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Research

Clinical Presentation of Celiac Disease in Children: A Single Center Experience

Çocuklarda Çölyak Hastalığının Klinik Prezentasyonu: Tek Merkez Deneyimi

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ABSTRACT

Objective: This study was an examination of the presenting complaints, clinical and laboratory data and biopsy reports of 174 celiac patients. The primary aims were to emphasize the presentation patterns of patients that certain complaints need to be queried even if they are not mentioned. Our secondary aim is to increase the awareness of investigating patients' first-degree family members, risk groups otherwise they have no complaints.

Methods: Presenting complaints, anthropometric data, biopsy reports were recorded by retrospectively examining the files of patients diagnosed with celiac disease (CD). In each diagnosis of CD, tissue transglutaminase IgA antibody, anti endomysium antibody titer and histopathological Marsh classification have been conducted.

Results: The prevalence of patients with weight and height below the 3rd percentile was 29.3%. In the order of frequency, the patients' most common presenting complaints were abdominal pain 64.4%, growth retardation 51.1%, diarrhea 36.8%, constipation 32.2% and halitosis 32.2%. It was found that 15.5% of the patients had no complaint. Physical examination was normal in 87.4% patients. When family members were questioned about the disease, it was determined that 20% of the patient families had one or more individuals with CD.

Conclusion: It was found that the rate of growth retardation is high in our population and increased with an increase in the duration of complaints. This shows the importance of early diagnosis and treatment for a quality of life. Additionally, particularly the first-degree relatives of CD patients should be questioned routinely, even if there are no complaints.

Keywords: Celiac disease, growth retardation, presentation, children

ÖZ

Amaç: Çalışmamızda 174 çölyak hastasının başvuru şikayetleri, klinik ve laboratuvar verileri ile biyopsi raporlarını inceledik. Çalışmadaki esas amacımız çölyak hastalarının prezentasyon şekillerini irdeleyerek, bazı şikayetlerin söylenmese de sorgulanması gerektiğini vurgulamaktır. Şikayeti olmasa da birinci derece aile bireylerinin ve riskli olan grupların tetkik edilmesi konusunda farkındalığı artırmaktır.

Gereç ve Yöntem: Çalışmaya dahil edilen hastaların dosyaları retrospektif olarak incelenerek başvuru şikayetleri, antropometrik verileri, biyopsi raporları kayıt altına alınmıştır. Çölyak hastalığı (ÇH) tanısında doku transglutaminaz IgA antikor, anti endomisyum antikor titresi ve histopatolojik olarak Marsh sınıflaması yapılmıştır.

Bulgular: Antropometrik veriler değerlendirildiğinde boy ve kilosu 3 persentil altında olan hasta oranı %29,3 idi. Hastaların en sık başvuru şikayeti sıklık sırasına göre, karın ağrısı %64,4, büyüme geriliği %51,1, ishal %36,8, kabızlık %32,2 ve halitozis %32,2 idi. Hastaların %15,5'inde hiçbir şikayet yoktu. Hastaların %87,4'ünde fizik muayenesi normal idi. Aile bireylerinde hastalık sorgulandığında %20'sinde ailede ÇH'si olan birey vardı.

Sonuç: Çalışmamızda hastaların şikayet süresi arttıkça büyüme geriliği oranları da artmaktadır. Bu da hastalığın erken tanı ve tedavisinin yaşam kalitesi üzerine olumlu etkisi ve tarama testlerinin önemini göstermektedir. Bazı riskli grupların ve özellikle ÇH olan bireylerin birinci derece akrabalarının şikayet olmasa da rutin sorgulanması gerekmektedir.

Anahtar Kelimeler: Çölyak hastalığı, gelişme geriliği, prezentasyon, çocuklar

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INTRODUCTION

Celiac disease (CD) is a chronic autoimmune enteropathy in genetically susceptible individuals that begins with the introduction of gluten into the diet, as well as the effects of environmental factors. It is characterized by the inflammation of the proximal intestine, and through the observation of clinical complaints associated with villus atrophy (1). The prevalence of CD has been gradually increasing with the screening of non-symptomatic risk groups (2). The prevalence of CD, which varied between 1:1000 and 1:3000 in Europe, increased to 1:150 and 1:300 after the tests began (3,4). Many prevalence studies were conducted on CD in European countries. When a systematic review was conducted, the prevalence of CD in Europe was found to be between 1/79 and 1/200 (5).

The results obtained in prevalence studies carried out in different regions of Türkiye were similar. In a study by Dalgic et al. (6), in school children, the prevalence of CD was reported to be 0.47%, in another study by Comba et al. (7), the prevalence was 0.46% in Çorum (1:216) and by Ertekin et al. (8) in the school-aged children in Erzurum, the prevalence of CD was found to be 1:115. For this reason, the study aimed to emphasize the importance of conducting research on CD, to make an examination of the presenting complaints and to query some findings, even if the patient does not report them.

In this study, we address certain parameters, in terms of early diagnosis, by examining the period that had elapsed between the first presentation complaints and diagnosis; some symptoms that the patient did not mention when questioned but which nevertheless existed, and the laboratory data and the endoscopic findings at the time of diagnosis. Our other aim is to highlight the need to evaluate the relatives of CD patients, even if they do not have any related complaints. To emphasize that to make a differential diagnosis, clinicians should consider CD when assessing and requesting etiological investigations for patients with non-specific gastric complaints.

METHODS

In this study, a retrospective analysis was made of the files of 174 patients diagnosed with CD who came for control to Adana City Training and Research Hospital, Pediatric Gastroenterology 1 Outpatient Clinic between June 1 and August 1, 2020. When patients initially present at the Pediatric Gastroenterology 1 Outpatient Clinic at Adana City Training and Research Hospital, a detailed file is started for each one of them. These patients are seen by me individually, as I do not have an assistant. After this study was planned, I have personally sought all information missing from the files from the patients directly during the two months of my involvement with them.

The patients' anthropometric data (height and weight values, percentiles) at the initial diagnosis, the age at diagnosis, gender, presenting complaints, some complaints questioned in detail [abdominal pain, combustion, heat (heart burn), halitosis, dyspepsia, presence of symptoms suggestive of reflux, vomiting, nausea, diarrhea, constipation, joint pain, fever, weight loss, growth retardation], duration of complaints, breastfeeding duration, months of first contact with gluten, additional diseases, the existence of CD in the family, socio-economic status, educational status of the mother and father, physical examination findings, the Marsh classification histopathological staging, *Helicobacter pylori* (Hp) positivity and some laboratory results (tissue transglutaminase IgA, serum IgA, anti endomysium antibody titer) in biopsy examination were obtained from the records in the file. The histopathological staging used for diagnosis was accomplished through the Marsh classification (9).

Among the patients who came to our outpatient follow-up, due to social or economic reasons, after being diagnosed in different centers, those without Marsh classification were additionally specified. Observer bias was an area that I have paid a considerable amount of attention to as well. I tried eliminating this by using the Marsh classification to standardize the results. These patients present with non-specific gastric complaints. Within the country's population Hp is very prevalent. I wanted to rule out other potential reasons and I wanted to prevent the patient from having to go through an other procedure. Therefore, I have followed the routine gastroscopy prosecures; taking 2 biopsies from the esophagus, the antrum, corpus, four biopsy from duodenum; and one biopsy was taken from the bulbus.

The diagnosis of those patients who were diagnosed in our center was performed in accordance with the items determined by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Union Committee in 2012 (10). The percentile values of height and weight were assessed using the percentile curves suggested by Neyzi et al. (11). After examining the height/age and weight/age curves of the patients, those under the 3rd percentile were evaluated as the growth retardation group. All patients who presented at the clinic were included in the study within the given timeframe; however, the patients with the following criteria were excluded: Patients who had been diagnosed elsewhere who do not carry the genes for CD. patients whose endoscopic biopsy records could

not be accessed for any reason. Patients who don't have a differentiating diagnosis of either CD or gluten allergy specifically.

The values of the tissue transglutaminase IgA, anti-endomysium IgA and serum IgA titers at the time of diagnosis and before starting the diet were examined. Serum IgA was studied using the nepholometric method (Beckman Coulter IMMAGE 800, Model: 4800). Tissue transglutaminase IgA levels were measured using the enzyme linked immune sorbent assay (ELISA) method (Dynex-Dsx instrument Orgentec Diagnostic GmbH, ORG 540A, Mainz, Germany). Serum anti-endomysium IgA was determined by the ELISA method (Alisei device Radim Diagnostic GmbH, Deutschland). All the hospitals in Adana use the same private laboratory to process celiac antibody titer. In our study population, patients diagnosed in another city were excluded.

This study followed the principles of the Declaration of Helsinki. Additionally, ethical committee approval (date: May 20, 2020, decision no: 879) from Adana City Training and Research Hospital, Scientific Research Ethics Committee was granted for the study. Independent of this study, patients continued their gastroenterological routine follow-up every three months in the first year and every 6 months in the subsequent years. Further studies are possible from the results of these follow-up appointments; nevertheless, I want to assure you that their care planning has not been negatively impacted by this study.

Statistical Analysis

The SPSS 23.0 licensed software package was used for the statistical analysis of the data. Categorical data were expressed as numbers and percentages, while continuous data were expressed as mean and standard deviation (median, and minimum-maximum values, where required). The chi-square test and Fisher's Exact test were applied for the comparison of categorical variables. After checking the distribution of normality in the comparison of continuous variables between the groups, the Mann-Whitney U test in paired groups. and the Kruskal-Wallis tests in more than two groups were used for parameters without a normal distribution. The level of statistical significance was set as 0.05 for all analyses.

RESULTS

The mean and median of the patients' ages of diagnosis were 8.26±4.37 years and 93 months (12-218 months), respectively. The sex of the patients was 64.9% (113 patients) female and 35.1% (61 patients) male. The number of patients of Turkish ethnic origin was 163 patients (93.7%) while 11 patients (6.6%) were of other ethnicities. When the patients' ages of diagnosis were grouped, it was found that the diagnosis was the highest between the ages of 5-10 years with 36.8%. The rate of diagnosis was 33.9% at ages more than 10 years, 23% between the ages of 2-5 and 6.3% in the first 2-5 years of life (Figure 1).

When anthropometric data of patients were evaluated, the rate of patients with weight and height below the 3rd percentile was 29.3% (51 patients). In the order of frequency, the most common presenting complaints of the patients were abdominal pain 64.4% (112 patients), growth retardation 51.1% (89 patients), diarrhea 36.8% (64 patients), constipation 32.2% (56 patients), and halitosis 32.2% (56 patients) (Figure 2).

In the patient group, it was noteworthy that 15.5% of the patients (27 patients) had no complaints; some of those had been examined only because of the disease in their family members. When the disease was queried among the family members, it was determined that 20% patients had an individual with CD in first-degree relatives. The aforementioned 35% is for all extended family members including cousins. Physical examination was normal in 87.4% patients (Figure 3).

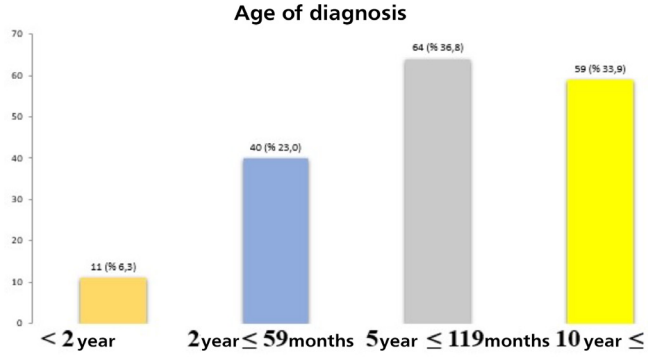

Figure 1. Age groups in which patients are diagnosed

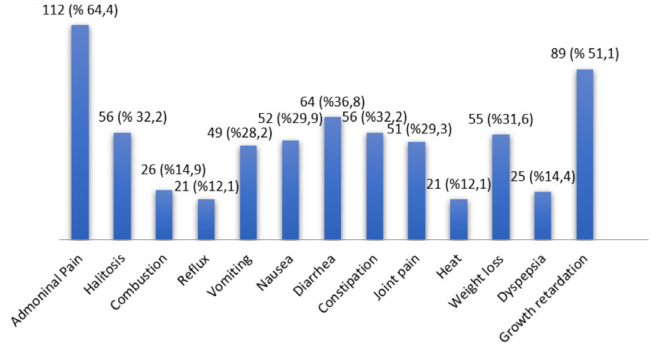

Figure 2. The percentage distribution of presenting complaints questioned in patients

When the biopsies of patients were evaluated, it was found that most biopsy results (45.6%) were compatible with Marsh 3b according to the Marsh classification (Figure 4). Patients with Marsh 0 and 1 were not excluded from the study because they have significantly high enough blood antibody titers (x10 upper limit of normal) to easily diagnose them. the gastroscopic examinations of those patients, we observed mucosal fissuring, villus destruction corresponding to CD. And we correlate with their genetic results that is HLA DQ2 and/or HLA DQ8 positive. The explanation for the difference between the macroscopic appearance and the biopsy is the patchy distribution pattern of the CD. No significant difference was found when comparing the complaint durations of patients with Hp positive and Hp negative in the biopsy material (p>0.05). The duration of the complaints was similar in both groups (12 months). In the evaluation of the material taken from the antrum and corpus area of the stomach by endoscopic biopsy, Hp was negative in 89 patients (70%), while it was positive in 38 patients (30%).

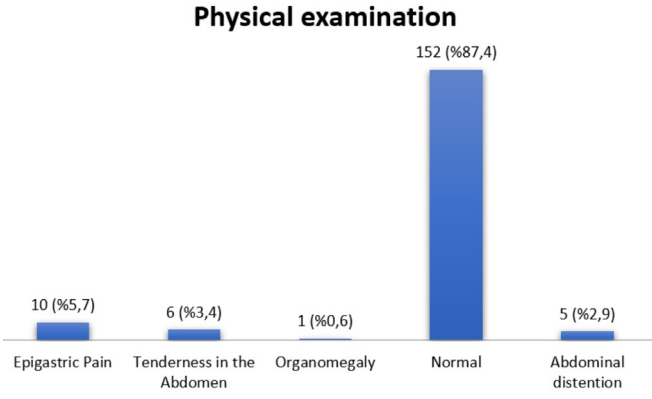

Figure 3. Physical examination results at admission

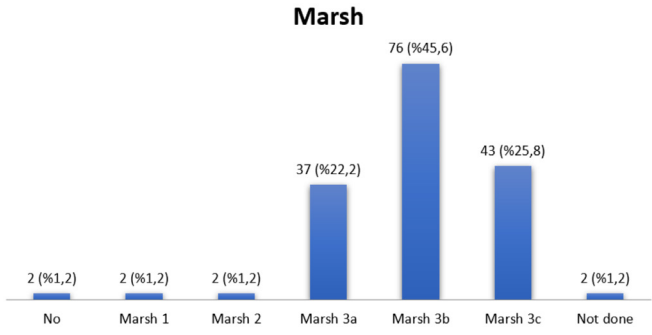

Figure 4. Marsh histopathological staging of the patients duodenal biopsy material

DISCUSSION

Over time, the presenting complaints of CD have changed from classic symptoms to nonclassical symptoms; the presentation has gradually increased, due to growth retardation; more advanced disease has been observed on histopathological examination; and the rate of autoimmune disease has decreased (12,13).

With CD, the presenting complaint of growth retardation is not rare. While the mechanism of growth retardation is not fully understood, it is considered to be caused by nutritional deficiencies, low-serum somatomedin activity, and a disruption in growth hormone release. In our study, when the anthropometric data of patients were evaluated, the rate of patients with growth retardation was found to be 29.3%. This result is consistent with other studies conducted in Türkiye (14).

When the growth retardation was associated with the age at diagnosis in our patients, the highest rate of growth retardatin (67.2%) was found in the group diagnosed between the ages of 5-10 years. Growth retardation was 64.4% in the patient group diagnosed after the age of 10 years. In contrast to the results reported in the literature, the rate of growth retardation was lower in our group of patients diagnosed in the first 2 years of life is 45.5%. When the relationship of growth retardation and the duration of complaints was evaluated, the complaint duration was 18 months in the patient group with growth retardation and 8 months in the patients without. As expected, as the duration of complaints increased, the rate of growth retardation also increased. This indicates the positive effect of early diagnosis and treatment on the quality of life and the importance of screening tests. Among our patients, the rate of patients with isolated short stature was 6.9%. When the results reported in the literature were examined, the rate of patients with isolated short stature was determined as 7.9% by Gokce and Arslantas (12) and 5.4% by Khatib et al. (15). Those results agreed with our data.

There are many studies in the literature, which support the claim that the age of diagnosis of CD has been increasing over the years (12,13,15,16). When compared, the age of diagnosis reported in the literature was found to be consistent with the age interval of our patients. Most diagnoses in our patients were in the 5-10 years old (36.8%).

While the age of admission in CD was gradually increasing, the symptoms related to the complaints of the gastrointestinal system, such as diarrhea, weight loss, abdominal pain and constipation dramatically decreased (14).

When the patient group was examined considering these studies, the most common presenting complaints of patients diagnosed before 2010 were abdominal pain (65.4%) and secondly, growth retardation (46.2%). The most common presenting complaints of the patients diagnosed after 2010 were abdominal pain (62.9%) and growth retardation (58.6%) respectively, similar to those of patients diagnosed before 2010. In a comparison of the patient groups with a CD diagnosis over the years, it was determined that the most important result was the reduction in heartburn and reflux. When these two groups were compared, while the heartburn and reflux symptoms were 22.1% and 18.3%, respectively in the patients diagnosed before 2010, the heartburn and reflux symptoms statistically and significantly decreased to 4.3% and 2.9%, respectively in the patients diagnosed after 2010 ($p<0.05$).

Because CD is an autoimmune disease, it should be considered that its prevalence increases in certain risk groups. There are many studies in the literature that have been conducted with these patient groups. In particular, Sari et al. (17) determined that 6.3% of patients with type 1 diabetes mellitus (DM) were found to have a CD association with the biopsy. In another study 4.9% of cases with autoimmune thyroiditis coexisted with CD (18). Similarly, the most common accompanying disease in our patient group was type 1 DM (7.4%) while autoimmune thyroiditis (2.2%) was the second most frequent disease. Other accompanying diseases were genetic syndromes (Turner syndrome, Down syndrome), cystic fibrosis, attention deficit and hyperactivity syndrome, and Familial Mediterranean fever, respectively.

In this study, 14.4% patients had an additional disease accompanying CD. In some studies, accompanying disease rates were found to be higher, such as 25.7% (12). According to the literature 4.6% of CD patients were found to have selective IgA deficiency, although no patient in our study group had selective IgA deficiency (16).

Foods containing gluten have an important place on the Turkish dining table and in Turkish cuisine. It is emphasized that breast feeding the infant during the first introduction of gluten and during the introduction period is important in terms of reducing CD risk (19).

In our patient group, the first introduction of gluten was mostly between the 4^{th} and 7^{th} month (69%). Then again, 28.7% of patients were introduced to gluten after reaching 7 months and 2.3% during the first 4 months of life. When it was questioned whether the patient received breast milk during the first contact with gluten, it was found that 75.9% patients were introduced to gluten while still being fed breast milk, whereas 24.1% were introduced to gluten after weaning.

In a study conducted in the Ankara region in 2015, the feeding of infants only their mother's milk was investigated. It was found that the rate of infants fed with only breast milk for 4 months was 49% and that of infants breastfed for 6 months was as low as 38% (20).

In our study, the duration of breast feeding in our patients was better, with an average of 13 months. It was concluded from this finding that increasing awareness by parents over time regarding the benefits of breast milk plays an important role.

While the prevalence of CD gradually increases over the years, the presenting complaints reduce and the severity eases. Approximately 25% of patients with no complaints can be detected with screening tests (14). In our study, while the rate of patients with no complaint was 15.5%, the rate of patients with one complaint was 47.1%. These results indicate the necessity of performing celiac screening tests on at-risk groups and those with a family history to prevent any delay in diagnosis.

The most common presenting complaints in our patient group were abdominal pain and growth retardation. Non-classical presenting complaints stated in the literature were not at the forefront. Khatib et al. (15) determined that the most common presenting complaints were abdominal pain (52.7%) and constipation (38.9%). These different results indicate that regional differences and genetics is applicable in presenting complaints. When the rate of growth retardation was compared according to the year of diagnosis in our patients, it was observed that while the growth retardation was detected in 30.8% of patients diagnosed before 2010, the rate of growth retardation was higher (44.3%) in patients diagnosed after 2010. No statistically significant difference was detected between the groups ($p>0.05$).

CONCLUSION

The prevalence of CH is known as 0.5-1%. The risk of CD increases in certain risk groups, particularly the first-degree relatives of individuals with CD and the people with autoimmune liver disease, autoimmune thyroiditis, type 1 diabetes, Down syndrome, Turner syndrome and Williams syndrome. With easy access to serological tests at the present time and their escalating use, the diagnosis of CD has been gradually increasing. In the existence of an individual with CD in the family, even if there is no complaint, other members of the family should be routinely examined. As we also specifically showed in our study, the early diagnosis of CD can be possible by screening first-degree family members, even if they have no complaints.

ETHICS

Ethics Committee Approval: Additionally, ethical committee approval (date: May 20, 2020, decision no: 879) from Adana City Training and Research Hospital, Scientific Research Ethics Committee was granted for the study.

Informed Consent: Retrospective study.

Financial Disclosure: The author declared that this study received no financial support.

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