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Different Clinical Features of Celiac Disease in Children, Adolescents, and Adults; a Cross-sectional Study

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ABSTRACT

BACKGROUND

Celiac disease is a common disorder but there are few studies comparing the clinical features of the disease in adults, adolescents and children.

METHODS

Demographic and clinical characteristics of all patients with celiac disease referred to the Celiac Clinic were evaluated and compared in different age groups.

RESULTS

Of 3416 participants, 473 patients were included. 302 (63.8%) were women and 171 (36.2%) were men. Overall, 325 (68.7%) and 411 (86.9%) patients had gastrointestinal (GI) and non-GI manifestations, respectively. The most common symptom in adults was psychiatric problems (66.5%), while abdominal discomfort was the most common symptom in adolescents (45.2%) and children (53.8%). According to age groups, GI manifestations were seen in 79 (66.4%), 119 (59.8%), and 127 (81.9%) children, adolescents, and adults, respectively. Adults had significantly more GI manifestations than the other groups (PR 1.167; 95% CI: 1.094-1.244; $p < 0.001$). Non-GI manifestations were seen in 90 (75.6%), 174 (87.4%), and 147 (94.8%) children, adolescents, and adults, respectively. Adults had significantly more non-GI manifestations than the other groups (PR 1.112; 95% CI: 1.060-1.168; $p < 0.001$).

CONCLUSION

Our study showed that there were significant differences in the clinical features of celiac disease between the different age groups. Considering these results may help plan for future studies.

KEYWORDS:
Celiac disease, Children, Adolescents, Adults, Southern Iran, Prevalence

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INTRODUCTION

Celiac disease (CD) is a common immune-mediated disease associated with small intestine atrophic enteropathy, which can occur with varying clinical patterns of gastrointestinal (GI) and non-GI symptoms.[1,2] The prevalence of CD in the

general population is approximately 1%, which can occur with women predominating at any age.[3] Although CD was traditionally believed to almost always affect European people, a high prevalence and incidence of CD has been reported in other areas including Asia, Africa, Oceania, and America.[4-8]

CD may present clinically with a wide range of manifestations in various organs. Recent studies have shown that on the one hand, the presentation of CD has changed from typical manifestations such as malabsorption syndrome to a milder form of the disease in past decades, and on the other hand, the age of onset of the symptoms has increased compared to the past. Based on the mentioned issues, it has been suggested that new studies be conducted on the clinical features of CD in children and adults in different countries.[1,9] To the best of our knowledge, there is no original study comparing the clinical features of CD in different age groups of children, adolescents, and adults in Iran, so we designed this study to evaluate the demographic and clinical characteristics of all patients with celiac disease referred to the Celiac Clinic and compare it in different age groups.

MATERIALS AND METHODS

Ethical approval/statement

This study was performed after obtaining the approval of the Ethics Committee and Institutional Review Board of Shiraz University of Medical Sciences (reference code:18977) and considering the Declaration of Helsinki on the ethical principles for medical research. Informed consent was obtained from all patients or their legal guardians to review their medical records.

Study design and population

This analytical cross-sectional study was performed to evaluate the clinical and demographic features in CD in Fars province, Southern Iran, from June 2017 to October 2019. All participants with the possibility of CD who were referred to the Celiac Clinic, a referral center in southern Iran for the diagnosis, treatment and counseling of patients with CD, were evaluated by a gastroenterologist. Patients suspected of CD were those who had been referred for CD evaluation because of suspicious clinical presentation or duodenal biopsy or positive serology. A checklist was completed by a physician including mode of presentation, physical examination, personal and family medical history, and medication use. GI symptoms including abdominal pain, abdominal discomfort or distention, bloating, constipation, gastroesophageal reflux disease, nausea, vomiting, and anorexia were evaluated. Non-GI manifestations including cutaneous, endocrine (history of diabetes mellitus or thyroid disease), hematologic, musculoskeletal, hepatic (hypertransaminasemia), neurological (history of headache or convulsion), psychiatric (history of depression or anxiety), and oral (aphthous stomatitis) manifestations were also evaluated.

On the other hand, an interviewer who was trained prior to the initiation of the study, collected and recorded different variables including age, sex, height, weight, laboratory data, histological reports, and early life information about breast-feeding from health care documentation during infancy. Patients with CD were then categorized, based on age of CD presentation into three groups of adults (> 19 years of age), adolescents (10-19 years of age), and children (< 10 years of age) according to the world Health Organization (WHO) criteria. Finally, the demographic and clinical characteristics of the three age groups were compared.

Serological and histological evaluation

In all participants, serum levels of IgA anti-transglutaminase antibodies (anti-tTG, Aeskulisa kit; Germany; along with ELISA method) and immunoglobulin A levels were measured. IgG based testing of anti-tTG was added to evaluate patients with selective serum immunoglobulin A deficiency. Upper GI endoscopy and small-bowel biopsies were performed in individuals with positive anti-tTG. Two and four biopsies were obtained from the bulb and second part of the duodenum, respectively, and stained by hematoxylin/eosin staining. The biopsies were read by an expert pathologist and then the histological findings were classified according to Oberhuber-modified Marsh classification.[10] A second pathologist was consult in revision if results were not concordant.

Celiac disease definition

According to published guidelines and studies, the diagnosis of CD was based on duodenal biopsy and positive CD serology.[1,3,11-13] Therefore, in our study CD was defined as an anti-tTG of 18 IU/mL or higher

in serology and Marsh type I or more in histology. The exclusion criteria were uncooperative patients, negative serological tests for CD, Marsh type 1 in histology with serological titer less than 10 times or negative HLA-DQ2 and DQ8 test, Marsh type 0 in histology, and other possible causes of villous atrophy such as Giardia lamblia infection. Finally, all patients with CD who had non-GI manifestations were referred to other specialists, such as a dermatologist, neurologist, endocrinologist, and rheumatologist, for confirmation of the diagnosis.

Statistical Analysis

Comparisons between the two groups were done using t-test for continuous variables and Chi square test for categorical variables. One-way ANOVA was also used to compare differences between three or more groups from a single independent variable. One-way ANOVA was used to compare differences between three or more groups from a single independent variable. Robust Poisson regression analysis was used for estimating prevalence ratios (PRs) and confidence intervals (CIs) to evaluate the association of various independent variables on CD. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software, version 25.0 (Chicago, USA).

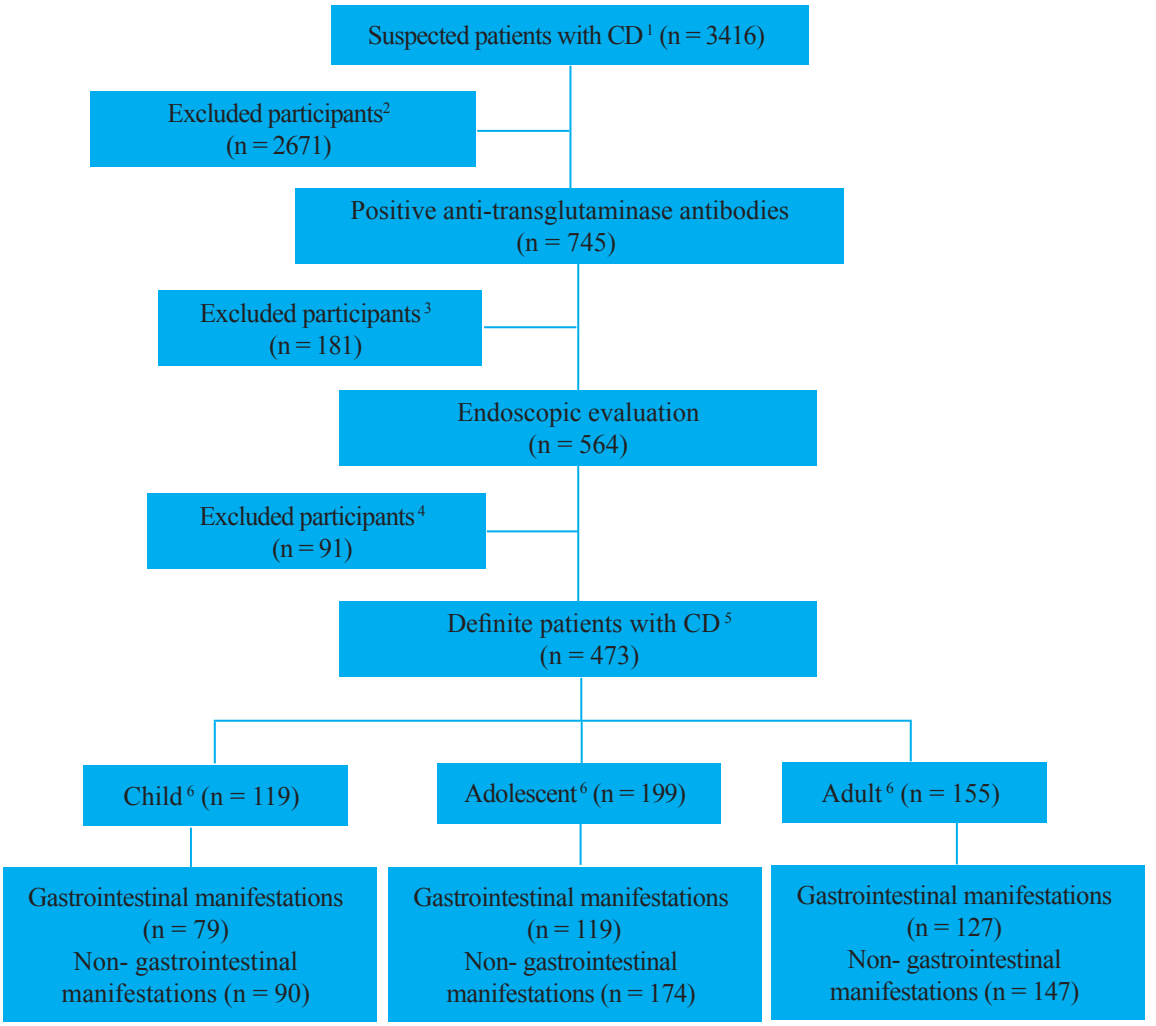
RESULTS

As shown in figure 1, of the 3416 patients referred to the clinic, 473 patients with definite CD were included in this study. 155 (32.77%), 199 (42.07%), and 119 (25.16%), of the patients were adults, adolescents, and children, respectively. Of the included patients, 302 (63.8%) were female and 171 (36.2%) were male with a female : male ratio of 1.77: 1. The mean ± SD age of patients was 18.72 ± 13.47 years (range: 2-70 years). Comparison of demographic and clinical features between different age groups is shown in table 1. Overall, 325 (68.7%) and 411 (86.9%) patients had GI and non-GI manifestations, respectively, some of which had more than one GI or non-GI manifestation. Abdominal discomfort (48.8%) including abdominal pain, bloating, and abdominal distention were the most common symptoms of patients with CD.

According to age groups (table 1), 79 (66.4%) children had GI symptoms and 90 (75.6%) had non-GI manifestations. Abdominal discomfort (53.8%) was the most common symptom in this group. Children had the lowest non-GI symptoms compared to other groups. 119 (59.8%) adolescents had GI symptoms and 174 (87.4%) of them had non-GI manifestations. This group had the lowest GI symptoms (59.8%) compared to other groups. Abdominal discomfort was the most common symptom in adolescents. In the adult group, 127 (81.9%) and 147 (94.8%) patients had GI and non-GI symptoms, respectively, which were more than the other groups. The most common symptom in adults was psychiatric problems (66.5%). The frequency of gastroesophageal reflux disease, nausea, and vomiting in adults was significantly lower than the other age groups.

As shown in table 2, the frequency of diarrhea and constipation, but not abdominal discomfort, was significantly different in the age groups. The difference between the frequency of chronic diarrhea (23.5%) as a classic symptom and constipation (25.8%) as a non-classic manifestation of CD was not statistically significant. Except for increased age, other variables such as sex, type of milk consumption during infancy, and family history of CD in parents had no significant association with the frequency of GI manifestations (table 3).

Non-GI manifestations and CD-associated diseases were observed in various systems including cutaneous (16.9%), endocrine (25.6%), hematological (39.5%), musculoskeletal (39.7%), hepatic (10.4%), neurological (30.4%), psychiatric (46.5%), and oral (14.2%) systems. Comparison of non-GI manifestations and associated diseases of CD by organ system between different age groups are shown in table 4. The frequency of all non-GI manifestations was significantly different between different age groups. Association between non-GI manifestations and demographic and other clinical features are shown in table 5. Except for increased age, other variables including sex, type of milk consumption during infancy, family history of CD, and familial marriage in the parents had no significant association with the frequency of non-GI manifestations. Overall, diabetes mellitus (including insulin and non-insulin-dependence) was seen in 66 (14.0%) of patients but by age groups, it was observed in 9.2%, 20.1% and 7.7% of the children, adolescents and adults, respectively. The frequency of diabetes mellitus in adolescents was significantly higher than in children



[1] All patients with suspected celiac disease who referred to the Celiac Clinic
[2] Participants with negative serological tests for celiac disease and uncooperative patients
[3] Participants who refused endoscopy
[4] Participants with Marsh type 0 in histology, other causes of villous atrophy, and uncooperative patients
[5] Definite celiac disease was defined as a positive anti-transglutaminase antibody in serology and Marsh type I or more in histology according to Oberhuber-modified Marsh classification
[6] Patients with celiac disease were then categorized, based on age category into three groups of more than 19 years as adults, 10-19 years as adolescents, and less than 10 years as children (according to WHO criteria)

Fig.1: Flow diagram for selection process of participants with celiac disease (CD)

and adults (p = 0.004). Thyroid diseases (including hypothyroidism and hyperthyroidism) was observed in 68 (14.4%) patients (in 3.4%, 11.6% and 26.5% of the children, adolescents, and adults, respectively). The frequency of thyroid disease in adults was significantly higher than in adolescents and children ($p < 0.001$).

Robust Poisson regression models was used for estimating the PRs and 95% CIs to evaluate the association of various independent variables on the GI and non-GI manifestations of CD (table 6). The adult age group was significantly associated with both GI (PR 1.167; 95% CI: 1.094-1.244; $p < 0.001$) and non-GI manifestations (PR 1.112; 95% CI: 1.060-1.168; $p < 0.001$) than the children and adolescent groups. However, other variables including sex, ethnicity, type of milk consumption during infancy, family history of CD, and familial marriage in the parents had no significant association with the frequency of GI or non-GI manifestations.

Table 1: Comparison of demographic and clinical characteristics of patients with celiac disease based on different age groups 1 (n = 473)

Variables	Children (n = 119)	Adolescents (n = 199)	Adults (n = 155)	*p* value
Sex [2]				
Female	70 (58.8%)	129 (64.8%)	103 (66.5%)	0.399
Male	49 (41.2%)	70 (35.2%)	52 (33.5%)	
Age (yrs.) [3]	7.07 ± 1.63	13.03 ± 2.67	34.97 ± 11.51	< 0.001
Ethnicity [2]				
Fars	91 (76.5%)	146 (73.4%)	127 (81.9%)	
Lor	21 (17.6%)	29 (14.6%)	13 (8.4%)	0.100
Turk	5 (4.2%)	18 (9.0%)	8 (5.2%)	
Others	2 (1.7%)	6 (3.0%)	7 (4.5%)	
Milk type [2,4]				
Breast-feeding	78 (65.5%)	130 (65.3%)	119 (76.8%)	0.058
Other	6 (5.0%)	8 (4.0%)	9 (5.8%)	
Both	35 (29.4%)	61 (30.7%)	27 (17.4%)	
Celiac disease in the family [2]	9 (7.6%)	10 (5.0%)	11 (7.1%)	0.598
Familial marriage in the parents [2]	11 (9.2%)	12 (6.0%)	30 (19.4%)	< 0.001
Gastrointestinal manifestations [2]	79 (66.4%)	119 (59.8%)	127 (81.9%)	< 0.001
Non-gastrointestinal manifestations [2]	90 (75.6%)	174 (87.4%)	147 (94.8%)	< 0.001

Notes: [1] The patients were categorized, based on age category into three groups of more than 19 years as adults, 10-19 years as adolescents, and less than 10 years as children; [2] Test: Chi-square test; [3] Test: One-way ANOVA; Mean ± Standard deviation; [4] Type of milk consumption during the first 12 months of infancy

Table 2: Comparison of gastrointestinal (GI) manifestations between different age groups 1 of the patients with celiac disease (n = 473)

GI manifestations	Children (n = 119); N(%)	Adolescents (n = 199); N(%)	Adults (n = 155); N(%)	*p* value[2]
Abdominal discomfort [3]	64 (53.8%)	90 (45.2%)	77 (49.7%)	0.325
Diarrhea	16 (13.4%)	29 (14.6%)	66 (42.6%)	< 0.001
Constipation	38 (31.9%)	39 (19.6%)	45 (29.0%)	0.028
Others [4]	94 (79.0%)	148 (74.4%)	74 (47.7%)	< 0.001

Notes: [1] The patients were categorized, based on age category into three groups of more than 19 years as adults, 10-19 years as adolescents, and less than 10 years as children; [2] Test: Chi-square test; [3] It included abdominal pain, bloating, and abdominal distention; [4] It included gastroesophageal reflux disease, nausea, vomiting and anorexia

Table 3: Comparison of demographic characteristics in patients with celiac disease with and without gastrointestinal (GI) manifestations (n = 473)

Variables; Number (%)	Positive GI manifestations	Negative GI manifestations	*p* value[1]
Sex			
Female	203 (67.2%)	99 (32.8%)	0.352
Male	122 (71.3%)	49 (28.7%)	
Different age groups			
Child	79 (66.4%)	40 (33.6%)	< 0.001
Adolescent	119 (59.8%)	80 (40.2%)	
Adult	127 (81.9%)	28 (18.1%)	
Milk type [2]			
Breast-feeding	223 (68.2%)	104 (31.8%)	0.844
Other	17 (73.9%)	6 (26.1%)	
Both	85 (69.1%)	38 (30.9%)	
Celiac disease in the family	20 (66.7%)	10 (33.3%)	0.803
Familial marriage in the parents	38 (71.7%)	15 (28.3%)	0.619
Ethnicity			
Fars	244 (67.0%)	120 (33.0%)	
Lor	46 (73.0%)	17 (27.0%)	0.154
Turk	21 (67.7%)	10 (32.3%)	
Others	14 (93.3%)	1 (6.7%)	
Non-GI manifestations	287 (69.8%)	124 (30.2%)	0.176

Notes: [1] Test: Chi-square test; [2] Type of milk consumption during the first 12 months of infancy

Table 4: Comparison of non- gastrointestinal (GI) manifestations and associated diseases of celiac disease by organ system between different age groups (n = 473)

Non- GI manifestations	Children (n = 119); N (%)	Adolescents (n = 199); N (%)	Adults (n = 155); N (%)	*p* value [1]
Cutaneous	13 (10.9%)	24 (12.1%)	43 (27.7%)	< 0.001
Endocrine	15 (12.6%)	59 (29.6%)	47 (30.3%)	0.001
Hematological	38 (31.9%)	70 (35.2%)	79 (51.0%)	0.002
Musculoskeletal	47 (39.5%)	65 (32.7%)	76 (49.0%)	0.008
Hepatic	7 (5.9%)	10 (5.0%)	32 (20.6%)	< 0.001
Neurological	24 (20.2%)	56 (28.1%)	64 (41.3%)	0.001
Psychiatric	31 (26.1%)	86 (43.2%)	103 (66.5%)	< 0.001
Oral	12 (10.1%)	19 (9.5%)	36 (23.2%)	< 0.001

Notes; [1] Test: Chi-square test

Table 5: Comparison of demographic characteristics in patients with celiac disease with and without non-gastrointestinal (GI) manifestations (n = 473)

Demographic and clinical features; Number (%)	Positive non-GI manifestations	Negative non-GI manifestations	*p* value [1]
Sex			
Female	269 (89.1%)	33 (10.9%)	0.062
Male	142 (83.0%)	29 (17.0%)	
Different age groups			
Child	90 (75.6%)	29 (24.4%)	< 0.001
Adolescent	174 (87.4%)	25 (12.6%)	
Adult	147 (94.8%)	8 (5.2%)	
Milk type [2]			
Breast-feeding	285 (87.2%)	42 (12.8%)	0.822
Other	19 (82.6%)	4 (17.4%)	
Both	107 (87.0%)	16 (13.0%)	
Celiac disease in the family	26 (86.7%)	4 (13.3%)	0.572
Familial marriage in the parents	49 (92.5%)	4 (7.5%)	0.203
Ethnicity			
Fars	321 (88.2%)	43 (11.8%)	0.128
Lor	49 (77.8%)	14 (22.2%)	
Turke	27 (87.1%)	4 (12.9%)	
Others	14 (93.3%)	1 (6.7%)	
GI manifestations	287 (88.3%)	38 (11.7%)	0.176

Notes: [1] Test: Chi-square test; [2] Type of milk consumption during the first 12 months of infancy

The mean ± SD body mass index (BMI, kg/m^2) in adults was 23.41 ± 4.75 kg/m^2 (range: 14.83 - 42.97 kg/m^2). There was no significant association between BMI and type of CD manifestations (GI or non-GI) in adults. There was no significant association between BMI and type of CD manifestations (GI or non-GI) in adults.

DISCUSSION

Our study showed that the clinical presentations of CD were significantly different between the three age groups of adults, adolescents, and children. Overall, the frequency of non-GI manifestations was higher than GI presentations, which is consistent with recent studies,[1,9,14,15] which supports the hypothesis that CD presentation with non-GI manifestations has increased. On the other hand, non-classical GI presentations were more than the classic manifestations, which supports another hypothesis that GI manifestations in CD are changing to non-classical presentations. Finally, the most common age for CD presentation, in our results, was in the adolescent and adult groups that support the hypothesis of increasing the age of CD presentation.[1,9,14]

CD, as an autoimmune disease, presents at any age and increases the mortality rate compared to the general population. Although CD primarily affects the small intestine, its clinical features can also be associated with extra-intestinal symptoms.[1,3,16,17] The prevalence of CD in the general population varies in different parts

Table 6: Robust Poisson regression models estimating prevalence ratio (PR) and 95% confidence interval (CI) to evaluate the association of various independent variables on the gastrointestinal (GI) and non-GI manifestations of patients with celiac disease (n = 473)

Variable	GI manifestations				Non-GI manifestations			
	Crude model		Adjusted model		Crude model		Adjusted model	
	PR (95% CI)	*p* value	PR (95% CI)	*p* value	PR (95% CI)	*p* value	PR (95% CI)	*p* value
Sex Male Female	0.969 (0.907-1.035) 1.0	0.349	0.964 (0.903-1.028) 1.0	0.260	1.054 (0.995-1.117) 1.0	0.072	1.050 (0.992-1.112) 1.0	0.090
Age Adults No-Adults [1]	1.167 (1.094-1.244) 1.0	< 0.001	1.167 (1.094-1.244) 1.0	< 0.001	1.112 (1.060-1.168) 1.0	< 0.001	1.112 (1.060-1.168) 1.0	< 0.001
Milk type [2] Breast-feeding Others	1.013 (0.945-1.085) 1.0	0.717	1.039 (0.972-1.110) 1.0	0.261	0.992 (0.936-1.052) 1.0	0.801	0.999 (0.943-1.059) 1.0	0.977
Celiac disease in the family Yes No	1.017(0.892-1.159) 1.0	0.805	1.021 (0.903-1.155)	0.740	1.002 (0.897-1.120) 1.0	0.970	1.013 (0.910-1.127) 1.0	0.818
Familial marriage in the parents Yes No	0.974 (0.881-1.077) 1.0	0.613	1.021 (0.926-1.125) 1.0	0.683	0.945 (0.879-1.016) 1.0	0.124	0.968 (0.899-1.043) 1.0	0.398
Ethnicity Fars Others	1.058 (0.982-1.140) 1.0	0.140	1.073 (0.997-1.155) 1.0	0.061	0.952 (0.890-1.019) 1.0	0.155	0.961 (0.899-1.028) 1.0	0.247
GI manifestations Yes No	-	-	-	-	0.961 (0.905-1.020) 1.0	0.194	0.974 (0.916-1.036) 1.0	0.409
Non-GI manifestations Yes No	0.938 (0.854-1.031) 1.0	0.184	0.960 (0.873-1.056) 1.0	0.406	-	-	-	-

Notes: [1] Non-adult patients including children and adolescents; [2] Milk type, type of milk consumption during the first 12 months of infancy

of the world.[4-7,18] Many studies show that the prevalence of CD was higher in women than men and in children more than adults.[3,4] In our study the most common age of presentation was in the adolescent group (42.07%). Moreover, the onset of symptoms in the adult group was higher than in children. The female:male ratio was 1.77: 1, which was similar to some studies that have shown ratios of 2:1 to 3:1.[3,14]

In addition to gluten and genetics, other potential risk factors for CD such as types of infant milk consumption, mode of delivery, smoking, age at gluten intake, and early life exposure to infection have also been investigated.[19-23] In our study, the type of milk consumption during infancy did not show a significant association with GI and non-GI manifestations (table 6). Although some studies have suggested that breastfeeding has protective effects on CD, others do not support these protective effects.[19,20,22] A case-control study on milk powder consumption during the first two years of life in genetically susceptible children for CD showed that milk powder intake was not associated with CD in Swedish children.[24] Another case-control research found that CD was not

statistically associated with the duration of breastfeeding, but was associated with skim milk consumption.[19] A randomized controlled trial showed that avoiding cow's milk- based formula for infants at risk for CD does not reduce the development of disease.[21]

Past studies have shown that 90% of children with CD have abdominal pain and many suffer from weight loss, diarrhea, weakness, nausea, and vomiting,[11] but recent reports show dramatic changes in CD presentation. In our study, chronic diarrhea was observed as a classic symptom in only about 14% of children and adolescents. On the other hand, constipation was observed as a non-classical symptom in about a quarter of our patients. These results are consistent with the results of recent studies that have shown that the symptoms of CD have changed from the classical type to mild and non-classical manifestations.[1,9,14] Due to the relatively high rate of constipation in our patients, it is recommended that people with chronic constipation with unknown cause be evaluated for CD.

In our study, similar to recent studies, the frequency of non-GI manifestations was higher than GI symptoms. The types of non-GI manifestations were cutaneous, endocrine, hematological, hepatic, musculoskeletal, psychiatric, neurological, and oral diseases, which were generally consistent with previous reports.[14,15]

Oral disorders such as aphthous stomatitis, delayed teeth eruption, lichen planus, cheilosis, and atrophic glossitis have been described in CD. Up to 46% of patients with CD have been reported to be affected by aphthous stomatitis,[15] which is higher than our report (14.2%).

One of the non-GI manifestations of CD is skin disease that is less common in children than in adults.[11, 15] In our study, cutaneous findings, including dermatitis herpetiformis, occurred in about one quarter of patients that was similar to some reports,[11] but its frequency was significantly higher in the adult group than in the children group.

Various types of musculoskeletal diseases in patients with CD have been described in the literature. Osteopenia and osteoporosis were reported in about 75% and 10–30% of children, respectively, while the prevalence of arthropathy was reported in about 5–10% of the children.15 Musculoskeletal diseases have been seen in about 40% of our patients.

Anemia is a common non-GI symptom in adults with CD, but occurs in approximately 15% of children.[15] Anemia is mainly caused by malabsorption, which may be associated with iron, folate, and B12 deficiency.[11] Hematological manifestations, including anemia, have been observed in half of our adult patients and in about one-third of adolescents and children.

Different types of psychological and neurological diseases have been described in patients with CD in the literature.[14] In our research, psychiatric disorders were the most common non-GI manifestation. A systematic review found that psychological comorbidities in children with CD were 1.2 to 1.8 times higher than children without CD.[25] Neurological manifestations have been described in patients with CD. Chronic malabsorption may be one of the mechanisms causing these symptoms.[11] In our study, about a third of patients had neurological manifestations including headache and convulsion.

CD is also linked to several different autoimmune and idiopathic disorders, including diabetes mellitus and thyroid diseases.[3,14,26] In a case-control study, autoimmune disorders were more common in patients with CD (35.3%) than in controls (15.2%).[27] The prevalence of diabetes mellitus as well as thyroid disease in our patients was about 14.0%.

Information on the prevalence of liver involvement in CD is very heterogeneous. Hypertransaminasemia (elevated alanine transaminase), as the most common hepatic manifestation in patients with CD,[15] has been reported in about 11-42% of adults and 15-57% of children.[28] In about 5% of the children and adolescents in our study, hypertransaminasemia was observed, which was almost similar to the results of another study reporting this condition in 3.9% of children.[28]

Although one of the main classic symptoms of CD is weight loss due to malabsorption,[11,26] many recent studies have shown that up to 40% of newly diagnosed patients with CD are obese.[14] A significant number of adult patients in our study were either overweight or obese at the time of diagnosis, confirming the fact that the weight distribution of these patients is increasing.

One of the strengths of our study was that we compared the demographic and clinical features with details in three age groups including children, adolescents, and adults, but most previous studies have only analyzed

one age group. Another strength of our study was the acceptable sample size with appropriate diagnostic evaluation for the participants. Our study had several limitations. Some participants who were excluded because of negative serological tests may be patients with seronegative CD. Although the specific antibodies for CD are detectable in most patients, a few participants are negative for serological markers.[3,29,30] Therefore, to clarify the clinical characteristics of this subgroup of CD, it is recommended to consider such patients in future studies. Another limitation of our research was that there was no control group to compare with patients with CD. Finally, our research was performed only in one center.

CONCLUSION

Our study showed that the frequency and types of clinical presentations of CD were significantly different between adults, adolescents, and children. The study also found that the frequency of non-GI manifestations in all three age groups was considerable and even more than GI presentations. Consideration of these results can help in planning for future studies.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018;**391**:70-81. doi: 10.1016/S0140-6736(17)31796-8.
2. Poddighe D, Turganbekova A, Baymukasheva D, Sadauakas Z, Zhanzakova Z, Abdrakhmanova S. Genetic predisposition to celiac disease in Kazakhstan: Potential impact on the clinical practice in Central Asia. *PLoS One* 2020;**15**:e0226546. doi: 10.1371/journal.pone.0226546.
3. Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, et al. Celiac disease: a comprehensive current review. *BMC Med* 2019;**17**:142. doi: 10.1186/s12916-019-1380-z.
4. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018;**16**:823-36. doi: 10.1016/j.cgh.2017.06.037.
5. Laass MW, Schmitz R, Uhlig HH, Zimmer KP, Thamm M, Koletzko S. The prevalence of celiac disease in children and adolescents in Germany. *Dtsch Arztebl Int* 2015;**112**:553-60. doi: 10.3238/arztebl.2015.0553.
6. Parra-Medina R, Molano-Gonzalez N, Rojas-Villarraga A, Agmon-Levin N, Arango MT, Shoenfeld Y, et al. Prevalence of celiac disease in latin america: a systematic review and meta-regression. *PLoS One* 2015;**10**:e0124040. doi: 10.1371/journal.pone.0124040.
7. Mohammadibakhsh R, Sohrabi R, Salemi M, Mirghaed MT, Behzadifar M. Celiac disease in Iran: a systematic review and meta-analysis. *Electron Physician* 2017;**9**:3883-95. doi: 10.19082/3883.
8. Ashtari S, Pourhoseingholi MA, Rostami K, Aghdaei HA, Rostami-Nejad M, Busani L, et al. Prevalence of gluten-related disorders in Asia-Pacific region: a systematic review. *J Gastrointestin Liver Dis* 2019;**28**:95-105. doi: 10.15403/jgld.2014.1121.281.sys.
9. Popp A, Maki M. Changing Pattern of Childhood Celiac Disease Epidemiology: Contributing Factors. *Front Pediatr* 2019;**7**:357. doi: 10.3389/fped.2019.00357.
10. N Marsh M, W Johnson M, Rostami K. Mucosal histopathology in celiac disease: a rebuttal of Oberhuber's sub-division of Marsh III. *Gastroenterol Hepatol Bed Bench* 2015;**8**:99-109.
11. Al-Bawardy B, Codipilly DC, Rubio-Tapia A, Bruining DH, Hansel SL, Murray JA. Celiac disease: a clinical review. *Abdom Radiol (NY)* 2017;**42**:351-60. doi: 10.1007/s00261-016-1034-y.
12. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al. Guideline for the 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. doi: 10.1097/00005176-200501000-00001.
13. Murch S, Jenkins H, Auth M, Bremner R, Butt A, France S, et al. Joint BSPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. *Arch Dis Child* 2013;**98**:806-11. doi: 10.1136/archdischild-2013-303996.
14. Hujoel IA, Reilly NR, Rubio-Tapia A. Celiac Disease: Clinical Features and Diagnosis. *Gastroenterol Clin North Am* 2019;**48**:19-37. doi: 10.1016/j.gtc.2018.09.001.
15. Nardecchia S, Auricchio R, Discepolo V, Troncone R. Extra-Intestinal Manifestations of Coeliac Disease in

Children: Clinical Features and Mechanisms. *Front Pediatr* 2019;**7**:56. doi: 10.3389/fped.2019.00056.

16. Ehsani-Ardakani MJ, Rostami Nejad M, Villanacci V, Volta U, Manenti S, Caio G, et al. Gastrointestinal and non-gastrointestinal presentation in patients with celiac disease. *Arch Iran Med* 2013;**16**:78-82.
17. Ganji A, Esmaielzadeh A, Aafzal Aghayee M, Goshayeshi L, Ghaffarzadegan K. The clinical presentation of celiac disease: experiences from northeastern iran. *Middle East J Dig Dis* 2014;**6**:93-7.
18. Shakeri MT, Ganji A, Mobarhan MG, Ghanbarabadi VG, Rahimi L. Pitfalls in Estimation of Celiac Disease Prevalence Using Serology: A Cross-Sectional Study. *Govaresh* 2017;**21**:266-71.
19. Bittker SS, Bell KR. Potential risk factors for celiac disease in childhood: a case-control epidemiological survey. *Clin Exp Gastroenterol* 2019;**12**:303-19. doi: 10.2147/CEG.S210060.
20. Gungor D, Nadaud P, Dreibelbis C, LaPergola CC, Wong YP, Terry N, et al. Infant milk-feeding practices and diagnosed celiac disease and inflammatory bowel disease in offspring: a systematic review. *Am J Clin Nutr* 2019;**109**:838S-51S. doi: 10.1093/ajcn/nqy371.
21. Hyytinen M, Savilahti E, Virtanen SM, Harkonen T, Ilonen J, Luopajarvi K, et al. Avoidance of Cow's Milk-Based Formula for At-Risk Infants Does Not Reduce Development of Celiac Disease: A Randomized Controlled Trial. *Gastroenterology* 2017;**153**:961-70 e3. doi: 10.1053/j.gastro.2017.06.049.
22. Meijer C, Shamir R, Szajewska H, Mearin L. Celiac Disease Prevention. *Front Pediatr* 2018;**6**:368. doi: 10.3389/fped.2018.00368.
23. Ludvigsson JF, Murray JA. Epidemiology of Celiac Disease. *Gastroenterol Clin North Am* 2019;**48**:1-18. doi: 10.1016/j.gtc.2018.09.004.
24. Hard Af Segerstad EM, Lee HS, Andren Aronsson C, Yang J, Uusitalo U, Sjoholm I, et al. Daily Intake of Milk Powder and Risk of Celiac Disease in Early Childhood: A Nested Case-Control Study. *Nutrients* 2018;**10**:550. doi: 10.3390/nu10050550.
25. Coburn SS, Puppa EL, Blanchard S. Psychological Comorbidities in Childhood Celiac Disease: A Systematic Review. *J Pediatr Gastroenterol Nutr* 2019;**69**:e25-e33. doi: 10.1097/MPG.0000000000002407.
26. Shannahan S, Leffler DA. Diagnosis and Updates in Celiac Disease. *Gastrointest Endosc Clin N Am* 2017;**27**:79-92. doi: 10.1016/j.giec.2016.08.011.
27. Bibbo S, Pes GM, Usai-Satta P, Salis R, Soro S, Quarta Colosso BM, et al. Chronic autoimmune disorders are increased in coeliac disease: A case-control study. *Medicine (Baltimore)* 2017;**96**:e8562. doi: 10.1097/MD.0000000000008562.
28. Benelli E, Naviglio S, De Leo L, Stera G, Giangreco M, Ronfani L, et al. Changing Epidemiology of Liver Involvement in Children With Celiac Disease. *J Pediatr Gastroenterol Nutr* 2019;**68**:547-51. doi: 10.1097/MPG.0000000000002209.
29. Dore MP, Pes GM, Dettori I, Villanacci V, Manca A, Realdi G. Clinical and genetic profile of patients with seronegative coeliac disease: the natural history and response to gluten-free diet. *BMJ Open Gastroenterol* 2017;**4**:e000159. doi: 10.1136/bmjgast-2017-000159.
30. Giorgio F, Principi M, Losurdo G, Piscitelli D, Iannone A, Barone M, et al. Seronegative Celiac Disease and Immunoglobulin Deficiency: Where to Look in the Submerged Iceberg? *Nutrients* 2015;**7**:7486-504. doi: 10.3390/nu7095350.