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Original Article

Evaluation of macular and retinal nerve fiber layer thicknesses in episodic-type cluster headache patients by optical coherence tomography

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Abstract

Aim: This study evaluated macular and retinal nerve fiber layer (RNLF) thicknesses using spectral domain optical coherence tomography (SD-OCT) in patients with episodic-type cluster headaches.

Material and Methods: In total, 33 eyes of 33 patients with episodic-type cluster headaches were included in this study. The eyes were ipsilateral to the pain, and all measurements were performed during attacks. The control group consisted of 33 eyes of 33 age- and sex-matched healthy individuals. The average RNFL thickness and macular thickness (MT) obtained from nine macular areas in the Early Treatment Diabetic Retinopathy Study (ETDRS) were evaluated using SD-OCT (RS-3000; Nidek Inc., Fremont, CA, USA) following a detailed ophthalmologic examination. The results of the two groups were then compared.

Results: The mean RNFL thickness was 104.73 ± 8.7 in the cluster headache patients and 106.86 ± 8.6 in the controls. The difference in RNFL thickness between the groups was not significant (p = 0.418). The MT measurements according to the ETDRS showed statistically significant thinning of the outer temporal area in the cluster headache patients (295.95 ± 13.5 vs. 312.77 ± 15.9 in the controls, p = 0.001). The differences between the two groups with respect to the other ETDRS areas (central macula, superior-inner, inferior-inner, nasal-inner, temporal-inner, superior-outer, inferior-outer, nasal-outer, and total average macula) were not significant (p = 0.482, p = 0.672, p = 0.65, p = 0.679, p = 0.062, p = 0.455, p = 0.818, p = 0.845, and p = 0.189, respectively).

Conclusion: Although the difference in thinning of the internal temporal region was not statistically significant between the patient and control groups, a vascular aetiology leading to thinning of the temporal region and thus to cell damage may contribute to the aetiology of episodic-type cluster headaches.

Keywords: Cluster Headache; Optical Coherence Tomography; Macular Thickness; Retinal Nerve Fiber Layer Thickness.

INTRODUCTION

Cluster headache is a less common type of headache than migraine and tension headaches, with an incidence of 0.1–0.5%. Although cluster headaches can start at any age, from childhood to adulthood, they most commonly develop in the third decade of life. Periodicity and clustering over the course of a year, their localised occurrence unilateral to the first branch of the fifth cranial nerve, and ipsilateral cranial autonomic symptoms are the distinguishing features of cluster headaches, which are the prototype of trigeminal autonomic cephalalgia. The two subgroups of cluster headaches are episodic-type and chronic-type. Most patients have episodic-type cluster headaches, which include painful periods of a few weeks or months interspersed by remission periods. Patients with pain lasting at least 1 year without intermittent remissions or with shorter remissions of 1 month are considered to have chronic-type cluster headaches. In both types, a unilateral headache, consistently localised on the same side, may be accompanied by autonomic manifestations such as an ipsilateral ocular discharge, redness, nasal discharge and obstruction, ptosis, and myosis. While the physiopathology of cluster headaches is not fully understood, genetic susceptibility, cavernous sinus pathologies, and the hypothalamus have been the focus of physiopathological studies (1-5).

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The distribution of pain in cluster headaches suggests the activation of trigeminovascular pathways, while the accompanying autonomic findings suggest changes in the blood flow of the cavernous sinus. Both cluster and migraine headaches involve activation of the trigeminovascular system. Calcitonin gene-related peptide (CGRP), a key neuropeptide that plays a role in the activation of the trigeminovascular nociceptive system, is expressed throughout the trigeminovascular system and acts as a vasodilator. CGRP also participates in the release of parasympathetic vasoactive intestinal peptide (VIP), which is involved in the activation of the cranial parasympathetic nervous system. The latter is associated with the facial vasomotor symptoms (nasal obstructions and discharge) associated with cluster headaches (6-8).

Due to the vascular aetiology of the attacks that characterise cluster headaches, microvascular and structural abnormalities may occur in the retina, which has a metabolic activity level much higher than that of other human tissues. Therefore, in this study, we evaluated the macular and retinal nerve fiber layer (RNFL) thicknesses in patients with episodic-type cluster headaches during attacks. The use of spectral domain (SD)-optical coherence tomography (OCT) allowed us to detect RNFL and macular changes at high resolution, even in patients without clinical symptoms.

MATERIAL and METHODS

In total, 33 eyes that were compatible with headache localisation during the episodic-type cluster headache attacks of 33 patients who were being followed up at Inönü University's Medical Faculty Neurology Department were included in this study. The control group included the eyes of 33 age- and sex-matched healthy individuals.

All study participants were Caucasian, and all gave informed consent before the study commenced, in adherence with the tenets of the Declaration of Helsinki.

Patients with a retinal disease (e.g., glaucoma, diabetes, and retinopathy), with open or closed globe rupture and a history of vitreoretinal surgery, with neurodegenerative diseases such as Alzheimer's or Parkinson's disease, with refractive errors >6 diopters, and with cataracts or any type of corneal disorder were excluded from the study.

Among the patients with episodic-type cluster headaches, during previous episodes 15 had received oral steroids, 14 triptan, and 4 verapamil because of pain resistant to steroids and triptans. OCT measurements were performed during the most recent episode, immediately before medical treatment. Thus, the patients did not receive any systemic treatment during the study.

The patients and controls underwent a comprehensive ophthalmologic examination that included refraction tests, best-corrected Snellen visual acuity testing, tonometry, fundus dilation, and biomicroscopic examination, as well as SD-OCT imaging (RS-3000; Nidek Inc., Fremont, CA, USA). OCT was performed independently by an experienced investigator blinded to the patient's history. Measurements were performed on the eyes ipsilateral to the pain in the patients and in a random eye in the controls.

To obtain a single RNFL thickness value using the software bundled with the OCT device, three consecutive RNFL thickness measurements were performed along a 3.45-mm diameter circle centered on the optic nerve head; the mean value was then calculated (Figure 1) and considered in the statistical analysis.

Macular thickness (MT) measurements were performed in the nine areas defined in the Early Treatment Diabetic Retinopathy Study (ETDRS) using the SD-OCT device's software. The ETDRS areas include a centralised 1-mm disc representing the central MT as well as inner and outer rings, with diameters of 3 and 6 mm, respectively. The two rings are divided into four quadrants: upper, nasal, lower, and temporal (Figure 2). The data from the two groups were compared.

Statistical analysis: SSPS for Windows (ver. 17.0; SSPS Inc., Chicago, IL, USA) was used. A power analysis showed that at least 33 participants were required in each group. The results are expressed as the mean ± standard deviation (SD). Based on the Kolmogorov-Smirnov test, non-parametric statistics were used because the data were not normally distributed. A Wilcoxon test was used to compare the data from the two groups. A p-value <0.05 was considered to indicate statistical significance.

RESULTS

There was no significant difference between the groups in terms of age and sex (p>0.05). The demographic and clinical characteristics of the study and control groups are summarised in Tables 1 and 2.

The mean RNFL thickness was 104.73 ± 8.7 in the cluster headache patients and 106.86 ± 8.6 in the controls. The difference was not statistically significant (p = 0.418).

Evaluation of the MT determined by examining the ETDRS areas showed statistically significant thinning only in the outer temporal area of the headache patients (295.95 ± 13.5 vs. 312.77 ± 15.9 in the controls; p = 0.001). The difference in the other ETDRS areas (central macula, superior-inner, inferior-inner, nasal-inner, temporal-inner, superior-outer, inferior-outer, nasal-outer, and total average macula) of the two groups was not statistically significant (p = 0.482, p = 0.672, p = 0.65, p = 0.679, p = 0.062, p = 0.455, p = 0.818, p = 0.845, and p = 0.189, respectively).

The mean RNFL thickness and MT values and the results of the statistical analyses for each ETDRS quadrant of both groups are shown in Table 3.

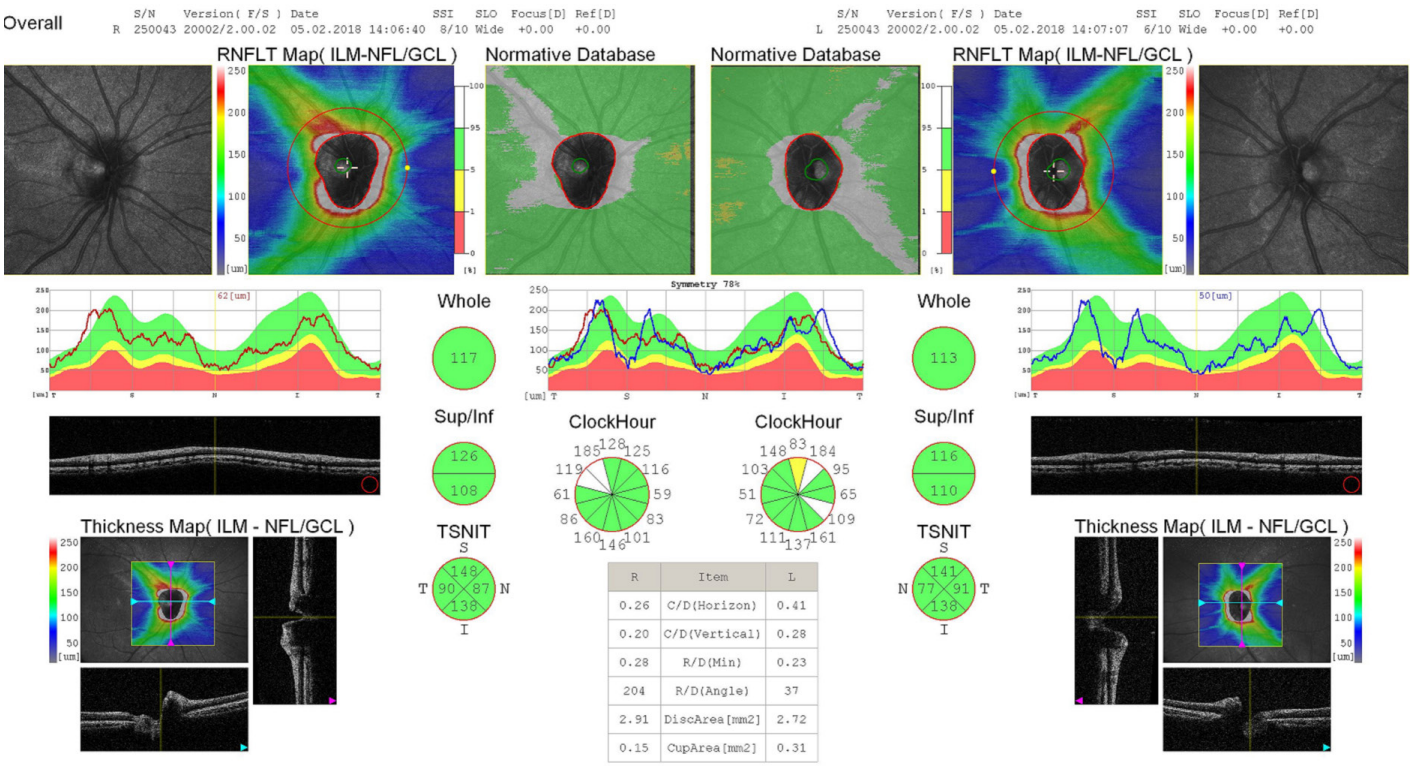

Figure 1. An SD-OCT image showing the RNFL thickness in a patient with episodic-type cluster headaches

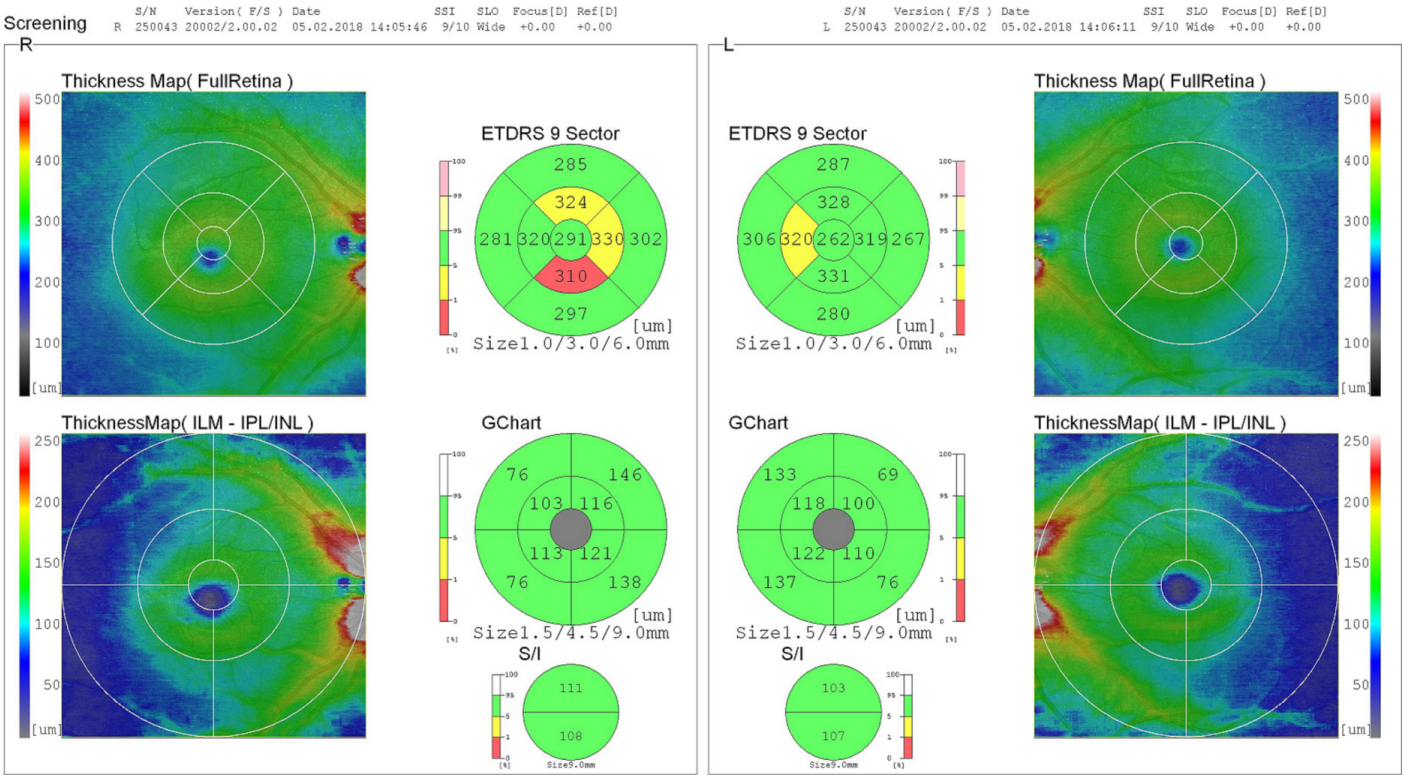

Figure 2. An SD-OCT image showing the MT in a patient with episodic-type cluster headaches

Table 1. Clinical characteristics of the cases in group 1 and group 2

	Group 1	Group 2	p value
Eyes/NOC	33/33	33/33	
Age, mean ± SD	44.54 ± 12.12	41.18± 11.5	0.351
Gender (F/M)	6/27	7/26	0.455
BCVA, snellen, de-cimal ± SD	0.9 ± 0.2	0.9 ± 0.03	0.645
IOP, mmHg, mean ± SD	15.7 ± 2.7	14.2 ± 2.8	0.089

NOC: Number of the cases, SD: Standard deviation, F: female, M: male, BCVA: best corrected visual acuity, IOP: intraocular pressure

Table 2. Clinical characteristics of the patients with episodic type cluster headache

Headache characteristics	
Mean duration of disease (years ± SD)	16.8 ± 9.2
Mean duration of cluster bouts (weeks ± SD)	7.9 ± 4.6
Mean number of attacks per day ± SD	3.2 ± 2.7
Mean duration of attacks (untreated) (min ± SD)	82.9 ± 71.3
Pain localisation (% of patients)	
Periorbital	90.4
Temporal	60.1
Upper jaw	53.9
Lower jaw	21.6
Frontal	38.2
Autonomic symptoms (% of patients)	
Lacrimation	91.8
Eyelid swelling	42.9
Rhinorrhoea	80.7
Facial sweating	48.4
Ptosis and/or miosis	30.6
Symptoms of aura (% of patients)	31.7
Current smoker (% of patients)	79.7

SD: Standard deviation

Table 3. The mean RNFL and macular thickness of the cases in group 1 and group 2

ETDRS area	Mean MT ± SD (µm)		p value
	Group 1	Group 2	
Central macula	275.5 ± 31.2	281.0 ± 17.3	0.482
SI	343.4 ± 16.7	341.0 ± 17.1	0.672
TI	329.4 ± 16.3	338.2 ± 14.1	0.062
II	341.1 ± 22.1	338.2 ± 17.9	0.65
NI	345.3 ± 18.4	347.5 ± 16.2	0.679
SO	308.8 ± 13.8	312.1 ± 14.1	0.455
TO	295.9 ± 13.5	312.7 ± 15.9	0.001
IO	301.4 ± 14.6	300.3 ± 15.3	0.818
NO	321.8 ± 13.1	322.7 ± 17.2	0.845
TAM	317.3 ± 11.9	321.3 ± 7.4	0.189
RNFL	104.7 ± 8.7	106.8 ± 8.6	0.418

ETDRS: early treatment diabetic retinopathy study, MT: macular thickness, SD: standard deviation, SI: superior-inner, TI: temporal-inner, II: inferior-inner, NI: nasal-inner, SO: superior-outer, TO: temporal-outer, IO: inferior-outer, NO: nasal-outer, TAM: total average macula, RNFL: retinal nerve fiber layer, statistically significance

DISCUSSION

In this study, OCT was used to examine 33 eyes of 33 patients with episodic-type cluster headaches and the data were compared to those obtained from 33 healthy controls. The results show that the RNFL values of the two groups did not differ significantly, but, among the nine ETDRS areas, a statistically significant difference between the patient and control groups was detected only for the outer temporal area, which was significantly lower in patients with episodic-type cluster headaches than in controls.

Primary headaches contain migraine, tension, cluster headaches, and paroxysmal hemicrania. The retino-hypothalamic-pineal (RHP) axis has been implicated in the pathophysiology of primary headaches in terms of retinal dysfunction, hypothalamic dysfunction and human circadian regression impairment, pineal melatonin dysfunction, and rostral limbic dysfunction mediated by the stress response. According to the combined RHP hypothesis, acute, periodic, or chronic circadian desynchronisation and the dysfunction of all or part of the RHP axis play an important role in the pathophysiology of primary headaches (9). Recent positron emission tomography studies showing alterations in the dorsal pons, hypothalamus, and rostral limbic structures provide supportive evidence for the RHP hypothesis (9,10). We therefore searched for evidence of retinal damage in patients with episodic-type cluster headaches.

Cluster headaches with ocular changes during attacks have been reported in several studies (11,12). Increased intraocular pressure and corneal indentation pulse amplitudes ipsilateral to the pain suggest the involvement of intraocular vasodilation leading to a volume increase

in the intraocular vascular bed (13). Pathological orbital phlebograms showed partial or complete contraction of the superior ophthalmic vein ipsilateral to the pain (14), while magnetic resonance angiography studies unclosed dilated ophthalmic arteries ipsilateral to the pain(15). Dilation of the internal carotid artery and its branches from the cavernous level can be elucidated by the inhibition of sympathetic vasocontractile fibers or the 'trigeminal-autonomic neurogenic vasodilator mechanism' associated with nonspecific pain (16).

Activation of the trigeminovascular system during cluster headaches causes the release of vasodilator agents such as CGRP and VIP into the bloodstream, where they affect ocular blood flow. The resulting tissue hyperperfusion can lead to microvascular changes in the retina, tissue damage (17), and ganglion cell damage, which manifests as a reduction in the thickness of the RNFL. OCT can be used to evaluate RNFL and macular thicknesses. It is a reliable, reproducible, and noninvasive imaging technique in the evaluation of retinal diseases. Although in our study of patients with cluster headaches there was no statistically significant difference in the RNFL thickness of patients and controls, an assessment of MT showed statistically significant thinning of the outer temporal area among the nine ETDRS areas.

Ewering et al. (18) also revealed a reduction in RNFL thickness in the temporal and temporal inferior regions in both eyes of patients with cluster-type headaches and a reduction in the temporal-inferior region ipsilateral to the pain. The same study showed a significant decrease in the MT of patients with chronic-type cluster headaches compared to healthy controls and patients with episodic-type cluster headaches. Moreover, the temporal RNFL thickness was reduced in patients who received 100% oxygen therapy compared to healthy controls and patients who did not receive oxygen therapy. In that study, RNFL thinning was shown to result from both the systemic effect of cluster headaches and the effect of treatment. Our patients with episodic cluster headaches, and thus with no history of no chronic drug or oxygen use, also had thinning of the outer temporal region. However, as they received systemic treatment only during attacks, alterations in retinal thickness due to systemic medications were unlikely. In addition, unlike in the study of Ewering et al. (18), we examined only eyes ipsilateral to the pain, not both eyes, and included only patients with episodic-type cluster headaches, not patients with chronic-type headaches. Thus, differences between the results of our study and the above-cited study can be expected.

Regional RNFL thinning has also been documanted in migraine patients. Cankaya and Tecellioglu (19) reported a decrease in foveal thickness in migraine patients, in particular in migraine with aura. Gipponi et al. (20) also found a decrease in RNFL thickness in migraine patients, regardless of the duration and frequency of the disease. The proposed mechanism of vasoconstriction in the retinal vessels leading to permanent structural changes in the retinal tissue (19,20) is similar to that suggested by our results for cluster type headaches: impaired ocular blood flow related to a trigeminovascular aetiology that leads to damage to the retinal layers.

Our study has several limitations. First, more statistically reliable results would have been obtained by the inclusion of more patients. Second, as the main goal of our study was to detect retinal changes during attacks, patients with chronic cluster headaches could have been included as a second study group. Third, various sources of error may be present in all OCT devices. To minimise the errors associated with the use of our device, all measurements were performed by the same operator and repeated three times, with the mean value then recorded. Fourth, although our patients did not use any systemic medication during the attacks, in previous episodes 15 patients had received oral steroids, 14 triptan, and 4 verapamil. Of these, tryptan is a particularly vasoactive agent and may have had an effect on ocular blood flow; however, Schmetterer et al. (21) found that this drug has no apparent effect on the ophthalmic artery. Verapamil is a calcium channel blocker and its neuroprotective effect on the retina has been reported (22). Thus, it was unlikely to have been a restrictive factor in retinal tissue in our study. The many effects of systemically used steroids on ocular tissues, including cataract formation, increased intraocular pressure, central serous chorioretinopathy, and diffuse retinal pigment epitheliopathy (23), are well known whereas topical, intravitreal, or systemic steroids have long been used in the treatment of many ocular diseases such as intraocular inflammation and macular edema.

CONCLUSION

In conclusion, in our study of patients with episodic-type cluster headaches, RNFL thinning, particularly in the outer temporal region, as measured by SD-OCT during attacks, supports a trigeminovascular aetiology and the involvement of the RHP axis in the physiopathology of the disease. Our results also demonstrate decreased retinal perfusion in these patients, as described in those with other types of primary headache.

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