European Journal of Therapeutics

DOI: 10.54614/eurjther.2022.0030

Original Article

A Review of Pediatric Celiac Patients in Southeastern Turkey: A Single-Center Experience

Sibel Yavuz[1], Halil Kocamaz[2], Şamil Hızlı[3]

[1]Department of Pediatric Gastroenterology, Adıyaman University Education and Research Hospital, Adıyaman, Turkey

[2]Department of Pediatric Gastroenterology, Pamukkale University Medical Faculty, Denizli, Turkey

[3]Department of Pediatric Gastroenterology, Yıldırım Beyazıt University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Celiac disease is an autoimmune enteropathy that primarily affects the small intestine. Celiac disease occurs with the ingestion of foods containing gluten and is characterized by malabsorption in individuals with a genetic predisposition. This study aimed to review the clinical, laboratory, radiological, and pathological findings of pediatric celiac patients who were followed in our clinic and to compare the data with previous reports in the literature.

Methods: A total of 509 patients who were diagnosed with celiac disease in the Pediatric Gastroenterology Clinic between 2010 and 2013 were included in this study. Medical records of the patients were reviewed retrospectively to collect their demographic characteristics, anthropometric and bone mineral density measurements, laboratory results, radiological imaging, endoscopic examinations, and pathology reports of the biopsy materials.

Results: Of the 509 patients enrolled in the study, 290 (57%) were females and 219 (43%) males. Among these patients, 441 (86.6%) presented with typical symptoms and 68 (13.4%) presented with atypical symptoms. A total of 479 (94.1%) patients were compliant with the gluten-free diet, whereas 30 (5.9%) patients were not. The chief complaint was growth retardation in the patient groups aged 61 to 144 months (44.6%) and >145 months (59%) and diarrhea (26.1%) in the patient group aged 0-60 months. In all patients, the most common physical examination findings at the time of presentation were normal (57.4%), and the most common comorbidities were iron deficiency anemia (35%) and osteoporosis (33%). While Marsh-Oberhuber stage 3c (52.5%) was most common in patients aged 0-60 months, Marsh-Oberhuber stage 3b was most common in patients aged 61-144 months and patients aged >145 months (51.9% and 63.8%, respectively).

Conclusions: Although growth and developmental retardation and chronic diarrhea are cautionary for celiac disease, patients may also present with extra-gastrointestinal (atypical) findings. The mainstay of celiac disease treatment is strict compliance with a gluten-free diet. Reviewing a relatively large number of cases, this study sheds some light on the current status of pediatric celiac disease patients in the southeastern part of Turkey.

Keywords: Celiac disease, child, Marsh

INTRODUCTION

Celiac disease (CD) is an autoimmune disease that results in damage to the intestinal mucosa and malabsorption after a series of immunological processes triggered by gluten intake in individuals susceptible to the gluten content in cereals such as wheat, barley, and oat. In addition to environmental factors such as gluten, immunological and genetic factors also play a role in the pathogenesis of CD. In this disease, there is a permanent intolerance to gluten, which continues for a lifetime.

According to screening studies, the prevalence of CD is increasing all over the world. Apart from the genetic background of a population, other factors are also responsible for the development of the disease. The global prevalence of CD has been estimated as 0.05-0.1%.[1] In Turkey, the prevalence of CD was found to be 0.9% in a study conducted in 1000 healthy children aged 2-18 years and 0.47% in another study conducted in 20 190 healthy children in the 7-18 age group.[2,3]

Clinical findings in CD patients include malabsorption due to damage to the intestinal mucosa and consequently growth and developmental retardation, diarrhea, abdominal distension, and fatty stools. In recent years, the frequency of occurrence of the non-classical findings, also called atypical or extra-gastrointestinal system findings, has increased.[4] These non-classical findings include short stature, delayed puberty, treatment-resistant iron deficiency anemia, aphthous stomatitis, elevated serum

Cite this article as: Yavuz S, Kocamaz H, Hızlı Ş. A review of pediatric celiac patients in southeastern Turkey: A single-center experience. *Eur J Ther*. 2022;28(1):67-72.

Corresponding author: Sibel Yavuz, e-mail: sibel_5163@hotmail.com

Received: March 12, 2021 **Accepted:** June 1, 2021

transaminases, arthritis, alopecia, dental enamel disorders, gastroesophageal reflux, and constipation.[5]

Studies reviewing the data on CD in large case series of Turkish children are limited. This study aimed to retrospectively evaluate 509 patients diagnosed with CD in Pediatric Gastroenterology Outpatient Clinic and compare them with available data in the literature.

METHODS

For this study, 509 patients who presented to the Pediatric Gastroenterology Clinic between 2010 and 2013 and were diagnosed with CD were reviewed retrospectively. The local ethics committee approved the study protocol which was implemented in accordance with the principles established in the Declaration of Helsinki Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Date: November 5, 2013, Decision no: 373). All patients were diagnosed with CD as per the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria.[6] The medical files of the patients were reviewed to record demographic data (age, sex), anthropometric measurements, clinical findings at the time of presentation, dietary compliance, medical history, family history of CD, physical examination findings, bone mineral density dual-energy x-ray absorptiometry (DEXA) measurements, laboratory results, pathology reports of the endoscopic examination and duodenal biopsy material, and follow-up findings in the case forms. The most common presenting complaints of the patients and current medical conditions were recorded. If any patient had multiple problems that could be associated with CD, those were also recorded as separate items. Patients with gastrointestinal symptoms such as chronic diarrhea and abdominal distension were considered as having typical CD, while those with additional extra-intestinal symptoms such as isolated short stature, headache, weakness, and pallor were considered as having atypical CD. The patients were divided into 3 age groups: 6-60 months, 61-144 months, and over 145 months. A DEXA Z-score between −1 and −2.5 SD was categorized as osteopenia, and Z-score of >−2.5 SD was categorized as osteoporosis. All patients underwent small intestine biopsy for definitive diagnosis, and histopathological evaluation was done according to Marsh criteria.

Main Points

- This study aimed to present the clinical and demographic features of pediatric patients with celiac disease (CD) followed at our center.
- Determining the risk factors for CD may be useful in the early diagnosis, prognosis, and treatment of the disease.
- In our study, patients were divided into age groups, and age groups were evaluated among themselves.
- The frequency of atypical CD increased over time; therefore, patients presenting with extra-intestinal symptoms as well as asymptomatic patients with risk factors should be screened for CD.

Statistical Analysis

The Kolmogorov–Smirnov test was used to check the goodness-of-fit of continuous variables to normal distribution. The Student's *t*-test was used to compare 2 independent groups of variables with normal distribution, and the Mann–Whitney *U* test was used for variables with non-normal distribution. For the comparison of more than 2 independent groups, Kruskal–Wallis test and Dunn's multiple comparison tests were used. The correlation between categorical variables was tested using the chi-square analysis, and the correlation between continuous variables was tested using Spearman's correlation analysis. Frequency, percentage, and mean ± standard deviation were used as descriptive statistics. The Statistical Package for the Social Sciences for Windows, version 11.5 (IBM Inc, Chicago, IL, USA) was used for statistical analysis, and a P value of $< .05$ was considered statistically significant.

RESULTS

A total of 509 patients diagnosed with CD were included in the study, of which 290 (57%) were females and 219 (43%) were males. The mean age of the patients was 129.4 ± 49.3 months, the mean age at onset of complaints was 76.5 ± 43.2 months, and the mean age at onset of gluten-free diet was 93.8 ± 46.7 months. The mean body weight of the patients was 19.4 ± 8.7 kg, the mean height was 111.1 ± 21.6 cm, and the mean body mass index was 15.0 ± 2.0 kg/m^2. Delayed bone age was detected in 28.3% of the patients. The mean tissue transglutaminase (tTG) value of the patients at baseline was 354.6 ± 71.1 IU/mL. Other laboratory parameters are presented in Table 1.

Of the patients, 441 (86.6%) presented with typical symptoms and 68 (13.4%) patients presented with atypical symptoms. Typical symptoms at presentation were also most common among the age groups. Of the patients, 479 (94.1%) were compliant with the gluten-free diet, whereas 30 (5.9%) patients were not (Table 2).

Table 3 shows presenting complaints, physical examination findings, and comorbid conditions of the patients and their distribution by age groups. Growth retardation was the most common presenting complaint in all patients (47.5%). Among age groups, the most common presenting complaint was growth retardation (44.6% and 59%) in the patient groups aged 61-144 months and >145 months, while it was diarrhea (26.1%) in the patient group aged 0-60 months. The number of patients screened due to having a sibling with CD and diagnosed with CD was 46 (9%). In all patients, the most common physical examination findings at the time of presentation were normal (57.4%), whereas pallor was the most common (21.4%) pathological physical examination finding. Pallor was also the most common pathological physical examination finding in the age groups of 0-60 months and 61-144 months (44.3% vs. 18.1%, respectively). Fatigue (21.8%) was the most common pathological physical examination finding in children over 145 months. Iron deficiency anemia (35%) and osteoporosis (33%) were the most common comorbidities. While the most common comorbidity disease was anemia in the patient groups aged 0-60 months and 61-144 months (67.2% vs. 33.1%, respectively), it was osteoporosis (51.1%) in the group

Table 1. Demographics and Laboratory Findings of the Cases

Parameters	All Patients (n = 509)
Sex, female, n (%)	290 (57%)
Age (months)	129.4 ± 49.3
Age of onset of complaint (months)	76.5 ± 43.2
Age of onset of gluten-free diet (months)	93.8 ± 46.7
Weight (kg)	19.4 ± 8.7
Height (cm)	111.1 ± 21.6
BMI (kg/m^2)	15.0 ± 2.0
Delayed bone age, n (%)	144 (28.3)
Laboratory parameters	
Hemoglobin (g/dL)	12.3 ± 1.6
Platelet count (×10^3/μL)	312 ± 95
White blood cell count (×10^3/mL)	7.5 ± 2.3
Iron (μg/dL)	62.1 ± 37.4
Iron binding capacity (μg/dL)	332 ± 82.1
Ferritin (ng/mL)	24.2 ± 29.8
AST (U/L)	32 ± 21.3
ALT (U/L)	21.9 ± 18.7
Albumin (mg/dL)	4.4 ± 0.4
Calcium (mg/dL)	9.6 ± 0.5
Phosphorus (mg/dL)	4.7 ± 0.7
Vitamin D (IU)	21.7 ± 9.6
Vitamin B12 (pg/mL)	370.7 ± 160.8
Folic acid (ng/mL)	9.2 ± 3.7
Initial tissue transglutaminase (IU/mL)	354.6 ± 71.1

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

aged over 145 months. Considering the distribution of comorbidities by sex, osteopenia was more common in girls, whereas type 1 diabetes mellitus (DM) was more common in boys. In addition, iron deficiency anemia was more common in patients who did not adhere to the diet.

Endoscopic findings of the patients showed that 448 (88%) had duodenitis, 118 (23.2%) had endoscopic gastritis, 53 (10.4%) had esophagitis Grade A, 26 (5.1%) had endoscopic nodular gastritis, 13 (2.6%) had esophagitis Grade B, 9 (1.8%) had cardio-esophageal sphincter failure, and 5 (1%) had bile reflux. Pathology reports of small intestine biopsies were most commonly consistent with Marsh stage 3b (55.4%). Among age groups, Marsh stage 3c (52.5%) was observed most commonly in patients aged 0-60 months, while Marsh stage 3b was most prevalent in 61-144 months and over 145 months (51.9% vs. 63.8%, respectively). A statistically significant association was found between Marsh-Oberhuber stage and dietary compliance of the patients ($P = .031$). Marsh stage 3b (56.8%) was most common in patients with dietary compliance, while Marsh stage 3c (50%) was most common in patients without dietary compliance.

DISCUSSION

Celiac disease is an autoimmune enteropathy that occurs in individuals with genetic predisposition as a result of eating foods containing gluten. The ESPGHAN guidelines are taken into account in the diagnosis of CD.[6] Diagnosis is made on the basis of serology testing and small intestine biopsy. Although the symptoms of CD may occur and the diagnosis may be made at any age, studies have shown that the prevalence of CD increases with age.[7] In the current study, the age of onset of complaints was 76.5 months; however, the age of onset of gluten-free diet was 93.8 months.

Celiac disease is among the leading causes of chronic diarrhea, especially in childhood. Classical CD symptoms include diarrhea, weight loss, and growth retardation. The most common extra-intestinal findings are iron deficiency anemia and metabolic bone disease. Other extra-intestinal findings include infertility, dermatitis herpetiformis, myocarditis, dilated cardiomyopathy, idiopathic pulmonary hemosiderosis, immunoglobulin A (IgA) nephropathy, neurological and psychiatric diseases such as depression and peripheral neuropathy due to vitamin deficiency, anemia due to iron, folate, and vitamin B12 deficiency, autoimmune diseases such as type 1 DM and autoimmune thyroiditis.[8-10]

In many published studies, the presenting complaints vary widely. In the current study, the most common presenting complaint was growth retardation in all patients, followed by abdominal pain. In a multi-center study, diarrhea was found to be the most common complaint at a rate of 51%.[11] In a study on 87 CD cases identified between 2000 and 2007, diarrhea was the most common complaint (96.3%) at the time of admission.[12] In a study by Kondolot et al[13] distributing the complaints of the patients

Table 2. Dietary Compliance and Distribution of Typical–Atypical Celiac Disease Symptoms by Sex

		All Patients	Female	Male	*P*
Dietary compliance	Yes, n (%)	479 (94.1)	276 (95.2)	203 (92.7)	.24
	No, n (%)	30 (5.9)	14 (4.8)	16 (7.3)	
Typical symptom	Yes, n (%)	441 (86.6)	253 (87.2)	188 (85.8)	.647
	No, n (%)	68 (13.4)	37 (12.8)	31 (14.2)	

Table 3. Presenting Complaints, Examination Findings, and Comorbidities by Age Group of the Cases

Parameters	All Patients (n=509)	0-60 months (n=61)	61-144 months (n=260)	>145 months (n=188)	*P*
Presenting complaint					
Growth retardation, n (%)	242 (47.5)	15 (24.6)	116 (44.6)	111 (59)	.001
Abdominal pain, n (%)	178 (35.0)	13 (21.3)	93 (35.8)	72 (38.3)	.05
Diarrhea, n (%)	133 (26.1)	34 (55.7)	64 (24.6)	35 (18.6)	.001
Abdominal distension, n (%)	119 (23.4)	32 (52.5)	70 (26.9)	17 (9)	.001
Loss of appetite, n (%)	56 (11)	9 (14.8)	31 (11.9)	16 (8.5)	.318
Sibling screening, n (%)	46 (9.0)	4 (6.6)	23 (8.8)	19 (10.1)	.694
Vomiting, n (%)	36 (7.1)	8 (13.1)	17 (6.5)	11 (5.9)	.14
Constipation, n (%)	26 (5.1)	3 (4.9)	14 (5.4)	9 (4.8)	.958
Other, n (%)	81 (15.9)	3 (4.9)	29 (11.1)	49 (65.9)	
Physical examination findings					
Normal physical examination, n (%)	292 (57.4)	19 (31.1)	160 (61.5)	113 (60.1)	.001
Pallor, n (%)	109 (21.4)	27 (44.3)	47 (18.1)	35 (18.6)	.001
Weakness, n (%)	97 (19.1)	17 (27.9)	39 (15)	41 (21.8)	.034
Abdominal distension, n (%)	82 (16.1)	24 (39.3)	41 (15.8)	17 (9)	.001
Other, n (%)	83 (16.5)	8 (13)	40 (15.5)	35 (18.5)	
Comorbidities					
Iron deficiency anemia, n (%)	178 (35)	41 (67.2)	86 (33.1)	51 (27.1)	.001
Osteoporosis, n (%)	168 (33)	5 (8.2)	67 (25.8)	96 (51.1)	.001
Osteopenia, n (%)	93 (18.3)	13 (21.3)	53 (20.4)	27 (14.4)	.214
Diabetes mellitus, n (%)	16 (3.1)	–	8 (3.1)	8 (4.3)	.253
Epilepsy, n (%)	13 (2.6)	3 (4.9)	9 (3.5)	1 (0.5)	.07
Gastroesophageal reflux, n (%)	10 (2)	–	5 (1.9)	5 (2.7)	.241
Other, n (%)	134 (14.5)	12 (16.4)	52 (19.8)	70 (26.3)	

by their ages, the complaint of diarrhea was found to decrease with age, and growth retardation was the most common presenting complaint in patients aged over 12 years. The presenting complaints in our study are comparable to those previously reported in the literature. Among age groups in our study, the most common presenting complaint was growth retardation in the patient groups aged 61-144 months and over 145 months, while it was diarrhea in the patient group aged 0-60 months. The number of patients who were screened due to having a sibling with CD and found to have CD was 46 (9%). In a study conducted by Telega et al.[4] more than half of the patients over the age of 7 years presented and were diagnosed with this form of the disease known as the atypical presentation. Balamtekin et al[14] investigated the frequency of symptoms in 220 patients with CD and found that 129 (58.6%) had gastrointestinal symptoms, 76 (34.6%) had extra-gastrointestinal symptoms, and 15 (6.8%) had silent symptoms. In our study, patients with atypical symptoms were older, with a higher mean age of onset of complaints, and a higher mean age of onset of a gluten-free diet compared to those with typical symptoms, which is in line with the data reported by Telega et al.[4] This finding suggests that the disease should be detected before the growth of the patient is adversely affected, and site-specific screening should be performed for this purpose. Early diagnosis and treatment are important for preventing growth and developmental retardation, osteoporosis, autoimmune diseases, and intestinal lymphoma that may develop in these patients.[15]

The hematologic system is an important system that is also affected in CD as with many diseases. Anemia is the most common hematological abnormality in the CD, with a prevalence at diagnosis varying between 12% and 69%, and may even be the

first clinical manifestation of subclinical/silent CD.[16] Consistent with previous reports, iron deficiency anemia was the most common comorbidity in our study. Guidelines recommend screening for CD with serological testing in patients presenting with iron deficiency anemia. Bone and skeletal systems may also be involved in CD. Due to mucosal damage in the proximal small intestine, calcium absorption is impaired and serum calcium concentration decreases. Zanchi et al[17] found osteopenia at a rate of 18% using DEXA measurements in 54 untreated children with CD. Osteoporosis is a well-known complication of untreated CD. In our study, osteoporosis was detected in 168 (33%) patients and osteopenia was detected in 93 (18.3%) patients.

Neurological complications are observed in 6-10% of celiac patients.[18] Headache, myelopathy, myopathy, dementia, perception disorders, attention deficit, and psychiatric disorders, in particular, cerebellar ataxia, peripheral neuropathy, and epilepsy have been reported in the course of CD. There are many studies reporting a higher incidence of epilepsy in children with CD compared to healthy children. Zelnik et al[19] showed that 8 (7.2%) of 111 CD children and 6 (2.8%) of 211 healthy control children had epilepsy. Dalgıç et al[20] found the prevalence of CD diagnosed with biopsy in 70 epileptic children at a rate of 1.17%, which was higher compared to the control group. In our study, the presenting complaint of 27 (5.3%) patients was headache and 13 (2.6%) patients had coexisting epilepsy.

Since CD is an autoimmune disease, it is frequently associated with diseases such as type 1 DM, thyroiditis, Sjögren's disease, sclerosing cholangitis, Addison's disease, rheumatoid arthritis, dermatitis herpetiformis, osteoporosis, primary biliary cirrhosis, Down syndrome, and selective IgA deficiency. About 5% of CD patients manifest with type 1 DM. Similarly, 5% of patients with type 1 DM have CD.[21] Therefore, individuals at risk for these diseases should be screened for CD. In our study, there were 16 patients with type 1 DM, 13 patients with epilepsy, 9 patients with thyroiditis, 5 patients with familial Mediterranean fever, 4 patients with rheumatoid arthritis, and 2 patients with dermatitis herpetiformis, suggesting the need for screening patients at risk for additional diseases, even when they are asymptomatic.

The only known treatment of CD is lifelong adherence to a gluten-free diet that requires avoidance of wheat, oat, and barley to provide symptomatic, serological, and histological remission.[22] This is the only way to achieve optimal quality of life in the light of current knowledge. Complications that may develop in the long term are prevented with early diagnosis and appropriate treatment. Problems related to malabsorption, such as growth retardation caused by the disease, resolve in the first 1-3 years, and patients reach normal weight and height percentiles for their age.[23] Adherence to a lifelong diet as a treatment method is challenging for both patients and families. Not surprisingly, the rate of non-compliance with diet is quite high. The most important factors in non-compliance with the diet include limited access to and high cost of gluten-free products, unavailability of gluten-free diet products, contamination with gluten and other prolamins in many products in the market (despite "gluten-free" label), and absence of alternative products, such as pure corn flour and rice flour. Failure to achieve a reduction in tissue transglutaminase levels after 6 months of a gluten-free diet suggests ongoing gluten intake from hidden sources. Adolescents do not often adhere to the diet. In our study, dietary compliance was lower in the adolescent age group (over 12 years old) compared to other age groups. Since the disease is silent in this age group, the adolescent may believe that the disease has improved. However, mucosal damage continues. Consequently, growth retardation and delayed sexual maturation will be observed when these patients follow a gluten-containing diet.

The present study has a number of limitations. First, this was a retrospective, single-center study. However, the sample size was relatively large, increasing the value of the study. Secondly, the study was designed as an analysis of the data from a single center collected retrospectively from a clinical registry and this may limit the generalizability of our findings.

CONCLUSION

Celiac disease causes a plethora of gastrointestinal and extra-intestinal symptoms. It should be kept in mind that although growth and developmental retardation and chronic diarrhea are cautionary for CD, patients may present with atypical extra-gastrointestinal symptoms. A multidisciplinary approach is required for the evaluation of CD patients. The mainstay of CD treatment is strict compliance with a gluten-free diet. Patients and caregivers should be trained during routine polyclinic controls to maintain compliance with treatment. Considering the number of cases, we believe that our study is an important study conducted in Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Date: November 5, 2013, Decision no: 373).

Informed Consent: Informed Consent: Informed consent was obtained from legal guardians to participate.

Peer-review: Externally peer-reviewed.

Author Contributions: Author Contributions: Concept – S.Y., Ş.H.; Design – S.Y., Ş.H.; Supervision – S.Y., Ş.H.; Resources – S.Y., H.K.; Materials – S.Y., H.K.; Data Collection and/or Processing – S.Y., H.K.; Analysis and/or Interpretation – S.Y., Ş.H.; Literature Search – S.Y., Ş.H., H.K.; Writing Manuscript – S.Y., Ş.H.; Critical Review – Ş.H., H.K.; Other – SY., Ş.H., H.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Lionetti E, Catassi C. New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. *Int Rev Immunol*. 2011;30(4):219-231. [CrossRef]
2. Demirçeken FG, Kansu A , Kuloğlu Z , Girgin N , Güriz H , Ensari A. Human tissue transglutaminase antibody screening by immunochomatographicline immunoassay for early diagnosis of celiac disease in Turkish children. *Turk J Gastroenterol*. 2008;19(1):14-21.

3. Dalgıç B, Sari S, Basturk B, et al. Prevalence of celiac disease in healthy Turkish school children. *Am J Gastroenterol*. 2011; 106(8):1512-1517. [CrossRef]. Epub 2011 Jun 21. Erratum in: *Am J Gastroenterol*. Yaşar, Aslan [corrected to Dogan, Yasar]. 2011;106(8):1565.
4. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc Med*. 2008;162(2):164-168. [CrossRef]
5. Doğancı T, Çocuklarda Çölyak Hastalığının Klinik Bulguları. In: Selimoğlu MA, ed. *Çölyak Hastalığı*. İstanbul: Logos yayıncılık; 2008:43-49.
6. Husby S, Koletzko S, Korponay-Szabó I, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70(1):141-156. [CrossRef]
7. Dixit R, Lebwohl B, Ludvigsson JF, Lewis SK, Rizkalla-Reilly N, Green PH. Celiac disease is diagnosed less frequently in young adult males. *Dig Dis Sci*. 2014;59(7):1509-1512. [CrossRef]
8. Harris LA, Park JY, Voltaggio L, Lam-Himlin D. Celiac disease: clinical, endoscopic, and histopathologic review. *Gastrointest Endosc*. 2012;76(3):625-640. [CrossRef]
9. Fasano A. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology*. 2005;128(4):S68-S73. [CrossRef]
10. Maki M, Lohi O. CeliacDisease. In: Walker WA, Goulet O, Kleinman RE, et al., eds. *Pediatric Gastrointestinal Disease*. 4th ed. Ontario: BC Decker; 2004:932-943.
11. Canales P, Alliende GF, Hunter MB, Diagnosis and clinical presentations of celiac disease. A multicenter study. *Rev Med Chile*. 2008; 136:296-303.
12. Dinler G, Atalay E, Kalaycı AG. Celiac disease in 87 children with typical and atypical symptoms in Black Sea region of Turkey. *World J Pediatr*. 2009;5(4):282-286. [CrossRef]
13. Kondolot M, Demirçeken F, Ertan Ü. 52 Vaka ile Türk Çocuklarında Çölyak Hastalığı. Türkiye Çocuk Hastalıkları. *Dergisi*. 2009;3(1):10-17.
14. Balamtekin N, Uslu N, Baysoy G, et al. The presentation of celiac disease in 220 Turkish children. *Turk J Pediatr*. 2010;52(3):239-244.
15. Shannahan S, Leffler DA. Diagnosis and updates in celiac disease. *Gastrointest Endosc Clin N Am*. 2017;27(1):79-92. [CrossRef]
16. Halfdanarson TR, Litzow MR, Murray JA. Hematologic manifestations of celiac disease. *Blood*. 2007;109(2):412-421. [CrossRef]
17. Zanchi C, Di Leo G, Ronfani L, Martelossi S, Not T, Ventura A. Bone metabolism in celiac disease. *J Pediatr*. 2008;153(2):262-265. [CrossRef]
18. Chin RL, Sander HW, Brannagan TH, et al. Celiac neuropathy. *Neurology*. 2003;60(10):1581-1585. [CrossRef]
19. Zelnik N, Pacht A, Obeid R, Lerner A. Range of neurologic disorders in patients with celiac disease. *Pediatrics*. 2004;113(6):1672-1676. [CrossRef]
20. Dalgiç B, Dursun I, Serdaroğlu A, Dursun A. Latent and potential celiac disease in epileptic Turkish children. *J Child Neurol*. 2006; 21(1):6-7. [CrossRef]
21. Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. *Aliment Pharmacol Ther*. 2014;40(10):1123-1132. [CrossRef]
22. Green PH, Jabri B. Celiac disease. *Annu Rev Med*. 2006;57:207-221. [CrossRef]
23. Kaukinen K, Lindfors K, Collin P, Koskinen O, Mäki M. Coeliac disease--a diagnostic and therapeutic challenge. *Clin Chem Lab Med*. 2010;48(9):1205-1216. [CrossRef]