typical CD *n* (%)	Atypical CD *n* (%)	*P* value
Diarrhea	53 (96.3)	-	-
Abdominal distention	36 (65.4)	-	-
Failure to thrive	33 (60.0)	10 (31.2)	0.014
Anemia	13 (23.6)	10 (31.2)	NS
Short stature	9 (16.3)	20 (62.5)	0.0001
Abdominal pain	20 (36.3)	8 (25.0)	NS
Vomiting	18 (32.7)	1 (3.1)	0.001
Constipation	2 (3.6)	1 (3.1)	NS
Pica	3 (5.4)	2 (6.2)	NS
Aphthous oral lesions	-	2 (6.2)	-
Chronic urticaria	-	1 (3.1)	-
Hepatosplenomegaly	2 (3.6)	1 (3.1)	NS
Edema	2 (3.6)	-	-
Delayed puberty	-	2 (6.2)	-

NS: not significant.

Table 3. Laboratory findings of patients in the typical and atypical celiac disease (CD) groups

Laboratory findings	Typical CD (*n*=55)	Atypical CD (*n*=32)	Total (*n*=87)	*P* value
Iron deficiency anemia	33/55 (60.0%)	15/30 (50.0%)	48/85 (56.5%)	NS
Vitamin B12 deficiency	1/42 (2.4%)	2/27 (7.4%)	3/69 (4.3%)	NS
Folic acid deficiency	10/44 (22.7%)	1/26 (3.8%)	11/70 (15.7%)	0.040
Hypertransaminasemia	14/49 (28.6%)	1/26 (3.8%)	14/75 (18.7%)	0.001
Hypoproteinemia	8/40 (20.0%)	0/14 (0.0%)	8/54 (14.8%)	NS

NS: not significant.

anemia and abdominal pain, and 3 (9.4%) had no complaint (Table 2).

Iron deficiency with low iron stores was the most common presentation of anemia in both groups. Folic acid levels were significantly lower in the typical group than in the atypical group ($P<0.05$). Only one patient with low serum folic acid level in the typical group had megaloblastic anemia. Fourteen patients (28.6%) in the typical group and 1 patient (3.8%) in the atypical group had elevated alanine aminotransferase (ALT) levels. The difference in elevated ALT levels was significant between the two groups ($P<0.05$). AGA (IgA and IgG) and anti-EMA IgA levels were as high as 71.6%, 92% and 88.3% in all patients with CD respectively. The positive rate of EMA was 87.5% in the typical and 89.6% in the atypical groups ($P>0.05$). AGA (IgA and IgG) was positive in 72.3% and 95.7% of the typical patients and 70.3% and 87.7% of the atypical patients respectively ($P>0.05$) (Table 3).

Histopathological evaluation of intestinal biopsies revealed total or subtotal VA in 40 patients (72.7%) in the typical group, and 12 patients (37.5%) in the atypical group. Partial VA was observed in 15 patients (27.3%) in the typical group and 20 (62.5%) patients in the atypical group. The presence of total or subtotal VA in intestinal biopsies was significantly higher in the typical group than in the atypical group ($P<0.02$) (Fig. 1). Patients with total or subtotal VA were more likely to have positive EMA-IgA results compared with those with partial VA, but statistical analysis revealed no significant difference between the two groups.

The most frequently associated disorder was IDDM. There were 8 patients with IDDM, of whom 5 presented with atypical symptoms and 3 had no complaints. Other associated disorders such as Behçet's disease, epilepsy, autoimmune thyroiditis, and osteoporosis were rarely seen (Table 4).

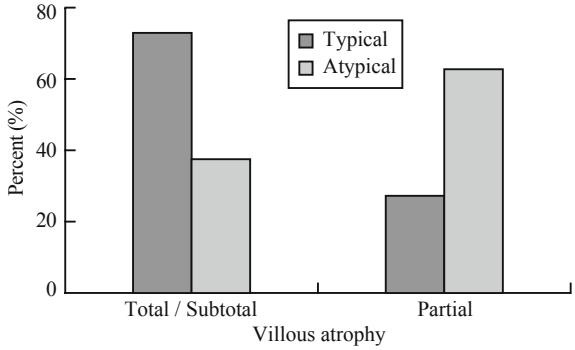

Fig. The percentage of patients with typical and atypical presentation and the intensity of mucosal damage.

Table 4. Associated disorders in the typical and atypical celiac disease (CD) patients

Associated disorders	Typical CD (*n*)	Atypical CD (*n*)
Diabetes mellitus type 1	-	8
Behçet's disease	-	2
Epilepsy	1	1
Autoimmune thyroiditis	1	-
Osteoporosis	-	1
Selective IgA deficiency	-	1
Down's syndrome	1	-
Chronic hepatitis	1	-
Chronic urticaria	-	1

Discussion

Celiac disease is an immunologically mediated enteropathy resulting from permanent gluten intolerance in genetically susceptible individuals. The reported prevalence of CD is approximately 1%-2% worldwide.[5,6] The prevalence of CD increases to more than 40% in patients presenting such typical symptoms as chronic diarrhea.[7] CD is characterized by symptoms of malabsorption such as weight loss, diarrhea, steatorrhea, or abdominal distension. But CD may present with a broad spectrum of clinical features such as isolated iron deficiency anemia,[8-10] short stature,[11] osteoporosis,[12] neurological disease,[13] non-specific abdominal symptoms or any associated disorders including autoimmune thyroiditis[14,15] and IDDM.[16]

Growth failure is one of the well known manifestations of overt CD.[1,2] Failure to thrive is common in young children with classical CD, whereas short stature is more likely to be seen in older children with atypical CD.[17-19] In our study, although no statistically significant differences were found in Z scores for height and weight between the two groups,

failure to thrive was more common in children with typical CD (60.0%) than in those with atypical CD (31.2%). On the other hand, short stature was the major symptom of children with atypical CD (62.5%), and these findings were statistically significant.

Most of our patients presented with two or more symptoms in each group. As a primary symptom of atypical CD, short stature was seen in 40.6% of the patients and anemia in 18.7%. Iron deficiency anemia was found in 60% and 50% of children with typical and atypical CD, respectively. There was no statistical significant difference in iron deficiency anemia between the two groups. In the typical group, only 23.6% of patients complained of anemia. This may be due to the fact that the parents of patients take care of symptoms other than anemia. We suggest that anemia is a common problem in CD.[20]

Immune-mediated diseases like IDDM and thyroid disorders are commonly associated with CD.[4,11,21] In this study the most frequently associated disorder was IDDM, but autoimmune thyroiditis was rarely seen. Transaminase activity normalized on a gluten-free diet in all patients, except one who presented with chronic hepatitis and portal hypertension at five months of age in the typical group. Although not confirmed by liver biopsy, 14 patients with normalized transaminase activity on a gluten-free diet were considered to have "celiac hepatitis" according to the reported criteria.[22] The mechanisms underlying liver injury in celiac disease are poorly understood. Although the spectrum of liver involvement in celiac disease is particularly wide, two main forms of liver damage have been suggested:[23] cryptogenic hepatitis (celiac hepatitis) caused by increased intestinal permeability with direct toxic effect of the substances on the liver and rarely autoimmune hepatitis. Celiac hepatitis develops in patients with overt malabsorption or those with hypertransaminasemia without other symptoms.[24] In our study, transaminase levels were higher in the typical group than in the atypical group and all normalized on gluten-free diet except one patient. We thought that the elevation of transaminase levels in celiac disease especially in the classical form may be due to the increasing intestinal permeability.

Folic acid is primarily absorbed in the jejunum, therefore folic-acid deficiency is frequent in diseases of the small intestine.[25] Many studies have confirmed that its deficiency is a frequent finding in CD patients.[26,27] Folic acid levels were lower in the typical patients with severe villous atrophy than in the atypically patients. We thought that severe mucosal damage may lead to folic acid malabsorption.

The severity of CD is based on the intensity of villous atrophy and the flattening of the villi.[4,28] A statistically significant correlation was observed between histological grade and clinical presentation. Brar et al[29] suggested however that the intensity of villous atrophy did not influence the mode of presentation in adult population. Contrarily, in another study,[28] total or subtotal VA was more common in CD patients with typical presentation, as found in our study.

In conclusion, approximately half of the patients with CD might present with atypical manifestations like iron deficiency anemia and short stature. These variable clinical presentations result in confusion in differential diagnosis. Delays in diagnosis of CD may predispose patients to complications such as reduced bone mineral density, autoimmune disorders and malignancies. Celiac disease should be investigated especially in patients with recurrent iron deficiency anemia, short stature, and autoimmune disorders.

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Contributors: Dinler G proposed the study, analyzed the data and wrote the first draft. Atalay E analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. Kalaycı Ayhan G is the guarantor.

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