

## The evaluation of factors and symptoms related to celiac disease in Turkish children

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### Summary

**Aim:** The aim of the study was to evaluate the factors that may affect occurrence of celiac disease and symptoms related to celiac disease in school age children between the ages of 6 and 17 years.

**Material and Method:** Between 2006 and 2008, 20190 school age children between the ages of 6 and 17 years (mean age, 11.6±2.9) in 139 schools in 62 cities of Turkey were included into the study. CD was screened using total serum IgA, IgA anti-tissue transglutaminase (tTG) and IgA anti-endomysial (EMA) antibodies. Subjects with selective IgA deficiency were further tested for IgG tTG. Small intestinal biopsy was offered to all subjects with tTG antibody positivity. The children who had intestinal biopsy compatible with CD composed the celiac group. Children with negative celiac antibodies composed the control group. Risk factors that may affect the occurrence of CD and symptoms related to CD were evaluated using a questionnaire in the celiac and control groups.

**Results:** 215 of 489 children with antibody positivity approved intestinal biopsy. CD was confirmed by histopathology in 95 subjects (the celiac group). In 19701 children, celiac antibodies were found to be negative (the control group). The mean age of the children in the celiac and control groups was similar (11.7±2.8 vs. 11.6±2.9, respectively) ( $p>0.05$ ). The ratio of girls was significantly higher in the celiac group than controls (61 (64.2%) vs. 10092 (51.2%), respectively) ( $p=0.012$ ). There were no significant differences in terms of gastrointestinal symptoms between the groups ( $p>0.05$ ). Extraintestinal symptoms including loss of appetite, history of pica and short stature were found to be significantly higher in children with CD ( $p=0.007$ ,  $p=0.012$ , and  $p=0.011$ ; respectively).

**Conclusions:** It was concluded that CD was more common in girls and mostly presented with extraintestinal symptoms among 6 to 17 years old children in Turkey. (*Turk Arch Ped* 2011; 46: 314-21)

**Key words:** Celiac disease, child, symptoms, risk

### Introduction

Celiac disease is a chronic intestinal disease occurring by a T cell-mediated mechanism triggered by gluten found in grains including wheat, barley and rye in individuals with genetic predisposition. The incidence of the disease shows geographical variations. The highest incidence is observed in countries where wheat takes an important place in nutrition including Turkey, West Europe, North America and Australia. Environmental, immunologic and genetic factors are involved in the pathogenesis (1-3). The variance of the incidence from population to population may be due to environmental factors including the period of breast-feeding, age at the time of

exposure to gluten, the amount of gluten consumed, the content of infant formulas and previous viral infections in addition to genetic factors (2).

This entity which is the most common disorder of absorption in the childhood affect the children and adults for a life time (1). Due to damage to the intestinal mucosa absorption is disrupted in the patients and thus classical findings including growth failure, diarrhea, abdominal distension and fatty stool are observed. In addition, the patients can present only with non-gastrointestinal symptoms including short stature, aphthous stomatitis, refractory seizures, migraine, iron deficiency anemia resistant to oral treatment, high serum transaminases, osteoporosis, infertility, delayed puberty, dental enamel defects, dermatitis

herpetiformis and vitamin deficiencies (4). In a group of patients, CD remains latent for a long period and displays clinical signs at any point in life or is found accidentally on screenings (4). In recent years, manifestations, clinic, frequency and age at presentation have changed substantially. In our study, the factors which may affect the occurrence of the disease and symptoms which may indicate the disease in school-aged children in the 6-17 years age group were investigated.

## Material and Method

The study was conducted in school-aged children between the ages of 6 and 17 between January 2006 and September 2008. The sample which would represent this age group in Turkey was selected by the Turkish Statistics Institution (TSI) with two-step cluster sampling method considering urban/ rural ratio. The school data related to 2005-2006 period were used by TSI after obtaining necessary permissions from the Ministry of Education. During the above mentioned educational year, 13.073.652 (6.987.045 male, 6.086.607 female) students between the ages of 6 and 17 were studying in the primary schools and high schools in Turkey. According to the international literature, the incidence of the disease was considered to be 1% and  $\alpha$  was considered to be 0.05. The sample volume was calculated to be 20 876 in the confidence interval of 895%. The following formula was used to calculate the sample volume:

$$n = \frac{t^2 pq}{d^2}$$

In this formula, n represents the total sample volume, t represents the value in the student-t table at the level of significance of 0.95 (taken as 1.96),  $\alpha$  represents the acceptable risk (error possibility=0.05), p represents the rate of units having a certain property (the incidence of the disease 0.01) and d represents the amount of sensitivity. q was calculated as  $q=1 - p$ .

To reach the sample volume which was determined from a total of 40 689 schools in the scope of the research in Turkey, 139 schools were selected from 63 provinces and 159 students were selected from each school. If the number of students was lower than 159, all students were included.

In selection of the schools, the number of students in the school was considered as magnitude and magnitude proportional contingent selection method was used. Systematical selection method was used when selecting students from sample schools.

According to the Turkish administrative structure, 107 of the schools were found in provinces and county centers, 10 schools were found in towns and 22 schools were found in villages. According to the level of school, 115 schools were primary schools (112 public, 3 private) and 24 schools were high schools. After excluding the children with chronic disease or known CD and the ones for whom no consent could be obtained, 20,190 children were included in the study. The study

protocol was approved by Gazi University Medical Faculty Local Ethics Committee (12.5.2005-103). Verbal and written information was given to the children and parents before the study and informed consent was obtained before invasive procedures. All children included in the study were given a questionnaire including factors which may affect the occurrence of CD and the findings of CD. Blood samples were taken from the children included in the study and serum samples which were centrifuged were stored at  $-80^{\circ}\text{C}$  until antibody tests were done. Screening for celiac disease was done using tissue transglutaminase (tTG) IgA and total serum IgA. Subjects whose serum total IgA levels were found to be lower than 0,05g/L were considered to have selective IgA deficiency. In children with selective IgA deficiency, tTG IgG was used. The sera of the subjects whose tissue transglutaminase IgA or IgG were positive were reevaluated with endomysial (EMA) IgA.

Tissue transglutaminase IgG and IgA were tested using human ELISA (Euroimmune, GmbH, Lubeck, Germany) kit. The kits were stored at  $+2 - +8^{\circ}\text{C}$ . Positive cut-off value for tissue transglutaminase IgA and IgG was considered to be 20 RU/mL (5). Total serum IgA level was tested nephelometrically (Dade Behring, Marburg/Germany).

Endomysial antibody was tested using indirect immunofluorescence method with the commercial kit (EUROPLUS™ Primate Liver and Gliadin (GAF-3X) BIOCHIPs, GmbH, Lubeck, Germany). 1/10 dilution and above was considered to be a positive value (5).

Small intestinal biopsy was planned in all children who were found to have positive tissue transglutaminase. In subjects who accepted biopsy, biopsy samples were evaluated by a single pathologist histopathologically in terms of CD. Marsh classification was used for histopathological evaluation (2). Gluten-free diet was started in the subjects who were diagnosed as CD with biopsy and these children were started to be followed up in local pediatric gastroenterology clinics.

## Statistical Analysis

The analysis of the data was done using SPSS for Windows 11.5 (SPSS Inc, Chicago, Illinois) package program. Descriptive statistics were given as mean  $\pm$  standard deviation for continuous variables and as subject number and (%) for numerical variables. The significance of the difference of possible risk factors between the group with celiac disease and the control group in terms of gastrointestinal and non-gastrointestinal symptoms was evaluated using single-variable logistic regression analysis, Pearson's chi-square or Fisher's exact test. Odds ratios and confidence intervals related to all possible risk factors which were thought to affect celiac disease were calculated. To determine the most determinative risk factors on celiac disease multi-variant retrospective stepwise logistic regression analysis was used. The variables with p values  $<0.25$  as a result of single-variant analyses were included in the regression analysis as candidate risk factors and a p value of  $<0.05$  was considered statistically significant.

## Results

Antibody positivity (only tTG IgA positive: 270 patients, tTG IgA and EMA IGA positive: 215 patients, tTG IgG positive: 4 patients) was found in 489 (2.4%) of 20 190 students included in the study. 215 of the patients with antibody positivity (only tTG IgA positive: 110 patients, tTG IgA and EMA IgA positive: 104 patients and tTG IgG positive: one patient) accepted small intestinal biopsy. In 95 of the children who were undergone small intestinal biopsy, the biopsy findings were compatible with CD. 95 children whose diagnoses were proved with biopsy constituted the celiac disease group and 19 701 children with antibody negativity constituted the control group.

The frequencies of possible risk factors which were thought to be effective on celiac disease according to groups are shown in Table 1. The mean age was 11.7±2.8 years in the celiac group and 11.6±.9 years in the control group. The celiac group was composed of 61 female (64.2%) and 34 male students (35.8%). The control group was composed of 10 092 female students (51.2%) and 9 609 male students (48.8%). Female gender was found with a significantly higher rate in the celiac group ( $p=0.012$ ). When monthly incomes

and the education levels of the parents were evaluated, no difference was found between the celiac group and control group ( $p>0,05$ ). When the effect of breast-feeding time on CD was evaluated, the number of children who were breastfed only for the first four months was found to be 34 (38.2%) in the celiac group and 5 438 (32%) in the control group. When the groups were compared, no significant difference was found ( $p=0.155$ ). When the groups were examined in terms of introducing foods containing gluten into the diet, the number of subjects who were started solid food during the first four months was found to be 9 (11.4%) in the celiac group and 2187 (13.5%) in the control group. No significant difference was found between the groups ( $p=0,615$ ). Familial CD history was found in only 2 patients (2.2%) in the celiac group and in 236 subjects (1.3%) in the control group. The presence of familial history was not found to be an efficient factor for occurrence of the disease ( $p=0.341$ ) (Table 1).

The groups were examined in terms of gastrointestinal and non-gastrointestinal symptoms. Diarrhea which is the classical sign of the disease was found in 7 (7.8%) children, abdominal distension was found in 10 (11.1%) children and weight loss was found in 26 (28.6%) children in the celiac group. In the control group, diarrhea was found in 1545 children (8.3%), abdominal distension was found in 1825 children (9.9%) and

**Table 1. The frequency of possible factors which are thought to have an effect on celiac disease**

	Control Group n (%)	Celiac Group n (%)	p	Odds ratio (%95 CI)
<b>Age</b>	11.6±2.9 <sup>a</sup>	11.7±2.8 <sup>a</sup>	0.778 <sup>†</sup>	1.010 (0.942-1.082)
<b>Gender</b>				
Male	9609 (48.8)	34 (35.8)	-	1.000 <sup>b</sup>
Female	10092 (51.2)	61 (64.2)	0.012 <sup>‡</sup>	1.708 (1.122-2.601)
<b>Monthly income of the family</b>				
>1500 TL	1319 (7.7)	4 (4.7)	-	1.000 <sup>b</sup>
500-1500 TL	7108 (41.3)	31 (36.5)	0.495 <sup>†</sup>	1.438 (0.507-4.081)
<500 TL	8779 (51.0)	50 (58.8)	0.226 <sup>†</sup>	1.878 (0.677-5.209)
<b>Maternal education level</b>				
Secondary school and higher	5316 (27.0)	19 (20.0)	-	1.000 <sup>b</sup>
Primary school and lower	14385 (73.0)	76 (80.0)	0.126 <sup>‡</sup>	1.478 (0.893-2.446)
<b>Paternal education level</b>				
Secondary school and higher	8901 (45.2)	41 (43.2)	-	1.000 <sup>b</sup>
Primary school and lower	10800 (54.8)	54 (56.8)	0.693 <sup>‡</sup>	1.085 (0.723-1.631)
<b>Breastfeeding time</b>				
>12 months	6235 (36.7)	27 (30.3)	-	1.000 <sup>b</sup>
0-12 months	5326 (31.3)	28 (31.5)	0.473 <sup>†</sup>	1.214 (0.715-2.062)
the first 4 months	5438 (32.0)	34 (38.2)	0.155 <sup>†</sup>	1.444 (0.870-2.396)
<b>Age of first exposure to gluten</b>				
>12 months	5198 (32.2)	26 (32.9)	-	1.000 <sup>b</sup>
4-12 months	8758 (54.3)	44 (55.7)	0.986 <sup>†</sup>	1.004 (0.618-1.633)
The first 4 months	2187 (13.5)	9 (11.4)	0.615 <sup>†</sup>	0.823 (0.385-1.759)
<b>Family history</b>				
Yes	17396 (98.7)	88 (97.8)	-	1.000 <sup>b</sup>
No	236 (1.3)	2 (2.2)	0.341 <sup>¶</sup>	1.675 (0.410-6.844)

a Mean ± standard deviation, b Reference category, CI confidence interval

† Single variant logistic regression analysis.

‡ Pearson's chi-square test.

¶ Fisher's exact test.

Table 2 The frequency of gastrointestinal symptoms in the study groups				
	Control group n (%)	Celiac group n (%)	p	Odds ratio (%95 CI)
<b>Diarrhea</b>				
No	16967 (91.7)	83 (92.2)	<b>0.846<sup>†</sup></b>	0.926 (0.427-2.007)
Yes	1545 (8.3)	7 (7.8)		
<b>Abdominal distension</b>				
No	16683 (90.1)	80 (88.9)	<b>0.691<sup>†</sup></b>	1.143 (0.591-2.209)
Yes	1825 (9.9)	10 (11.1)		
<b>Flatulence</b>				
No	15623 (82.6)	74 (82.2)	<b>0.935<sup>†</sup></b>	1.023 (0.595-1.758)
Yes	3226 (17.4)	16 (17.8)		
<b>Weight loss</b>				
No	14343 (77.2)	65 (71.4)	<b>0.194<sup>†</sup></b>	1.351 (0.856-2.132)
Yes	4246 (22.8)	26 (28.6)		
<b>Vomiting</b>				
No	16822 (90.9)	86 (95.6)	<b>0.126<sup>†</sup></b>	0.465 (0.171-1.270)
Yes	1681 (9.1)	4 (4.4)		
<b>Abdominal pain</b>				
No	12278 (66.1)	52 (57.1)	<b>0.073<sup>†</sup></b>	1.461 (0.963-2.215)
Yes	6303 (33.9)	39 (42.9)		
<b>Constipation</b>				
No	16451 (89.0)	77 (85.6)	<b>0.299<sup>†</sup></b>	1.365 (0.757-2.461)
Yes	2035 (11.0)	13 (14.4)		

† Pearson's chi-square test.

Table 3. The frequency of non-gastrointestinal symptoms in the study groups				
	Control group n (%)	Celiac group n (%)	p	Odds ratio (%95 CI)
<b>Academic success</b>				
High	12054 (65.9)	53 (60.2)	-	1.000
Moderate	5767 (31.5)	32 (36.4)	0.300 <sup>†</sup>	1.262 (0.813-1.959)
Poor	477 (2.6)	3 (3.4)	0.548 <sup>†</sup>	1.430 (0.445-4.594)
<b>Fatigue</b>				
No	11097 (59.8)	50 (54.9)	0.351 <sup>‡</sup>	1.217 (0.805-1.842)
Yes	7475 (40.2)	41 (45.1)		
<b>Restlessness</b>				
No	14113 (76.1)	63 (69.2)	0.123 <sup>‡</sup>	1.418 (0.908-2.217)
Yes	4422 (23.9)	28 (30.8)		
<b>Unhappiness</b>				
No	14363 (77.6)	70 (77.8)	0.968 <sup>‡</sup>	0.990 (0.601-1.629)
Yes	4146 (22.4)	20 (22.2)		
<b>Nervousness</b>				
No	8397 (45.1)	41 (45.1)	0.993 <sup>‡</sup>	1.002 (0.662-1.516)
Yes	10221 (54.9)	50 (54.9)		
<b>Loss of appetite</b>				
No	12984 (70.2)	52 (57.1)	0.007 <sup>‡</sup>	1.763 (1.163-2.674)
Yes	5523 (29.8)	39 (42.9)		
<b>Pica</b>				
No	18062 (97.3)	83 (92.2)	0.012 <sup>¶</sup>	3.010 (1.385-6.544)
Yes	506 (2.7)	7 (7.8)		
<b>Short stature</b>				
No	15042 (80.9)	64 (70.3)	0.011 <sup>‡</sup>	1.785 (1.136-2.802)
Yes	3556 (19.1)	27 (29.7)		
<b>Dental staining</b>				
No	13876 (75.2)	69 (75.8)	0.891 <sup>‡</sup>	0.967 (0.598-1.564)
Yes	4575 (24.8)	22 (24.2)		

† Single variant logistic regression analysis

‡ Pearson's chi-square test

¶ Fisher's exact test

**Table 4. Multiple retrospective stepwise regression analysis of all possible risk factors which are thought to be involved in celiac disease**

	Beta	Odds Ratio	p	%95 CI	
				Lower limit	Upper limit
Female gender	0.544	1.723	0.014	1.115	2.661
Loss of appetite	0.514	1.672	0.023	1.075	2.603
Pica	1.145	3.143	0.004	1.428	6.919
Short stature	0.494	1.639	0.044	1.013	2.652
Vomiting	-1.084	0.338	0.038	0.122	0.941

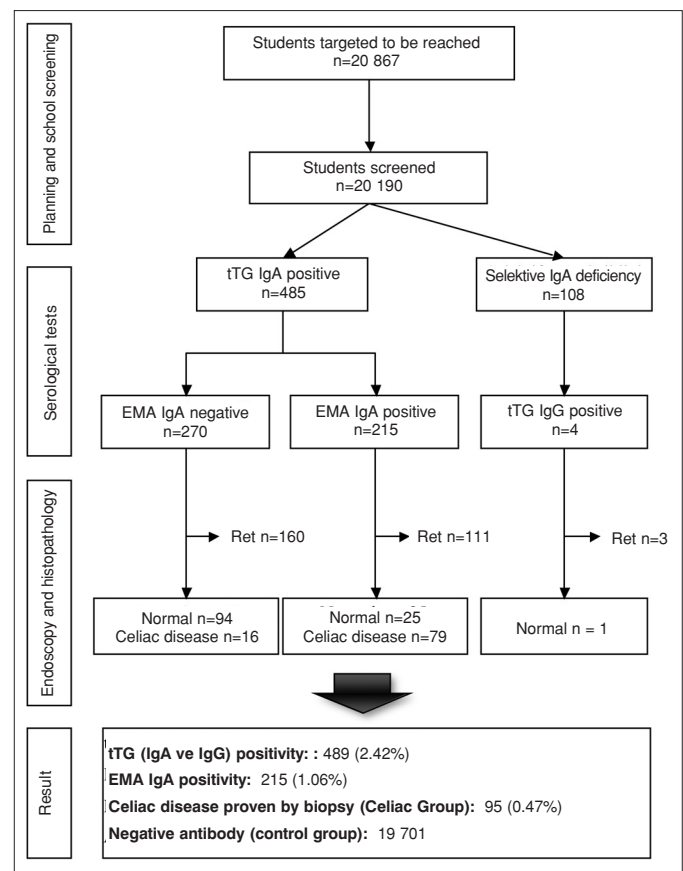
weight loss was found in 4246 children (22.8%). No significant difference was found between the groups in terms of gastrointestinal symptoms ( $p>0.05$ ) (Table 2).

Non-gastrointestinal symptoms including academic success, fatigue, restlessness, unhappiness, nervousness, loss of appetite, pica, short stature and dental staining were examined in the groups (Table 3). Loss of appetite which was a non-gastrointestinal symptom was found with a significantly higher rate in the celiac group compared to the control group ( $p=0.007$ ). A history of pica which is an indication for iron deficiency anemia was found in 7 patients (7.8%) in the celiac group and 506 children (2.7%) in the control group. The difference between the groups was significant ( $p=0.012$ ). Short stature which is one of the atypical findings of celiac disease was found in 27 patients (29.7%) in the celiac group and in 3556 children (19.1%) in the control group. The difference between the groups was significant ( $p=0.011$ ) (Table 3).

The effects of all possible risk factors which were thought to be involved in celiac disease and the symptoms together were examined using multi-retrospective stepwise regression analysis (Table 4). According to this, a positive correlation was found between the diagnosis of CD and mainly the presence of pica ( $p=0.004$ ), female gender ( $p=0.014$ ), loss of appetite ( $p=0.023$ ) and short stature ( $p=0.044$ ). A negative correlation was found between CD and vomiting (Table 4). In multi-variant analyses of socio-economical risk factors including a parental education level of primary school or below and low income, no statistically significant effects on CD were found (Table 4).

## Discussion

CD which was previously known as a primary malabsorption disease is now considered to be a systemic autoimmune disease which can show gastrointestinal and non-gastrointestinal symptoms. This disease which is the most common cause of malabsorption in the childhood affects the children and adults for a life time (1). The disease is observed with a higher rate in Europe, North America, Australia and South West Asia where wheat has an important place in nutrition compared to Africa and Far East (2). The reasons for the difference between populations may be environmental factors including breast-feeding time, age at exposure to gluten, the amount of gluten consumed, the content of infant



**Figure 1. Serological and pathological results of the study group (tTG: Tissue transglutaminase antibody, EMA: endomysial antibody)**

formulas and previous viral infections in addition to genetic factors (2). In this study which screened school age children between the ages of 6 and 17 years, serologic test positivity which was used for screening the disease was found to be 1:94 and the frequency of biopsy-proven CD was found to be 1:212. The incidence of the disease in our country was found to be 1:158 in a regional study (6) and 1:144 in adult blood donors (7). In studies from different countries of the world, the incidence of CD has been reported to range between 1:99 and 1:210 (8,9). The mean age of the celiac group was found to be  $11.7\pm 2.8$  years. Mean ages of the celiac and control group were similar. Celiac disease can occur at any age after



gluten is added to the diet. However, its incidence increases below the age of 5 and between the ages of 30 and 40 years (10). According to our study, the disease was found to occur frequently in the age groups outside the limits mentioned in the literature in our country. Many studies have reported that CD is observed more frequently in men compared to women (11,12). Bardella et al.(13) proposed that the diagnosis is missed in men and actually the both genders are affected equally. Despite different views in the literature, most studies report a higher incidence of CD in female patients compared to male patients and our study also supports this view.

The change in the age of occurrence of CD is thought to be related to differences in infant nutrition. Studies have reported that lengthening of breastfeeding time and delayed introduction of gluten into the diet are effective in the occurrence of the symptoms at advanced ages (12,14). However, in our study, no relation was found between breastfeeding time and time of starting foods containing gluten and CD in contrast to the literature.

Familial history is a significant factor in the occurrence of celiac disease. In children who have a first-degree relative with CD, the incidence of the disease is 1-18% (15). In the study performed in celiac patients between the ages of 1 and 60 in USA, the incidence of the disease was found to be 1:39 in first-degree relatives and 1:56 in second-degree relatives (15). In a study performed in our country, CD was found with a rate of 7.1% in asymptomatic parents of children with CD and with a rate of 9.3 in the siblings (16). In the international literature, the incidence of CD in first-degree relatives of celiac patients has been reported to be 4-5% (17,18). The presence of the disease in relatives of our celiac patients was found with a lower rate compared to the literature. This suggests that awareness of the population and healthcare workers about the disease is not adequate. We think it is highly probable that there are missed cases among the relatives of our celiac patients in our study and thus we could not find a correlation between familial history and CD.

Population screenings have found more asymptomatic and atypical cases compared to symptomatic cases. Thus, symptomatic cases have been compared to an iceberg (18). We interrogated the frequency of gastrointestinal and non-gastrointestinal symptoms and whether these symptoms can be an indication for the disease in our celiac patients. Various studies still report that diarrhea is the most common symptom in celiac patients (19-21). While one of the most common causes of chronic diarrhea in Middle East and North Africa is CD, the incidence of CD was reported to be 4.7% in patients presenting with diarrhea and growth failure in Egypt (22-24). On the other hand, some studies have reported that diarrhea has been observed with a lower frequency in recent years (25,26). Similarly, gastrointestinal symptoms including abdominal distension, weight loss, constipation, vomiting and abdominal pain have been reported to gradually decrease in recent years (12,20,27). In accordance with the literature, we found these gastrointestinal symptoms with a lower rate in our celiac group compared to the control group. We think this is related to the fact

that our study group was in the age group when atypical symptoms of the disease are frequently observed and that the classical picture of the disease has decreased similar to the literature. Some studies have reported mood and behaviour disorders including loss of appetite, fatigue, restlessness, unhappiness, nervousness, poor academic success and depression may be observed in some celiac patients and these findings have been reported to improve with gluten-free diet (28-30). On the other hand, we observed that non-gastrointestinal symptoms including fatigue, restlessness, unhappiness and nervousness and excluding loss of appetite had similar frequencies in celiac patients as in healthy children in our study. The fact that these symptoms were observed frequently also in our control group suggested that our children were in negative mood and behavior states and the causes underlying this fact should be examined. However, significantly higher frequency of loss of appetite in the celiac group suggested that children with this complaint should also be examined. Various studies have reported that CD should be investigated especially in individuals with iron deficiency anemia which is resistant to treatment. Ackerman et al.(31) found the incidence of CD to be 3% in adults who were undergone endoscopy performed to investigate the cause of iron deficiency anemia. Howard et al.(32) found the incidence to be 5% and Ransford et al.(33) found it to be 12%. In our study, we found pica which is an indication of iron deficiency anemia was a significant complaint for CD, though this finding was not definite, since hemoglobin and iron levels of the subjects were not measured. This finding showed that interrogation for pica should not be omitted during interrogation of the systems in pediatric patients. In accordance with the literature, CD was found to be correlated with short stature alone also in our study (34-36).

In our study which was based on a questionnaire, the answers to the questions in the questionnaire of the subjects included in the study were reevaluated, since gastrointestinal symptoms were reported with a higher rate in the control group. When the answers of all families were examined, it was found that individuals with low income and low education level answered more "yes" to the questions related to loss of appetite, short stature, pica, diarrhea, abdominal pain, weight loss, vomiting and abdominal distension and this was found to be statistically significant. However, multi-variant analyses of risk factors including a parental education level of primary school or lower and low income showed that these factors did not have statistically significant effect on CD. In addition, when we examined the effects of possible risk factors which were thought to be effective on CD and symptoms together by multiple retrospective stepwise regression analysis, a positive relation was found between the disease and mainly the presence of pica, female gender, loss of appetite and short stature.

Evaluation of short stature based on the questionnaire data owing to the fact that our study was based on the questionnaire, absence of anemia and iron profiles of the children with a history of pica and the fact that small intestinal biopsy could not be performed in all children with positive antibody tests are thought to be the limiting properties of our study.

With these results it was concluded that CD is observed more frequently in female gender in Turkey and the clinical presentation is mostly manifested by non-gastrointestinal symptoms in the 6-17 age group similar to the literature.

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### Turkish Celiac Disease Study Group

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