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Our Celiac Disease Experience: Demographic Characteristics, Laboratory Findings and Concomitant Diseases of 94 Patients

Çölyak Hastalığı Deneyimimiz: 94 Hastanın Demografik Özellikleri, Laboratuvar Bulguları ve Eşlik Eden Hastalıklar

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Abstract

Objective: Celiac Disease (CD) which is an autoimmune disease affecting 1% of the population is associated with other autoimmune diseases and has extraintestinal manifestations. In the present study, we investigated the demographic and laboratory data of 94 patients and the association of celiac disease with anemia, osteoporosis and other autoimmune diseases.

Material and Method: This study was conducted retrospectively by examining the records of 94 patients who were followed up with the diagnosis of CD between January 2014 and December 2019.

Results: Of the patients, 74 were female (79%), 20 were male (21%). The mean age of the patients was 35 (18-73). The average disease duration was 6.6 years (0-29). Anti-endomysium Ig A positivity in 81 patients (86%), tissue transglutaminase Ig A positivity in 87 patients (93%), and tissue transglutaminase IgG positivity in 45 patients (48%) were detected. 14 patients had hypothyroidism (15%) and 8 patients had diabetes mellitus (9%). Osteoporosis or osteopenia was detected in 61 patients as the result of bone mineral densitometry (65%). According to the ferritin results, half of the patients and according to the transferrin saturation result, 47% had iron deficiency. 13 patients had B12 deficiency (14%) and 24 patients had folic acid deficiency (26%). Vitamin D deficiency was found in 74% of the patients. TSH value was found over 4.5 mIU/L in 10 patients.

Conclusion: CD is associated with iron, folate, vitamin B12, and vitamin D deficiency and is associated with anemia and osteoporosis, and the disease is often accompanied by autoimmune thyroid diseases and diabetes.

Keywords: Celiac disease, hypothyroidism, osteoporosis, anemia

Öz

Amaç: Çölyak Hastalığı (ÇH) toplumun yüzde %1'ini etkileyen, diğer otoimmun hastalıklarla birliktelik gösteren ve ekstraintestinal manisfestasyonlara sahip otoimmun bir hastalıktır. Bu çalışmada 94 hastanın demografik ve laboratuvar bulgularını, kansızlık, osteoporoz ve diğer otoimmun hastalıklar ile ilişkisini araştırdık.

Gereç ve Yöntem: Bu çalışma Ocak 2014-Aralık 2019 tarihleri arasında ÇH tanısı ile takipli 94 hastanın hasta kayıtları incelenerek retrospektif olarak yapılmıştır.

Bulgular: Hastaların 74'ü kadın (%79), 20'si erkekti (%21). Hastaların ortalama yaşı 35 idi (18-73). Ortalama hastalık süresi 6.6 yıldı (0-29). 81 hastada anti-endomisyum Ig A pozitifliği (%86) ,87 hastada doku transglutaminaz Ig A pozitifliği (%93) ve 45 hastada doku transglutaminaz Ig G pozitifliği saptandı (%48). 14 hastada hipotiroidi (%15) ve 8 hastada diabetes mellitus (%9) saptandı. 61 hastada kemik mineral dansitometri sonucunda osteoporoz veya osteopeni saptandı (%65). Ferritin sonuçlarına göre hastaların yarısında, transferrin saturasyonunu sonucuna göre ise %47'sinde demir eksikliği mevcuttu. 13 hastada B12 eksikliği (%14), 24 hastada folik asit eksikliği mevcuttu (%26). Hastaların %74'ünde D vitamin eksikliği saptandı. 10 hastada TSH değeri 4.5 mIU/L'den büyük saptandı. Hipotiroidi oranı %10'larda iken anti-TPO antikor pozitifliği %40, anti-TG pozitifliği ise %38 idi.

Sonuç: ÇH demir, folat, vitamin B12 ve vitamin D eksikliği ve bunlara bağlı kansızlık ve osteoporoz ile ilişkili olup hastalığa sıklıkla otoimmun tiroid hastalıkları ve diyabet eşlik etmektedir.

Anahtar Kelimeler: Çölyak hastalığı, hipotiroidi, osteoporoz, anemi

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INTRODUCTION

Celiac disease (CD) is an autoimmune disease related to gluten found in food items such as wheat, barley and rye. [1] The basis and the key finding of the diagnosis stage of the disease is gluten-sensitive enteropathy, which is a non-specific inflammation of small intestine mucosa, improved with a gluten-free diet.[2] Just like other autoimmune diseases, it is more common in females.[3] The disease is characterized by symptomatic and asymptomatic enteropathy, as well as various extra-intestinal symptoms and other potentially serious complications.[4] The most widely-known extra-intestinal findings are osteoporosis, anemia, skin and joint symptoms. Besides, CD patients are at a high risk of cancer, with a four-times increased risk of non-Hodgkin lymphoma, a more than 30-times increased risk of small intestine adenocarcinoma, and their mortality possibility increases 1.4 times.[5] Although diagnosed cases are rare, the CD affects about 1% of the population.[6] With up-to-date knowledge and diagnostic methods, the confirmed diagnosis rates in the last couple of years, especially the atypical and subclinical form, have been increasing steadily both in developed and developing countries. Other autoimmune diseases, especially autoimmune thyroid diseases and diabetes mellitus are also seen in Celiac Disease.[7] Clinical findings are quite variable and different in Celiac Disease.[8] Today, manifestations of diseases such as diarrhea, abdominal swelling, loss of appetite become less common, and even the patients with mild symptoms can be diagnosed with the introduction of serological tests.

The number of studies conducted on celiac patients involving demographic and laboratory data is insufficiently low. Furthermore, there is not much information about the association with vitamin-mineral deficiencies, osteoporosis and other autoantibodies. In the present study, we investigated the demographic and laboratory data of a total of 94 patients, and the association of celiac disease with anemia, osteoporosis and other autoimmune diseases.

MATERIAL AND METHOD

The present study is a retrospective study conducted by examining the records of patients followed-up for CD in the Gastroenterology Clinic of our hospital between January 2014 and December 2019. Patients whose demographic data, autoantibody results, laboratory results, and bone mineral densitometry results were missing were not included in the study. A detailed medical history was obtained from the patients to evaluate concomitant diseases. A total of 110 patients were found, 16 of them were excluded from the study because of insufficient information, and the study was carried out with 94 patients.

Four main categories were taken into consideration according to the modified Marsh-Oberhuber histological classification. [9] New diagnostic fields for CD are also addressed. Levels of 180 pg/ml for B12 deficiency, 20 ml/ng for ferritin deficiency, 4 ng/mL for folate deficiency and 20 ng/mL for vitamin D were considered. Those with a transferrin saturation below 10% and ferritin values below 20 ml/ng were considered iron deficiency anemia. The upper limit for AST and ALT was dedicated to be 40 U/L, 105 U/L for ALP, and 60 U/L for GGT. The normal range of TSH has been accepted as 0.5-4.5 mIU/L. Patients with an anti-TPO value higher than 9 IU/mL and an anti-TG value higher than 2 IU/mL were considered antibody positive.

Statistical evaluation was conducted using Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., Chicago, IL)software for Windows 10. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Normally distributed data in numerical valuables were shown as mean±standard deviation, non-normally distributed data were presented as median (min-max). Categorical variables were presented as numbers and percentages.

As the study was retrospective, no written consent was obtained from the patients. The study was carried out by following the ethical standards set out in the 1964 Helsinki Declaration. Research and publication ethics were strictly followed in our study and the rules were respected. Ethics approval for the study was obtained from the ethics board of our hospital dated 06.01.2021 and numbered E1-20-1426.

RESULTS

Of the participating patients, 74 were female (%79), and 20 were male (%21). The mean age of the patients was 35 (18-73). The mean duration of disease was 6.6 years (0-29). 25 patients had just been diagnosed with CD (26%). According to the modified Marsh-Oberhuber histological classification, 12 patients were Stage 1 (13%), 29 patients were stage 2 (31%), 30 patients were stage 3a and 3b (32%), and 13 patients were Stage 3c-4 (14%). It was found that 81 patients had anti-endomysium Ig A (86%), 87 patients had tissue transglutaminase Ig A (93%), and 45 patients were tissue transglutaminase IgG positive (48%). Hypothyroidism (15%) was detected in 14 patients and diabetes mellitus (9%) was detected in 8 patients. Inflammatory bowel diseases and rheumatological diseases were rarely found. Pathology was detected in bone mineral densitometry of 61 patients (65%). Values between 0-1 (23%) in 22 patients, between 1-2 (19%) in 18 patients, between 2-3 (15%) in 14 patients and between 3-4 in 7 patients were observed. (7%). Demographic characteristics, concomitant diseases, bone mineral densitometry and celiac test results of the patients are given in **Table 1**.

Laboratory test results of the patients can be found in **Table 2**. The mean hemoglobin value of the patients was 12 g/dl (7-18), mean white blood cell count was 8.7 103/µL and mean platelet count was 308 103/µL. The mean ferritin value of the patients was 22 ml/ng and the mean transfer saturation was 13.5%. According to the ferritin results, half of the patients had iron deficiency, and 47% of them had iron deficiency according to transferrin saturation. 13 patients had B12 deficiency (14%), and 24 patients had folic acid deficiency (26%). Elevated ALT values were seen in 14 patients (15%), high AST in 10 patients

(11%), and high ALP in 20 patients (21%). Elevated bilirubin or GGT were not seen in patients. 3 patients had low albumin and total proteins (3%). In 17 patients, creatinine values were below 0.5 (18%) while no patients had high values. Only 3 patients had low adjusted calcium values, while 74% of patients had vitamin D deficiency. In 44% of the patients, values below 10 ng/mL were seen. Hypothyroidism was detected in 10 patients due to TSH values greater than 4.5 mIU/L. In one patient, the TSH value was above 30 mIU/L. Hyperthyroidism was not detected in any patients. While hypothyroidism rates were at 10%, the anti-TPO positivity rate was 40% and anti-TG positivity was 38%.

Table 2. Laboratory results

Hemoglobin (g / dL), median	12
White Blood Cell Count (Thousand / µL), median.	8.7
Platelet (Thousand / µL), median	308
Ferritin (ml/ng), median	22
<20 ml / ng	47/94 (50%)
Transferrin saturation (%), median	13.5%
<10%	44/94 (47%)
Vitamin B12 (pg/ml), median	330
<180pg/ml	13/94 (14%)
Folate (ng/mL), median	8.6
<4 ng/mL	24/94 (26%)
ALT (U/L), median	26
41 -80U/L	13/94 (14%)
>80U/L	1/94 (1%)
AST (U/L), median	26
41-80U/L	10/94 (11%)
>80U/L	0
ALP (U/L), median	111
>105U/L	20/94 (21%)
>500U/L	2/94 (2%)
GGT (U/L), median	14
>60U/L	0
Total Billuribine (mg / dL), median	0.9
>1.4mg/dL	0
Albumin (g/dL), median	4.3
<3.5g/dL	3/94 (3%)
Total Protein (g / dL), median	7.3
<6.2g/dL	3/94 (3%)
Creatinine (mg / dL)	
<0.5 mg / dL	17/94 (18%)
> 1.2 mg / dL	0
Adjusted calcium (mg / dL), median.	9.33
<8mg / dL	3/94 (3%)
Vitamin D (ng/mL), median	15
<20ng / mL	70/94 (74%)
<10ng / mL	41/94 (44%)
TSH (mIU/L), median	2.3
>4.5mIU/L	10/94 (11%)
>30mIU/L	1/94 (1%)
<0.5mIU/L	0
Anti-TPO (IU/ml)	
>9	38/94 (40%)
>100	10/94 (11%)
Anti-TG (IU / ml)	
>2	36/94 (38%)

Table 1. Demographic characteristics, comorbid diseases, bone mineral densitometry test results and celiac test results

Gender, Female (%) / Male (%)	74 (79%)/20(21%)
Age, median (min-max)	35 (18-73)
Duration of disease,median(min-max)	6.6 years (0-29 years)
Recently diagnosed	25 (26%)
Marshall classification	
1	12 (13%)
2	29 (31%)
3a-3b	30 (32%)
3c-4	13 (14%)
Anti-endomysium IgA	
Negative	13 (14%)
Positive	81 (86%)
Tissue Transglutaminase IgA	
Negative	7 (7%)
Positive	87 (93%)
Tissue Transglutaminase IgG	
Negative	49 (52%)
Positive	45 (48%)
Comorbid disease	
Hypothyroidism	14/94 (15%)
Diabetes Mellitus	8/94 (9%)
Inflammatory Bowel Disease	3/94 (3%)
Ankylosing spondylitis and rheumatoid arthritis	3/94 (3%)
Membranous glomerulonephritis	2/94 (2%)
Down Syndrome	2/94 (2%)
Phenylketonuria	1/94 (1%)
Hyperparathyroidism	1/94 (1%)
Bone Mineral Densitometry (Pathological)	61/94 (65%)
0-(-1)	22/94 (24%)
(-1)-(-2)	18/94 (19%)
(-2)-(-3)	14/94 (15%)
(-3)-(-4)	7/94 (7%)

DISCUSSION

In the present study, it is shown that celiac disease cause iron, folate, vitamin B12 and vitamin D deficiencies, and patients develop anemia and osteoporosis. It is also presented that celiac disease are commonly seen together with diabetes and autoimmune thyroid diseases.

In our study, most of the patients were females. It has been an expected situation as CD is an autoimmune disease. Furthermore, the mean age of the patients was low as expected. The follow-up duration of our study was 6.6 years, and it was sufficient. A quarter of our patients were newly diagnosed.

The antibody with the highest positivity was found to be transglutaminase Ig A in our study. In the second place, anti-endomysium antibody Ig A was often found to be highly positive in diagnosis. Tissue transglutaminase IgG was negative in half of the patients. These results were consistent with the literature findings.[10] According to these results, we recommend that tissue transglutaminase Ig A should be initially requested for celiac diagnosis.

The most common concomitant diseases were found to be hypothyroidism and diabetes mellitus. In a previous study by Freeman, it was similarly found that these two diseases often accompany each other.[11] One of the other important comorbid diseases is Down Syndrome.[12] In our study, only one patient had down syndrome. This may be because our study was conducted with adult patients. Also, the

relationship between inflammatory bowel disease (IBD) and celiac disease had been shown in the literature.[13] In our study, IBD was detected in 3 patients. In a previous study, Lodhi et al.[14] showed the association of Celiac and RA or AS. In our study, rheumatological diseases were observed in 3 patients.

Almost two-thirds of the patients in our study had osteopenia or osteoporosis. With these results we can say that patients diagnosed with CD should be applied to bone densitometry as soon as possible. Similarly, the literature states that osteoporosis is often observed in celiac patients.[15] One of the most likely causes of this is Vitamin D deficiency.[16] As a matter of fact, in our study, vitamin D deficiency was found in the vast majority of patients. It is recommended that these patients should receive Vitamin D replacement even earlier.

Anemia seen in Celiac disease patients can be the result of various factors. The most commonly known causes are iron, folate and B12 deficiency.[17] Almost half of the patients in our study had iron deficiency and a quarter had B12 or folate deficiency. Although deficiencies were seen, significant anemia was not detected in the patients. In any case, as one of the most important symptoms in these patients is weakness and fatigue, it is recommended to apply replacement treatments for patients with deficiencies.

Despite being not very frequent, mildly elevated values of AST, ALT and ALP were seen in our patients. This shows that celiac disease disrupts liver functions and CD should be considered when there are high enzyme levels without any known cause.

Although no albumin or protein deficiency was indicating a nutritional deficiency in our patients, a decrease in creatinine values, which we believe is due to muscle loss, was observed. Although vitamin D values were very low, calcium values were normal in patients, but this condition still could not prevent osteoporosis. To this extent, we recommend Vitamin D and calcium supplements to patients with Vitamin D deficiency.

Hypothyroidism is commonly seen in celiac patients. The most common cause of this condition is Hashimoto thyroiditis.[18] As a supporting indicator, thyroid antibodies were found to be positive in our patients at high rates. If we could have assessed other antibodies, we think that they would be high as well.

The most important limitations of our study are being retrospective and having a low number of patients. However, since the CD is a not a frequently-seen disease, we think that our study group was sufficient in terms of the number of patients.

CONCLUSION

The present study has revealed that celiac disease has a relationship with vitamin and mineral deficiencies and related anemia and osteoporosis. Besides, it is shown that celiac patients often had other positive autoantibodies, and commonly the disease is accompanied by hypothyroidism and diabetes.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics approval for the study was obtained from the Ethics Board of our hospital on 06.01.2021 with the issue number E1-20-1426.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: OO and MK contributed in designing the study and performed critical revision of the manuscript; MK and VG: analyzed and interpreted the statistical results; BH, NCÜ and İT collected data; DAand EA reviewed the manuscript.

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