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Retinal nerve fiber layer thickness in patients with essential tremor and Parkinson's disease

Esansiyel tremoru ve Parkinson hastalığı olan hastalarda retina sinir lifi tabaka kalınlığı

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Abstract

Aim: Essential tremor (ET) and Parkinson's disease (PD) are common movement disorders. In PD, visual problems such as impaired color vision and decreased visual acuity have been reported. Studies have shown that retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) is decreased in PD and some neurodegenerative diseases. Due to the similarities of ET and PD, we aimed to evaluate RNFL measured by OCT in ET and PD patients.

Methods: PD, ET and control groups were formed in this prospective case-control study. Each group included 30 individuals, and 180 eyes were examined. In these groups, RNFL quadrants, macula and fovea were evaluated with OCT. In the ET group, tremor severity was included in the analyses. The severity of disease in PD was assessed with the Unified Parkinson's Disease Rating scale and the Hoehn and Yahr scale.

Results: In the control, ET and PD groups, the mean RNFL thicknesses of the right eye were 93.2 (8.1), 86.7 (9.7), 86.8 (10.2) µm, respectively. These values were lower in the PD and ET groups compared to the control group (P=0.026, P=0.025). There was no correlation between disease severity and RNFL thickness in ET.

Conclusion: Decreased RNFL thickness in ET may indicate that ET is a neurodegenerative disease, such as PD. There may be subclinical retinal impairment in ET.

Keywords: Essential tremor, Optical coherence tomography, Parkinson's disease, Retinal nerve fiber layer

Öz

Amaç: Esansiyel tremor (ET) ve Parkinson hastalığı (PH) yaygın hareket bozukluklarındandır. PH'de renkli görmede bozulma ve görme keskinliğinde azalma gibi görme sorunları bildirilmiştir. Çalışmalar, optik koherens tomografi (OKT) ile ölçülebilen retina sinir lifi tabaka (RSLT) kalınlığının PH ve bazı nörodejeneratif hastalıklarda azaldığını göstermiştir. ET ve PH hastalığının benzer özellikleri olması nedeniyle, ET ve PH hastalarında OKT kullanarak RSLT'yi değerlendirmeyi amaçladık.

Yöntemler: Bu prospektif vaka-kontrol çalışmasında PH, ET ve kontrol grupları oluşturuldu. Her grupta 30 kişi mevcuttu ve 180 göz incelendi. Bu gruplarda, RSLT kadranları, makula ve fovea OKT ile değerlendirildi. ET grubunda titreme şiddeti analizlere dahil edildi. PH'de hastalığın şiddeti Birleşik Parkinson Hastalığı Değerlendirme Ölçeği ve Hoehn ve Yahr ölçeği ile değerlendirildi.

Bulgular: Kontrol, ET ve PH gruplarında sağ gözün ortalama RSLT kalınlığı sırasıyla 93,2 (8,1), 86,7 (9,7), 86,8 (10,2) µm idi. PH ve ET gruplarında bu değerler kontrol grubuna göre daha düşüktü (P=0,026, P=0,025). ET'de hastalık şiddeti ile RSLT kalınlığı arasında ilişki bulunmadı.

Sonuç: ET'de azalmış RSLT kalınlığı, ET'nin PH gibi bir nörodejeneratif hastalık olduğunu gösterebilir. ET'de subklinik retinal bir etkilenme olabilir.

Anahtar kelimeler: Esansiyel tremor, Optik koherens tomografi, Parkinson hastalığı, Retinal sinir lifi tabakası

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Introduction

Essential tremor (ET) and Parkinson's disease (PD) are common movement disorders with similar clinical features. PD is characterized by rest tremor, rigidity, bradykinesia, and postural instability. Postural and kinetic tremor is typical in ET. Rest tremor can be seen in ET as the disease progresses. Nonmotor clinical features are seen in both diseases. Visual impairments including impaired contrast sensitivity, decreased visual acuity and impaired color vision is one of the nonmotor symptoms in PD [1,2]. It was shown that the concentration of retinal dopamine decreased in PD [2-5]. In PD, it is thought that some visual impairments may develop as a result of dopamine deficiency in retina. Although the correlation between the retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) and the dopamine present in retinas is not fully established, studies have shown that RNFL thickness in PD patients is also thinner compared to controls, as in other neurodegenerative diseases such as Alzheimer's disease [6-9]. ET, including postural and kinetic tremor, is a chronic progressive disease that typically progresses slowly over time. Clinical progression in ET, development of rest tremor and ataxia in some patients, the risk of developing PD and the presence of Lewy bodies in brainstem in autopsy studies show that ET has similar aspects to PD [10-13]. Some nonmotor symptoms such as cognitive impairment or neuropsychiatric problems are seen in ET as in PD [14,15]. In the literature, there are very few researches on visual functions in ET, and color vision abnormalities have not been detected [16,17]. The studies determining RNFL thickness with OCT in ET had different results [18-20]. However, we did not find any study comparing RNFL thickness in both PD and ET patients. In addition, few studies on RNFL thickness in ET did not investigate whether there was a correlation between RNFL thickness and tremor severity. In our study, we wanted to evaluate RNFL thickness in ET and PD with OCT based on their similar characteristics.

Materials and methods

Subjects

Healthy individuals who were referred to the Neurology Department of the Faculty of Medicine in Mersin University between September 2013 and May 2014, patients with definite ET diagnosis according to the Washington Heights-Inwood Genetic Study of ET (WHIGET) diagnostic criteria and patients with definite PD diagnosis according to the United Kingdom Brain Bank diagnostic criteria were included in this prospective case-control study. Ethical approval for this study was obtained from the ethical committee of the Faculty of Medicine in Mersin University (year: 2013, number: 2013/339). Written consent was obtained from all participants. The age of onset of idiopathic PD was taken into consideration and participants were included in the study if the age of the participants was over 40 years in all groups. Individuals with Parkinsonism-causing toxic substance exposure, history of encephalitis, meningitis or head trauma and those with diabetes mellitus, thyroid disease, vasculitis, retinal detachment, glaucoma and cataract were excluded from the study. The severity of postural, kinetic and rest tremor was evaluated in ET patients. Postural tremor severity was scored after 30 seconds of observation, with arms extended straight forward. It was scored as 0 for no tremor, 1 for mild, 2 for moderate amplitude and 3 for high amplitude and severe cases. Kinetic tremor was scored by pouring water from glass to glass, using spoon, drinking and finger-nose test. It was scored as 0 for no tremor, 1 for mild degree, 2 for moderate amplitude, 3 for high jump mode and 4 for extremely high amplitude. While evaluating tremor severity, the value on the extremity with the most severe tremor was recorded. ET patients were separated in subgroups as with and without rest tremor. In ET patients with rest tremor, frequency of rest tremor was lower than the frequency of postural tremor, and rest tremor did not occur at the early stages of the disease. Patients with a family history of PD were not included in the ET group. In the PD group, disease severity was measured by the Hoehn and Yahr scale (HYS) and Unified Parkinson's Disease Rating Scale (UPDRS). PD patients with a suspected or definite history of ET were not included. All PD patients were included in the study during on periods. Patients in the PD group were receiving dopaminergic or levodopa therapy. An experienced ophthalmologist examined participants, and those with findings consistent with ophthalmologic conditions that would affect the retina were not included in the study. Visual acuity using Snellen chart was 20/30 or higher in all subjects. Intraocular pressure of all subjects was lower than 21 mmHg.

OCT examination

Carl Zeiss Cirrus 4000 OCT was used to measure RNFL and macular thickness. Each individual focused on a bright point set by OCT. OCT examination consisted of three circular scans with a diameter of 3.4 mm centered on optic disk. The software was enabled to measure the thickness data of each quadrant automatically. RNFL superior (RNFLs; $46\text{-}135^0$), inferior (RNFLi; $226\text{-}315^0$), nasal (RNFLn; $136\text{-}225^0$), temporal (RNFLt; $316\text{-}45^0$) quadrants thickness and foveal thickness values were obtained in the evaluation of both eyes and these values were recorded as micron (μm), and the macular cube volume was recorded as cubic millimeter (mm^3). Mean of RNFL (RNLFm; 360^0) and central foveal thickness were also calculated. RNFLm values were obtained by averaging RNFLs,i,n,t quadrants. Because a small number of studies reported that asymmetry may be present in OCT measures, both eyes of the individuals were examined with OCT [18-21].

Statistical analysis

The distribution of the variables was checked by the Kolmogorov-Smirnov test. ANOVA (Tukey test), Kruskal-Wallis and Mann-Whitney U tests were used in the analysis of quantitative data; the Chi-squared test was used in the analysis of qualitative data, and Spearman's correlation was used in the correlation analysis. Bonferroni correction was used for post-hoc analysis and multiple comparisons. Considering the previous studies and power analysis (95% confidence interval and level 0.05 type 1 error), it was planned to include 30 participants in each group [8,9,18]. *P*-value <0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS IBM Corp; Armonk, NY, USA) 22.0 was used to perform the statistical analysis.

Results

Each group included 30 individuals, and a total of 180 eyes were examined. Mean age (standard deviation) was detected as 61 (11.3) years in ET patients, 62 (10.4) years in PD patients and 60.5 (11.9) years in the control group. 12 ET patients (40%), 11 Parkinson's patients (36.7%) and 16 patients (53.3%) in the control group were females. There was no difference between the groups with respect to age and gender. Family history of ET was present in 19 ET patients (63.3%) and family history of PD was present in 8 PD patients (26.7%). Demographic features of PD and ET patients are shown in Table 1. The mean durations of the disease in Parkinson's and ET patients were 4.1 (2.4) and 8.7 (5.4) years, respectively. Postural and kinetic tremor severities in the ET group were shown in Table 1. There was a positive correlation between kinetic tremor severity (most affected side considered) and duration of disease in the ET group (P=0.15, r=0.440). Five ET patients had rest tremor without bradykinesia or rigidity or re-emergent tremor or jaw tremor. Asymmetric clinical findings were present in 20 patients with ET and 25 patients with PD. The mean HYS score was 2.1 (0.9) in the PD group. UPDRS mental status, daily life, motor examination and treatment complication scores were 4.6 (2.3), 15.6 (10.3), 20.3 (10.8) and 2.7 (4.3), respectively. The mean UPDRS total score was 43.2 (25.4). There was a significant positive correlation between the duration of the disease and the HYS of the patients (P=0.019, 0.425). There was also a significant positive correlation between the duration of the disease and UPDRS mental status, daily living activities and scores related to treatment complications (P=0.019, r=0.426; P=0.002, r=0.534; P=0.002, r=0.537, respectively). A similar positive correlation was found between UPDRS total score and the duration of the disease (P=0.004, r=0.509).

The RNFLs, i, n, t, m values among groups are shown in Table 2. Right RNFLm was 93.3 (8.1), 86.7 (9.7) and 86.8 (10.2) μm in the control, ET and PD groups, respectively, and significantly lower in the ET and PD groups compared to the control group (P=0.025 and P=0.026 with Bonferroni correction, respectively). The mean RNFL thickness of the right eyes among groups was shown in Figure 1. Similarly, the left RNLFn of ET patients was thinner than the left RNLFn of PD patients and controls (Table 2). In the control, PD and ET groups, mean of macular volumes were 10.0 (0.7), 9.7 (0.6) and 9.7 (1.0) mm^3, respectively, and mean values of foveal thickness were 263.2 (16.3), 266.6 (19.7) and 262.7 (12.1) μm, respectively, and there was no significant difference between the groups (table 2).

In the PD group, a negative correlation was found between HYS scores and RNFLn in the right eye (P=0.005, r=-0.498). There were also negative correlations between right RNFLn and UPDRS mental (P=0.007, r=-0.484), daily life (P=0.005, r=-0.498), motor (P=0.018, r=-0.429) and total (P=0.018, r=-0.429) scores. A negative correlation between RNFLi and UPDRS motor score in the left eye was found (P=0.015, r=-0.442). There was no correlation between macular volume and UPDRS / HYS scores in PD patients. No correlation was found between RNFL parameters, foveal thickness, and tremor severity in the ET group.

Table 1: Demographic characteristics and disease severity of PD, ET and Control groups

	PD group	ET group	Control group	*P*-value
Age mean (SD) (years)	62 (10.4)	61 (11.3)	60.5 (11.9)	0.901
Gender (female/male)	11 / 19	12 / 18	16 / 14	0.387
Duration of disease mean (SD) (years)	4.1 (2.4)	8.7 (5.4)	-	
Side of onset* (right/left/bilateral)	14 / 11 / -	11 / 6 / 7	-	
HYS scores mean (SD)	2.1 (0.9)	-	-	
UPDRS total scores mean (SD)	43.2 (25.4)	-	-	
Postural tremor severity mean (SD) (right/left)	-	2.1 (0.6)/ 2.1 (0.7)	-	
Kinetic tremor severity mean (SD) (right/left)	-	2.5 (0.9) / 2.3 (0.9)	-	

PD: Parkinson's disease, ET: essential tremor, HYS: Hoehn and Yahr scale, SD: standard deviation, *: the side of onset of symptoms was unknown in some patients

Table 2: Comparison of RNFL thickness in PD, ET and Control groups

	PD group Mean(SD)	ET group Mean (SD)	Control group Mean (SD)	*P*-value
RNFLm (μm)				
Right eye	86.8 (10.2)	86.7 (9.7)	93.2 (8.1)	0.010
Left eye	85.7 (12.9)	84.5 (15.9)	91.7 (8.9)	0.076
RNFLs (μm)				
Right eye	103.6 (18.1)	103.5 (16.1)	110.1 (16.5)	0.206
Left eye	103.9 (25.5)	105.3 (25.1)	112.1 (17.3)	0.341
RNFLi (μm)				
Right eye	113.7 (20.3)	112.5 (20.0)	123.7 (15.3)	0.064
Left eye	110.7 (23.9)	108.3 (25.9)	118.0 (21.8)	0.266
RNFLn (μm)				
Right eye	70.2 (9.1)	68.3 (11.7)	73.4 (12.7)	0.216
Left eye	65.1 (12.4)	64.7 (14.7)	73.2 (12.5)	0.023
RNFLt (μm)				
Right eye	59.9 (12.9)	62.3 (8.9)	65.3 (14.8)	0.243
Left eye	60.2 (18.3)	59.9 (15.2)	63.7 (10.2)	0.554
Foveal thickness (μm)				
Right eye	257.6 (13.9)	267.8 (24.2)	260.8 (18.3)	0.156
Left eye	268.2 (16.5)	266.0 (24.3)	264.9 (19.5)	0.089
Macular volume (mm^3)				
Right eye	9.7 (1.1)	9.6 (0.7)	9.9 (0.7)	0.162
Left eye	9.7 (1.1)	9.8 (0.6)	10.0 (0.7)	0.407

SD: standard deviation, RNFLs/i/n/t/m: retinal nerve fiber layer thickness superior / inferior / nasal / temporal / mean. Anova Tukey and Kruskal-Wallis tests were used. P<0.05 was considered statistically significant.

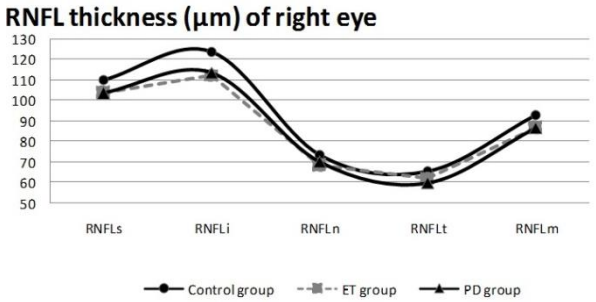

Figure 1: Mean RNFL thickness value of right eyes among groups (RNFLs/i/n/t/m: Retinal nerve fiber layer thickness superior / inferior / nasal / temporal / mean)

Discussion

Inzelberg [8] first showed that RNFL of PD patients measured by OCT was thinner than that of controls. Similar results of other studies supported this result [9, 22-24]. In a meta-analysis, it was found that all RNLF quadrants might be thinner in PD patients than in controls with different OCT devices. However, subgroup analysis showed a statistically significant decrease in RNFLt thickness and RNFLm thickness in all OCT types [25]. Akin to these previous studies [8,25,26], in our study, peripapillary RNFL thickness in all quadrants was thinner in Parkinson's patients compared to the controls. Although all these findings were not significant, right RNFLm thickness was significantly smaller compared to the controls. Although temporal quadrant was thought to be affected early in neurodegenerative diseases [27], it was lower than the control group in our study, but this was not significant. We think that, if the number of patients increase, this difference will become more significant. Interestingly, we also found similar decreases in

RNFL thickness in the ET group. We found few studies in the literature where RNFL of ET patients was assessed by OCT [18-20]. One of these studies was a pilot study with a small number of patients where it was found that foveal thickness decreased in ET patients compared to the controls, but this difference was not statistically significant [18]. Although we did not find such a result, it may indicate that retinal involvement may be present in ET patients. Similar to our results, Tak et al. found that RNFL was thinner in ET patients compared to the control group [19]. However, in another study, RNFL thickness of ET patients was not significantly different compared to the control group, in contrast to our results [20]. This may be due to methodological differences, such as the age of the patients included in the study. We have difficulty in explaining these different results, but we believe that more studies on this topic will result in clearer findings.

In a small number of studies, color vision impairment was not detected in ET [16,17], but the retinal thinning we found may indicate a subclinical visual effect. It is known that there is a retinal dopamine deficiency in PD [3,4]. Retinal dopamine deficiency leads to decreased visual contrast sensitivity. OCT can measure RNFL thickness but does not measure the amount of dopamine. It is not known whether dopamine deficiency affects the RNFL thickness or whether there is a correlation between the RNFL and the amount of dopamine. In addition, lack of direct connection between dopaminergic amacrine cells and ganglion cells suggests that dopamine deficiency alone may not be responsible for the reduction of RNFL thickness [3,4,28]. However, the improvement of retinal activity measured by electroretinogram or improvement of color vision with levodopa treatment suggests that dopamine has a significant retinal effect [29,30]. Lewy bodies (LB) or phosphorylated α-synuclein may have contributed to this retinal involvement. As is well known, LB and other pathological findings occur in brainstem and olfactory nucleus before they occur in substantia nigra, and these pathological findings are spread from brainstem to the cortex and other regions, as described in the Braak staging [31]. LB are not specific to PD but also occur in other neurodegenerative diseases such as corticobasal degeneration and Lewy body dementia. Alpha-synuclein, which plays a role in dopamine release, is important in the formation of LB. Phosphorylated alpha-synuclein was found in the retinas of PD patients, which is thought to be a biomarker of PD [32,33]. Visual problems seen in PD can be caused by LB or phosphorylated α-synuclein present in retina. In postmortem studies performed on ET patients, LB were detected in brainstem [11]. Decrease in RNFL thickness determined by OCT may also occur in ET as a result of these pathologies. Regardless of the cause, RNFL thickness in measured by OCT decreased in neurodegenerative disorders such as PD, Alzheimer's disease and multiple sclerosis. Similar to these neurodegenerative diseases, the presence of thinner RNFL suggests that ET may be a neurodegenerative disease.

As expected, there was a correlation between disease severity identified by UPDRS, HYS in PD, tremor grade in ET and the duration of illness. The correlation between RNFL thickness, macula or fovea and severity of PD has been determined in some studies [6,22]. Satue et al. [6] found a negative correlation between HYS and macular parameters. We did not find such a correlation. In our study, an inverse correlation was found between RNFLn, RNFLi and UPDRS scores in PD patients. Jimenéz et al. [34] found a negative correlation between UPDRS scores and average RNFL thickness. Unlike the PD group, we did not obtain a similar correlation in the ET group. In fact, this finding was not surprising, because the severity of tremor was based on motor symptoms, and a retinal pathology that may be present in ET may be a nonmotor symptom.

Limitations

There were some limitations of our study. First, some of the ET patients may develop PD. The risk of developing PD in ET patients can be four times higher than controls [35]. The prevalence of rest tremor in ET varies between 1% and 50% [36,37]. Five ET patients (16.7%) had rest tremor in our study. It should be noted that the ET patients included in our study were > 40 years old and had a longer duration of disease. There were no re-emergent tremor, jaw tremor, bradykinesia or rigidity in ET patients included in our study. However, there may be a possible overlap between ET and PD. Second, all PD patients were receiving dopaminergic or levodopa therapy, and these treatments may affect RNFL thickness. In addition, the PD group was not divided into subgroups according to treatment.

Conclusion

In conclusion, our study has shown that RNFL thickness measured by OCT was reduced in ET as in neurodegenerative diseases such as PD and Alzheimer's disease. This finding may indicate that ET is a neurodegenerative disease and subclinical retinal impairment occurs in ET.

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