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Extraintestinal Manifestations Associated with Celiac Disease

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ABSTRACT

Celiac disease (CD) can affect almost all organs of the body, including the nervous system, liver, skin, reproductive and musculoskeletal systems. In this study, it is aimed to determine the prevalence of extra-intestinal manifestations (EIMs) in adult celiac patients and to investigate the factors affecting the development of EIMs.

The study included 230 celiac patients who were diagnosed and followed-up in our clinics between 2015-2019. The demographic and anthropometric characteristics, initial admission complaints, disease duration and dietary compliance of the patients were documented. All EIMs that accompanied the celiac disease were recorded, and their relationship with risk factors was analyzed.

The age range of the patients was 18-72 years, and the mean age was 33.4±10.6 years. One hundred seventy two (74.8%) patients were female and disease follow-up was 4.8±3.5 years. The number of patients with accompanying EIMs was 202 (87.8%). Osteoporosis/osteopenia was found in 146(63.5%) patients, oral involvement in 116(50.4%) patients, arthritis/arthralgia in 96(41.7%) patients as the most common comorbidities. It was determined that, there was a significant relationship between EIM and body mass index. Although the EIMs development was less in patients who had strict diet; however, this was not statistically significant.

The majority of adult celiac patients were found to be accompanied by EIMs. The diagnosis is delayed due to various clinical presentations. Lack of delay in diagnosis of celiac disease and consequently reduced gluten exposure seem to be the only factor in preventing some EIMs

Key Words: Celiac Disease, Extra-intestinal Manifestations, Gluten Free Diet

Introduction

Classically, celiac patients present with diarrhea, steatorrhea, weight lost and growth retardation which is predominant in malabsorption. However, malabsorption related symptom ratio decreased in newly diagnosed patients and became prominent non-classical or even asymptomatic celiac disease (CD) (1). Celiac patients can be affected almost all organs of the body, including the nervous system, liver, skin, reproductive and musculoskeletal systems (2,3). Diagnosis of CD with the use of highly sensitive and specific serological test, has become more common. There have been many clinical presentations from the presence of gastrointestinal symptoms (diarrhea, abdominal pain, and abdominal distension) to growth retardation in children (4), prolonged fatigue (5), unexpected weight loss, recurrent aphthous stomatitis, anemia (6), increased liver enzymes (7) and unexplained neuropsychiatric disorders (8). In addition, studies have shown that CD should be investigated in patients with autoimmune thyroid disease, dermatitis herpetiformis, type 1 diabetes and irritable bowel syndrome (6- 9). The most common extra-intestinal symptom in children is growth retardation and iron deficiency anemia in adults (10).

Although CD is a gastrointestinal disease with small intestinal mucosal lesion, small intestinal mucosal damage develops gradually during the course of the disease and mucosal deterioration can take many years. Therefore, it is reported that extra-intestinal manifestations (EIMs) may develop before the diagnosis of CD (11). Studies have shown that the prevalence of EIMs in celiac patients is around 60%, similar between pediatric and adult populations (12,13).

Although it is known that CD is more common in women, it is seen that the data related to gender distribution of EIMs are contradictory (13). In addition, some EIMs recovered completely after early strict diet, while some of them recovered partially and somewhere not affected at all (12,13).

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While the gluten free diet has an obvious effect on skin diseases and bone mineral density, it has been shown to be less effective for further EIMs such as liver diseases and infertility (3,14,15). Other autoimmune diseases associated with CD should be investigated due to common gene polymorphism, except for EIMs secondary to gluten sensitivity (16-19). In this study, it is aimed to determine the prevalence of EIMs in adult celiac patients and to investigate the factors affecting the development of EIMs.

Materials and Methods

Study Design: The patients who were diagnosed and followed-up in the clinics of Gastroenterology were included in the present study. The records of celiac patients were taken from the hospital database between 2015 and 2019. For all patients who were diagnosed with CD, the inclusion criteria for the study were having positive results of the Antibody level test (Anti-Endomysium and Tissue Transglutaminase Antibody (anti-TTG)), which is having consistent results of the tissue samples taken in endoscopy in histopathological examination according to the Marsh classification (20). The patients who did not continue follow-ups in our clinic, whose data could not be obtained were not included in the study. A total of 230 patients with CD, whose ages varied between 18 and 72 years were included in the study.

Evaluation of Demographic and Clinic Features: The demographic and anthropometric characteristics (age, gender, onset of disease, duration of disease, educational status, marital status, smoking use, body mass index (BMI)) of the patients who included in the study were documented. Height (meter) and weight (kg) measurements were made to calculate the BMI of the patients. The BMI was calculated with the following formula: Weight/Height x Height. The waist circumference, hip circumference, waist/hip rates were also documented. In men, 0.9 waist/hip rate was considered to be risky for abdominal obesity and chronic diseases in men, and 0.85 in women (21). The symptoms of the participants at admission were documented. Diarrhea, constipation, reflux, bloating, abdominal pain, nausea, vomiting were evaluated as gastrointestinal system (GIS) symptoms.

Dietary Compliance: In patients who had CD, gluten-free diet compliance was questioned retrospectively in the patient records in patient visits by the responsible physician and dietician. In addition, compliance with gluten-free nutrition was evaluated by analyzing the questionnaire that was given to the patients. The diet was classified as two categories; strict diet (complete dietary compliance) and normal gluten-containing diet.

Extra-intestinal Manifestations: The presence of EIM in celiac patients, a structured questionnaire and patient records were reviewed. EIMs; anemia, arthritis / arthralgia, dermatitis herpetiformis, oral involvement (gum disease, aphthous ulcer, aphthous stomatitis), neurological involvement (headache, migraine, epilepsy, neuropathy), liver involvement, osteoporosis / osteopenia, infertility and the presence of alopecia were documented.

Ethics declaration: To conduct this study, ethical approval was obtained from the Ethics Committee of our hospital. All the applied procedures were complied with the ethical standards of human testing committee of our institution and the Helsinki Declaration. Written informed consent forms were received from all participants.

Statistical Analysis: The results of our study were analyzed with "The Statistical Package for Social Sciences 19.0 (SPSS Armonk, NY: IBM Corp.)" program. The data that had continuous values were given as (mean ± standard deviation), and the categorical data were given as frequency and percentage (n, %). The data were tested for compliance to normal distribution with the Kolmogorov-Simirnov Test, Histogram and ± SD. The nonparametric data of the groups were compared by using the Mann Whitney U-test; and the parametric data were compared with the Parametric T-test. The Chi-square Test was employed to test the categorical data. A P value < 0.05 was considered to be statistically significant.

Results

A total of 230 patients who were followed-up with CD were included in the study. A total of 172 (74.8%) of the patients were female, and the mean age was 33.4±10.6 years (range between 18-72 years). Although the mean BMI level of the patients was 22.6±4.2; only 146 (63.5%) patients had normal BMI. The waist-hip rate of the patients ranged between 0.63 and 0.98 with a mean of 0.81±0.07 (0.87±0.06 in males, and 0.8±0.06 in females). In 54 (%24.5) of the patients, it was determined that the waist-hip rate was above normal. EIMs were detected in the celiac patients were evaluated. It was determined that; 202 (87,8%) patients had EIMs. Osteoporosis/osteopenia was determined in 146

Table 1. Accompanying Extraintestinal Manifestations in Celiac Patients

	N[1] - (%)		N - (%)
Anemia	65 (28.3%)	Osteoporosis / Osteopenia	146 (63.5%)
Arthritis / arthralgia	96 (41.7%)	Infertility	10 (4.3%)
Dermatitis Herpetiformis	10 (4.3%)	Alopecia	38 (16.5%)
Oral Involvement	116 (50.4%)	Neurological Involvement	46 (20%)
Liver Involvement	94 (40.9%)	Total	202 (87.8%)

[1]N: Number of patients

(63.5%) patients, oral involvement in 116 (50.4%) patients, arthritis/arthralgia in 96 (41.7%) patients, liver involvement in 94 (40.9%) patients, anemia in 65 (28.3%) patients, neurological involvement in 46 (20%) patients, alopecia in 38 (16.5%) patients, infertility in 10 (4.3%) patients and dermatitis herpetiformis in 10 (4.3%) patients (Table 1).

The factors that might affect the development of EIMs in celiac patients are considered. It was determined that; there was a statistically significant relation between EIMs development and BMI. The BMI levels in individuals who had EIM accompanying CD was 22.3±4.1, and in individuals who did not have EIM was 24.4±4.3 (p=0.016). Although the EIMs development was less in patients who had strict diet; however, this was not statistically significant. No significant relations were detected between EIM development and other factors (Table 2).

Discussion

Clinical presentation is heterogeneous and often ambiguous, as many extra-intestinal tracts are affected in CD (22). Although the presence of EIMs in celiac disease has been known for decades, its prevalence is still unclear. The prevalence rates of the patients were different due to different age ranges and symptoms which were evaluated as EIM of the patients included in the study. However, some studies have reported that the prevalence of EIM in celiac patients is approximately 60% (12,13). In our study, we found the EIM prevalence in 87% of adult celiac patients.

CD is frequently reported to be accompanied by bone, joint, liver, skin involvement and anemia (23). Osteoporosis is one of the most common EIM in adult celiac patients, especially in elderly patients and postmenopausal women. Studies have reported a prevalence of 4-23% in adult celiac patients (12,24). In our study, osteoporosis / osteopenia was found to be 63.5% as the most common EIM in patients. In particular, the delay in diagnosis of pediatric celiac patients prevents the formation of peak bone mass emphasizes the importance of delay in diagnosis in celiac patients. Joint symptoms are also frequently reported in CD. Along with recent studies reported the prevalence of arthritis between 2-9%, in our study which arthralgia is added, joint involvement was found as 41.7% (12,13,25,26). In addition, the prevalence of oral involvement in studies is very contradictory, it has been reported in the range of 1-83% (13,26). It is thought that the different symptoms which were evaluated as oral involvement of the patients included in the study. In our study, 50.4% of celiac patients had oral involvement. Gluten exposure time, dietary compliance, iron, vitamin and mineral deficiencies as well as immunological disorders are suggested as the causes of oral involvement (27).

Elevated liver enzymes and autoimmune liver diseases such as autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis are also frequently reported in celiac patients (2). The incidence of hypertransaminemia in celiac patients has been reported in 9-14% of recent studies. In our study, in which evaluated autoimmune liver diseases, non-alcoholic fatty liver disease and the cause of unknown hypertransaminasemia, we found liver involvement in 40% of patients. One of the most common EIMs in all age groups in CD is anemia and is becoming more common (28). Iron deficiency as a result of iron absorption disorder, vitamin B12 and folic acid deficiency play a role in this case (29). In our study, 28.3% of the celiac patients were found to be anemic. Other EIMs such as dermatitis herpetiformis, alopecia and infertility are also seen in celiac patients. Dermatitis herpetiformis is a dermatologic symptom of CD usually seen in adulthood (24,30). In addition, approximately 20% of celiac patients had neurological findings (12,13). The most common of these is headache which usually occur without accompanying gastrointestinal symptoms, gluten ataxia and peripheral neuropathy (31). In our study, we found that 20% of the patients had

Table 2. Risk Factors Associated with the Presence of Extraintestinal Manifestations

Variables	Celiac Disease EIM (-) (n=28)	Celiac Disease EIM (+) (n=202)	Total (n=230)	P value
Age (mean ± Sd)	35.9±14.4	33±10	33,4±10,6	0,181
Onset age of the disease (years) (mean ± Sd)	30.7±14.5	28,2±10,1	28,5±10,7	0,254
Disease duration (years) (mean ± Sd)	5.21±3.9	4,82±3,4	4,8±3,5	0,578
BMI (kg/m²) (mean ± Sd)	24.4±4.3	22,3±4,1	22,6±4,2	0,016*
Waist/hip rate				
Below the limit	20 (71.4%)	156 (%77,2)	176 (%76,5)	0,497
Above the limit	8 (28.6%)	46 (%22,8)	54 (%24,5)	
Disease stage				
Mild (Stage 2-3a)	16 (57.1%)	110 (%54,5)	126 (%54,8)	0,789
Severe (Stage 3b,3c,4)	12 (%42,9)	92 (%45,5)	104 (%45,2)	
Dietary Compliance				
Strict	14 (%50)	74 (%36.6)	92 (%40)	0,173
None	14 (%50)	128 (%63.4)	138 (%60)	
Gender				
Female	18 (%64,3)	152 (%75,2)	170 (%73,9)	0,216
Male	10 (%35,7)	50 (%24,8)	60 (%26,1)	
Immunologic Remission				
Yes	14 (%50)	86 (%42,6)	100 (%43,5)	0,458
No	14 (%50)	116 (%57,4)	130 (%56,5)	
Family History				
Yes	18 (%64,3)	160 (%79,2)	178 (77,4)	0,077
No	10(%35,7)	42 (%20,8)	52 (22,6)	
Educational Status				
Illiterate	2 (%7,1)	39 (%19,3)	41 (%17,8)	0,204
Primary Education	16 (%57,2)	113 (%55,9)	129 (%56,1)	
High School and over	10(%35,7)	60 (%26,1)	60 (%26,1)	
Marital Status				
Married	18 (%64,3)	144 (%71,3)	162 (%70,4)	0,447
Single	10 (%35,7)	58 (%28,7)	68 (%29,6)	
Working Status				
Working	4 (%14,3)	42 (%20,8)	46 (%20)	0,420
Unemployed	24 (%85,7)	160 (%79,2)	184 (%80)	
Smoking Status				
Smoking	2 (%7,1)	43 (%21,3)	45 (%19,6)	
Non-smoking	24 (%85,7)	138 (%68,3)	162 (%70,4)	0,147
Quit	2 (%7,1)	21 (%10,4)	23 (%10)	
Complaints at First Admission				
GIS symptoms	22 (%78.6)	144 (%71.3)	166 (%72.2)	0.719
Non-GIS symptoms	4 (%14.3)	40 (%19.8)	44 (%19.1)	
GIS+Non GIS symptoms	2 (%7.1)	18 (%8.9)	20 (%8.7)	

EIM: Extra Intestinal Manifestations
BMI: Body Mass Index,
Sd: Standard Deviation,
GIS: Gastrointestinal System
*: Statistically significant ($p<0.05$)

neurological involvement, 16.5% had alopecia, 4.3% had infertility and 4.3% had dermatitis herpetiformis.

Although it is known that CD is more common in women, the gender distribution of EIMs is currently mostly unclear. The pathogenesis of most of the EIMs is unclear. There is some evidence that their existence is generally associated with a more serious clinical and histological presentation, but it does not appear that the appearance or violence is only a direct result of intestinal damage. Since even identical twins with CD may have completely different phenotypes, the balance between genetic and environmental factors is considered to be important. At least partially different pathogenic background of variable presentations of CD is supported by the unique appearance of serological markers in some of these cases (23). Also delayed in diagnosis of CD it was stated that as a result of the increase in gluten exposure, the rate of EIM increased and some findings regressed after diet compliance (2,32). In our study, we did not find any significant relationship between age and sex with the presence of EIMs. However, we found a significant relationship between the development of EIMs and low BMI. Although it was not statistically significant, it was seen that the rate of EIMs was lower in those with dietary compliance.

In conclusion, the majority of adult celiac patients were found to be accompanied by EIMs. The diagnosis is delayed due to various clinical presentations. Lack of delay in diagnosis of celiac disease and consequently reduced gluten exposure seem to be the only factor in preventing some EIMs. In patients with symptoms that do not respond to a gluten-free diet, accompanying autoimmune diseases should be screened. Therefore, in addition to gastroenterologists, a multidisciplinary approach is required, including general internal medicine, rheumatologist, dermatologist, ophthalmologist, gynecologist and family physicians.

References

1. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014; 63: 1210-1228.
2. Äärelä L, Nurminen S, Kivelä L, et al. Prevalence and associated factors of abnormal liver values in children with celiac disease. Digestive and Liver Disease 2016; 48: 1023-1029.
3. Tersigni C, Castellani R, De Waure C, et al. Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. Human reproduction update 2014; 20: 582-593.
4. Guandalini S, Assiri A. Celiac disease: a review. JAMA pediatrics 2014; 168: 272-278.
5. Sanders DS, Evans KE, Hadjivassiliou M. Test for coeliac disease first? Bmj 2010; 341: 5161.
6. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. The American journal of gastroenterology 2013; 108: 656.
7. Sainsbury A, Sanders DS, Ford A. Meta-analysis: coeliac disease and hypertransaminasaemia. Alimentary pharmacology & therapeutics 2011; 34: 33-40.
8. Addolorato G, Leggio L, D'Angelo C, et al. Affective and psychiatric disorders in celiac disease. Digestive diseases 2008; 26: 140-148.
9. Pinto-Sánchez MI, Bercik P, Verdu EF, Bai JC. Extraintestinal manifestations of celiac disease. Digestive Diseases 2015; 33: 147-154.
10. Jericho H, Guandalini S. Extra-Intestinal manifestation of celiac disease in children. Nutrients 2018; 10: 755.
11. Mustalahti K. Unusual manifestations of celiac disease. The Indian Journal of Pediatrics 2006; 73: 711-716.
12. Jericho H, Sansotta N, Guandalini S. Extraintestinal manifestations of celiac disease: effectiveness of the gluten-free diet. Journal of pediatric gastroenterology and nutrition 2017; 65: 75-79.
13. Nurminen S, Kivelä L, Huhtala H, Kaukinen K, Kurppa K. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. Acta Paediatrica 2019; 108: 681-687.
14. Zanini B, Baschè R, Ferraresi A, et al. Factors that contribute to hypertransaminasemia in patients with celiac disease or functional gastrointestinal syndromes. Clin Gastroenterol Hepatol 2014; 12: 804-810.
15. Kalayci AG, Kansu A, Girgin N, Kucuk O, Aras G. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. Pediatrics 2001; 108: 89.
16. Majorana A, Bardellini E, Ravelli A, Plebani A, Polimeni A, Campus G. Implications of gluten exposure period, CD clinical forms, and HLA typing in the association between celiac disease and dental enamel defects in children. A case–control study. Int J Paediatr Dent 2010; 20: 119-124.
17. Sansotta N, Amirikian K, Guandalini S, Jericho H. Celiac disease symptom resolution: Effectiveness of the gluten-free diet. J Pediatr Gastroenterol Nutr 2018; 66: 48-52.

18. Laurikka P, Salmi T, Collin P, et al. Gastrointestinal symptoms in celiac disease patients on a long-term gluten-free diet. Nutrients 2016; 8: 429.
19. Hervonen K, Salmi T, Kurppa K, Kaukinen K, Collin P, Reunala T. Dermatitis herpetiformis in children: a long-term follow-up study. Br J Dermatol 2014; 171: 1242-1243.
20. Marsh MN. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102: 330-354.
21. Chamberlain JJ, Rhinehart AS, Shaefer CF, Neuman A. Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med 2016; 164: 542-552.
22. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med 2002; 346: 180-188.
23. Laurikka P, Nurminen S, Kivelä L, Kurppa K. Extraintestinal manifestations of celiac disease: Early detection for better long-term outcomes. Nutrients 2018; 10: 1015.
24. Bottaro G, Cataldo F, Rotolo N, Spina M, Corazza G. The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. Am J Gastroenterol 1999; 94: 691.
25. Roma E, Panayiotou J, Karantana H, et al. Changing pattern in the clinical presentation of pediatric celiac disease: a 30-year study. Digestion 2009; 80: 185-191.
26. Mubarak A, Spierings E, Wolters VM, Otten HG, Kate FJ, Houwen RH. Children with celiac disease and high tTGA are genetically and phenotypically different. World J Gastroenterol 2013; 19: 7114.
27. Cheng J, Malahias T, Brar P, Minaya MT, Green PH. The association between celiac disease, dental enamel defects, and aphthous ulcers in a United States cohort. J Clin Gastroenterol 2010; 44: 191-194.
28. Kivelä L, Kaukinen K, Lähdeaho M-L, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. J Pediatr 2015; 167: 1109-1115.
29. Repo M, Lindfors K, Mäki M, et al. Anemia and iron deficiency in children with potential celiac disease. J Pediatr Gastroenterol Nutr 2017; 64: 56-62.
30. Green PH, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001; 96: 126.
31. Luostarinen L, Pirttilä T, Collin P. Coeliac disease presenting with neurological disorders. Eur Neurol 1999; 42: 132-135.
32. Canova C, Pitter G, Zanier L, Simonato L, Michaelsson K, Ludvigsson JF. Risk of fractures in youths with celiac disease-A population-based study. J Pediatr 2018; 198: 117-120.