

# Choroidal thickness and retinal nerve fiber layer analysis in chronic spontaneous urticaria

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## ABSTRACT

**Aim:** In this study, we investigated the effects of chronic spontaneous urticaria on the choroid and retinal nerve fiber layer.

**Material and Method:** The patient group consisted of newly diagnosed 54 chronic spontaneous urticaria (CSU) patient and the control group consisted of 54 healthy volunteer. Choroidal and retinal nerve fiber layer (RNFL) thickness measurements were performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after pupil dilation with 0,5% tropicamide.

**Results:** In the patient group, nasal choroidal thickness (NCT) was  $290.11 \pm 43.16 \mu\text{m}$ , subfoveal choroidal thickness (SFCT) was  $339.17 \pm 37.709 \mu\text{m}$ , temporal choroidal thickness (TCT) was  $296.00 \pm 42.859 \mu\text{m}$ , mean choroidal thickness (MCT) was  $308.33 \pm 35.923 \mu\text{m}$  and RNFL thickness was  $91.11 \pm 7.393 \mu\text{m}$ . NCT was  $248.42 \pm 35,742 \mu\text{m}$ , SFCT  $276.56 \pm 40.04 \mu\text{m}$ , TCT  $253.69 \pm 37.384 \mu\text{m}$ , MCT  $259.50 \pm 32,986 \mu\text{m}$  and RNFL thickness  $92.19 \pm 8.719 \mu\text{m}$  in the control group. When we examine the p value, it is seen that both groups are similar to each other in terms of RNFL thickness ( $p=0.326$ ), while there is a significant thickening in all choroidal regions of patients with CSU, including NCT, SFCT, TCT, MCT ( $p=0.000$ ,  $p=0.000$ ,  $p=0.000$ ,  $p=0.000$ , respectively).

**Conclusion:** The choroid is affected in CSU and choroidal thickness can be a noninvasive method that can be used in diagnosis CSU. However, studies of longer disease durations may provide more illuminating information about CSU and choroid and RNFL.

**Keywords:** Choroidal thickness, chronic spontaneous urticaria, EDI-OCT, histamine, retinal nerve fiber layer

## INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disease that lasts for at least 6 weeks and is characterized by itching and swelling without a triggering factor (1). Although the exact etiopathogenesis of the disease has not been determined yet, there is perivascular infiltration of inflammatory cells at the lesion site in CSU and blebs are known to contain prostaglandins and leukotrienes, platelet-activating factors, histamine, cytokines and proteases released by degranulation of skin mast cells (2). As these inflammatory mediators increase vascular permeability, redness, itching and edema occur (3).

The choroid is a network of vessels that serves as nutrition for the fovea, outer retina and optic nerve. The choroid contains dense plexuses of nerve fibers controlled by the autonomic nervous system (4). Parasympathetic and sympathetic nervous system activation and the

inflammation can produce changes in the choroidal circulation and thus changes in thickness. With the new generation of advanced deep imaging optical coherence tomography (EDI-OCT) devices, the choroid can now be visualized and choroidal thickness and thickness changes can be measured. For this reason, changes in choroidal thickness have been the subject of many studies in recent years, and the effects of various systemic diseases on choroidal thickness have been studied (5). Choroidal thickness examinations were performed on the diseases with skin involvement such as vitiligo, rosacea, and Behçet's disease (6-8).

New generation OCT devices can detect changes in the retinal nerve fiber layer (RNFL) by performing retinal nerve fiber analysis. RNFL thickness changes, which are generally used in the diagnosis and follow-up of glaucoma, have been studied in many retinal

and systemic diseases (8-10). RNFL analysis has been evaluated in inflammatory diseases with skin involvement such as Vogt Koyanagi Harada and vitiligo (11,12). As far as we know, no retina examination has been done in CSU. Since retinal dysfunction has been reported in patients with an inflammatory disease such as vitiligo, we wanted to analyze RNLF in CSU (12). At the same time, the inflammatory process in CSU can cause an increase in ganglion cell apoptosis. We think that inflammation caused by inflammatory cell infiltration and inflammatory mediator release in CSU may affect the choroidal thickness and RNFL. Therefore, in our study, we examined the choroidal thickness and RNFL analysis of our CSU patients who have not yet been treated.

### MATERIAL AND METHOD

This study was carried out by dermatology and ophthalmology departments as cross-sectional. The study was carried out with the permission of Niğde Ömer Halisdemir University Noninvasive Clinical Researches Ethics Committee (Date: 26.05.2022 Decision No: 2022/69). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Oral and written consent was obtained from each patient before the eye examination.

The study group was formed by determining patients who were diagnosed with CSU by the dermatology department of our hospital and have not been treated yet. Fifty-four CSU patients without any eye disease or complaint and 54 healthy individuals as a control group were included in the study. The patient and control groups consisted of volunteers with 10/10 vision according to the Snellen chart and no eye pathology except refractive error. The axial lengths of our participants were between 22-24mm. In both groups; patients older than 18 years of age were included in the study, those with systemic disease other than CSU, pregnancy and lactation, myopia and hyperopia greater than 3D, astigmatism greater than 2D, and those with a history of ocular surgery were excluded from the study. At the same time participants with smoking and alcohol use were excluded. Body max index of our participants was between 18.5-24.9.

Demographic information of all cases were recorded. All individuals were questioned about their detailed medical history. A full ophthalmoscopic examination including best corrected visual acuity, eye pressure measurement with a pneumatic tonometer (corrected according to pachymeter), color vision, light reflexes, eye movements, anterior and posterior segment examination with slit lamp slit lamp was performed. Both eyes of all participants were included in the study.

### Choroidal thickness measurement and RNFL analysis with Optical Coherence Tomography Examination

Measurements were made with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after administration of 0,5% tropicamide. Measurements with a signal quality of 6 and above in both choroidal thickness and RNFL analysis were included in the study.

Choroidal thickness was measured with the device's single line HD 5 Line Raster protocol and depth imaging system (EDI) mode. The first measurement was subfoveal choroidal thickness (SFCT). The thickness was found by measuring the distance between the retinal pigment epithelium (RPE) hyperreflective band and the choroido-scleral junction. Then, measurements were made from 6 points in the temporal and nasal directions from the subfoveal region at 500 micron intervals and up to 1500 microns, 3 temporally (TCT) and 3 nasally (NCT). Mean choroidal thickness (MCT) was calculated by taking the average of the measurements from 7 points.

For RNFL measurement, three-dimensional (3D) cube OCT data were obtained using the optic nerve head-centered "Optical Disc Cube 200 X 200 Scan" model. After the RNFL map formed, the RNFL thickness is determined by an automatic computer algorithm.

### Statistical Analysis

Statistical analyzes were performed using the STATA 14 package program. In the descriptive table, numerical variables were summarized with mean±standard deviation [minimum – maximum] values, and categorical variables were shown as numbers and percentages. The Kolmogorov-Smirnov test was used to evaluate normal distribution, and the homogeneity of the variances was examined with the Levene test. Significance level was taken as p<0.05.

### RESULTS

The patient group consisted of 108 eyes, 72 female and 36 male eyes, and the mean age of the group was 43.06±14.007. In the control group, 66 eyes were female and 42 were male of 108 eyes, and the mean age of the group was 43.94±13,593. Differences between the patient and control groups were examined in **Table 1** and it was found that the two groups were similar to each other in terms of age and gender (p=.0.636 and p=0.395 respectively).

	Chronic spontaneous urticaria group n: 108	Control group n:108	P
Age	43.06±14.007	43.94±13.593	0.636
Gender			0.395
Female N (%)	72 (66.7%)	66 (61.1%)	
Male N (%)	36 (33.3%)	42 (38.9%)	

In **Table 2**, NCT, SFCT, TCT, MCT and RNFL values were compared between patients with CSU and the control group. In the patient group, NCT was  $290.11 \pm 43.16 \mu\text{m}$ , SFCT was  $339.17 \pm 37.709 \mu\text{m}$ , TCT was  $296.00 \pm 42.859 \mu\text{m}$ , MCT was  $308.33 \pm 35.923 \mu\text{m}$  and RNFL thickness was  $91.11 \pm 7.393 \mu\text{m}$ . NCT was  $248.42 \pm 35.742 \mu\text{m}$ , SFCT  $276.56 \pm 40.04 \mu\text{m}$ , TCT  $253.69 \pm 37.384 \mu\text{m}$ , MCT  $259.50 \pm 32.986 \mu\text{m}$  and RNFL thickness  $92.19 \pm 8.719 \mu\text{m}$  in the control group. When we examine the p value, it is seen that both groups are similar to each other in terms of RNFL thickness ( $p=0.326$ ), while there is a significant thickening in all choroidal regions of patients with CSU, including NCT, SFCT, TCT, MCT ( $p=0.000$ ,  $p=0.000$ ,  $p=0.000$ ,  $p=0.000$ , respectively).

	CSU group (n=108)	Control group (n=108)	p
Subfoveal Choroidal Thickness ( $\mu\text{m}$ )	$339.17 \pm 37.709$	$276.56 \pm 40.04$	0.000
Nasal Choroidal Thickness ( $\mu\text{m}$ )	$290.11 \pm 43.16$	$248.42 \pm 35.742$	0.000
Temporal Choroidal Thickness ( $\mu\text{m}$ )	$296.00 \pm 42.859$	$253.69 \pm 37.384$	0.000
Mean Choroidal Thickness ( $\mu\text{m}$ )	$308.33 \pm 35.923$	$259.50 \pm 32.986$	0.000
RNFL Thickness ( $\mu\text{m}$ )	$91.11 \pm 7.393$	$92.19 \pm 8.719$	0.326

## DISCUSSION

Although the etiology of CSU is not known exactly, it has been recently revealed that mechanisms such as immunological, inflammatory and coagulation play a role in its pathogenesis (13). As far as we know, our study is the first to examine the effects of this state of inflammation on the choroid and RNFL in patients with CSU. In our study, we found the choroids of CSU patients to be significantly thicker than the control group, but we did not observe any effect on RNFL thickness.

In the studies conducted in recent years, it is observed that a systemic proinflammatory state is dominant in CSU. It has been reported that adiponectin levels are lower in patients with chronic urticaria, and the levels of molecules such as IL-10, IL-6 and TNF-alpha have increased (14). In addition, autoimmunity plays a role in the pathogenesis and high-affinity IgE receptor-specific IgG antibodies have been found in CSU patients. These autoantibodies contribute to inflammation by activating the complement system, mast cells in the skin, and circulating basophils (15). In the pathogenesis of CSU, pathologies have also been found in the coagulation system. Studies have reported that the coagulation cascade is activated in the patients with CSU, and thus an increase in vascular permeability occurs with the effect of thrombin (16). Activation of the coagulation

cascade has also been reported in the skin diseases characterized by increased vascular permeability, such as bullous pemphigoid characterized by increased vascular permeability and angioedema due to C1-inhibitor deficiency (13). It has also been a matter of curiosity whether these existing pathologies are only characterized by the skin. It has been reported that systemic effects due to increased plasma histamine levels in patients with CSU can also be observed (17). Headache, increased gastric acid secretion, tachycardia, decreased arterial pressure, and bronchospasm has been reported as other systemic findings that may occur in CSU (18). Weigert et al. (19) reported that intravenous histamine injection caused an increase in human choroidal blood flow and retinal vessel diameters. In our study, the choroidal thickness of the patients with CSU was found to be thicker than healthy individuals. As far as we know, there is no other study examining choroidal thickness in CSU, so we could not compare our results, but choroidal thickness was examined in various skin diseases. Demirkan et al. (6) reported that the choroidal thickness was thinned in vitiligo patients. Şahin et al. (7) found no change in choroidal thickness in their study of rosacea patients. In addition, the literature has demonstrated that the choroid of patients has been thickened in the active phases of inflammatory diseases with vascular involvement such as lupus and Behçet's disease (20).

The relationship between urticaria and the neurological system has also been investigated in the literature. Wang et al. (21) investigated the functional and structural changes of the striatum in 40 CSU patients and 40 healthy controls and demonstrated striatum dysfunction in CSU. Fumal et al. (22) reported a migraine attack that was presumed to be associated with the systemic release of vasoactive substances such as histamine. Harada et al. (23) presented a case of a 10-year-old boy with cholinergic urticaria associated with epileptic seizures. The neuroectoderm-derived retina, which is an extension of the brain, is also likely to be affected in CSU, but there is no study yet on this subject. Örnek et al. (11) examined RNFL thickness in vitiligo patients and found no difference in RNFL thickness, similar to our study. In our study, we found that the RNFL thickness of the patients with CSU was thinner than healthy controls, but there was no significant difference. We found an increase in choroidal thickness in our study but the absence of any change in RNFL may be due to the difference in the amount of histamine in the tissues. In their tissue study conducted with the eyes that were enucleated secondary to various causes, Nowak et al. (24) reported that the lowest amount of histamine was in the optic nerve and retina and the highest amount of histamine was in the choroid and sclera. Rogosic et al. (25), in a study conducted about vitiligo, it was suggested that there may

be a possible relationship between the duration of vitiligo and glaucoma. They reported that this may be a glaucoma secondary to steroid therapy. Steroids used to treat CSU are likely to affect RNLF. However, patients who have not yet received treatment were examined in our study. This may be why no change has been tracked in the RNFL.

A limitation of the study was the manual measurement of choroidal thickness due to OCT device capability. Therefore, in our study, measurements were made and compared by two independent researchers to check the reliability.

## CONCLUSION

The choroid is affected in CSU and choroidal thickness may be a noninvasive method that can be used in diagnosis and treatment follow-up in CSU. However, data on longer disease durations may provide more illuminating information about CSU and choroid and RNFL.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Niğde Ömer Halisdemir University Noninvasive Clinical Ethics Committee (Date:26.05.2022 Decision No: 2022/69).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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