

Investigating Nerve Fiber Layer and Retinal Ganglion Layer Cells in Patients with Essential Tremor

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Article Info

 [10.30699/jambs.31.148.441](https://doi.org/10.30699/jambs.31.148.441)

Received: 2023/01/17;

Accepted: 2023/04/24;

Published Online: 29 Oct 2023;

Use your device to scan and read the article online



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ABSTRACT

Background & Objective: Based on literatures, the patients with essential tremor have a thinner Retinal Nerve Fiber Layer (RNFL) layer in Optical Coherence Tomography (OCT) imaging, compared to the healthy population. Thus, we decided to examine the ocular-neural state of patients with essential tremor, by examining RNFL and Retinal Ganglion Cell Layer (RGCL) in the OCT reports of patients referred to Hazrat Rasool Akram Hospital in the years 2020 to 2022.

Materials & Methods: This research was implemented in the form of case-control study. 50 patients were recruited into each group of tremor, and healthy controls. OCT parameters, including thickness of RNFL and RGCL were evaluated and recorded.

Results: The study findings revealed a significant difference in the mean superior, superior nasal, superior temporal sections of the right eye and superior temporal and inferior temporal regions of the left eye in RNFL between the control group and all patients ($P < 0.01$). Moreover, the results showed that there was a significant difference in the GCL in superior 6 mm of the right and left eye between the control group, and all patients ($P < 0.01$).

Conclusion: Regarding the results this study, it seems that patients with essential tremor have a significant decrease in some RNFL and GCL factors compared to healthy people. However, the majority of variables examined from RNFL and GCL in our study did not show significant differences. Moreover, this thinning could be associated with the neurodegenerative nature of the disease.

Keywords: Essential Tremor, Optical Coherence Tomography, Retinal Ganglion Cell Layer, Retinal Nerve Fiber Layer

Introduction

A part of the body that is relatively rhythmic and oscillating is said to have a tremor, which is defined as abnormal, hyperkinetic, rhythmic, and involuntary motions induced by the alternating contraction of agonist and antagonist muscles. The most typical involuntary movement that may affect the hands, arms, head, face, voice chords, chest, and legs is a tremor. In many people, tremors are a sign or symptom of a neurological disorder in the body (1, 2). Essential tremor is a chronic and progressive disease in the form of kinetic tremors in the hands and arms with a frequency of 4-12 Hz, which usually involves both sides of upper limbs and occurs during voluntary movements such as writing or eating (3, 4). Based on studies, essential tremor was found to be the most common movement disorder. This tremor can

remain mild and benign in some people, whereas it can slowly progress in others; in which it starts first on one side of the body, and progresses to the other side in less than three years, with a minimum duration of 3 years. This tremor may occur in different parts of the body, such as the head (neck), vocal cords, mandible and lower limbs. It is not followed by other associated symptoms, such as parkinsonism, ataxia or dystonia (4, 5).

Although essential tremor may occur at any age, its prevalence increases with age. Studies report a prevalence of approximately 0.9% in all ages, and 4.6% particularly in people over 65. The patient's medical history and results of any neurological exams are used to establish the disease's diagnosis. No particular laboratory indicator or unique imaging technique may be used to confirm the

diagnosis (4, 6). Genetic transmission of essential tremor is mostly autosomal dominant with incomplete penetrance, and sometimes it is seen in other family members as well. However, polygenic inheritance was shown in some families (7).

The pathogenesis of essential tremors was not fully understood yet. Researchers have suggested that essential tremors may be caused by abnormal central dysfunction in Guillain-Mollaret triangle. The cerebellum plays an important role in the pathogenesis of this disease (8-10). Researchers think that essential tremor has a brain origin, while brain scans of these patients are completely normal. As a result, the pathogenesis is still not completely understood. Recent studies (11-14) have found the immobility of this condition, including cerebellar symptoms, olfactory dysfunction, hearing disorder, cognitive impairments, sleep abnormalities, behavioral symptoms, and other personality features.

The thickness of retinal nerve fiber layer (RNFL) in the patients with Parkinson's disease was documented in several studies, and the results are reported as decrease in the thickness of the RNFL (8, 13, 14). Optical coherence tomography (OCT) is a tool used to evaluate retinal nerve fiber layer of the anterior visual pathway.

Abnormal OCT was noticed in other neurodegenerative diseases, such as Alzheimer's disease, multiple sclerosis and cerebellar spinal ataxia, which is most likely related to the loss of retinal ganglionic cells (RGCs) and axons, thereby decreasing the thickness of RNFL (15, 16). The diagnostic utility of RNFL and macular inspection as a technique to monitor the course of neurodegenerative disorders including Parkinson's disease and multiple sclerosis has been shown in earlier research. The neurodegenerative aspect of essential tremor disorder is covered in few publications. As observed by OCT tool, the thickness of the retinal nerve fiber layer, ganglion cell layer, internal plexiform layer and choroid plexus in these patients is significantly less than normal people (17).

Considering these findings, and the importance of accurate diagnosis of essential tremor disease, and to rule out other causes of tremor in the patients, we decided to conduct a case-control study to examine an ocular-neurological examination of patients with essential tremor, based on which early diagnosis of the patients is facilitated and necessary measures are taken in time.

Materials and Methods

This study was conducted in the form of a case-control study. The required approvals were secured before the research could commence in order to gather different data from patients at the Hazrat Rasool Akram (PBUH) Hospital who had neurological diseases and had essential tremor disease. The researchers adhered to the principles

of Declaration of Helsinki throughout the study. The study was registered at the ethics committee of Iran University of Medical Sciences with the code IR.IUMS.FMD.REC.1399.881.

The study consisted of two groups of 50 patients each, one as healthy control and one as the patients with essential tremor (case group). The control group was made up by recruiting as many healthy individuals as the same number of the patients in case group. The individuals were randomly selected from the community and had no nervous or ocular diseases in addition to normal OCT results.

Patients who referred to the neuromuscular disorder clinic of Rasul Akram Hospital from 2020 to 2022, in terms of the tremors for diagnosis or follow-up, were assessed for inclusion. Further inclusion criteria were: clinical approval of essential tremor, and essential tremor plus by two movement disorders specialists. Exclusion criteria were diseases with signs and symptoms of neurodegenerative disease, alcohol consumption, history of Parkinson's disease or dyskinesia disorders based on UK bank criteria (18), and retinal nerve fiber layer disease (glaucoma, ischemic optic neuropathy...), present of a significant cognitive impairment (Mini-Mental Status Examination <24), and the presence of diseases with pain, anxiety and depression symptoms (19).

Age, gender, and family history of essential tremor were collected, as well as information on the subtype of the disease (essential tremor or essential tremor plus), the thickness of the RNFL layer in the quadrants (superior, inferior, temporal, and nasal), and the thickness of the RGC layer in the quadrants (superior, inferior, temporal, and nasal) in thicknesses of 1, 3, and 6 mm (the latter two via OCT imaging).

Statistical Analysis

Frequency statistics, and frequency percentages were used to describe qualitative variables and mean, standard deviation, median and range of changes were used to describe quantitative variables (20). Based on the type of variable (qualitative-nominal, qualitative-rank and quantitative with normal distribution based on the Kolmogorov-Smirnov test), Pearson correlation coefficients was used. A significance level of $p < 0.05$ was considered (21).

Results

53 patients were screened, out of which 3 were removed in terms of glaucoma and retinal nerve fiber diseases. Out of 50 patients studied, 19 (38%) patients had essential tremor and 31 (62%) had essential tremor plus. [Table 1](#) depicts demographic data of the patients.

Table 1. Demographic data

Variables	Group	Mean	Standard Deviation	Range (min-max)
Age	Control	56.62	10.63	33-75
	Patients	57.03	10.73	30-72
	Essential Tremor	58.68	8.67	39-72
	Essential Tremor Plus	55.38	11.05	30-71
Gender	Group	Gender	Frequency	Percent
	Control	Female	29	58
		Male	21	42
	Patients	Female	27	54
		Male	23	46
	Essential Tremor	Female	10	52.6
		Male	9	47.4
	Essential Tremor Plus	Female	17	54.8
Male		14	45.2	

The results of comparing the average age of participants in different groups showed that there is a significant difference between the age of essential tremor group, and essential tremor plus (P value =0.018), but there is no significant difference between the control group, and all patients (P value =0.489). The results of comparing the gender of participants in the study in different groups showed that there is no significant difference between any of the groups (P value >0.050).

[Table 2](#) contains the findings of the comparison of RNFL variables between the groups. The findings revealed that the upper quadrant, upper nasal sector, and upper temporal sector of the right eye in the control group were significantly thicker than those of the case (essential tremor plus subtype); similarly, the upper temporal sector and lower temporal sector of the left eye were significantly thicker than those of both subtypes.

Table 2. Mean (standard deviation) and significance level of RNFL layer between different groups.

Variables	Patients	Control	Significance level	Essential tremor	Essential tremor plus	Significance level	
Right Eye	Mean Superior	120.64 (15.93)	127.81 (10.15)	0.009	125.10 (18.23)	117.90 (13.96)	0.122
	Superior Nasal	121.98 (19.52)	113.93 (11.57)	0.015	125.52 (21.82)	119.80 (17.99)	0.320
	Superior Temporal	119.46 (28.71)	141.79 (15.03)	0.001	124.78 (32.49)	116.19 (26.15)	0.340
	Mean Inferior	124.34 (16.35)	129.66 (13.30)	0.081	122.26 (16.65)	125.61 (16.31)	0.430
	Inferior Nasal	113.86 (22.66)	117.89 (21.55)	0.369	108.73 (20.98)	117 (23.41)	0.214
	Inferior Temporal	134.72 (23.66)	141.22 (14.36)	0.102	135.94 (19.37)	133.96 (26.23)	0.777
	Nasal Mean	81.84 (13.21)	78.27 (10.96)	0.150	83.05 (15.67)	81.09 (11.67)	0.670
	Mean Temporal	71.84	72.89	0.590	74.15	70.41	0.215

	Variables	Patients	Control	Significance level	Essential tremor	Essential tremor plus	Significance level
Left Eye		(10.27)	(8.97)		(9.88)	(10.40)	
	Mean Superior	122.92 (16.20)	125.50 (9.85)	0.344	121.63 (12.50)	123.70 (18.25)	0.665
	Superior Nasal	118.98 (20.31)	120.14 (11.64)	0.727	116.05 (18.57)	120.77 (21.40)	0.431
	Superior Temporal	124.5 (20.64)	139.16 (13.24)	0.001	127.42 (20.41)	122.70 (20.92)	0.312
	Mean Inferior	129.04 (14.65)	127.89 (13.41)	0.648	127.42 (15.52)	130.03 (14.27)	0.532
	Inferior Nasal	126.44 (21.71)	124.14 (19.57)	0.548	129.94 (24.66)	124.29 (19.80)	0.393
	Inferior Temporal	132.04 (25.39)	143.91 (13.71)	0.005	124.73 (25.57)	136.51 (24.61)	0.112
	Nasal Mean	74.64 (13.02)	73.95 (10.32)	0.775	76.57 (14.48)	73.45 (12.14)	0.416
	Mean Temporal	68.88 (10.42)	68.16 (6.47)	0.333	72.89 (9.51)	68.03 (10.66)	0.110

Results of RGC layer examined *via* OCT are depicted in [Table 3](#). In the right eye, there was a significant higher mean thickness of 6 mm in the upper sector between the control group and the case (both subtypes). This significant mean difference of 6 mm was also observed in the upper sector between the

control group and the case (both subtypes) in the left eye as well.

Based on obtained results, no significant difference was observed in the OCT parameters (RNFL and GCL) between different sectors in each group separately.

Table 3. Mean (standard deviation) and significance level of GCL layer between different groups.

	Variables	Patients	Control	Significance level	Essential tremor	Essential tremor plus	Significance level
Right Eye	Central 1mm	13.04 (3.88)	12.86 (1.14)	0.756	13.22 (4.18)	12.93 (3.77)	0.806
	Superior 3mm	47.04 (7.51)	48.16 (3.14)	0.339	46.27 (8.94)	47.48 (6.66)	0.593
	Superior 6mm	31.12 (7.17)	35.02 (4.88)	0.002	30.44 (8.65)	31.51 (6.27)	0.619
	Inferior 3mm	46.28 (9.39)	48.24 (6.79)	0.240	44.33 (10.57)	47.41 (8.61)	0.272
	Inferior 6mm	29.44 (6.90)	30.64 (3.69)	0.289	29.44 (8.28)	29.45 (6.11)	0.997
	Nasal 3mm	45.08 (10.34)	45.82 (4.16)	0.644	42.83 (11.97)	46.38 (9.23)	0.251
	Nasal 6mm	34.71 (7.27)	35.06 (3.57)	0.766	33.72 (8.47)	35.29 (6.56)	0.473
	Temporal 3mm I	40.24 (9.89)	42.74 (3.92)	0.105	38.50 (12.23)	41.25 (8.29)	0.373

Variables	Patients	Control	Significance level	Essential tremor	Essential tremor plus	Significance level
Temporal 6mm	33.30 (7.09)	34.82 (6.14)	0.259	32.83 (9.06)	33.58 (5.80)	0.726
Central 1mm	12.97 (4.19)	12.42 (1.03)	0.368	12.94 (4.51)	13.0 (4.07)	0.965
Superior 3mm	46.69 (9.79)	47.86 (3.08)	0.429	48.27 (7.29)	45.77 (10.99)	0.345
Superior 6mm	32.46 (5.38)	35.74 (2.41)	0.001	32.77 (5.70)	32.29 (5.27)	0.769
Inferior 3mm	44.75 (11.24)	47.36 (2.64)	0.120	44.27 (12.44)	45.03 (10.69)	0.824
Inferior 6mm	28.30 (7.79)	30.20 (1.88)	0.104	28.72 (7.81)	28.06 (7.89)	0.779
Nasal 3mm	43.55 (11.13)	44.20 (2.30)	0.691	43.44 (13.78)	43.61 (9.53)	0.960
Nasal 6mm	34.10 (7.80)	35.90 (2.45)	0.129	34.66 (8.05)	33.77 (7.77)	0.704
Temporal 3mm l	39.81 (10.43)	41.80 (3.95)	0.218	40.38 (10.96)	39.48 (10.28)	0.773
Temporal 6mm	33.44 (6.21)	34.92 (3.37)	0.149	34.44 (6.77)	32.87 (5.90)	0.399

Discussion

This study compares the results of OCT in two groups of 50 patients with essential tremors and healthy individuals between 2020 to 2022 in Rasool Akram Hospital. The study's findings showed that there is a significant difference in the mean superior, superior nasal, and superior temporal regions of the right eye and superior temporal and inferior temporal sections of the left eye in RNFL between the control group and all patients. Furthermore, the results showed that there is a significant difference between the control group and all patients, with essential tremor and with essential tremor plus in GCL in the superior 6 mm of the right and left eye. Based on the results of this study, it appears that patients with essential tremors have a meaningful reduction in some RNFL and GCL sectors compared to healthy subjects. Essential tremor is a disorder of nervous system that causes involuntary and rhythmic tremors. Although tremors may affect practically any area of the body, they are most often felt in the hands, particularly when doing routine actions like tying a shoelace or drinking from a glass (16, 22). Although essential tremor is often not harmful, it may become worse with time and eventually become uncontrolled and severe. Essential tremor is not the result of other complications, although essential tremor is sometimes confused with Parkinson's disease (2).

There is a possibility of essential tremor occurring at any age, but the percentage of its prevalence increases after the age of 40. About half of cases of essential tremor are the result of a genetic mutation, although no specific gene was identified. This type of tremor is called familial tremor. The causes of essential tremors in people without genetic mutations are not known (1, 3, 7).

Electrophysiological tests can be helpful before the onset of clinical symptoms because vision disorders may not be associated with obvious changes in routine ophthalmological examinations. In fact, the thickness of the RNFL can be used as a diagnostic variable in the patients mentioned above (23, 24). In OCT, special laser light is shined on the eye and this light is finally reflected after passing via the different layers of the eye, and the device's sensor analyzes the light reflection of different layers of the eye and separates the normal layers from the abnormal ones. It detects and shows the type of lesion with micron clarity and precision (25).

In a study by Tugcu *et al.*, 2020, patients were divided into four groups of essential tremor, Parkinson's disease, both essential tremor and Parkinson's disease, and healthy control; in terms of the RNFL factor. Patients with Parkinson's disease were shown to have a thinner RNFL than patients with

essential tremor and healthy people. However, not all of the studied quadrants had this problem. On the other hand, a slightly significant difference was observed between the RNFL thickness of group with essential tremor and the healthy group in some quadrants. In our study, though parkinsonian patients were not examined, similar results were obtained (14).

In a study by Fidanci et al., 2019, RNFL changes were examined in three groups of 30 individuals each, with essential tremor, Parkinson's disease and healthy. It was also shown in various research quadrants that the average RNFL thickness was considerably lower in the parkinsonian and essential tremor groups than in the healthy group. Moreover, the study did not report a significant correlation between the severity of the disease and the thickness of RNFL in the group with essential tremor, which was not addressed in our study since the severity of the disease was not evaluated. Eventually, it can be concluded from both of the studies, that changes in RNFL thickness observed in the patients with essential tremor could possibly be associated with the neurodegenerative nature of the disease (8).

Similar to our study, in the study by Tak et al., 2018, RNFL and RGC layer was assessed in a case-control manner in two groups of essential tremor and healthy people (40 people each). The results of their study was in accordance with ours, in which RNFL thickness was significantly decreased in the patients with essential tremor compared to the control group. Additionally, most of the RGC layer's components were reduced, although only three factors were significantly altered by our research. OCT is useful in identifying the neurodegenerative component of essential tremor, according to the study's final finding (17). The general phenomenon of age-related neuronal loss in the inner retina is well established. The effects of aging were studied by histological analysis of RGCs or their axons in the optic nerve and by optical measurements of the RNFL. Studies of the number of axons in the optic nerve showed a systematic age-related loss at rates of 0.3% to 0.6% per year, while age-related thinning of the RNFL occurs to some extent. Therefore, age can be an effective factor in comparative studies. We tried to prevent the influence of the intervening age on the parameters by roughly matching people in terms of age in each group (26, 27).

One of the most significant constraints was the lack of willing patients to undertake OCT tests, which was mostly caused by patients' ignorance of the benefits of this diagnostic tool in the course of therapy. This problem was mainly addressed by educating the patients. Furthermore, the lack of similar indigenous domestic studies to accurately, and correctly compare the differences could be the other limitation of the study. Considering the importance of this issue, it is suggested that studies with higher statistical populations, cohort studies and a longer follow-up period be conducted so that more variables, and

confounding variables can be recognized and evaluated.

Conclusion

Based on the results of this study, it seems that the patients with essential tremor have a significant decrease in some RNFL and GCL factors compared to healthy individuals. This difference was evident in variables, such as the average thickness in the right upper quadrants and left upper and lower temporal sectors in the RNFL, as well as the left and right upper 6 mm thickness in the RGC layer. Nevertheless, the majority of RNFL and GCL variables examined in this study did not show significant differences.

Acknowledgments

The authors would like to thank the patients for making this study possible through their participation.

Funding

None.

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Conflict of Interest

The authors assert that there is no conflict of interest.

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How to Cite This Article:

Nasiri S M, Habibi S A H, Rohani M, Sedaghat A, Goudarzi S. Investigating Nerve Fiber Layer and Retinal Ganglion Layer Cells in Patients with Essential Tremor. *J Adv Med Biomed Res.* 2023; 31(138):441-8.

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