Evaluation of Eye Involvement in Pediatric Celiac Disease Patients

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Abstract

Background: The nonclassic presentation of pediatric celiac disease (CD) becomes increasingly common in daily practice, which requires an awareness of its extraintestinal clinical findings. To evaluate eye involvement and effect of gluten free diet on ocular involvement in pediatric CD patients by measuring the thicknesses of choroid and ganglion cell complex(GCC) composed of retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL) using enhanced depth imaging optical coherence tomography (EDI-OCT). Methods: Forty-three CD patients aged between four and 16 years (mean age;9.9 $\pm$ 4.1, 12 boys and 31 girls), and 48 healthy children (mean age; 11.3 $\pm$ 4.1,17 boys and 31 girls) were compared. Following comprehensive eye examinations, thicknesses of choroid at three points and GCC layers (RNFL at five points, GCL and IPL) were obtained using EDI-OCT. Measurement of thicknesses of choroid and GCC layers by a trained EDI-OCT technician and an ophthalmologist who were not aware about group of children in pediatric CD patients with one year gluten free diet. Results: All layers of subfoveal, nasal, temporal choroid were significantly thinner in CD than in the control group ($p < .001$, $p < .001$, and $p < .001$, respectively). No significant difference were observed between the CD and control groups in terms of GCC thicknesses ($p > .05$). Conclusion: Pediatric CD causing thinning of subfoveal, nasal and temporal areas of choroid, and this change is apparent even after one year gluten free diet. This extraintestinal involvement should be more closely screened at diagnosis and long term clinical results of thin choroid should be determined. Thicknesses of GCC layers were not different in CD group may be revealing the effect of diet or not involvement.

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Results: All layers of subfoveal, nasal, temporal choroid were significantly thinner in CD than in the control group ($p < .001$, $p < .001$, and $p < .001$, respectively). No significant difference was observed between the CD and control groups in terms of GCC thicknesses ($p > .05$).

Conclusion: Pediatric CD causing thinning of subfoveal, nasal and temporal areas of choroid, and this change is apparent even after one year gluten free diet. This extraintestinal involvement should be more closely screened at diagnosis and longterm clinical results of thin choroid should be determined. Thicknesses of GCC layers were not different in CD group may be revealing the effect of diet or not involvement.

Keywords: Children, Celiac disease, choroid thickness, ganglion cell complex, retinal nerve fiber layer, ganglion cell layer, inner plexiform layer

What is known?

1.Most of autoimmune inflammatory diseases effect eye.
2.CD is also an autoimmune inflammatory disease that would affect eyes of patients as an extraintestinal finding,
2.CT of pediatric CD patients at gluten free diet for 5 years decreased at subfoveal area.

What is new?

1.Pediatric CD causing thinning of subfoveal, nasal and temporal areas of choroid, and this change is apparent even after or
2. Thickneses of GCC layers were similar in CD and control groups may be revealing the effect of diet or these layers are no

1 | INTRODUCTION

Celiac disease (CD) is a gluten-induced multisystemic autoimmune disease in genetically susceptible individuals.[1] In recent years, there has been increasing recognition that the pattern of presentation of pediatric CD may be changing.[1,2]

Classic CD manifesting with diarrhea, malabsorption and failure to thrive may be less common than the more subtle presentations such as oligosymptomatic, latent, potential, and extraintestinal system findings related with nervous, otologic, dermatological, dental and musculoskeletal findings.[3,4] If undiagnosed extraintestinal findings remain untreated, leaving individuals exposed to the risk of long-term complications.[5-7]

Recent studies eye involvement in systemic and autoinflammatory diseases such as inflammatory bowel disease, diabetes mellitus, rheumatoid arthritis and Behçet's disease.[8-11] Mostly reflected as a change in thicknesses of choroid and ganglion cell complex (GCC). Choroid is highly vascular tissue present between retina and sclera and providing main blood flow to the optical structures effected by circulatory factors, such as intraocular and perfusion pressure, endogenous nitric oxide production and inflammation.[12,13]

In the acute inflammatory phase, cytokines increase the choroidal vascular permeability and choroidal thickness (CT) usually increases, while atrophic changes in recurrent inflammatory conditions result in decreased CT.[8-11,14] CD is also an autoimmune inflammatory disease that would affect eyes of patients. Ocular findings due to CD occupy an important place among these extraintestinal findings because of the direct effect of visual function and ocular comfort on quality of life.[5-7] Bölükbaşı et al. has revealed that mean CT measurements at all seven areas of subfoveal, nasal, and temporal points were found to be higher in the adult celiac group.[15] There is only one study by Doğan et al. that have found insignificant decrease in thickness of choroid in pediatric CD patients at only subfoveal area. The studies about eye involvement and effect of gluten free diet on ocular findings in CD patients are scarce.[1]

Optical coherence tomography (OCT) calculates delays in reflected light in different layers of the eye, allowing the reflected light to be converted into 3D images showing depth dimensions. The axial resolution of OCT has currently reached the very low value of 3 microns, and this convenient, non-contact technique can yield images similar to biopsy material viewed under a microscope. OCT can therefore be described as a non-invasive tissue biopsy. Enhanced depth imaging optical coherence tomography (EDI-OCT), a software application that can be installed on spectral domain optical coherence tomography (SD-OCT) devices, is

a non-invasive method that provides deeper cross-sectional information about vascularization of choroid, thicknesses of; choroid and GCC which is composed of retinal nerve fibre layer (RNFL), ganglion cell layer (GCL) and ınner plexiform layer (IPL).[17,18]

Ganglion cell comple is the sum of the three innermost layers: the retinal nerve fiber layer RNFL, which is composed of axons; the GCL, which is composed of cell bodies; and the IPL, which contains the retinal ganglion cells dendrites.[12] Early and initial signs of systemic and autoimmune diseases can also be evaluated by measuring the thickness of GCC layers by the help of EDI-OCT.[8-11] In Behçet's disease, systemic lupus erythematosus (SLE), multiple sclerosis (MS) and obesity patients thicknesses of GCC layers are decreased due to effects of autoinflammatory diseases and metabolic stress.[11,14,19,20] There is only one study in adult and one small size pediatric study reporting thinning of RNFL layer in CD patients.[21,22] In the present study, measurement of thicknesses of choroid (at subfoveal, nasal and temporal points) and GCC (RNFL at seven points GCL and IPL) in pediatric CD and control group in order to evaluate eye findings and effect of gluten free diet on ocular involvement which is an important extraintestinal finding of CD.

2 | METHODS

2.1 | Clinical setting

A total of 43 children with CD diagnosed and followed up at the Department of Pediatric Gastroenterology of Adıyaman University (Adıyaman,Turkey) were evaluated prospectively and compared with 48 controls who were recruited from the hospital well child outpatient clinic.

Diagnosis of CD is based on pathology results of biopsy material taken from the duodenum according to European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic criteria.[23]

Measurement of thicknesses of choroid and GCC layers (the thickness of RNFL, GCL and IPL) of optic nerve by using EDI-OCT by a trained OCT technician and ocular examination of participants were made by an ophthalmologist who were not aware about group of children in pediatric CD patients with one year gluten free diet. Informed consent was obtained from all participants parents before procedures. The study was approved by hospital ethics committee (22.05.2018/4-4).

Systemic examinations and measurements of blood pressures were made in both groups and were within normal limits for age. All participants underwent comprehensive ocular examinations, including standard slit-lamp examination, refractive error evaluation and best-corrected visual acuity determination, intraocular pressure measurement with pulse tonometry, detailed fundoscopy and perimetry. Blood tests measuring hemoglobin, iron, vitamin D, vitamin B12, C-reactive protein, and sedimentation were within normal ranges in the CD and healthy control groups.

Children with; acute or chronic, and local or systemic, infection under four years of age who were unable to adapt to OCT, and the patients with corneal abnormality, intraocular pressure greater than 21 mm Hg, retinal disease, glaucoma, strabismus, optic disc disorder, history of ocular surgery or trauma, refraction error greater than 3 diopters and chronic use of any medication, were not included into the study.

2.2 | Optical coherence tomography technique

Scans were obtained by a trained OCT technician using an SD-OCT device (Spectralis OCT®; Heidelberg Engineering, Heidelberg, Germany) without pupil dilatation. All EDI-OCT measurements were performed at specific times (between 09:00 and 12:00 a.m.) in order to avoid the effect of diurnal variation. A 9 mm high-resolution line scan passing the horizontal fovea was recorded. This datum was measured using the software (Heidelberg Eye Explorer®, Version 1.7.0.0; Heidelberg Engineering) installed on the device. Thicknesses of choroid at three points and GCC layers (RNFL at five points, GCL and IPL) were obtained manually by the same experienced ophthalmologist using EDI-OCT (Figure 1,2). Choroidal thickness was measured manually at the foveal center and within the nasal and temporal quadrants at 500 μm intervals from the foveal center Three measurement values taken from at every point of measurement and the average of this measurements taken into statistical analysis.

2.3 | Statistical Analysis

SPSS®, Version 21, software (Chicago, IL, USA) was used for statistical analyses. Descriptive and comparative analysis was employed to characterize the study population. The variables were investigated using visual and analytical methods to determine normality. The Student'st -test and Mann–Whitney U test were used to compare these parameters between groups.

3 | RESULTS

Eighty-six eyes of children diagnosed with CD, 31 (72.1%) girls and 12 (27.9%) boys, with a mean age of 9.9 ± 4.1 years, were enrolled in the study. Ninety-six eyes of control children, 31 (64.6%) girls and 17 (35.4%) boys, with a mean age of 11.3 ± 4.1 years, were enrolled as the control group. No statistically significant difference was determined between the groups in terms of age and percentage of sex (Table 1).

All thicknesses of choroid at nasal, temporal and subfoveal points were significantly lower in patients with CD (as mean±SD; 317.24±82, 320.1±81.86, 333.13±81.29μm, respectively) than in the control group (as mean±SD; 379.35±62, 383.66±64.03, 400.93±64.98, respectively μm), ($p < .001$, $p < .001$, p and $p < .001$, respectively). No significant difference was observed between CD and control groups in terms of GCC (as mean±SD of CD and control group; superior RNFL: 125.18±19.06 and 129.62±17.34, nasal RNFL: 70.76±16.80 and 75.31±13.88, inferior RNFL: 131.08±19.40 and 133.26±15.81, temporal RNFL: 75.17±11.41and 73.63±9.71, global RNFL: 100.51±11.76 and 103.13±9.72, GCL: 1.13±0.86 and 1.14±0.09, IPL: 0.93±0.11and 0.93±0.06 μm, $p > .05$ for all) (Table 2).

4 | DISCUSSION

This is the first pediatric research studying CT at three different areas of choroid in order to evaluate the immunopathologic processes within choroid in pediatric CD patients reflecting eye involvement in this autoimmune disease by the help of EDI-OCT. There are studies in literature with different results; Bölükbaşı et al. found an increase in adult CD patients at seven areas (one subfoveal, three nasal, three temporal)[15], but Doğan et al. found an insignificant decrease at subfoveal area in pediatric CD patients at gluten free diet for 5 years.[16]

According to our study results in pediatric CD patients who made gluten free diet for one year after endoscopic diagnosis, CT were thinner at all subfoveal, nasal and temporal points compared to control group. Our findings were supporting the study results of Dogan. Although they made the CT measuements at only one point at subfoveal area, in our study, CT measurements were made at three different points of choroid. Baltmr A et al. reported that, in the acute inflammatory phase, CT usually increases, while atrophic changes in recurrent inflammatory conditions result in decreased CT in local ocular inflammation.[24]Tekin et al. found a significant decrease in CT in pediatric malnutrition cases.[25] Our findings may be reflecting that the immunopathologic changes in choroid did not recover with gluten free diet since intestinal mucosa recovery is incomplete at one year or may be reflecting atrophic changes in CT without recovery with gluten free diet or may be due to effect of malnutrition and malabsorbtion of vitamin A and D. There is a need for follow up studies measuring CT at diagnosis time and after gluten free diet in follow-up period.

Early and initial signs of systemic and autoimmune diseases can also be evaluated by measuring the thickness of GCC complex composed of; RNFL, GCL and IPL of optic nerve by the help of EDI-OCT.[8,9,10,11] Our measurement results of GCC layer thicknesses (Five points of RNFL, GCL and IPL) revealed similar results in CD and control groups. There are papers reporting decreased thicknesses of these layers in Behçet's disease, SLE, MS and obesity patients due to effects of autoinflammatory diseases and metabolic stress.[11,14,19,20] There is only one adult CD study by Hazar et al. reporting that superior and nasal RNFL was decreased.[22] There is only one pediatric CD study by Hashas, reporting a decrease in global, temporal, superior temporal and superior nasal RNFL.[23]

GCC is a continuation of optic nerve. In our study we did not found a decrease in thicknesses of GCC layers which may reflect neural tissue involvement is a more complicated issue.[12] Study by Hazar et al was in adults and study by Hashas in pediatric were with a small number study.[21,23] Their theory accepts that the immune

antibodies would be causing that decrease in RNFL, GCL and IPL, but these layers are not in direct contact with these antibodies. There are Behçet's disase, SLE and MS studies reporting decreased thicknesses of GCC layers, which inflammatory effects of these diseases are directly influencing neural tissue.[11,14,20] But antibodies causing Celiac disease

In conclusion, our study shows that Pediatric CD causing thinning of subfoveal, nasal and temporal areas of choroid, and this change is apparent even after one year gluten free diet as an extraintestinal finding. This finding may be a new form of nonclassical presentation of CD. Thickneses of GCC layers were similar in CD and control groups may be revealing the effect of diet or these layers are not involved in CD eye findings pathogenesis. Eye findings as an extraintestinal involvement should be more closely screened at diagnosis and longterm clinical results of thin choroid and GCC should be determined in pediatric CD.

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Table 1. Comparison of the demographic characteristics of the groups

Table 2. Optical coherence tomography results of celiac disease and control group of eyes.

Figure 1. Choroidal thickness measurements obtained by spectral-domain coherence tomography in a patient with celiac disease. The thickness was measured manually at the foveal center ,nasal and temporal points 500 μm from the foveal center.

Figure 2. Spectral domain optical coherence tomography Retinal nerve fiber layer normal imaging of a CD

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