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Effects of Laboratory Parameters on Tear Tests and Optical Coherence Tomography Findings in Pediatric Celiac Disease

Çocuk Çölyak Hastalarında Laboratuvar Parametrelerinin Göz Yaşı Testleri ve Optik Koherens Tomografi Bulguları Üzerindeki Etkisi

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ABSTRACT

Aim: The aim of this study was to evaluate the tear parameters and optical coherence tomography (OCT) findings in children with celiac disease (CD) and to investigate the relationship between these findings and laboratory data.
Material and Methods: The study included 100 eyes of 50 CD patients as well as 110 eyes of 55 healthy subjects with no ocular pathology as a control group. Best corrected visual acuity was evaluated, baseline tear volume was estimated using standard Schirmer's test, and fluorescein tear film break-up time (TBUT) was determined for all participants. Pupillary dilation was induced and macular sections and optic disc sections were obtained with OCT.
Results: The patient and control groups showed no statistically significant differences in terms of age and gender distribution (p=0.490, and p=0.930, respectively). Mean Schirmer's test measurement was significantly lower in the CD patients compared to the control group (14.07±5.14 mm vs. 20.20±3.93 mm, p<0.001). TBUT was also shorter in the CD patients compared to the control subjects (10.86±3.51 s vs. 15.25±2.49 s, p<0.001). Mean total retinal thickness and outer retinal thickness values were significantly lower in the patient group than in the control group (p<0.001, for both parameters). In addition, the mean retinal nerve fiber layer (RNFL) thickness measurement was significantly thinner in the patient group than in the control group (p<0.001).
Conclusion: In the presented study, it was observed that macular and RNFL thickness were decreased in children with CD compared to the control group, and tear tests were also impaired.
Keywords: Celiac disease; laboratory parameters; tear film; optical coherence tomography; pediatric patients.

ÖZ

Amaç: Bu çalışmanın amacı çölyak hastalığı (ÇH) olan çocuklarda gözyaşı parametreleri ve optik koherens tomografi (OKT) bulgularını değerlendirmek ve bu bulgular ile laboratuvar verileri arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Çalışmaya ÇH nedeniyle takip edilen 50 hastanın 100 gözü ile herhangi bir oküler patolojisi olmayan 55 sağlıklı katılımcının 110 gözü dahil edildi. Tüm katılımcıların en iyi düzeltilmiş görme keskinliği değerlendirildi, standart Schirmer testi kullanılarak gözyaşı miktarı belirlendi ve floresein ile gözyaşı kırılma zamanı (GKZ) belirlendi. Pupiller dilatasyon sağlandıktan sonra maküla kesitleri ve optik disk kesitleri OKT cihazı ile alındı.
Bulgular: Yaş ve cinsiyet dağılımı bakımından hasta ve kontrol grupları arasında istatistiksel olarak anlamlı farklılık yoktu (sırasıyla, p=0,490 ve p=0,930). Ortalama Schirmer testi değeri kontrol grubu ile karşılaştırıldığında ÇH hastalarında anlamlı olarak daha düşüktü (14,07±5,14 mm'ye karşı 20,20±3,93 mm, p<0,001). Ayrıca GKZ değeri sağlıklı katılımcılar ile karşılaştırıldığında ÇH hastalarında anlamlı olarak daha kısaydı (10,86±3,51 s'ye karşı 15,25±2,49 s, p<0,001). Ortalama total retina kalınlığı ve dış retina kalınlığı değerleri hasta grubunda kontrol grubuna göre anlamlı olarak daha düşüktü (her iki parametre için p<0,001). Ayrıca, ortalama retina sinir lifi (ORSL) kalınlığı kontrol grubu ile karşılaştırıldığında hasta grubunda anlamlı olarak daha inceydi (p<0,001).
Sonuç: Sunulan bu çalışmada ÇH olan çocuklarda maküla ve ORSL kalınlığının kontrol grubuna göre azaldığı ve gözyaşı testlerinin de bozulduğu görülmüştür.
Anahtar kelimeler: Çölyak hastalığı; laboratuvar parametreleri; gözyaşı filmi; optik koherens tomografi; çocuk hastalar.

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INTRODUCTION

Celiac disease (CD) is an autoimmune disease of the small intestine that occurs in genetically predisposed individuals due to the ingestion of gluten-containing foods (1). It was first described by Samuel Gee in 1888, and the importance of gluten ingestion in its pathophysiology emerged in 1953 (2,3). Gluten ingestion causes intestinal mucosal damage and malabsorption of nutrients in these patients. Onset can occur in childhood or adulthood and the disease is a lifelong condition (4). The prevalence of CD varies regionally, with reports ranging from 0.47% to 1% (5,6). Although the classical findings involve the gastrointestinal tract, CD is recognized as a syndrome that can affect various systems and manifest along a broad clinical spectrum (7). The main reason for this is that pediatric patients present with milder and extraintestinal findings (8-11). These patients seem to be more prone to certain ocular conditions, especially dry eye, cataract, retinopathy, orbital myositis, uveitis and they may develop ocular involvement as an extraintestinal manifestation (12).

The present study was conducted to evaluate tear parameters and optical coherence tomography (OCT) findings in CD patients and to investigate the relationship between these findings and laboratory parameters.

MATERIAL AND METHODS

This study was designed as a prospective, randomized controlled study, and approval was obtained from the Mersin University Clinical Research Ethics Committee (dated 11.05.2017, numbered 153) prior to initiating the study. The study was conducted in accordance with the 1997 Declaration of Helsinki and informed consent forms were obtained from the parents of the patients included in the study.

One hundred eyes of 50 patients who were being followed up for CD in the Division of Pediatric Gastroenterology comprised the patient group. Patients with systemic disease other than CD and diagnosed with ocular disease other than dry eye were excluded from the study. The control group included 110 eyes of 55 healthy subjects with no ocular pathology other than a refractive error (-6.00 diopters (D) to 4.00 D.). All patients underwent best corrected visual acuity assessment, followed by Schirmer tear test II (5 minutes) under topical anesthesia to determine baseline tear quantity and fluorescein dye test to determine tear film break-up time (TBUT). After slit-lamp examination, 1% tropicamide was instilled to dilate the pupils and 9x9 mm macular sections and 6x6 mm optic disc sections were taken with a spectral domain OCT device (Nidek RS 3000; Nidek Co. Ltd, Aichi, Japan) capable of modal image acquisition from 53,000 different points. The macular sections were evaluated based on the ETDRS map, while the peripapillary retinal nerve fiber layer (RNFL) thickness was evaluated separately on the map in clock hours. In addition, inner retinal thickness (IRT; from the RNFL to the posterior of the outer plexiform layer) and outer retinal thickness (ORT; posterior of the outer plexiform layer to the posterior retinal pigment epithelium) using the software included in the device. All OCT images were acquired at the same time in the morning (10-12 am) by the same experienced technician and scans were repeated when necessary. The body mass index (BMI) of CD patients was calculated, and their hematocrit, ferritin, vitamin B12, folate, vitamin D, albumin, total cholesterol, and triglyceride levels in venous blood samples drawn after night fasting for at least 12 hours were recorded. The samples were analyzed by using fully automatic analyzers in the centralized laboratory. Lipid profile and albumin measures were done by spectrophotometric methods. Ferritin, vitamin B12, and folate measures were done by ELISA method, and 25 (OH) vitamin D measure was done by liquid chromatography-mass spectrometry technique. We compared the tear and OCT data of the CD patients with those of the healthy subjects, and also evaluated the relationship between the patients' ocular data and laboratory parameters.

Statistical Analysis

Normality of the data distributions was tested for each group using the Shapiro-Wilk test. Normally distributed parameters were summarized with the descriptive statistics mean and standard deviation. Categorical variables were expressed using the descriptive statistics number and percentage. The Student's t-test was used to compare the means of the parameters between the patient and control groups, and the Pearson correlation coefficient was used to evaluate the relationships between the parameters. All data analyses were performed using the SPSS v.11.5 package program, and $p<0.05$ was considered significant.

RESULTS

The patient and control groups showed no statistically significant differences in terms of gender distribution and age ($p=0.930$ and $p=0.490$, respectively). The mean follow-up period of the patients was 3.58±2.04 years. It was observed that vitamin D levels were below the normal limit in the patients.

Mean Schirmer's test measurement was significantly lower in the CD patients compared to the control group (14.07±5.14 mm vs. 20.20±3.93 mm, $p<0.001$). TBUT was also shorter in the CD patients compared to the control group (10.86±3.51 s vs. 15.25±2.49 s, $p<0.001$, Table 1). Schirmer's test results were not significantly associated with laboratory data; however, TBUT was significantly correlated with vitamin D ($r=0.250$, $p=0.021$) and total cholesterol ($r=-0.220$, $p=0.041$) levels.

Total retinal thickness (TRT) values were significantly lower in the CD patients compared to the control group (252.33±21.66 μm vs. 262.58±17.63 μm, $p<0.001$, Figure 1). The CD patient group also showed significantly lower ORT values compared to the control group (196.69±14.93 μm vs. 214.87±11.84 μm, $p<0.001$). The separate retinal thickness values in the inner and outer rings and the data on the relationship of retinal layers with systemic data were presented in Table 2 and Table 3, respectively.

RNFL thickness was significantly thinner in the patient group compared to the control group ($p<0.001$). Significant correlations were observed between cup/disc ratio and vitamin B12 ($r=-.0450$, $p<0.001$) and triglyceride ($r=0.310$, $p=0.004$) levels, as well as between RNFL and ferritin ($r=0.540$, $p<0.0001$) levels. Cup/disc ratio data and segmental RNFL measurements were summarized in Table 4.

Table 1. Comparison of age, gender, and tear parameters

	Control (n=55)	Patient (n=50)	p
Gender, n (%)			
Male	18 (32.7)	16 (32.0)	0.930
Female	37 (67.3)	34 (68.0)	
Age (years)	12.82±3.58	12.34±3.58	0.490
Schirmer (mm)	20.20±3.93	14.07±5.14	**<0.001**
TBUT (sec)	15.25±2.49	10.86±3.51	**<0.001**

TBUT: tear film break-up time

Table 2. Comparison of retinal thickness parameters

	Control (n=55)	Patient (n=50)	p
TRT (µm)	262.58±17.63	252.33±21.66	**<0.001**
CRT (µm)	227.68±15.38	223.63±17.80	0.078
IRT (µm)	28.58±5.88	27.24±6.43	0.110
ORT (µm)	214.87±11.84	196.69±14.93	**<0.001**
External Ring			
Superior	303.42±12.85	301.34±17.05	0.320
Temporal	292.49±14.33	287.85±17.94	**0.039**
Inferior	299.06±15.16	294.11±16.27	**0.023**
Nasal	318.85±12.77	315.44±18.25	0.120
Internal Ring			
Superior	341.86±17.28	334.69±23.63	**0.014**
Temporal	329.93±16.87	319.66±18.72	**<0.001**
Inferior	332.59±33.55	328.64±21.14	0.310
Nasal	339.56±18.62	333.67±17.50	**0.019**

TRT: total retinal thickness, CRT: central retinal thickness, IRT: inner retinal thickness, ORT: outer retinal thickness

DISCUSSION

Studies have demonstrated altered tear parameters and ocular surface changes in CD (13,14). The results of the present study are consistent with the literature, but in contrast to previous studies, we investigated the association between tear parameters and laboratory results. Although it was observed that no relationship between Schirmer's test results and laboratory parameters, TBUT was correlated with vitamin D and total cholesterol levels. A positive correlation between TBUT and systemic vitamin D levels has also been reported by Jin et al (15). In the present study, TBUT was positively correlated with systemic vitamin D levels in patients with CD. In contrast, it was detected that a negative correlation between TBUT and total cholesterol level. This is consistent with existing knowledge that increased systemic cholesterol alters lipid profiles in meibomian gland secretions, which increases the probability of developing dry eye (16).

In the present study, CD patients had lower TRT, CRT, IRT, ORT, and RNFL values compared to the control group. Different from previous studies, we have measured these layers separately to understand which layer causes thinning. We think that deficiency of the micronutrients or cross reaction of the autoantibodies may be the cause of the retinal layers thinning. At the same time, children with CD exhibited a significantly higher cup/disc ratio when compared to the control group.

Aksoy et al. (17) reported a negative correlation between serum ferritin levels and peripapillary RNFL thickness in

Table 4. Comparison of optic nerve parameters

	Control (n=55)	Patient (n=50)	p
C/D ratio	0.28±0.13	0.41±0.12	**<0.001**
RNFL	109.15±9.94	100.11±13.85	**<0.001**

C/D ratio: cup/disc ratio, RNFL: retinal nerve fiber layer

Table 3. Correlations between retinal thickness parameters and laboratory findings

	Central Retinal Thickness		Total Retinal Thickness		Inner Retinal Thickness		Outer Retinal Thickness	
	r	p	r	p	r	p	r	p
Ferritin	-0.200	0.070	-0.140	0.180	0.160	0.340	-0.230	**0.035**
B12	0.210	0.054	0.140	0.180	-0.100	0.340	0.310	**0.004**
D Vitamin	0.270	**0.012**	0.140	0.190	0.060	0.540	0.220	**0.039**
Total Cholesterol	-0.300	**0.006**	-0.260	**0.017**	-0.040	0.720	-0.280	**0.008**
Triglyceride	-0.340	**0.001**	-0.220	**0.041**	-0.060	0.550	-0.350	**0.001**

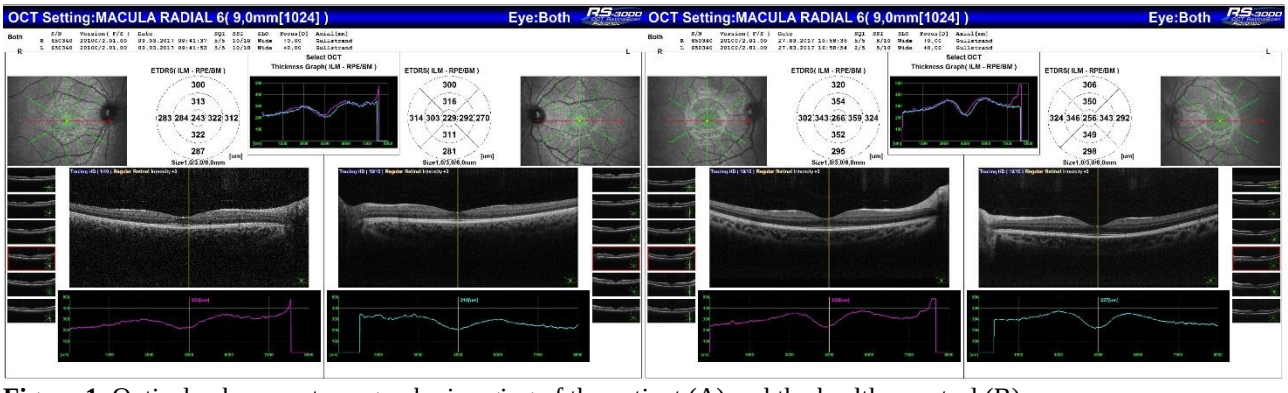

Figure 1. Optical coherence tomography imaging of the patient (A) and the healthy control (B)

children with iron deficiency and thalassemia major. In the present study, serum ferritin levels were negatively correlated with ORT and positively correlated with RNFL in children with CD. In contrast to the findings of Aksoy et al. (17), our results indicate that serum ferritin levels in patients with CD do not affect IRT but are inversely associated with ORT. The discrepancies between these results may be due to the evaluation of different patient groups. Furthermore, it is important to note that the ferritin levels observed in the current patient series were within normal limits.

A study evaluating patients with vitamin B12 deficiency revealed a positive correlation between peripapillary RNFL thickness and serum vitamin B12 levels (18). In the same study, however, RNFL thickness measurements were not associated with serum folate levels. In the present study, there were positive correlations between serum B12 vitamin levels and ORT, and between serum folate levels and IRT. There was also a negative correlation between serum B12 level and cup/disc ratio. Vitamin B12 deficiency is known to potentially lead to optic neuropathy and optic atrophy, which may explain this relationship between cup/disc ratio and serum vitamin B12 levels (19). However, it should be noted that the B12 and folate levels of the patients included in the study were within normal limits, and these findings may be related to the laboratory data or to the natural disease course in patients with CD.

Graffe et al. (20) demonstrated a positive association between serum vitamin D levels and CRT in the elderly. In contrast, Uro et al. (21) reported that vitamin D level was positively associated with ganglion cell complex thickness, but not with RNFL thickness. In the present study, we found that serum vitamin D levels were positively correlated with CRT and ORT but were not associated with optic nerve parameters in CD patients. These findings are similar to those in the literature.

One of the interesting findings of the present study is the negative correlation between total cholesterol and triglyceride levels and CRT, TRT, and ORT. There are studies in the literature with different results regarding the effect of blood lipid profile on OCT results (22-25). The present study suggests that serum lipid profile has different effects on these parameters in CD patients than those reported in the literature. Atherosclerosis begins in childhood even during the intrauterine period. Lipid accumulation in the aorta can be seen at the age of 3 years. We think that high cholesterol and triglyceride levels may accelerate the ischemic process and be subclinically reflected as thinning in the OCT measurements (26).

CONCLUSION

Tear parameters and OCT measurements may be altered in patients with CD. For this reason, it should be kept in mind that celiac patients should be followed up closely and subclinical eye involvement may occur. Therefore, monitoring of patients with OCT is more important for follow-up rather than diagnosis. Furthermore, the results of this study suggest that tear parameters and OCT measurements are associated with systemic variables. For this reason, systemic parameters of the patients should be closely monitored by gastroenterology specialists and nutritional parameters should be replaced. Hereby, subclinical eye involvement may be prevented.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Mersin University (11.05.2017, 153).

Conflict of Interest: None declared by the authors.

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