Optical Coherence Tomography Findings Locates Essential Tremor in Neurodegenerative Disease Spectrum

Refika Hande Karakahya[1], *Tuba Şaziye Özcan*[2]

ABSTRACT

Purpose: The essential tremor (ET) is considered as a part of neurodegenerative disease spectrum. The evaluation of the retina and choroid via Spectral Domain- optical coherence tomography (OCT) in patients with ET, was aimed.

Material and Methods: This study enrolled 60 eyes of 30 patients with ET and 60 eyes of 30 age and gender matched healthy controls (HC). All patients underwent full ophthalmological examination including OCT.

Results: Measurements of the thickness of the ganglion cell-innerplexiform layer (GC-IPL) of the macular area demonstrated significant decrease in average, minimum and inferotemporal sector for right and left eyes and in the superonasal sector of the left eye in ET group. The average retinal nerve fiber layer (RNFL) thickness in ET group was significantly lower than the values in HC group. Quadrant evaluation revealed RNFL thickness in the inferior and temporal quadrants for right and left eyes were statistically lower in ET group. Correlation analysis revealed a negative association between duration of ET and RNFL thickness in the temporal quadrant in both eyes.

Conclusion: Supporting the neurodegenerative theory, ET patients, demonstrated a selective inferior and temporal retinal involvement correlated with the disease duration. OCT may also be an invaluable biomarker for evaluating these patients, in addition to its use in other neurodegenerative disorders.

Key words: Essential tremor, Neurodegenerative disorder, Optical coherence tomography, Retinal ganglion cell.

INTRODUCTION

Essential tremor (ET), is relatively common with a 4.0% prevalence over 40 years of age. [1,2] Most common clinical presentation of ET is an 8–12 Hz kinetic tremor of the arms followed by the involvement of head and voice.[3] The onset of ET shows bimodal distribution, pointing out to two distinct phenotypes; early and late onset (<24 and >46 years of age, respectively) [4], with the latter exhibiting a more rapid clinical progression.[5]

Once considered as a mono-symptomatic disease, definition of ET has evolved according to the criteria published in 2017 by the MDS Task Force. [6] In addition to motor symptoms, wide ranges of non-motor symptoms are defined in ET.[7] Indicating a clinical heterogeneity, the presence, evolution, and severity of neurological signs, and even response to pharmacological agents differ in ET patients. Furthermore, some postmortem studies revealed pathological heterogeneity, either.[8] In the basis of these etiological, clinical, therapeutic response, and pathological heterogeneity, Louis et al. regarded ET as a member of neurodegenerative disorder family instead of a single disease entity.[9-11] Furthermore, greater incidence of other neurodegenerative disorders was reported in patients with ET.[12-14]

Although the exact pathophysiologic mechanism of ET is not clearly defined, it is proposed that ET is characterized with increased oscillatory activity in the cortico-thalamo-olivo-cerebellar circuit owing to inferior olive dysfunction, cerebellar pathology or GABAergic dysfunction or all, caused by genetic and/or environmental factors.[15] Due to its insidious onset, progressive character, increasing of its incidence by age, association with cognitive deficits, association with Purkinje cell loss and other histopathological changes such as Lewy body formation conventionally found in neurodegenerative disorders, as well as the constellation of non-motor findings, locate ET

1- Ophthalmologist, MD, Lösante Hospital, Ophthalmology Department, Ankara, Türkiye

2- Prof. MD, Sancaktepe Şehit Prof.Dr. İlhan Varank Training and Research Hospital, Neurology, İstanbul, Türkiye

Received: 20.04.2022
Accepted: 25.07.2022

Ret-Vit 2022; 31: 271-277

DOİ:10.37845/ret.vit.2022.31.53

Correspondence Adress:
Refika Hande Karakahya
Lösante Hospital, Ophthalmology Department, Ankara, Türkiye
Phone: +90 530 777 8435
E-mail: handekarakahya@gmail.com

in the neurodegenerative disease spectrum.[8,16,17]

Previous studies revealed the role of retinal evaluation by optic coherence tomography (OCT) in diagnosis, severity, progression and prognosis in neurogenerative diseases.[18-21] Currently there are few reports in the literature evaluating the OCT parameters in ET with conflicting results.[22-24] Hypothesizing the possible retinal involvement as in the case with other neurodegenerative diseases, the evaluation of the patients with ET, by Spectral Domain-OCT (SD-OCT) was aimed in this study.

2. MATERIALS AND METHODS

This study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All participants provided written informed consent.

Patients with ET diagnosis based on the criteria defined by MDS task force [6] were included.

History of optic nerve disease, glaucoma; uveitis; any retinal diseases, amblyopia, ocular surgery except phacoemulsification, trauma, tumor; automated refraction of > 3.0 diopters; axial length (AL) of > 25 mm; best corrected visual acuity (BCVA) of <6/10; intraocular pressure of >21 mmHg; signal strength of <7/10; systemic disorders such as diabetes mellitus, hypertension, pulmonary disorders, sleep apnea and obesity of >25 body mass index were excluded.

A total of 120 eyes of 60 patients were included in the study, consisting of 60 eyes of 30 patients with ET and 60 eyes of 30 healthy controls.

All of the patients who referred from neurology department with the diagnosis of ET underwent a full ophthalmologic examination including Snellen BCVA assessment, spherical equivalent, 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 dilation of pupil, central macular thickness (CMT), RNFL thickness, GCIPL and subfoveal choroidal thickness (SCT) was assessed with OCT (Cirrus HD-OCT, Carl Zeiss Ophthalmic System Inc, Zeiss-Humphrey, Dublin, California, USA). Single physician manually measured the SCT by EDI-OCT over the thinnest foveal zone between 10 AM and 11 AM to avoid diurnal variations. The peri-papillary RNFL thickness was measured by an optic disc cube scan 200 × 200 protocol. The macular cube scan 512×128 protocol was used to evaluate total retinal thicknesses in ETDRS protocol centered on the fovea. GCIPL thickness was measured by GCA software.

2.1. Statistical Analyses

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. The continuous data were described as mean ± SD and categorical data were described as number (%) of cases. Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t test, Mann Whitney U test were applied for comparisons of the not normally distributed data. Pearson or Spearman correlation analysis was used to evaluate the degrees of relation between variables. A p-value < 0.05 was accepted as significance level.

RESULTS

The ET group included 14 (46.7%) females and 16 (53.3%) with a mean age of 52.80 ± 15. 57 years. Healthy control (HC) group included 13 (43.3%) females and 17 (56.7%) with a mean age of 51.73±4.08 years. Ten (33.33%) patients in Group ET had a family history of ET. Mean disease duration was 5.17 ± 4.01 years in Group ET. Mean BCVA in the right and left eye was 0.97 ± 0.07, and 0.97 ± 0.08 in Group ET whereas 0.96 ± 0.09 and 0.98 ± 0.07 Group HC, respectively (p: 0.685 and p: 0.950). Mean IOP was measured as 13.97 ± 3.22, and 14.30 ± 2.78 mmHg in right and left eyes of group ET and 12.97 ± 3.05 and 13.43 ± 2.22 mmHg of Group HC, respectively (p: 0.222 and p: 0.188). Mean AL in the right and left eyes was 21.93 ± 1.44, and 21.93 ± 1.41 mm in group ET and 22.11 ± 1.28 and 22.25 ± 1.69 mm in Group HC, respectively (p:0.612 and p:0.436). There were no differences in respect to age, gender, BCVA, IOP, and AL between the groups (Table1).

Macular thickness parameters provided by the ETDRS protocol are demonstrated in Table 2. No statistically significant difference was found between groups in terms of macular thickness parameters.

Measurements of the thickness of the GC-IPL of the macular area demonstrated thinning in both eyes of ET group, however significant differences yielded in average, minimum and inferotemporal sector for both eyes and in the superonasal sector of the left eye (Table 3). The average RNFL thickness in the ET group was significantly lower than the values in HC group (Right eye p value: 0.003, left eye p value: 0.003). The average RNFL thickness in the ET group was measured as 89.97 ± 8.82 μm and 90.03 ± 8.73 μm in the right and left eyes, respectively. The

Table 1: *Characteristics of patients.*

		Essential Tremor Group		Healthy Control Group		P
Gender ‡	Male	16	53.3%	17	56.7%	0.795
	Female	14	46.7%	13	43.3%	
Age (years)*		52.80	±15.57	51.73	±4.08	0.655
Family History		10	33.33%	-	-	-
Duration (years)		5.17	±4.01	-	-	-
BCVA-R (Snellen) †		0.97	±0.07	0.96	±0.09	0.685
BCVA-L (Snellen) †		0.97	±0.08	0.98	±0.07	0.950
IOP-R (mmHg)*		13.97	±3.22	12.97	±3.05	0.222
IOP-L (mmHg)*		14.30	±2.78	13.43	±2.22	0.188
AL-R (mm)*		21.93	±1.44	22.11	±1.28	0.612
AL-L (mm)*		21.93	±1.41	22.25	±1.69	0.436

Continuous variables are expressed as either the mean ± standard deviation (SD).
R: Right eye, L: left eye, BCVA: Best Corrected Visual Acuity, IOP: Intraocular Pressure, AL: Axial Length

Table 2: *Macular thickness parameters.*

	Essential Tremor Group		Healthy Control Group		P
	mean	sd	mean	sd	
CST-R †	245.30	±10.27	245.17	±10.14	0.953
CST-L †	244.87	±10.96	245.40	±11.10	0.773
N6-R*	294.73	±6.44	295.20	±7.10	0.791
N6-L*	294.40	±7.06	294.77	±6.78	0.838
N3-R †	318.23	±22.45	318.77	±33.05	0.249
N3-L †	318.03	±22.16	318.87	±33.08	0.231
T6-R*	266.50	±16.73	266.50	±16.92	1.000
T6-L*	266.90	±16.76	266.43	±17.21	0.916
T3-R*	306.87	±10.72	307.50	±12.29	0.832
T3-L*	307.13	±11.58	307.50	±12.29	0.906
S6-R*	276.73	±17.77	280.40	±18.45	0.436
S6-L*	278.27	±16.52	280.67	±18.35	0.596
S3-R*	319.40	±20.01	319.03	±32.66	0.816
S3-L*	319.77	±20.08	318.67	±34.27	0.902
I6-R*	271.87	±19.10	274.30	±22.32	0.652
I6-L*	270.53	±19.74	276.53	±21.90	0.270
I3-R*	317.33	±19.93	318.80	±12.57	0.734
I3-L*	317.93	±20.00	318.80	±12.57	0.842
MV-R	243.34	±16.2	244.01	±14.11	0.771
MV-L	244.07	±12.8	244.11	±11.13	0.803

Continuous variables are expressed as either the mean ± standard deviation (SD).
R= Right eye, L= Left eye, CST = central subfield thickness, N3 = nasal inner macula, N6 = nasal outer macula, T3 = temporal inner macula, T6= temporal outer macula, S3 = superior inner macula, S6 = superior outer macula, I3 = inferior inner macula, I6 = inferior outer macula, MV: macular volume

average RNFL thickness in the HC group was measured as 96.27 ± 6.85 µm and 96.43 ± 6.95 µm in the right and left eyes, respectively. When quadrants were evaluated, RNFL thickness in the inferior (Right eye p value: 0.001, Left eye p value: 0.002) and temporal quadrants (Right eye p value: 0.022, Left eye p value: 0.029) for both eyes were statistically lower in group ET (Table 3). There was no difference between groups for both eyes in terms of SCT despite nonsignificant thickening in ET group (Table 3).

No significant difference was determined when OCT parameters were compared for right and left eyes ($p>0.05$). Presence of family history of ET did not reveal a correlation between any of the OCT parameters for both eyes. However, duration of ET was found to be negatively correlated with average GCIPL thickness in the left eye and minimal GCIPL thickness, GCIPL in superior, inferior, superonasal, superotemporal and inferotemporal sectors and RNFL thickness in the temporal quadrant in both eyes (Table 4).

Table 3: *Peri-papillary RNFL thicknesses, GCIPL and SCT thicknesses in the groups.*

	Essential Tremor Group		Healthy Control Group		P
GCIPL thickness (µm)	**Mean**	**Sd**	**Mean**	**Sd**	
Minimum-R*	75.23	±2.66	77.17	±2.57	**0.006**
Minimum-L*	75.47	±2.58	77.60	±2.79	**0.003**
Average-R*	76.53	±2.62	78.70	±2.67	**0.002**
Average -L*	76.93	±2.30	78.57	±2.42	**0.010**
Superior-R*	79.13	±2.33	80.07	±2.26	0.121
Superior-L*	79.40	±2.03	80.03	±2.28	0.260
Inferior-R*	77.37	±3.51	78.33	±2.47	0.222
Inferior-L*	77.17	±4.13	78.23	±2.43	0.228
Superonasal-R*	80.93	±1.91	80.80	±2.06	0.796
Superonasal-L*	80.60	±1.94	81.60	±1.50	**0.029**
Superotemporal-R*	78.10	±1.65	78.43	±1.57	0.425
Superotemporal-L*	78.17	±1.80	78.33	±1.45	0.694
Inferonasal-R*	77.43	±1.85	78.30	±1.58	0.056
Inferonasal-L*	77.70	±1.76	78.57	±1.65	0.055
Inferotemporal-R*	79.30	±1.86	80.43	±2.22	**0.036**
Inferotemporal-L*	79.40	±2.03	80.53	±2.32	**0.048**
RNFL thickness (µm)					
Average-R*	89.97	±8.82	96.27	±6.85	**0.003**
Average-L*	90.03	±8.73	96.43	±6.95	**0.003**
Superior-R*	111.73	±6.42	111.73	±6.42	1.000
Superior-L*	111.23	±6.43	111.60	±6.29	0.824
Inferior-R*	112.73	±9.16	119.63	±6.53	**0.001**
Inferior-L	112.77	±9.43	119.67	±6.65	**0.002**
Nasal-R*	75.57	±4.89	75.30	±4.71	0.830
Nasal-L*	75.30	±4.27	75.20	±4.78	0.932
Temporal-R*	63.00	±3.95	65.13	±3.00	**0.022**
Temporal-L*	63.10	±3.86	65.17	±3.28	**0.029**
SCT-R †	273.10	±11.70	270.73	±13.01	0.328
SCT-L*	273.60	±10.40	270.50	±12.57	0.302

Continuous variables are expressed as either the mean ± standard deviation (SD).
R= Right eye, L= Left eye, RNFL= Retinal Nerve Fiber Layer, GCIPL= Ganglion Cell Inner Plexiform Layer, SCT: Subfoveal choroidal thickness

DISCUSSION

Postulated as a member of neurodegenerative family with heterogenous presentation, progression and etiopathogenesis rather than a mono-symptomatic single disease entity [9-11,17] , ET, was shown to exhibit overlapping clinical features with Parkinson's Disease (PD) and other neurodegenerative diseases.[25-27] Although the mechanisms are unclear, as in the case with other neurodegenerative diseases, there is preliminary evidence that a pre-motor phase in ET including, cognitive dysfunction, depression, sleep dysregulation, restless leg syndrome, premorbid personality, or olfactory dysfunction, preceeds the tremor.[28]

The role of retinal evaluation by optic coherence tomography (OCT) in diagnosis, severity, progression and prognosis in neurodegenerative diseases was demonstrated in previous studies.[18-21,29]

Currently there are some reports in the literature evaluating the OCT parameters in ET. Cubo et. al. [22], using time domain-OCT (TD-OCT), notified the asymmetry between the eyes, with detection of thinner foveal retinal thickness in the eye contralateral to the more affected side in ET

Table 4: *Correlation analysis (significant parameters are demonstrated only).*

GCIPL thickness		**Duration**
Minimum-R	r	**-0.549**
	p	**0.002**
Minimum-L	r	**-0.444**
	p	**0.014**
Average-L	r	**-0.404**
	p	**0.027**
Superior-R	r	**-0.563**
	p	**0.001**
Superior-L	r	**-0.511**
	p	**0.004**
Inferior-R	r	**-0.441**
	p	**0.015**
Inferior-L	r	**-0.363**
	p	**0.048**
Superonasal-R	r	**-0.381**
	p	**0.038**
Superonasal-L	r	**-0.471**
	p	**0.009**
Superotemporal-R	r	**-0.393**
	p	**0.032**
Superotemporal-L	r	**-0.439**
	p	**0.015**
Inferotemporal-R	r	**-0.550**
	p	**0.002**
Inferotemporal-L	r	**-0.511**
	p	**0.004**
RNFL thickness		
Temporal-R	r	**-0.420**
	p	**0.021**
Temporal-L	r	**-0.420**
	p	**0.021**

GCIPL: ganglion cell interplexiform layer, RNFL: Retinal nerve fiber layer, R: Right eye, L: Left eye

and PD, however, without any significant difference in ET patients in relation to control eyes. Turkel et al. [23], also declared that there is no global RNFL and foveal retinal thickness difference between ET eyes and control eyes, except thinner RNFL in the nasal quadrant in ET eyes. However, Tak et al. [24] demonstrated a significant difference in global RNFL, GCL and IPL thicknesses with a significant thinning of RNFL only in the nasoinferior quadrant, in addition to thickening of the choroid compared to controls.

Decrease in RNFL thickness, related with axonal disturbance pointing out an indirect measure of RGC loss, was demonstrated in PD, Alzheimer's Disease (AD), Multiple Sclerosis (MS) and other neurodegenerative disorders. [30-36]

In addition, RNFL was used for prediction of disease progression in neurodegenerative diseases.[29,37,38] RNFL thickness was found to be associated with degree of cognitive impairment in AD, as well.[34,39] In this regard, it is accepted that neurodegeneration in the retina may occur in parallel to neurodegeneration in brain.[40] In this current study a significant reduction in average RNFL thickness and in the inferior and temporal quadrants via SD-OCT was detected in ET group. Consistent with neurodegeneration, our findings resembles Parkinsonian-type peripapillary RNFL thinning. The subclinical optic neuropathy affecting selectively inferotemporal quadrant in ET group, may also point out the possible role of mitochondrial pattern.[41]

However, GC-IPL thickness was found to be superior to RNFL thickness with regard to structure-function relationships with visual function and disability in MS.[42] In addition, GCL was found to be associated with the duration and severity of the disease in AD and GCIPL thickness presents higher sensitivity than RNFL[20,43], and in regression analysis predicts subjects at risk for AD axonal atrophy.[20] In this current study, despite reduction in thickness in all sectors in both eyes, significant reduction was detected in minimum, average GCIPL thickness and in inferotemporal sector for both eyes and superonasal sector for the left eye. In this aspect the results of the current study may support the neurodegenerative theory in ET pathogenesis. Being a model of brain, retina, may demonstrate changes in the brain tissue. However, despite a significant reduction in RNFL and GC-IPL thicknesses, we did not observe significant differences in macular thickness. Segmentation analysis may provide more information about the relative thickness differences for ET patients. Moreover, Cubo et al. postulated the foveal thickness, which is not affected in ET patients when compared to controls, as a diagnostic tool for differentiating PD from ET. However significant, the results are less pronounced when the retinal findings demonstrated in other neurodegenerative diseases are taken into consideration. In this regard, ET may be hypothesized as a less severe form in neurodegenerative disease spectrum.

Tak et al. [24] demonstrated thickening of the choroid compared to controls which was linked to neuro-inflammation in ET patients. However, the choroid thickness did not demonstrate any significant difference between ET subjects and control subjects in this current study, despite nonsignificant thickening. This may be regarded as the small contribution of the vascular components in ET neurodegeneration or due to manual measurement of the choroidal thickness in our study by EDI-OCT. The mean

age was older and the duration of the disease was shorter in our study compared to Tak et al's study.

Limitations of this study are the small size of the study group and the manual measurement of the subfoveal choroidal thickness. Unfortunately, there was no tremor scale and the correlation of findings with the severity of disease could not be performed. Presence of family history of ET did not reveal a correlation between any of the OCT parameters for both eyes. However, duration of ET was found to be negatively correlated with average GCIPL thickness in the left eye and minimal GCIPL thickness, GCIPL in superior, inferior, superonasal, superotemporal and inferotemporal sectors and RNFL thickness in the temporal quadrant in both eyes.

CONCLUSION

In conclusion ET, due to the lack of biomarkers or definitive imaging findings, is still a clinical diagnosis, with growing pathological and clinical evidences, strengthening its position among the neurodegenerative disorder spectrum. OCT is an invaluable tool in evaluating these potential neurodegenerative changes in a fast, inexpensive, reliable and repeatable way.

REFERENCES

1. Dogu O, Sevim S, Camdeviren H et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. Neurology 2003; 61:1804–6.
2. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder estimates of the prevalence of essential tremor throughout the World? Movement Disorders 1998; 13:5–10.
3. Bhalsing KS, Saini J, Pal PK. Understanding the pathophysiology of essential tremor through advanced neuroimaging: a review. Journal of the Neurological Sciences 2013; 335:9–13.
4. Hopfner F, Ahlf A, Lorenz D et al. Early- and late-onset essential tremor patients represent clinically distinct subgroups. Movement Disorders 2016;31: 1560-6.
5. Louis ED, Faust PL, Vonsattel JP et al. Older onset essential tremor: more rapid progression and more degenerative pathology. Movement Disorders 2009;24: 1606-12.
6. Bhatia KP, Bain P, Bajaj N et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Movement Disorders 2018;33:75-87.
7. Louis ED. Non-motor symptoms in essential tremor: a review of the current data and state of the field. Parkinsonism & Related Disorders 2016;22:115-8.
8. Louis ED. Re-thinking the biology of essential tremor: from models to morphology. Parkinsonism & Related Disorders 2014;20:88-93.
9. Louis ED. Essential tremor or the essential tremors: is this one disease or a family of diseases? Neuroepidemiology 2014;42: 81-9.
10. Louis ED. The Essential Tremors: A Family of Neurodegenerative Disorders? Archives of neurology 2009;66:1202-8.
11. Louis ED. The evolving definition of essential tremor: What are we dealing with? Parkinsonism & Related Disorders 2018;46:87-91.
12. Benito-León J, Louis ED, Bermejo-Pareja F. Elderly-onset essential tremor is associated with dementia. Neurology 2006;66: 1500-5.
13. Benito-León J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. Journal of Neurology, Neurosurgery & Psychiatry 2009;80: 423–5.
14. Bermejo-Pareja F, Louis ED, Benito-Leon J. Risk of incident dementia in essential tremor: a population-based study. Movement Disorders 2007;22: 1573–80.
15. Hopfner F, Helmich RC. The etiology of essential tremor: Genes versus environment. Parkinsonism & Related Disorders 2018;46:92-6.
16. Louis ED, Faust PL, Vonsattel JP et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007;130:3297-307.
17. Bonuccelli U. Essential tremor is a neurodegenerative disease. Journal of Neural Transmission 2012;119:1383–7.
18. Satue M, Obis J, Rodrigo MJ et al. Optical Coherence Tomography as a Biomarker for Diagnosis, Progression, and Prognosis of Neurodegenerative Diseases. Journal of Ophthalmology 2016;2016:8503859.
19. Doustar J, Torbati T, Black KL et al. Optical Coherence Tomography in Alzheimer's Disease and Other Neurodegenerative Diseases. Frontiers in Neurology 2017;19:701.
20. Garcia-Martin E, Bambo MP, Marques ML et al. Ganglion cell layer measurements correlate with disease severity in patients with Alzheimer's disease. Acta Ophthalmologica 2016;94:454-9.
21. Garcia-Martin E, Polo V, Larrosa JM et al. Retinal layer segmentation in patients with multiple sclerosis using spectral domain optical coherence tomography. Ophthalmology 2014;121:573-9.
22. Cubo E, Tedejo RP, Rodriguez Mendez V et al. Retina thickness in Parkinson's disease and essential tremor. Movement Disorders 2010;25: 2461–2.
23. Turkel Y, Ornek N, Dag E et al. Retinal nerve fiber layer thickness in patients with essential tremor. Neurology Asia 2015;20:363–6.
24. Tak AZA, Şengül Y, Karadağ AS. Evaluation of thickness of retinal nerve fiber layer, ganglion cell layer, and choroidal thickness in essential tremor: can eyes be a clue for neurodegeneration? Acta Neurologica Belgica 2018;118:235-41.
25. LaRoia H, Louis ED. Association between essential tremor and other neurodegenerative diseases: what is the epidemiological evidence? Neuroepidemiology 2011;37:1-10.
26. Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism & Related Disorders 2007;13:67-76.
27. Fekete R, Jankovic J. Revisiting the relationship between essential tremor and Parkinson's disease. Movement Disorders 2011;15;26:391-8.

28. Lenka A, Benito-León J, Louis ED. Is there a Premotor Phase of Essential Tremor? Tremor and Other Hyperkinetic Movements (NY) 2017;5:498.

29. Martinez-Lapiscina EH, Arnow S, Wilson JA et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurology 2016;15:574–84.

30. Satue M, Seral M, Otin S et al. Retinal thinning and correlation with functional disability in patients with Parkinson's disease. British Journal of Ophthalmology 2014;98:350–5.

31. Garcia-Martin E, Larrosa JM, Polo V et al. Distribution of retinal layer atrophy in patients with Parkinson disease and association with disease severity and duration. American Journal of Ophthalmology 2014;157:470–8.

32. Satue M, Obis J, Alarcia R et al. Retinal and Choroidal Changes in Patients with Parkinson's Disease Detected by Swept-Source Optical Coherence Tomography. Current Eye Research 2018;43:109-15.

33. Paquet C, Boissonnot M, Roger F et al. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neuroscience Letters 2007;420: 97–9.

34. Cunha LP, Lopes LC, Costa-Cunha LV et al. Macular thickness measurements with frequency domain-OCT for quantification of retinal neural loss and its correlation with cognitive impairment in Alzheimer's disease. PLoS One 2016;11:e0153830.

35. Parisi V, Restuccia R, Fattapposta F et al. Morphological and functional retinal impairment in Alzheimer's disease patients. Clinical Neurophysiology 2001;112:1860–7.

36. Talman LS, Bisker ER, Sackel DJ et al. Longitudinal study of vision and retinal nerve fiber layer thickness in MS. Annals of Neurology 2010;67: 749–60.

37. Jimenez B, Ascaso FJ, Cristobal J et al. Development of a prediction formula of Parkinson disease severity by optical coherence tomography. Movement Disorders 2014;29: 68–74.

38. Costello F, Coupland S, Hodge W et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Annals of Neurology 2006;59:963–9.

39. Oktem EO, Derle E, Kibaroglu S et al. The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness. Neurological Sciences 2015; 36: 1141–6.

40. Ferrari L, Huang SC, Magnani G et al. Optical coherence tomography reveals retinal neuroaxonal thinning in frontotemporal dementia as in Alzheimer's disease. Journal of Alzheimer's Disease 2017;56: 1101–7.

41. Unal Gulsuner H, Gulsuner S, Mercan FN et al. Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease. Proceedings of the National Academy of Sciences U S A 2014;111:18285-90.

42. Saidha S, Syc SB, Durbin MK et al. Visual dysfunction inmultiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. Multiple Sclerosis 2011;17: 1449–63.

43. Cheung CY, Ong YT, Hilal S et al. Retinal ganglion cell analysis using high-definition optical coherence tomography in patients with mild cognitive impairment and Alzheimer's disease. Journal of Alzheimers Disease 2015;45:45-56.