Does The Presence of Photophobia Affect Optical Coherence Tomography Findings in Tension-Type Headache?

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ABSTRACT

Purpose: The retinochoroidal evaluation in tension type headache (TTH) was aimed in this study.

Materials and Methods: This case-controlled study conducted in Ordu University Training and Research Hospital included 92 patients, 62 of whom with TTH. Group 1 included 30 (32.6%) TTH patients with photophobia, Group 2 included 32 (34.8%) TTH patients without photophobia and Group 3 included 30 (32.6%) healthy control (HC) subjects. All patients underwent complete neurological and ophthalmological examinations including optical coherence tomography (OCT).

Results: Subfoveal choroidal thickness (SCT) value was measured significantly higher, whereas average ganglion cell-innerplexiform layer (GCIPL) thickness, GCIPL in the superior and superonasal sectors were measured significantly lower in Group 1 compared to Group 3. Comparing Group 1 and 2, SCT was significantly thicker and GCIPL thickness in the superonasal sector was significantly thinner in Group 1. When total patients with TTH taken into consideration, TTH patients demonstrated a thicker SCT and thinner GCIPL thickness in the superior and superonasal sector than the controls.

Discussion: TTH seems to demonstrate thicker SCT and thinner GCIPL in selected sectors, with the photophobia accentuating these effects.

Keywords: Choroid, Optical coherence tomography, Photophobia, Retina, Tension type headache.

INTRODUCTION

Tension-type headache (TTH), is the most prevalent primary headache disorder worldwide, with a high economic burden over society decreasing quality of life and productivity.[1,2] TTH affect up to 46 % of world population, with a female dominance, however, unlike migraine male-to-female ratio is 4:5. The highest prevalance is between the ages of 30 and 39 for both genders, and diminishes thereafter.[1,3,4] According to the most recent classification by International Classification of Headache Disorders (3th edition) in 2013, physical activity does not aggrevate pain but mild nausea, photophobia, or phonophobia may accompany pain.[5]

Eventhough the pathogenesis of TTH has not been enlightened yet, environmental factors possess more impotance than in migraine. TTH has been linked to a complex interaction of peripheral [6] and central factors[7], as well as genetic[8] and psychological factors.[9] Possible associations had been demonstrated such as vitamin D deficiency[10] and elevated interleukin-1 levels proposing the role of neurovascular inflammation[11] and oxidative stress[12] in the pathogenesis.

With regard to a recent review, migraine patients are prone to ischemic type injury in the optic nerve, retina, and choroid owing to the transient recurrent vasoconstriction in the retinal and ciliary arteries during attacks.[13] Meta-analysis by Feng et al. demonstrated that retina seems to be altered in patients with migraine, especially if aura exists, correlated with severity of migraine.[14] According to continuum severity model, due to similarities between migraine and TTH, they are regarded as points on a severity scale, with migraine representing a more severe form.[15] However, there is no report in the literature reporting choroidal involvement in addition to retinal involvement in TTH.

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In context of these, the evaluation of the retina and choroid via optical coherence tomography (OCT) in TTH was aimed.

MATERIALS AND METHODS

This study conducted in neurology and ophthalmology departments of a tertiary university hospital, was performed in accordance with the Declaration of Helsinki and was approved by the local ethics commitee. All participants provided written informed consent.

The inclusion criteria were defined as diagnosis of TTH according to "The International Classification of Headache Disorders".[5]

The exclusion criteria were defined as history of significant ocular disease, ocular surgery, ocular trauma or tumour; refractive measurement of more than 3.0 diopters; best corrected visual acuity (BCVA) of less than 8/10, axial length (AL) of more than 25 mm, intraocular pressure (IOP) of more than 21 mm Hg, with a cup-to-disc ratio of more than 0.4, any kind of amblyopia, history of glaucoma, uveitis, any retinal diseases, any opacities leading to poor image quality (signal strength of less than 7/10), chronic obstructive pulmonary diseases, smoking, sleep apnea, optic disc anomaly, history of optic neuritis, peripapillary atrophy, body mass index of more than 25 and history of neurogenerative diseases.

A total of 92 patients were enrolled in the study, 62 of whom with TTH. Group 1 included 30 (32.6%) TTH patients with photophobia, Group 2 included 32 (34.8%) TTH patients without photophobia and Group 3 included 30 (32.6%) healthy control (HC) subjects.

All of the patients were recruited from Neurology department with the diagnosis of TTH. A detailed medical history was obtained from each patient and present medications were recorded. Patients underwent a full ophthalmologic examination including BCVA assessment, slit-lamp examination, hand-held tonometry (i-Care TA01i, Tiolat Oy, Helsinki, Finland) and fundus examination. All of the measurements and ocular examination were executed by a single physician. AL was measured with combined biometric pachymeter (PacScan 300AP Digital Biometric Ruler; SonoMed, Lake Success, NY). Following pupil dilation with tropicamide 1% central macular thickness (CMT), retinal nerve fiber layer (RNFL) thickness, ganglion cell-innerplexiform layer (GCIPL) thickness and subfoveal choroidal thickness (SCT) was assessed with OCT (Cirrus HD-OCT, Carl Zeiss Ophthalmic System Inc, Zeiss-Humphrey, Dublin, California, USA).

An experienced single physcian manually measured the SCT by EDI-OCT between 10 AM and 11 AM. The macular cube scan 512 × 128 protocol was used to evaluate CMT. The peripapillary RNFL thickness was measured by an optic disc cube 200x200 scan protocol centered on the optic disc. GCA software was used to evaluate the thickness of the GC-IPL.

Statistical analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distributions of continuous variables were normal or not was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± SD. Categorical data were described as number of cases. Categorical variables were compared using Fisher's exact test Pearson's chi-square test. Statistical analysis differences in normally distributed variables between three independent groups were compared by one way anova test were applied for comparisons of the not normally distributed data. When the p-value from One-Way ANOVA test statistics were statistically significant post hoc tukey test were used to know which group differ from which others. The diagnostic accuracy of parameters to differentiate between normal and patient eyes was determined by calculating the areas under the receiver-operating characteristic (ROC) curves. It was accepted p-value < 0.05 as significant level on all statistical analysis.

RESULTS

A total of 92 eyes of 92 patients who met the inclusion criteria were enrolled in this study.

Group 1 consisted of 24 female (80.0 %) and 6 male (20.0 %) TTH patients with photophobia and the mean age was 33.83 ± 9.71 (mean±SD; SD: Standart Deviation) years. Group 2 included 26 female (81.0 %) and 6 male (19.0 %) TTH patients without photophobia and the mean age was 33.53 ± 13.65 years. Group 3 included 27 female (90.0 %) and 3 male (10.0 %) healthy controls and the mean age was 32.90 ± 10.29 years.

No statistically significant differences were observed among the groups in terms of age, gender, BCVA, IOP, and AL (p=0.949; p=0.598; p=0.411; p=0.763; p=0.537). The characteristics of patients in groups are demonstrated in Table 1.

OCT parameters in groups are demonstrated in Table 2. Mean SCT in Group 1, Group2, and Group 3 was measured as 283,13±16,41 (241-307), 266,72±28,76 (218-308), and 265,73±20,64 (222-299) respectively. Mean SCT in Group 1 was found to be statistically higher than Group 2 and

Table 1: *Characteristics of patients.*

		Group 1		Group 2		Group 3		P
Gender	Male	6	20.0%	6	19.0%	3	10.0%	0,598
	female	24	80.0%	26	89.0%	27	90.0%	
Age (years)		33.83	±9.71	33.53	±13.65	32.90	±10.29	0.949
BCVA (snellen)		0.99	±0.04	0.99	±0.04	1.0	±0.0	0.411
IOP (mmHg)		15.17	±3.71	14.50	±3.89	14.60	±3.83	0.763
AL (mm)		22.28	±1.26	22.02	±1.27	22.22	±1.27	0.537

Continuous variables are expressed as either the mean ± standard deviation (SD) and categorical variables are expressed as either frequency or percentage and the p value was set at 0.05. Statistically significant p-values are in bold. Abbreviations: BCVA: Best corrected visual acuity; IOP: Intraocular pressure; AL: Axial length

Table 2: *OCT parameters in groups.*

	Group 1		Group 2		Group 3		p
SCT	283.13	16.41	266.72	28.76	265.73	20.64	1-2=0.015 1-3=0.011 2-3=0.984
CMT	251.77	12.34	251.78	19.89	252.57	15.25	0.976
RNFL							
Average	98.47	6.48	99.78	7.23	100.57	7.60	0.516
Superior	108.53	7.28	111.47	8.16	112.10	6.23	0.134
Inferior	121.37	7.49	122.13	8.46	123.77	5.06	0.419
Nasal	74.60	5.70	74.00	9.78	73.97	5.37	0.930
Temporal	68.80	6.70	68.78	6.00	68.10	5.87	0.882
GCIPL							
Average	79.47	2.92	81.47	4.87	82.03	2.71	1-2=0.086 1-3=0.022 2-3=0.817
Minimum	76.30	2.65	76.53	2.50	77.27	2.53	0.315
Superior	79.17	2.63	79.69	3.26	81.43	3.20	1-2=0.780 1-3=0.014 2-3=0.068
Inferior	78.77	3.87	79.72	3.13	79.23	1.76	0.474
Superonasal	79.37	3.27	81.19	2.35	82.43	2.31	1-2=0.024 1-3<0.001 2-3=0.165
Superotemporal	81.80	1.95	81.38	1.34	82.33	1.45	0.067
Inferonasal	78.80	1.97	78.47	1.67	79.10	1.65	0.375
Inferotemporal	80.50	1.59	80.63	2.32	80.93	2.00	0.690

Continuous variables are expressed as either the mean ± standard deviation (SD) and categorical variables are expressed as either frequency or percentage and the p value was set at 0.05. Significant differences were found between; Statistically significant p-values are in bold. Abbreviations: SCT: Subfoveal choroidal thickness; CMT: Central macular thickness; RNFL= Retinal Nerve Fiber Layer; GCIPL= Ganglion Cell Inner Plexiform Layer

Group 3 (p=0,015 ve p=0,011), whereas, there was no statistically significant difference between Group 2 and Group 3 (p=0,984).

No statistically significant difference was detected betweeen groups regarding CMT and RNFL thicknesses (p>0.05), despite lower values are recorded in Group 1 in average RNFL thickness and in the superior and inferior quadrants.

Mean average GCIPL thickness was measured as 79,47±2,92 (72-86), 81,47±4,87 (71-94), and 82,03±2,81 (71-86) in Group 1, Group 2, and Group 3, respectively. Mean average GCIPL thickness in Group 1 was found to be statistically lower than Group 3 (p=0.022), whereas, there was no statistically significant difference between Group 1 and Group 2 (0.086) and between Group 2 and Group 3 (p=0,817).

Mean GCIPL thickness in superior sector was measured as 79,17±2,63 (70-83), 79,69±3,26 (69-85), and 81,43±3,20 (72-85) in Group 1, Group 2, and Group 3, respectively. Mean GCIPL thickness in superior sector in Group 1 was found to be statistically thinner than Group 3 (p=0,014), whereas there was no statistically significant difference between Group 1 and Group 2 (0.780) and between Group 2 and Group 3 (p=0,068).

Mean GCIPL thickness in superonasal sector was measured as 79,37±3,27 (72-85), 81,18±2,35 (76-85), and 82,43±2,31 (78-89) in Group 1, Group 2, and Group 3, respectively. Mean GCIPL thickness in superonasal sector in Group 1 was found to be statistically thinner than Group 2 and Group 3 (p=0,024 and p>0,001), whereas, there was no statistically significant difference between Group 2 and Group 3 (p=0,165).

The comparison of total patients with TTH with the control group regarding OCT parameters is demonstrated in Table 3. No statistically significant differences were observed among the groups in terms of age, gender, BCVA, IOP, and AL (p=0.983; p=0.370; p=0.157; p=0.748; p=0.429).

Table 4 shows the OCT characteristics of patients with TTH and HCs. Mean SCT in patients with TTH and HCs was measured as 274,66±24,84 and 265,73±20,64 respectively. Mean SCT in TTH patients was found to be statistically higher than the HCs (p=0,015).

No statistically significant difference was detected betweeen groups regarding CMT and RNFL thicknesses (p>0.05), despite lower values are measured in TTH patients in average RNFL thickness and in the superior and inferior quadrants, compared to HCs.

Table 3: *Comparison of parameters in patients with TTH and controls.*

		TTH		Control		P
Gender	Male	12	19.35%	3	10.0%	0.370
	Female	60	80.65%	27	90.0%	
Age (years)		33.67	±11.81	32.90	±10.29	0.983
BCVA (snellen)		0.99	±0.04	1.0	±0,0	0.157
IOP (mmHg)		14.82	±3.79	14.60	±3.83	0.748
AL (mm)		22.14	±1.26	22.22	±1.27	0.429

Continuous variables are expressed as either the mean ± standard deviation (SD) and categorical variables are expressed as either frequency or percentage and the p value was set at 0.05. Statistically significant p-values are in bold. Abbreviations: BCVA: Best corrected visual acuity; IOP: Intraocular pressure; AL: Axial length

Table 4: *Comparison of OCT parameters in patients with TTH and controls.*

	TTH		Control		P
SCT	274.66	24.84	265.73	20.64	0.015
CMT	251.77	16.54	252.57	15.25	0.426
RNFL					
Average	99.15	6.85	100.57	7.60	0.411
Superior	110.05	7.82	112.10	6.23	0.213
Inferior	121.76	7.95	123.77	5.06	0.337
Nasal	74.29	8.01	73.97	5.37	0.844
Temporal	68.79	6.3	68.10	5.87	0.448
GCIPL					
Average	80.5	4.14	82.03	2.71	0.069
Minimum	76.42	2.56	77.27	2.53	0.076
Superior	79.44	2.96	81.43	3.20	<0.001
Inferior	79.26	3.52	79.23	1.76	0.260
Superonasal	80.31	2.96	82.43	2.31	0.002
Superotemporal	81.58	1.66	82.33	1.45	0.051
Inferonasal	78.63	1.81	79.10	1.65	0.206
Inferotemporal	80.56	1.99	80.93	2.00	0.535

Continuous variables are expressed as either the mean ± standard deviation (SD) and categorical variables are expressed as either frequency or percentage and the p value was set at 0.05. Significant differences were found between; Statistically significant p-values are in bold. Abbreviations: SCT: Subfoveal choroidal thickness; CMT: Central macular thickness; RNFL= Retinal Nerve Fiber Layer; GCIPL= Ganglion Cell Inner Plexiform Layer

Mean GCIPL thickness in superior sector was measured as 79,44±2,96, and 81,43±3,20 in patients with TTH and HCs, respectively. Mean GCIPL thickness in superior sector in TTH patients was found to be statistically thinner than the HCs ($p<0.001$).

Mean GCIPL thickness in superonasal sector was measured as 80,31±2,96 and 82,43±2,31 in patients with TTH and HCs, respectively. Mean GCIPL thickness in superonasal sector in TTH patients was found to be statistically thinner than the HCs ($p=0.002$).

Further analysis of ROC curves regarding cutoff values for SCT, GCIPL in the superior and superonasal sectors in the diagnosis of TTH and cutoff values for SCT, average GCIPL and GCIPL in the superior and superonasal sector in determination of photophobia are shown in Figure 1 and Figure 2, respectively.

DISCUSSION

Central sensitization owing to the sustained input generated in pericranial muscles by inflammation, diminished blood flow, muscle hyperactivity, and finally muscular atrophy, seems to be the major determinants in the pathogenesis of TTH. [7,16,17,18]

Considerable overlap between migraine and TTH regarding symptoms such as neck pain, photophobia and phonophobia, response to treatment, and pathophysiology including central sensitization, introduced the continuum severity model, situating the migraine at the end of the spectrum.[13] Although pathophysiology of migraine is not clear yet, the trigeminal vascular system through vasoactive neurotransmitters is thought to be involved in migraine attacks.[19,20] The retina and choroid may be involved during these vasospasm related hypoperfusion episodes in migraine. In fact, in a recent review, OCT changes demonstrated retrograde trans-synaptic neuronal degeneration (RTSD) of the retinal ganglion cells (RGCs) possibly due to cerebral and retrobulbar vasospasm episodes suggesting OCT as a biomarker of RTSD of the RGCs.[14] Although there are discrepancies in different studies, a recent meta-analysis reported thinner peripapillary RNFL in migraine compared to controls, in correlation with duration of the migraine, more prominent in patients with aura.[15] There are conflicting results over choroidal thickness in migraine patients, in the literature.[21,22]

Following the demonstration of similar visual field defect patterns in the attack periods of migraine and TTH[23], authors evaluated migraineurs and TTH patients using the Swept source-OCT[24], however could not be able to demonstrate a difference between the headache groups and control patients. In the current study, despite lower in the superior and inferior quadrants, no significant difference regarding RNFL thickness was demonstrated between groups. On the other hand, in respect to macular GCIPL, significant reduction in superior and superonasal sectors was detected in the TTH patients compared to controls.

In definition, photophobia is light-induced discomfort in the eye or head and /or avoidance reaction without overt pain[25],

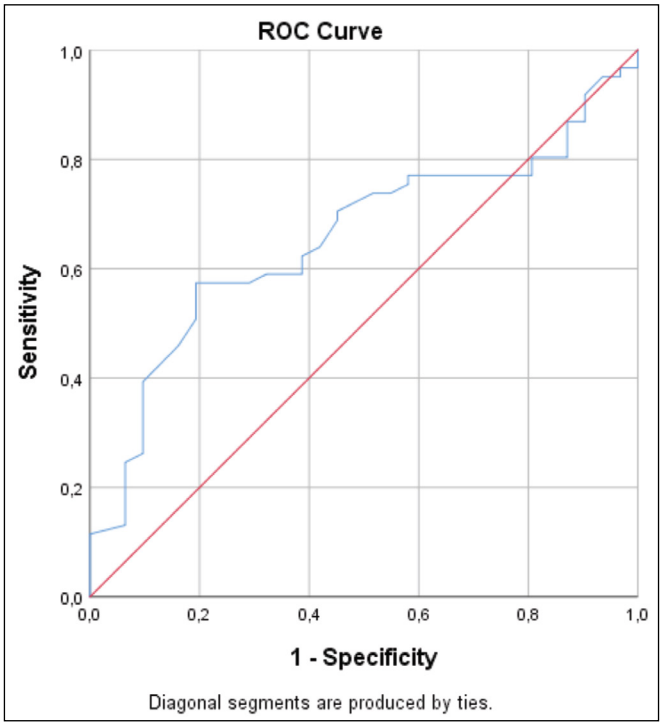

Figure 1: *Receiver-operating characteristic (ROC) curves for SCT in tension type headache patients.(AUC:0.657).*

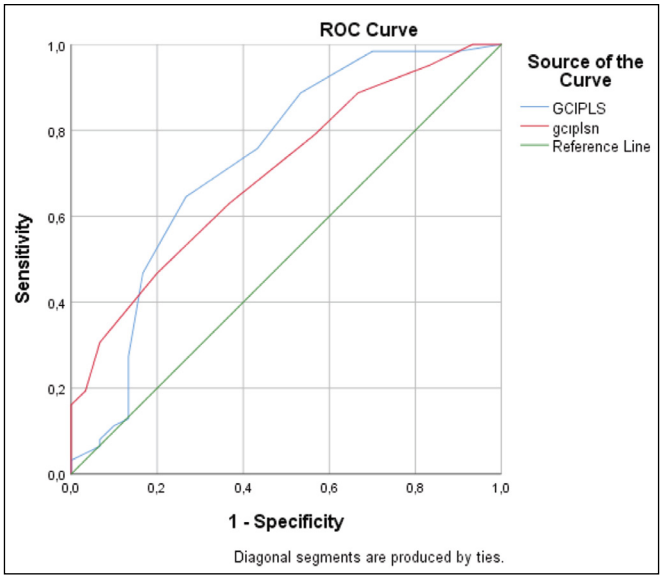

Figure 2: *Receiver-operating characteristic (ROC) curves for macular GCIPL thickness in superior and superonasal sectors in tension type headache patients (AUC:0.730, AUC:0.701).*

due to the action of transducers known as intrinsically photosensitive retinal ganglion cell (ipRGC), containing pigment melanopsin[26], in addition to known retinal photoreceptors. Three pathways converting light to painful stimulus are described as the pathway between ipRGCs and pain centers in the thalamus[27], trigeminal nerve and trigeminal nerve efferents through retinal photoreceptors, with the consequent ocular vasodilation and activation of pain-sensing neurons in blood vessels[28], and direct stimulation of the trigeminal afferents, possibly via ipRGCs and/or ipRGC-like melanopsin-containing neurons of the iris.[29] Neuropeptides playing role in synaptic transmission are calcitonin gene related peptide (CGRP) and pituitary adenylate cyclase activating polypeptide which are also involved in migraine type headache.[30] ipRGCs comprise only 1% of total RGCs; and sparsely distributed among the classically defined RGCs related with vision[31], with the superior and temporal retinal predilection.[32,33] Involved in non-image forming functions of the eye, ipRGCs are relatively more durable than other subtypes of RGC.[34] In this current study we also evaluated the TTH patients with photophobia and compared with TTH patients who do not experience photophobia. Despite thinner in the superior and inferior quadrants, no significant difference regarding RNFL thickness was demonstrated between groups, including the controls. On the other hand, in respect to macular GCIPL, significant reduction in superior and superonasal sectors and in average GCIPL was detected in the TTH group with photophobia compared to controls. TTH patients with photophobia revealed significantly lower GCIPL thickness in the superonasal sector compared to TTH patients without photophobia.

RGCs, most abundant in the macular area forms stratified multicellular layers within the central 6 degrees of visual field. Hence, any insult resulting in loss of axons and the corresponding soma in this location will cause thinning in the RGC layer. Besides axons, blood vessels and glial elements, may also affect the RNFL thickness. However, the lack of large retinal vessels in the macular area makes the ganglion cell layer measurements more accurate.[35] Therefore, this reduction observed in the current study in macular GCIPL thickness in the absence of RNFL involvement, may be attributed to the anatomic characteristics of macular area which is devoid of vasculature and glial elements and/or the insufficient time elapsed from the beginning of the insult to the evaluation. Increase in blood flow may be hypothetized to obscure the changes in the RNFL layer especially in the short term, in other words, in the beginning of the disease process. However further investigations may demonstrate different results in patients with longer disease duration or more frequent attacks of TTH than our study. This may also be the reason why conflicting results are measured in migraineurs. Photophobia seems to exaggarate the results obtained in GCIPL parameters.

Mean SCT in TTH patients with photophobia was found to be statistically higher than TTH patients without photophobia and control group. In addition the mean SCT in total TTH patients was found to be statistically higher than the controls. The choroidal blood flow is under neural control, with parasympathetic, sympathetic and sensorial innervation. Sensory nerve fibers of trigeminal ganglion contain neurotransmitters substance P and CGRP[36] causing ocular and choroidal vasodilatation. The sensory input conveys pain centrally and cause vasodilation with an increase in choroidal blood flow. The continuous stimulation from multiple trigger points from multiple sensitive muscles in TTH may be the result of this increase in SCT in TTH patients prominent in the photophobia subgroup.

The limitations of this study are the absence of the OCT parameters relation with the severity of the pain and photophobia and relatively small size of the groups. This is the first study regarding choroidal evaluation in addition to retinal assesment in TTH patients with and without photophobia.

CONCLUSION

TTH results in significant increase in SCT and thinning in GCIPL on OCT recordings, more exaggarated in TTH patients with photophobia, in relation with the pathogenesis. These findings may render OCT a contributory tool for enlightening the pathogenesis.

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