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Research

Clinical Assessment of Children with Celiac Disease Compliant to Diet by Age

Diyete Uyum Sağlayan Çölyak Hastalığı Olan Çocukların Yaşa Göre Klinik Olarak Değerlendirmesi

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ABSTRACT

Objective: The aim of this study was to evaluate pediatric patients with celiac disease (CD) compliant with gluten-free diet (GFD) by age groups and determine the relationship between the duration of compliance with diet, anthropometric measurements, and laboratory parameters.

Methods: A total of 195 children with CD (mean age: 7.3±4.4, male/female: 0.69) who were compliant with GFD were enrolled in this retrospective study. Clinical and demographic characteristics, laboratory examinations, serological tests, histopathological findings, and genetic analysis of the patients were examined according to age groups at diagnosis, 6 months, and 1st and 2nd years of follow-up.

Results: 19.5% of the patients were ≤2 years old, and most of the patients were between 5 and 9 years of age. 68.2% of the patients were typical, 26.2% were atypical, and 5.6% were asymptomatic. The most common presenting symptoms were growth retardation, diarrhea, and abdominal distension in children ≤2 years of age. When the patients were classified according to height and weight standard deviation scores, no statistically significant differences were observed during follow-up (p>0.05). As the duration of compliance to GFD increased, the number of patients who were normal and overweight increased. Additionally, significant differences were observed in body mass index Z-scores among age groups during follow-up.

Conclusion: Growth retardation, diarrhea, and abdominal distension are the predominant symptoms in infants. As age increases, atypical presentation becomes more common. Longer the duration of compliance with GFD, improvement in anthropometric measurements and laboratory parameters are more prominent.

Keywords: Celiac disease, children, gluten-free diet, age group

ÖZ

Amaç: Çalışmanın amacı glutensiz diyete (GD) uyumlu çölyak hastalığı (ÇH) olan çocukları yaş gruplarına göre değerlendirmek ve diyete uyum süresi, antropometrik ölçümler ve laboratuvar parametreleri arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, GD'yle uyumlu toplam 195 ÇH tanılı çocuk (ortalama yaş: 7,3±4,4, erkek/kız: 0,69) dahil edildi. Hastaların klinik ve demografik özellikleri, laboratuvar muayeneleri, serolojik testleri, histopatolojik bulguları ve genetik analizleri tanı anındaki yaş gruplarına, 6. ay, 1. ve 2. yıl takiplerine göre incelendi.

Bulgular: Hastaların %19,5'i ≤2 yaş grubunda olup, çoğunluğu 5-9 yaş aralığındaydı. Hastaların %68,2'si tipik, %26,2'si atipik ve %5,6'sı asemptomatikti. ≤2 yaş çocuklarda en sık görülen semptomlar büyüme geriliği, ishal ve karın şişliğiydi. Hastalar boy ve kilo standart sapma skorlarına göre sınıflandırıldığında takip sırasında istatistiksel olarak anlamlı farklılık elde edilmedi (p>0,05). GD'ye uyum süresi arttıkça normal ve aşırı kilolu hasta sayısı da arttı. Ayrıca takip sırasında yaş grupları arasında vücut kitle indeksi Z-skorlarında anlamlı farklılık gözlendi.

Sonuç: Büyüme geriliği, ishal ve karın şişliği bebeklerde halen en sık görülen semptomlardır. Yaş arttıkça atipik seyir daha sık görülür. GD'ye uyum süresi uzadıkça antropometrik ölçümlerde ve laboratuvar parametrelerinde iyileşme daha belirgindir.

Anahtar Kelimeler: Çölyak hastalığı, çocuklar, glutensiz diyet, yaş grubu

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INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy induced by dietary gluten in genetically predisposed individuals and is characterized by abdominal distention, diarrhea, and growth retardation. CD can occur at any age and its prevalence is estimated to be 1% worldwide and varies depending on geographical and ethnic variations (1).

Environmental, immunological, and genetic factors play a role in the pathogenesis of the disease (2). Dietary gluten intake causes a natural and acquired immune response in the body, which leads to intestinal villi atrophy, crypt hyperplasia, and lymphocyte infiltration. Approximately 90-95% of the patients are human leukocyte antigen (HLA) DQ2 positive, whereas the rest are HLA-DQ8 positive (3).

The diagnosis of CD is based on serological tests and biopsy, the gold standard in diagnosis. CD is classified according to clinical findings as typical (classical), atypical, asymptomatic (silent), latent, or potential (2). Typical disease occurs in the first 6-24 months of life after dietary gluten intake begins and is characterized by growth retardation, gastrointestinal symptoms such as chronic diarrhea or watery stool, vomiting, abdominal pain, and distention. The atypical form is more common in older children and adults and is characterized by extraintestinal symptoms such as delayed puberty, short stature, iron deficiency anemia, and abnormal liver function.

The only effective treatment is a lifelong gluten-free diet (GFD). Children on a strict GFD show faster and higher rates of gastrointestinal and extraintestinal symptom resolution. Early diagnosis is important to prevent long-term complications such as growth retardation and nutritional deficiencies (2). In this study, children with CD compliant with GFD were evaluated by age, and the relationship between the duration of compliance with diet, anthropometric measurements, and laboratory parameters was determined.

METHODS

A total of 195 CD patients who were followed-up in the pediatric gastroenterology department between January 2000 and December 2018 and who were compliant with GFD for at least 2 years were enrolled in this prospective study. Patients older than 18 years of age, those diagnosed at a different center, and those noncompliant to GFD were excluded from the study.

The diagnosis of CD was based on the ESPGHAN criteria (2). Compliance with GFD was questioned verbally in a standard form, and the patients whose growth improvements were observed at one month of follow-up were considered compliant with GFD.

Clinical and demographic characteristics, laboratory examinations, serological tests, histopathological findings, and genetic analysis of the patients were examined according to age groups at diagnosis and 6th month, 1st, and 2nd year controls.

The application created by the Pediatric Endocrine and Diabetes Association for children (CHILD METRICS) was used for anthropometric measurements of patients at admission and during follow-up. The standard deviation score (SDS) of the patients' height (cm), weight (kg), and body mass index (BMI) were established according to references of Neyzi et al. (4). The patients with a weight below -2 SDS were defined as wasting, -2 to -1 SDS as underweight, 1 to 1 SDS as normal, 1 to 2 SDS as overweight, and those >2 SDS as obese. If the height was <2 SDS, it was regarded as stunted, -2 to -1 SDS as short, -1 to 1 SDS as normal, 1 to 2 SDS as tall, and >2 SDS as very tall. If BMI was <-2, it was defined as malnutrition, -2 to 1 as normal, 1 to 2 as overweight, and >2 as obese (4).

Iron deficiency anemia was based on the Second National Health and Nutrition Examination Survey (NHANES-II) and the Nutrition Committee of the American Academy of Pediatrics (5). Accordingly, the reference values of hemoglobin (Hb) were 10.5 g/dL between 6 months and 2 years of age, 11.5 g/dL between 2 and 12 years of age, 12 g/dL in girls, and 13 g/dL in boys between 12 and 18 years of age. Ferritin levels were significant <12 µg/dL for children ≤5 years and <15 µg/dL for those <5 years. Platelet count <130,000/mm^3 was defined as thrombocytopenia, and >400,000/mm^3 as thrombocytosis (3).

Patients with at least one of the serological tests [antigliadin immunoglobulin A (IgA) and IgG, antiendomisyum IgA and IgG, tissue transglutaminase IgA and IgG] positive were defined as serology positive.

According to the modified Marsh classification (6); grade 0 is defined as normal, grade 1 as intraepithelial lymphocyte increase, grade 2 as intraepithelial lymphocyte increase and crypt hyperplasia, grade 3a as partial villous atrophy, grade 3b as subtotal villous atrophy, and grade 3c as total villous atrophy. Grade ≥2 was considered CD (6).

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Research and Application Center (no: 3207, date: 30.03.2021). Written informed consent was obtained from all parents.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 15.0 package program (SPSS Inc, Chicago, Illinois, U.S.A.). The descriptive statistics were given as numbers and percentages for categorical variables and as mean, standard deviation, and median for numerical variables. Repeated measures variance analysis was used in analysis of numerical variables in dependent groups when the differences satisfy normal distribution, and if it was not met, the Friedman test was used. Analysis of subgroups was performed using the Wilcoxon test and interpreted with Bonferroni correction. The rates in the dependent groups were compared using Cochran's Q test. Analysis of subgroups was performed using the McNemar test and interpreted with Bonferroni correction. P<0.05 was considered significant for all results.

RESULTS

The mean age of patients with CD was 7.3±4.4 (range 0-17 years), and the male/female ratio was 0.69. Of the patients, 19.5% were diagnosed at ≤2 years old, 8.2% were 3-4 years old, 42.1% were 5-9 years old, 24.6% were 10-14 years old, and 5.6% were ≥15 years old. The most common complaint at admission was growth retardation (44.6%), followed by diarrhea (29.7%), abdominal pain (21%), and abdominal distention (18.5%). When the complaints at admission were evaluated by age group, it was found that diarrhea (60.5%) and abdominal distention (36.8%) were higher in patients ≤2 years of age than in the other age groups (p<0.001 and p=0.025, respectively). The clinical and demographic characteristics and laboratory findings of the patients according to age groups are shown in Table 1.

68.2% of the patients had typical, 26.2% had atypical, and 5.6% had asymptomatic CD. 10% of asymptomatic CD patients had a family history and were referred to us for screening. 20.5% of the patients had accompanying disease, of which the most common was type 1 diabetes mellitus (3.1%), followed by protein losing enteropathy (2.5%). The most common accompanying genetic diseases were Down syndrome (1%) and Turner syndrome (1%).

When the patients were classified according to height SDSs, no significant difference was observed between height SDSs at diagnosis and 6 months of follow-up (p=0.22). In total, 37.4% of the patients stunted at diagnosis, 33.8% at 6 months of follow-up, 28.7% at 1st year, and 18.5% at 2nd year (Table 2). According to weight SDSs, no statistically significant differences were observed at diagnosis, 6 months, 1st year, and 2nd year of follow-up. As the duration of compliance to GFD increased, the number of patients who were normal and overweight increased and those who were underweight decreased (Table 2). In addition, a significant difference was observed in BMI Z-scores during follow-up (Table 2).

Table 1. The clinical and demographic characteristics, and laboratory findings of the patients with celiac disease according to age groups

	≤2 years (n=38)	3-4 years (n=16)	5-9 years (n=82)	10-14 years (n=48)	≥15 years (n=11)	p-value
Gender (M/F)	0.58 (14/24)	1 (8/8)	0.6 (31/51)	0.7 (21/27)	1.2 (6/5)	0.71
Complaint admission						
Gastrointestinal						
Growth retardation	15 (39.5%)	9 (56.3%)	30 (36.6%)	29 (60.4%)	4 (36.4%)	0.07
Diarrhea	23 (60.5%)	7 (43.8%)	17 (20.7%)	9 (18.8%)	2 (18.2%)	<0.001
Abdominal pain	4 (10.5%)	4 (25%)	20 (24.4%)	11 (22.9%)	2 (18.2%)	0.49
Abdominal distention	14 (36.8%)	3 (18.8%)	12 (14.6%)	6 (12.5%)	1 (9.1%)	0.025
Poor weight gain	6 (15.8%)	3 (18.8%)	12 (14.6%)	4 (8.3%)	1 (9.1%)	0.74
Constipation	3 (7.9%)	2 (12.5%)	13 (15.9%)	5 (10.4%)	-	0.61
Nausea	3 (7.9%)	-	4 (4.9%)	4 (8.3%)	1 (9.1%)	0.68
Poor appetite	2 (5.3%)	1 (6.3%)	7 (8.5%)	-	-	0.22
Vomiting	1 (2.6%)	1 (6.3%)	3 (3.7%)	1 (2.1%)	-	0.82
Extraintestinal						
Refractory anemia	2 (5.3%)	2 (12.5%)	11 (13.4%)	12 (25%)	3 (27.3%)	0.07
Short stature	1 (2.6%)	-	5 (6.1%)	3 (6.3%)	1 (9.1%)	0.73
Fatigue	1 (2.6%)	-	2 (2.4%)	1 (2.1%)	-	1.00
Other	-	-	2 (2.4%)	1 (2.1%)	-	1.00
Screening	1 (2.6%)	-	6 (7.3%)	2 (4.2%)	1 (9.1%)	0.65

Table 1. Continued

	≤2 years (n=38)	3-4 years (n=16)	5-9 years (n=82)	10-14 years (n=48)	≥15 years (n=11)	p-value
Type of disease						
Typical	27 (71.1%)	12 (75%)	52 (63.4%)	35 (72.9%)	7 (63.6%)	0.89
Atypical	10 (26.3%)	4 (25%)	23 (28%)	11 (22.9%)	3 (27.3%)	
Asymptomatic	1 (2.6%)	-	7 (8.5%)	2 (4.2%)	1 (9.1%)	
Marsh classification						
Grade 1	-	-	-	-	-	0.82
Grade 2	4 (10.5%)	-	3 (3.7%)	1 (2.1%)	-	
Grade 3a	10 (26.3%)	3 (18.8%)	19 (23.2%)	10 (20.8%)	4 (36.4%)	
Grade 3b	14 (36.8%)	9 (56.3%)	36 (43.9%)	26 (54.2%)	5 (45.5%)	
Grade 3c	10 (26.3%)	4 (25%)	24 (29.3%)	11 (22.9%)	2 (18.2%)	
Hemoglobin (g/dL)						
Normal	20 (52.6%)	4 (25%)	41 (50%)	24 (50%)	6 (54.5%)	0.39
Low	18 (47.4%)	12 (75%)	41 (50%)	24 (50%)	5 (45.5%)	
Hematocrit (%)						
Normal	21 (55.3%)	4 (25%)	37 (45.1%)	24 (50%)	7 (63.6%)	0.23
Low	17 (44.7%)	12 (75%)	45 (54.9%)	24 (50%)	4 (36.4%)	
MCV						
Normal	25 (65.8%)	8 (50%)	35 (42.7%)	25 (52.1%)	5 (45.5%)	0.22
Low	13 (34.2%)	8 (50%)	47 (57.3%)	23 (47.9%)	6 (54.5%)	
Platelet count						
Normal	22 (57.9%)	10 (62.5%)	54 (65.9%)	45 (93.8%)	10 (90.9%)	<0.001
High	16 (42.1%)	6 (37.5%)	27 (32.9%)	2 (4.2%)	1 (9.1%)	
Low	-	-	1 (1.2%)	1 (1.2%)	-	
Serology						
At diagnosis						
Positive	38 (100%)	16 (100%)	81(98.8%)	47 (97.9%)	11 (100%)	1.00
Negative	-	-	1 (1.2%)	1 (2.1%)	-	
At 6th months						
Positive	23 (60.5%)	11 (68.8%)	57 (69.5%)	36 (75%)	7 (63.7%)	0.69
Negative	15 (39.5%)	5 (31.3%)	25 (30.5%)	12 (25%)	4 (36.4%)	
At 1st year						
Positive	14 (36.8%)	6 (37.5%)	31 (37.8%)	25 (52.1%)	4 (36.4%)	0.52
Negative	24 (63.2%)	10 (62.5%)	51 (62.2%)	23 (47.9%)	7 (63.6%)	
At 2nd year						
Positive	10 (26.3%)	3 (18.8%)	16 (19.5%)	13 (27.1%)	1 (9.1%)	0.62
Negative	28 (73.7%)	13 (81.3%)	66 (80.5%)	35 (72.9%)	10 (90.9%)	

MCV: Mean corpuscular volume, M/F: Male/female
P<0.05 is statistically significant

51.7% of the patients with height <-2 SDS had growth retardation at admission (p<0.001). No significant differences were observed in terms of complaints at admission and height SDSs, except that 40% of the patients who were diagnosed with CD at screening had normal height (p=0.003) (Table 3). When the complaint at diagnosis and weight SDSs were evaluated, it was observed that the patients with growth retardation and diarrhea were mostly wasting and underweight patients (p<0.001, p=0.038, respectively) (Table 4). It was remarkable that the patients with constipation were of normal weight (p=0.03). No statistically significant differences were found between

Table 2. Evaluation of patients' height, weight, and BMI SDS, and laboratory parameters according to compliance to diet

	Diagnosis	6th months	1st year	2nd year	p-value
Height (SDS)					
Stunted (<-2)	73 (37.4%)	66 (33.8%)	56 (28.7%)	36 (18.5%)	<0.001
Short stature (-2 and -1)	51 (26.2%)	51 (26.2%)	48 (24.6%)	56 (28.7%)	
Normal (-1 and 1)	58 (29.7%)	65 (33.3%)	74 (37.9%)	81 (41.5%)	
Tall (1 and 2)	11 (5.6%)	10 (5.1%)	15 (7.7%)	18 (9.2%)	
Very tall (>2)	2 (1%)	3 (1.5%)	2 (1%)	4 (2.1%)	
Weight (SDS)					
Wasting (<-2)	71 (36.4%)	51 (26.2%)	35 (17.9%)	32 (16.4%)	<0.001
Underweight (-2 and -1)	52 (26.7%)	55 (28.2%)	52 (26.7%)	44 (22.6%)	
Normal (-1 and 1)	64 (32.8%)	79 (40.5%)	92 (47.2%)	100 (51.3%)	
Overweight (1 and 2)	7 (3.6%)	9 (4.6%)	15 (7.7%)	18 (9.2%)	
Obese (>2)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	
BMI (SDS)					
Malnutrition (<-2)	36 (18.5%)	12 (6.2%)	13 (6.7)	15 (7.7%)	<0.001
Normal (-2 and 1)	152 (77.9%)	164 (84.1%)	153 (78.5%)	163 (83.6%)	
Overweight (1 and 2)	6 (3.1%)	18 (9.2%)	25 (12.8%)	16 (8.2%)	
Obese (>2)	1 (0.5%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	
Hemoglobin (g/dL)					
Normal	95 (48.7%)	133 (68.2%)	151 (77.4%)	164 (84.1%)	<0.001
Low	100 (51.3%)	62 (31.8%)	44 (22.6%)	31 (15.9%)	
Hematocrit (%)					
Normal	93 (47.7%)	137 (70.3%)	152 (77.9%)	170 (87.2%)	<0.001
Low	102 (52.3%)	58 (29.7%)	43 (22.1%)	25 (12.8%)	
MCV (fL/dL)					
Normal	98 (50.3%)	120 (61.5%)	143 (73.3%)	162 (83%)	<0.001
Low	97 (49.7%)	75 (38.5%)	52 (26.7%)	33 (16.9%)	
Ferritin					
Normal	74 (37.9%)	114 (58.5%)	127 (65.1%)	144 (73.8%)	<0.001
Low	121 (62.1%)	81 (41.5%)	68 (34.9%)	51 (26.2%)	
Vitamin B12					
Normal	192 (98.5%)	193 (99.5%)	194 (99.5%)	194 (99.5%)	0.57
Low	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	
Folic acid					
Normal	174 (89.2%)	189 (96.9%)	194 (99.5%)	193 (99%)	<0.001
Low	21 (10.8%)	6 (3.1%)	1 (0.5%)	2 (1%)	

BMI: Body mass index, MCV: Mean corpuscular volume, SDS: Standard deviation score
P<0.05 is statistically significant

other complaints at diagnosis and weight SDSs (p<0.05) (Table 4).

51.3% of the patients had Hb levels lower than the reference range according to age and 50.3% of the patients had mean corpuscular volume (MCV) levels lower than the reference range according to age. 26.7% had thrombocytosis, whereas only two patients had thrombocytopenia. 42.1% of the patients ≤2 years of age had thrombocytosis (p<0.001).

The comparison of Hb, MCV, and platelet counts according to age groups is shown in Table 1 and according to follow-up periods in Table 2. When the patients with low ferritin at diagnosis evaluated, a significant decrease in the number of patients was observed during follow-up (p<0.001) (Table 2).

None of the patients had an IgA deficiency. It was found to be statistically significant that the number of patients with positive serology started to decrease and became

Table 3. Comparison of complaints at admissions according to height SDS

	Stunted (<-2 SDS)	Short stature (-2 and -1 SDS)	Normal (-1 and 1 SDS)	Tall (1 and 2 SDS)	Very tall (>2 SDS)	p-value
Gastrointestinal						
Growth retardation						
No	28 (25.9%)	24 (22.2%)	44 (40.7%)	10 (9.3%)	2 (1.9%)	<0.001
Yes	45 (51.7%)	27 (31%)	14 (16.1%)	1 (1.1%)	-	
Diarrhea						
No	49 (35.8%)	32 (23.4%)	47 (34.3%)	7 (5.1%)	2 (1.5%)	0.19
Yes	24 (41.4%)	19 (32.8%)	11 (19%)	4 (6.9%)	-	
Abdominal pain						
No	62 (40.3%)	39 (25.3%)	42 (27.3%)	10 (6.5%)	1 (0.6%)	0.22
Yes	11 (26.8%)	12 (29.3%)	16 (39%)	1 (2.4%)	1 (2.4%)	
Abdominal distention						
No	59 (37.1%)	41 (25.8%)	46 (28.9%)	11 (6.9%)	2 (1.3%)	0.6
Yes	14 (38.9%)	10 (27.8%)	12 (33.3%)	-	-	
Poor weight gain						
No	65 (38.5%)	43 (25.4%)	49 (29%)	10 (5.9%)	2 (1.2%)	0.87
Yes	8 (30.8%)	8 (30.8%)	9 (34.6%)	1 (3.8%)	-	
Constipation						
No	67 (39%)	47 (27.3%)	49 (28.5%)	8 (4.7%)	1 (0.6%)	0.08
Yes	6 (26.1%)	4 (17.4%)	9 (39.1%)	3 (13%)	1 (4.3%)	
Nausea						
No	69 (37.7%)	46 (25.1%)	56 (30.6%)	10 (5.5%)	2 (1.1%)	0.51
Yes	4 (33.3%)	5 (41.7%)	2 (16.7%)	1 (8.3%)	-	
Poor appetite						
No	71 (38.4%)	47 (25.4%)	56 (30.3%)	9 (4.9%)	2 (1.1%)	0.18
Yes	2 (20%)	4 (40%)	2 (20%)	2 (20%)	-	
Vomiting						
No	69 (36.5%)	50 (26.5%)	58 (30.7%)	10 (5.3%)	2 (1.1%)	0.17
Yes	4 (66.7%)	1 (16.7%)	-	1 (16.7%)	-	
Extraintestinal						
Refractory anemia						
No	64 (38.8%)	41 (24.8%)	48 (29.1%)	10 (6.1%)	2 (1.2%)	0.77
Yes	9 (30%)	10 (33.3%)	10 (33.3%)	1 (3.3%)	-	
Short stature						
No	69 (37.3%)	49 (26.5%)	55 (29.7%)	10 (5.4%)	2 (1.1%)	0.8
Yes	4 (40%)	2 (20%)	3 (30%)	1 (10%)	-	
Fatigue						
No	71 (37.2%)	50 (26.2%)	58 (30.4%)	10 (5.2%)	2 (1%)	0.22
Yes	2 (50%)	1 (25%)	-	1 (25%)	-	
Other						
No	72 (37.5%)	51 (26.6%)	56 (29.2%)	11 (5.7%)	2 (1%	0.58
Yes	1 (33.3%)	-	2 (66.7%)	-	-	
Screening						
No	71 (38.4%)	51 (27.6%)	53 (28.6%)	9 (4.9%)	1 (0.5%)	0.004
Yes	2 (20%)	-	5 (50%)	2 (20%)	1 (10%)	

SDS: Standard deviation score, p<0.05 is statistically significant

Table 4. Comparison of complaints at admissions according to weight SDS

	Wasting (<-2 SDS)	Underweight (-2 and -1 SDS)	Normal (-1 and 1 SDS)	Overweight (1 and 2 SDS	Obese (>2 SDS)	p-value
Gastrointestinal						
Growth retardation						
No	28	23 (21.3%)	50 (46.3%)	6 (5.6%)	1 (0.9%)	<0.001
Yes	43 (25.9%)	29 (33.3%)	14 (16.1%)	1 (1.1%)	-	
Diarrhea						
No	41(29.9%)	42 (30.7%)	47(34.3%)	6 (4.4%)	1 (0.7%)	0.038
Yes	30 (51.7%)	10 (17.2%)	17 (29.3%)	1 (1.7%)	-	
Abdominal pain						
No	60 (39%)	40 (26%)	49 (31.8%)	4 (2.6%)	1 (0.6%)	0.36
Yes	11 (26.8%)	12 (29.3)	15 (36.6%)	3 (7.3%)	-	
Abdominal distention						
No	54 (34%)	48 (30.2%)	49 (30.8%)	7 (4.4%)	1 (0.6%)	0.06
Yes	17 (47.2%)	4 (11.1%)	15 (41.7%)	-	-	
Poor weight gain						
No	63 (37.3%)	44 (26%)	54 (32%)	7 (4.1%)	1 (0.6%)	0.80
Yes	8 (30.8%)	8 (30.8%)	10 (38.5%)	-	-	
Constipation						
No	68 (39.5%)	46 (26.7%)	52 (30.2%)	5 (2.9%)	1 (0.6%)	0.03
Yes	3 (13%)	6 (26.1%)	12 (52.2%)	2 (8.7%)	-	
Nausea						
No	68 (37.2%)	49 (26.8%)	58 (31.7%)	7 (3.8%)	1 (0.5%)	0.67
Yes	3 (25%)	3 (25%)	6 (50%)	-	-	
Poor appetite						
No	68 (36.8%)	47 (25.4%)	63 (34.1%)	6 (3.2%)	1 (0.5%)	0.16
Yes	3 (30%)	5 (50%)	1 (10%)	1 (10%)	-	
Vomiting						
No	69 (36.5%)	49 (25.9%)	63 (33.3%)	7 (3.7%)	1 (0.5%)	0.63
Yes	2 (33.3%)	3 (50%)	1 (16.7%)	-	-	
Extraintestinal						
Refractory anemia						
No	60 (36.4%)	44 (26.7%)	53 (32.1%)	7 (4.2%)	1 (0.6%)	0.90
Yes	11 (36.7%)	8 (26.7%)	11 (36.7%)	-	-	
Short stature						
No	66 (35.7%)	50 (27%)	61 (33%)	7 (3.8%)	1 (0.5%)	0.85
Yes	5 (50%)	2 (20%)	3 (30%)	-	-	
Fatigue						
No	69 (36.1%)	51 (26.7%)	63 (33%)	7 (3.7%)	1 (0.5%)	1.00
Yes	2 (50%)	1 (25%)	1 (25%)	-	-	
Other						
No	71 (37%)	52 (27.1%)	61 (31.8%)	7 (3.6%)	1 (0.5%)	0.17
Yes	-	-	3 (100%)	-	-	
Screening						
No	70 (37.8%)	50 (27%)	60 (32.4%)	5 (2.7%)	-	
Yes	1 (10%)	2 (20%)	4 (40%)	2 (20%)	1 (10%)	0.003

SDS: Standard deviation score, p<0.05 is statistically significant

negative related with the compliance to diet during follow-up ($p<0.001$). Although the rate of patients with negative serology increased among age groups, the difference was not statistically significant (Table 2). Serology did not differ by gender and laboratory parameters such as Hb, hematocrit, MCV, and vitamin B12 levels at the time of diagnosis, 6 months, 1st year, and 2nd year ($p>0.05$), except for ferritin and folic acid levels. Ferritin levels at 6 months were significantly lower in patients with positive serology than in those with negative serology ($p=0.047$), and normal levels were higher in patients with negative serology at 1 year ($p=0.03$). In patients with negative serology, folic acid levels were significantly within normal limits at the 2nd year ($p=0.048$).

HLA typing was performed in 111 patients and revealed that 58.6% of those had HLA DQ2, 20.7% had HLA DQ8, 10.8% had both HLA DQ2 and HLA DQ8 positivity, and only 9.9% had both HLA DQ2 and HLA DQ8 negativity. No significant differences were observed, except that asymptomatic patients diagnosed during screening had higher positivity for both HLA DQ2 and HLA DQ8 compared with the other HLA groups ($p=0.01$).

DISCUSSION

In recent studies on CD, it has been reported that the mean age of the patients at diagnosis was increased (7-9). Similarly, the mean age of our patients was 7.3±4.4 years and 42% of those patients were 5-9 years of age. Increased age at diagnosis is thought to be due to increased awareness of the disease, widespread screening, and earlier diagnosis of patients presenting with atypical symptoms.

Similar to other studies (7,9) reporting female predominance (67% and 68.6%, respectively), 58.9% of the patients were girls in our study. CD is more common in females because autoimmune diseases are more common in females, they have more hospital admissions and examinations, and they are more symptomatic than males (10). We found no significant difference in gender according to age groups, similar to the study by Tanpowpong et al. (11).

A family history of CD was found in 6.9% and 18% of the patients in the studies of Oliveira et al. (9) and Stone et al. (8), respectively. In total, 8.7% of our patients had a family history. Oliveira et al. (9) reported that the most common presenting symptom was abdominal pain, followed by diarrhea, growth retardation, and abdominal distention. They also observed that diarrhea and abdominal distention were significantly more common in patients younger than 5 years and abdominal pain in children older than 5 years (9). Van Kalleveen et al. (7) reported that abdominal distention (72.1%), growth retardation (60.5%), and diarrhea (48.8%) among 0-3 years of age, abdominal pain (37.2%), fatigue (36%), and short stature (22%) among 4-12 years of ages, abdominal pain (83.3%) among patients older than 12 years of age were the most common when the symptoms were evaluated according to age groups. In our study, the most common presenting symptom was growth retardation (44.6%), followed by diarrhea (29.7%), and abdominal pain (21%). Although growth failure and diarrhea were common in our children ≤2 years, similar to the literature, our study differed from those studies in that the most common symptoms were atypical symptoms such as refractory anemia and short stature as age increased. It has been shown that long-term breastfeeding, addition of very small amounts of gluten-containing foods to the diet <12 months, and continuation of breast milk when starting to give foods containing gluten reduce the risk of developing CD in children <2 years (12). Breastfeeding was not questioned in our study.

The most common type of disease was the classical type in our study, consistent with other studies (9,13). It has been reported that most of the patients had Marsh 3 classification in their histopathological examination in studies conducted by Ziv-Baran et al. (14), Vivas et al. (15), and Oliveira et al. (9). Tanpowpong et al. (11) reported that villous atrophy is more common between 0 and 5 years of age. In our study, histopathological examinations of the patients revealed Marsh grade 3, but no statistically significant difference was obtained according to age groups, similar to the study of Vivas et al. (15).

Sansotta et al. (16) evaluated the relationship between anthropometric measurements of CD patients at diagnosis and during follow-up and response to GFD. They observed that both height and weight SDSs measured at follow-ups after starting the diet significantly increased; however, the increase in BMI did not make a statistical difference. Więch et al. (17) reported a significant difference only in weight SDSs and not in height and BMI SDSs. They observed that the increase in height was higher in patients compliant with GFD than in the uncompliant group, but the difference was not significant, whereas the difference in weight gain was statistically significant between these groups. In our study, both height and weight SDSs were found to be increased during follow-up in patients compliant with GFD, and increased numbers of normal weight and overweight children were observed.

It has been stated that the best way to evaluate the developmental delay of patients following a GFD is by BMI (18,19). Valletta et al. (18) compared BMI Z-scores at

the time of diagnosis and 1 year after starting GFD and found that the number of overweight children significantly increased with compliance to GFD (11% to 21%). Cheng et al. (19) reported that 66% of their patients on GFD who were underweight gained weight, whereas 54% of overweight and 47% of obese patients lost weight. In our study, the number of malnourished patients decreased, and the number of normal weight and overweight patients increased while on GFD. Although the number of obese patients in our study did not change, it should be noted that the number of overweight and obese patients increased immediately both at diagnosis and with dietary compliance (18,19).

Abnormalities in platelet counts have been reported to be secondary to iron deficiency anemia, hyposplenism, and/or inflammatory mediators (20). Thrombocytosis is more common than thrombocytopenia and is normalized with GFD (20). Bansal et al. (21) and Çatal et al. (22) reported that 33% and 16.5% of their patients had thrombocytosis, respectively, and stated a significant improvement in thrombocytosis with GFD. It was remarkable that a significant difference was observed in thrombocytosis among the age groups in our study, especially ≤2 years of age.

It has been reported that iron deficiency anemia is common in CD patients and may sometimes be the only presenting symptom of the disease. Additionally, Hb levels may not be normal for up to 1 year and iron stores are low for up to 2 years despite GFD and iron supplementation (23). Although we observed that ferritin levels increased as the duration of compliance to GFD was prolonged, especially in the 6th month-2nd year of follow-up, it was not statistically significant. Ferritin levels were low in 34.9% of the patients in the first year and 26.2% of our patients in the second year of follow-up.

Vitamin and mineral deficiencies have been reported to decrease with compliance with GFD (24). In our study, vitamin B12 deficiency was detected in only three patients at the time of diagnosis. Folate deficiency was higher and its decrease with GFD was consistent with the literature.

Histopathological recovery of CD is faster in children than in adults, with a complete recovery rate of 88-96% over 2 years (25). In our study, it was determined that 31% of the patients on GFD at 6 months, 58.9% at 1st year, and 77.9% at 2nd year of follow-up had negative serology, consistent with the study conducted by Gidrewicz et al. (26). No significant differences were obtained in serological results between age groups in our study, which may be due to unequal distribution of patients and non-standardized serological parameters among patients.

It has been reported that most patients with CD have HLA DQ2 positivity, followed by HLA DQ8 (9,27). The rates of both HLA DQ2 and HLA DQ8 positivity were reported to be 11% and 42.9%, respectively (9,27). Similarly, 58.6% of our patients had HLA DQ2 positivity. HLA tissue typing has a high negative predictive value (28). However, 9.9% of our patients, those who had tissue transglutaminase levels at least 10 times higher and Marsh 2 and 3 (a, b, c) grades, were negative for both HLA DQ2 and HLA DQ8, a higher rate than that reported in the literature. It has been stated that the disease has a more serious course in HLA DQ2-positive patients than in DQ8-positive patients; even DQ2.5 homozygous alleles had clinically more severe disease, serological titers, and Marsh classification than the other alleles (27,29,30). No statistically significant differences were obtained between HLA typing and Marsh grades according to age groups in our study, which may be related to the lower number of HLA DQ2-positive patients than in other studies.

The limitations of this study were being a single-center retrospective study, unavailability of determining HLA alleles, and non-standardized serological parameters among patients.

CONCLUSION

In conclusion, we observed an increase in the number of patients diagnosed at older ages with atypical symptoms. As the duration of compliance to GFD increases, the number of overweight patients increases and the normalization of anthropometric measurements. Therefore, early diagnosis of CD and maintenance of compliance with GFD are essential because of gradual improvement in both laboratory and anthropometric measurements observed in patients compliant with GFD.

ETHICS

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Research and Application Center (no: 3207, date: 30.03.2021).

Informed Consent: Written informed consent was obtained from all parents.

Authorship Contributions

Surgical and Medical Practices: B.Ö.A., N.U., M.U., D.G., Concept: B.Ö.A., N.U., Design: B.Ö.A., N.U., Data Collection or Processing: B.Ö.A., N.U., M.U., D.G., Analysis or Interpretation: B.Ö.A., N.U., M.U., D.G., Literature Search: B.Ö.A., N.U., Writing: B.Ö.A., N.U.

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