Research Article / Araştırma Makalesi

Celiac Disease Among Preschool Children: A Retrospective Analysis

Okul Öncesi Çocuklarda Çölyak Hastalığı: Retrospektif Bir Analiz

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Abstract

Background: The aim of this study is to evaluate the medical parameters of celiac disease cases in the preschool age group in terms of public health and to make recommendations to health professionals, policy makers and the society.
Materials and Methods: This study was conducted between February 2017 and December 2018 in Şanlıurfa Education and Research Hospital, Pediatric Gastroenterology Clinic. Clinical and laboratory findings of preschool children diagnosed with celiac disease were retrospectively analyzed. Anamnesis, physical examination findings, laboratory findings, endoscopic biopsies and pathology results of patients were evaluated.
Results: The most common presenting complaint was growth retardation (96.3%), followed by chronic diarrhea (32.5%) and constipation (27.5%). Height-for-age and weight-for-age values were found to be lower in patients with chronic diarrhea and duodenitis compared to those without ($p<0.05$). Patients with strong positive tissue transglutaminase-IgA (tTG IgA) levels had significantly higher Marsh scores ($p<0.05$).
Conclusions: For preschool-age children, initiating the diet via early diagnosis and ensuring adherence to diet are the main objectives. Children adhering to the diet have a higher success in elementary school and a shorter adaptation period.

Key Words: Child, Celiac disease, Malnutrition, Clinic

Öz

Amaç: Bu çalışmanın amacı, okul öncesi yaş grubundaki çölyak hastalığı vakalarının tıbbi parametrelerini halk sağlığı açısından değerlendirmek ve sağlık profesyonellerine, politika yapıcılara ve topluma önerilerde bulunmaktır.
Materyal ve Metod: Bu çalışma Şubat 2017-Aralık 2018 tarihleri arasında Şanlıurfa Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Kliniği'nde yapıldı. Çölyak hastalığı tanısı konan okul öncesi çocukların klinik ve laboratuvar bulguları geriye dönük olarak incelendi. Hastaların anamnezleri, fizik muayene bulguları, laboratuvar bulguları, endoskopik biyopsileri ve patoloji sonuçları değerlendirildi.
Bulgular: En sık başvuru şikayeti gelişme geriliği (%96.3) olup, bunu kronik ishal (%32.5) ve kabızlık (%27.5) izlemektedir. Kronik ishali ve duodeniti olanlarda, olmayanlara göre yaşa göre boy ve yaşa göre ağırlık değerleri daha düşük bulunmuştur (p<0.05). Güçlü pozitif doku transglutaminaz-IgA (tTG IgA) düzeylerine sahip hastaların Marsh skorları anlamlı olarak daha yüksek tespit edilmiştir (p<0.05).
Sonuç: Okul öncesi çağındaki çocuklarda erken tanı ile diyete başlanması ve diyete uyumun sağlanması temel hedeflerdir. Diyete bağlı kalan çocukların ilkokulda başarıları daha yüksek ve uyum süreleri daha kısadır.

Anahtar Kelimeler: Çocuk, Çölyak hastalığı, Malnütrisyon, Klinik

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Introduction

Celiac disease develops as a result of the damage in the mucosa of the small intestine after the autoimmune inflammation following the gluten intake of individuals having genetic susceptibility. Recovery is observed in the small intestine mucosa and symptoms after the gluten-free diet treatment (1).

Celiac disease is a chronic disease and its prevalence is reported to vary between 0.5 and 1% throughout the world (2). Girls are affected twice as boys are (3). Its lower prevalence in developing countries might be related to the limited use of diagnostic tests (4). However, its prevalence rapidly increases in the countries, where the level of consciousness is high and the use of scanning test (5).

Most of the patients have minimum of 1 of Human Leukocyte Antigen (HLA) DQ2/DQ8 alleles (4). It was reported that celiac disease is observed more frequently among those having celiac disease history of first-degree relatives and those having conditions such as immunoglobulin A (IgA) deficiency, autoimmune thyroiditis, and type 1 diabetes mellitus (DM) (6).

Clinical findings range in a wide spectrum from asymptomatic disease to severe malnutrition and celiac attack. The most common (typical) symptoms among children include stomachache, diarrhea, flatulence, constipation, weight loss, and developmental retardation (7). Atypical symptoms are mode commonly seen among adults. Atypical symptoms include osteoporosis, dermatitis herpetiformis, exhaustion, anemia, short stature, delayed puberty, and moderately high level of liver enzymes (6).

Celiac disease diagnosis has 99% sensitivity to the tissue transglutaminase IgA (tTG IgA) antibody level (7). Small intestine biopsy is still considered as the golden standard for the diagnosis (6).

In the present study, anthropometric, clinical, and laboratory findings of pediatric cases diagnosed within 2-year period in a tertiary healthcare facility in the Southeastern Anatolian region, where celiac disease is widely seen in Turkey, and the pathological results of endoscopic biopsies were retrospectively examined. It was aimed to offer suggestions to healthcare professionals, policymakers, and society regarding the medical, sociological, and cultural approaches to celiac disease from the aspect of public health perspective, as well as raising awareness.

Materials and Methods

Study design and subjects

In the present study having a descriptive and cross-sectional design, anthropometric, clinical, and laboratory findings of 80 preschool (0-6 years of age) pediatric cases, who were diagnosed with celiac disease between February 2017 and December 2018 in Pediatric Gastroenterology Department of Şanlıurfa Training and Research Hospital, and the pathological results of endoscopic biopsies were retrospectively examined. The patients, who were diagnosed with celiac disease in another medical facility before and started receiving diet therapy, were excluded from the study (11 patients).

Data collection

The files of cases were retrospectively examined and their ages, genders, clinical findings at the moment of application, comorbidities, laboratory results, endoscopic findings, and anthropometric measurement results were recorded in case record form. Using the body height and weight data, body weight and body z scores, weigh-at-age (WAA), height-at-age (HAA), weight-for-height (WFH), and body mass index (BMI) values were calculated. The data obtained were analyzed according to the Gomez and Waterlow classifications. According to Gomez classification, the ones having WAA values between 90 and 110% were classified as normal, those having WAA values between 75 and 89% as mild malnutrition, those having WAA values between 60 and 74% as moderate malnutrition, and those having WAA values below 60% as severe malnutrition. According to Waterlow classification, those with WFH levels lower than 90% and HAA levels higher than 95% were classified as acute malnutrition (thin), whereas the cases with WFH levels higher than 90% and HAA levels lower than 95% were defined as chronic malnutrition (short) and those having WFH levels lower than 90% and HAA values lower than 95% as acute malnutrition (thin and short) (8, 9). The tissue transglutaminase Ig A (tTG IgA) levels of 100 IU/ml and higher were accepted to be strong positivity. The endoscopic assessments and histological findings of the cases were classified according to Marsh classification.

Ethical Approval and Permissions

Before the study, the ethics committee approval was obtained from Fırat University's Non-Interventional Researches Ethics Committee (Date: 07.19.2018, No: 13/13) and the necessary administrative permissions were obtained from the Chief Physician of Şanlıurfa Training and Research Hospital. All the procedures were conducted in compliance with Helsinki Declaration and ethical standards of our institution's human experiment committee.

Statistical Analysis

The data obtained were analyzed statistically using IBM SPSS Statistics v.22.0 (IBM Corp.; Armonk, NY, USA) package program. In statistical analyses, continuous variables were analyzed using mean ± standard deviation or median, whereas nominal variables were analyzed using numbers and percentages. The normality of continuous variables' distribution was tested using the Kolmogorov-Smirnov test, normal distribution diagrams, skewness, and kurtosis coefficients. The significance of difference regarding the continuous variables was tested using independent sample t-test, while the relationship between categorical variables was examined using

the Chi-Square test. The degree and direction of the relationship between two numerical variables were determined using Pearson's correlation analysis. Statistical significance was set at $p<0.05$.

Results

Of 80 cases involved in the present study, 43 (53.8%) were girls and 37 (46.2%) were boys. The mean age was found to be 4.1±1.5 (min: 1, max: 6) years (Table 1). Mean age of girls was 4.0±1.4 years and that of boys was 4.2±1.6 years.

Table 1. Demographic and anthropometric characteristics of subjects

Characteristics	n (%)
Gender	
Boys	37 (46.2)
Girls	43 (53.8)
Mean age ± SD (min-max) (years)	4.1 ± 1.5 (1-6)
Mean height ± SD (cm)	98.9 ± 15.7
Mean weight ± SD (kg)	14.5 ± 4.1
Mean height-at-age ± SD (%)	95.7 ± 7.6
Mean weight-at-age ± SD (%)	85.2 ± 12.7
Weight-for-height ± SD (%)	95.4 ±10.9
BMI ± SD (kg/m^2)	14.7 ± 1.9

***SD**: Standard deviation, **BMI**: Body mass index*

Among the cases, the most common complaint for application was developmental retardation (96.3%), followed by chronic diarrhea (32.5%) and constipation (27.5%). As a result of the endoscopic examination, the vast majority of patients were found to have duodenitis (93.8%) and gastritis (68.8%) (Table 2). Two (2.5%) of cases were found to have Type 1 Diabetes mellitus, 1 (1.2%) case was found to have Ig A deficiency, 1 (1.2%) case was found to have epilepsy, 1 (1.2%) case was found to have multiple food allergies, and 1 (1.2%) case was found to have Pica history.

Examining the effect of complaints at the moment of diagnosis on the anthropometric measurements, it was found that the cases with chronic diarrhea were found to have lower HAA levels in comparison to those having none (88.9±7.1 and 95.6±6.2, respectively, $p=0.006$). Examining the effect of endoscopic examination on anthropometric measurements, it was found that the cases with duodenitis had lower WAA levels in comparison to those not having (79.2±16.5 and 85.6±12.4, respectively, $p=0.045$). Given the laboratory findings of patients, it was determined that 11 cases (13.8%) had anemia, 1 case (1.2%) had leukocytosis, 6 cases (7.5%) had leukopenia, and 8 cases (10) had a high level of transaminase.

Table 2. Complaints and endoscopic findings of cases

Complaints	n (%)
Developmental retardation	77 (96.3)
Chronic diarrhea	26 (32.5)
Constipation	22 (27.5)
Stomachache	6 (7.5)
Vomiting	4 (5.0)
Nausea	2 (2.5)
Familial history	6 (7.5)
Findings	
Duodenitis	75 (93.8)
Gastritis	55 (68.8)
Esophagitis	4 (5.0)
Nodularity	3 (3.8)
Irregularity in duodenum	2 (2.5)

Examining the patients classified by Marsh classification, no relationship with age was observed. However, it was also determined that the patients with strong positive tTG IgA level had higher Marsh scores ($p<0.05$) (Table 3).

Age, height, and weight of cases were found to have a positive and significant relationship with hemoglobin (HG) and hematocrit (HCT) values ($p<0.05$). These parameters were found to have a negative and significant relationship with white blood cells (WBC), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels. Besides that, tTG IgA was found to have negative relationships with HG, HTC, and red blood cell count (RBC) (Table 4).

Examining the malnutrition grades by the Gomez classification, it was determined that 36 (45.0%) of cases had mild malnutrition, 16 (20.0%) had moderate malnutrition, and 1 (1.2%) had severe malnutrition. Considering the Waterlow classification, 12 (15.0%) cases were classified as acute malnutrition (weak), 29 (36.25%) cases as chronic malnutrition (short), and 10 (12.5%) cases as chronic acute malnutrition (short-weak) (Table 5).

Table 3. Distribution of Marsh classes by the age groups and strong positive tTG IgA levels of cases

	Marsh Classification, n (%)			
	Marsh 2	**Marsh 3a**	**Marsh 3b**	**Marsh 3c**
Age groups				
1-2 years of age	0	6 (40)	8 (53.3)	1 (6.7)
3-4 years of age	0	15 (46.9)	16 (50)	1 (3.1)
5-6 years of age	2 (6.1)	15 (45.5)	14 (42.4)	2 (6)
χ^2=3.669, p=0.721				
tTG IgA Level (IU/mL)				
<100 IU/mL	1 (50.0)	1 (2.8)	1 (2.6)	0 (0.0)
≥100 IU/mL	1 (50.0)	35 (97.2)	37 (97.4)	4 (100)
χ^2=12.235, p=0.007				

***tTG IgA:** Tissue transglutaminase Ig A*

Table 4. Correlation between laboratory results and ages and anthropometric measurements of cases

	Age (years)	Height (cm)	Weight (kg)	tTG IgA level (IU/ml)
HG (g/dl)	0.38 (0.001)†	0.34 (0.002)†	0.39 (0.001)†	-0.23 (0.039)*
HCT (%)	0.30 (0.006)†	0.28 (0.010)†	0.32 (0.004)†	-0.20 (0.072)
RBC (10^6/µL)	0.01 (0.922)	0.08 (0.449)	0.09 (0.399)	-0.15 (0.180)
WBC (K/mm3)	-0.12 (0.275)	-0.20 (0.063)	-0.20 (0.065)	0.03 (0.772)
ALT (IU/L)	-0.12 (0.254)	-0.12 (0.262)	-0.21 (0.060)	0.12 (0.269)
AST (IU/L)	-0.17 (0.129)	-0.23 (0.039)	-0.22 (0.042)*	0.05 (0.601)
MPV (fL)	0.07 (0.503)	0.08 (0.431)	0.14 (0.215)	-0.16 (0.133)

*The correlation coefficient was expressed as **r (p),** *p<0.05, †p<0.01, **HG**: Hemoglobin, **HCT:** Hematocrit, **RBC:** red blood cell count, **WBC:** White blood cell count, **MPV:** Mean platelet volume, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase*

Table 5. Classification of malnutrition among cases

Gomez Classification	**WAA (%), n (%)**	
Normal	27 (33.8)	
Mild malnutrition	36 (45.0)	
Moderate malnutrition	16 (20.0)	
Severe malnutrition	1 (1.2)	
Waterlow Classification	**HAA (%), n (%)**	
WFH (%)	**>95%**	**<95%**
>%90	29 (36.25)	29 (36.25)
<%90	12 (15.0)	10 (12.5)

WAA: weight-at-age, WFH: weight for height, HAA: height-at-age

Discussion

Celiac disease is more frequently seen among girls (3). Of 80 cases involved in the present study, 53.8% were girls. In the previous studies carried out in Turkey, it was determined that the share of girls among the cases with celiac disease was higher (10-13). The same also applies to studies throughout the world (2,14-17).

In the present study, the most common complaint at the moment of application of cases diagnosed with celiac disease was developmental retardation (96.3%). Given the studies carried out on this subject in Turkey, it can be seen that the most prominent complaint of children having celiac disease at the moment of application to polyclinic is the other gastrointestinal system complaints accompanying the developmental retardation (10, 11, 13, 18-20). Examining the studies carried out on this subject outside Turkey, the most prominent clinical reflections of celiac disease among the children with celiac disease were reported to be growth and development retardations (16, 17, 21). Celiac disease must be taken into account for the differential diagnosis of children applying to the polyclinic with developmental retardation or found to have developmental retardation during the physical examination. Especially for preschool children, early beginning diagnosis and initiating the therapy and rehabilitation process after the diagnosis in the early period are very important for the biopsychosocial development of individuals.

Chronic diarrhea, which has a predisposing effect in terms of development and growth in celiac disease, was found in 32.5% of the cases involved in the present study. In previous studies carried out in Turkey, chronic diarrhea complaint was reported in 20.9-78.0% of children diagnosed with celiac disease (10, 12, 13). In previous studies carried out in Holland (16) and Italy (17), the prevalence of chronic diarrhea among the children found to have celiac disease was reported to be 28.6% and 16.7%, respectively. In a study carried out on children with chronic diarrhea in Iran, the prevalence of celiac disease was reported to be 6.5% (22). Chronic diarrhea is one of the classical symptoms of celiac disease. Malnutrition may develop as a result of chronic disease in case of any delay in diagnosis of celiac disease (23). In the present study, when compared to the cases with no chronic diarrhea, the HAA levels of cases with chronic diarrhea were reported to be statistically significantly lower (p<0.05. Low HAA levels of cases may originate from malnutrition due to chronic diarrhea arising from the late diagnosis. Malnutrition is a reason for death in 60.7% of children with diarrhea, 53.2% of children with pneumonia, 44.8% of children with measles, and 57.3% of children with malaria worldwide (24). This finding indicates that diarrhea continuing for a long time is one of the important of malnutrition that should be investigated (25).

Since the symptoms and signs of celiac disease may significantly vary, it should be noted that patients may apply with constipation rather than diarrhea. Constipation is one of the most frequently seen symptoms among celiac patients. The prolongation of orocecal transition time due to a motor function disorder of the upper gastrointestinal system is thought to be the reason for constipation seen in celiac disease (26). In the present study, constipation complaint was detected in one-third of cases diagnosed with celiac disease. Given the studies carried out on this subject, the prevalence of constipation complaint was reported to vary between 0.0% and 21.3% (10, 12, 13, 18-20).

Other typical findings among celiac disease include stomachache and vomiting-nausea. Among the cases involved in the present study, the prevalence of stomachache and vomiting-nausea was found to be 7.5%. In a previous study examining the clinical presentation of celiac disease, it was reported that 12.8% of cases applied to the polyclinic for stomachache and 1.4% for vomiting-nausea at the moment of diagnosis (12). In case of a clinical presentation coursing with complaints such as loss of appetite, stomachache, and vomiting-nausea, loss of weight, developmental retardation, or severe malnutrition may develop as a result of any delay in diagnosis especially for breastfeeding children or toddlers.

Genetic susceptibility is of significant importance in the etiopathogenesis of celiac disease and its prevalence among first-degree relatives is approx. 10% (27). In the present study, celiac-positive familial history was found 6 of 80 cases (7.5%). In the previous studies carried out in different provinces and different samples in Turkey, the same parameter was reported to vary between 3.4% and 6.4% (10, 12, 28). In a study carried out in Italy (29), the prevalence of celiac disease among the first-degree relatives of children having celiac disease was reported to be 9.5%. In a study carried out by Farre et al. (30) in Spain, the rate of celiac disease among the cases having a positive familial history of celiac was reported to be 5.5%. This rate was reported to be 4.8% by Almeida et al. (31) for Brazil, 11.0% by Rubio-Tapia et al. (32) for the USA, and 7.7% by Dehbozorgi et al. (33) for Iran. Especially for the cases thought to have celiac disease, considering the familial history of celiac may facilitate the decision-making process in terms of early diagnosis.

Celiac disease may co-exist with other autoimmune dişe ases. In a clinical research carried out on the children having Type-1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, selective Ig A deficiency, or autoimmune liver disease, even if they are found to be asymptomatic in clinical examinations, they should be examined by considering that they have a higher risk of celiac disease in comparison to the healthy population (34). Regarding this subject, Type-1 diabetes mellitus was found in 2 (2.5%) of cases and IgA was found in 1 case (1.2%) from their previous medical records and the examinations investigating the celiac disease were expanded.

Malnutrition is one of the most important complications of celiac disease leading to mortality and morbidity. In a previous study carried out on this subject, preschool children diagnosed with celiac disease were classified using the classification of Gomez, and 45.0% were found to have mild malnutrition, 20.0% were found to have moderate malnutrition, and 1.2% of cases were found to have severe malnutrition. Using the Waterlow classification, 15.0% of cases were found to have acute malnutrition, 36.3% were found to have chronic malnutrition, and 12.5% were found to have chronic acute malnutrition. Regardless of all the indicators, the nutritional statuses of these pediatric cases with continuing biological, psychological, and sociological development show a negative presentation at the moment of diagnosis. Given the previous studies carried out on this subject in İzmir, Soylu et al. (11) reported that 68.0% of children diagnosed with celiac disease were thin and 76.0% were found to be short. Emiroğlu et al. (19), in their mono-center study carried out on children diagnosed with celiac disease in Konya province, reported 35.0% of cases to have mild malnutrition, 20.0% to have moderate malnutrition, and 3.8% to have severe malnutrition. In another study carried out in India (35), severe acute malnutrition was reported in 14.4% of children having celiac disease. In a study carried out by Setavand et al. (36) in Iran, authors reported malnutrition in 28.8% of children diagnosed with celiac disease. Nutritional statuses of children, who were diagnosed with celiac disease, at the moment of diagnosis and during the follow-up period are not at the desired level. Low level of health literacy, socioeconomic variables, difficulties in access to healthcare services, cultural approaches related with geographical differences, and other environmental factors may be the main factors explaining this condition.

In celiac disease, the prevalence of iron deficiency increases and this condition is in correlation with the severity of damage in the intestinal mucosa (37). The prevalence and severity of malnutrition increase with increasing severity of damage in intestinal mucosa. Examining this subject, a positive and significant relationship was found between age, height, and weight of cases and hemoglobin and hematocrit levels (p<0.05). Moreover, it was reported that there was a positive correlation between the severity of damage in intestinal mucosa and the level of serum tTG IgA (38). In this study, it was found that the patients having strong positive tTG IgA levels had significantly higher Marsh scores (p<0.05). During the endoscopic examinations in the present study, 93.8% of cases were found to have duodenitis. Examining the effect of endoscopic examination on the anthropometric measurements, WAA levels of cases with duodenitis were found to be lower in comparison to those having no duodenitis. The deterioration in absorbance surfaces due to the damage in intestinal mucosa and the consequent chronic diarrhea are the main reasons of this condition (39).

In conclusion, among the cases involved in the present study, the most common complaint for applying to the clinic was found to be developmental retardation and they were found to have poor nutritional status at the moment of diagnosis. The laboratory findings also support this situation. Endoscopic and pathologic results confirm the damage in intestinal surfaces, where an important level of absorption occurs. Celiac disease is an important public health problem and its only treatment is the gluten-free diet. Celiac disease requires a life-long diet; diet therapy can prevent the growth and development retardation, malnutrition, and bone disorders that may develop due to the celiac disease. Especially for the children in this age group, the main objective is, thanks to the early diagnosis, to initiate the diet and ensure adherence to diet. For preschool children, adherence to the

diet should be ensured and this adherence should be maintained throughout life. The children adhering to the diet had a higher level of academic achievement and a shorter adaptation time in elementary school. Moreover, it is also necessary for a healthier future. For human, a bio-psychosocial creature, maintaining a complete wellness depends on the achievements gained in this period.

The fact that the patients diagnosed with celiac disease in the preschool age group could not be evaluated in a multicenter manner and considering socioeconomic-sociocultural variables was considered as a limitation of the study.

Ethical Approval: *The ethics committee approval was obtained from Fırat University's Non-Interventional Researches Ethics Committee (Date: 07.19.2018, No: 13/13).*

Author Contributions:
Concept: U.A., U.D.
Literature Review: U.A., U.D.
Design : U.A., U.D.
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