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ORIGINAL PAPER

Retinal vessel diameter obtained by optical coherence tomography is spared in Parkinson's disease

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Abstract

Purpose To define the alterations in retinal vessel diameter in Parkinson's disease (PD) by optical coherence tomography (OCT).

Methods This is a case-control study including 41 eyes of 41 patients with diagnosis of PD and 35 eyes of 35 age- and sex-matched control subjects. All subjects underwent complete neurological and ophthalmological examinations before measurements. Retinal vessel diameters and peripapillary retinal nerve fiber layer (pRNFL) thicknesses were evaluated with spectral domain OCT (SD-OCT) with a circular scan centered at the optic disc. The diameters of the superior nasal and temporal arteries and veins, and inferior nasal and temporal arteries and veins were measured and then compared between the groups. Correlations with the duration of the disease, usage of levodopa, and pRNFL thicknesses between retinal vessel diameters were examined with Pearson and Spearman correlation analysis.

Results Average pRNFL thickness is significantly decreased in PD compared to age- and sex-matched controls ($p < 0.05$). At all measurement points, retinal artery diameter measurements were decreased in the PD group compared to controls, but the differences did not reach statistical significance. Diameters of the retinal veins also did not show any significant difference in the PD and control groups. Superior temporal artery diameter was significantly decreased in patients using levodopa compared to nonusers ($p = 0.022$). There were no statistically significant correlations between pRNFL thicknesses or disease duration with retinal vessel diameters in PD group.

Conclusions Parkinson's disease does not seem to have an impact on the retinal vessel diameters obtained by SD-OCT.

Keywords Optical coherence tomography · Parkinson's disease · Retina · Retinal nerve fiber layer · Retinal vessel diameter

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Introduction

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease, characterized by the loss of dopaminergic neurons in the nigrostriatal complex [1]. The main underlying pathology is neurodegeneration and accumulation of the Lewy bodies as cytoplasmic inclusions. Although extent and progression of cerebral small vessel disease is associated with focal cerebral atrophy and research

suggests contribution of hypertensive microangiopathy as the underlying etiology, vascular components in the pathogenesis of PD still remain largely unknown [2, 3]. Retinal blood vessels are the only part that allows for the direct and noninvasive visualization as part of the central circulation system. Spectral-domain OCT is a noninvasive and reproducible tool with high-resolution images for evaluating the retinal and optic disc anatomy in central nervous system diseases. Retinal involvement, including RNFL, macular thickness, volume, and choroidal thickness changes have been documented with OCT in the literature in PD [4–9]. Examining the retinal vessels in PD may contribute to the underlying etiology of the disease. The objective of this study is to investigate the retinal vessel diameters in PD and their correlation with the duration of the disease and the use of levodopa.

Subjects and methods

This is a non-randomized prospective case-control study including 41 eyes of 41 patients with a diagnosis of PD according to the Brain Bank criteria of the UK Parkinson's Disease Society and 35 eyes of 35 healthy controls. Subjects with systemic disease (i.e., hypertension, diabetes mellitus, stroke, ischemic heart disease, collagen disease, renal disease/failure, migraine), dependency on alcohol or smoking habit, and autoimmune inflammatory diseases of the central nervous system were excluded. A single eye was chosen randomly for inclusion in the study. Where the image quality was not of sufficient quality for measurement, the other eye was included. The study was approved by the Institutional Review Board of Medical School of Erciyes University (No: 2016/24, date: August 1, 2016) and was conducted in adherence with the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. All of the patients with PD were diagnosed by a board-certified neurologist specialized in movement disorders (MG). Duration of the disease and patients' usage of levodopa was noted. Healthy participants of similar age and gender were recruited as controls from the volunteers admitted to ophthalmology clinic for routine examination, and they were also examined by the neurologists and diagnosed healthy for neurological disorders. A complete ophthalmologic examination through dilated pupils was performed to all patients and controls, and features of detailed ophthalmologic examination were obtained by DGS and MU. The patients' eyes with any ophthalmologic pathology (i.e., glaucoma, retinal pathology, narrow anterior chamber, refractive disorders greater than $\pm$ 3.0 Diopters, poor image due to cataract or unstable fixation, and prior intraocular surgery) were excluded from the study.

Spectral domain: optical coherence tomography measurements

This study used SD-OCT with a $\sim$ 840 nm wavelength (Spectralis; Heidelberg Engineering, Heidelberg, Germany) to measure pRNFL thickness and retinal vessel diameters. An experienced technician who was blinded for the groups of the participants of the study performed all SD-OCT scans with an eye tracking system using high-resolution mode and automatic real-time averaging 9 B-scan frames in order to improve image quality and reduction of noise speckles.

To obtain pRNFL measurements and peripapillary retinal vessel measurements, a 3.4-mm ring scan was manually centered on the middle of the optic disc (Fig. 1a). The pRNFL Spectralis protocol generates a map showing the average thickness [10]. All vessel analyses were obtained from those peripapillary scans.

Retinal vessel diameter measurements

All of the measurements were carried out manually by two masked, independent clinicians (DGS, SS) on the OCT images as described previously (Fig. 1b) [11, 12]. Vessels in which these landmarks were undistinguishable were excluded from the analysis. Reproducibility is reported as the inter-rater variability between two independent clinicians.

Vessels were grouped as upper nasal arteries, upper temporal arteries, inferior nasal arteries, inferior temporal arteries, and upper nasal veins, upper temporal veins, inferior nasal veins, and inferior temporal veins based on their appearance on the simultaneously taken fundus photograph. Vessel diameters were indirectly measured, and their shadow width from the hyperreflective signal inferiorly to the hyperreflective signal superiorly (i.e., lumen plus vessel walls) was determined.

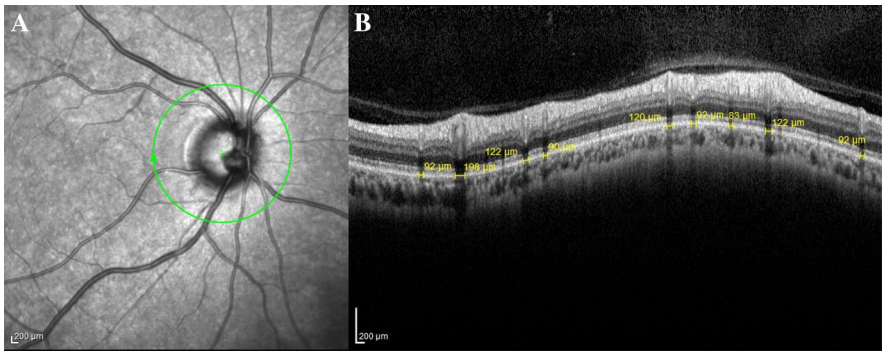

Fig. 1 Image of retinal vessel diameter measurement with spectral domain OCT **a** the position of the 3.4-mm ring scan centered in the middle of the optic disc, **b** measurements of the shadow width of the corresponding vessels

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 22.0 package program (IBM Corp., Armonk, New York, USA). Shapiro–Wilk's test was used, and histogram and q–q plots were examined to assess the data normality. Data were expressed as mean ± standard deviation (SD) for metric variables, and as frequency (percentage) for categorical variables. Intraclass correlation coefficients were used to determine the reproducibility. For comparisons, Mann–Whitney U test or T test was performed according to data distributions. Correlations with the duration of the disease, usage of levodopa, and pRNFL thicknesses between retinal vessel diameters were examined with Pearson and Spearman correlation analysis. A value of $p < 0.05$ was determined as statistically significant.

Results

Forty-one eyes of 41 subjects with PD (20 females, 21 males, 59.64 ± 9.94 years) and 35 eyes of 35 subjects in control group (16 females, 19 males, 59.44 ± 7.59 years) were evaluated. There were no differences between participants in the PD and control groups with respect to age or gender ($p > 0.05$). The median disease duration for PD was 4 years (range 1–25 years).

Although at all measurement points, retinal artery diameter measurements were decreased in the PD group compared to controls, the difference did not reach statistical significance (Table 1).

The diameters of the retinal veins in the eyes of PD group and controls showed no difference statistically (Table 2).

Eight patients did not have levodopa in their treatment regimen and were treated with dopamine agonists (five patients were on pramipexole and three patients were on ropinirole). Superior temporal artery diameter was significantly decreased in patients using levodopa compared to nonusers ($p = 0.022$), while other retinal vessel diameters showed no statistical difference between patients with and without levodopa in their treatment regimen (Table 3). Retinal vessel diameters did not show any significant difference according to the duration of the disease.

Average pRNFL thickness in the PD group was found as 89.58 ± 8.71 µm, while in the control group, it was 98.74 ± 11.32 µm ($p = 0.033$). There were no significant relationships between pRNFL thickness and mean retinal artery ($p = 0.755$) and vein ($p = 0.629$) diameter and levodopa use ($p = 0.118$) within the PD group.

Inter-rater correlation coefficients were significant for all parameters ($p < 0.05$).

Discussion

Parkinson's disease is a primary neurodegenerative disorder, yet there has been shown in the literature suggesting PD patients have an increased risk of developing comorbid cerebrovascular disease compared to healthy subjects [13]. In a study, comparing early-to-moderate Parkinson's disease patients to age-matched healthy controls revealed that Parkinson's disease is characterized by widespread cortical hypoperfusion [14]. In Alzheimer's disease, also another age-related neurodegenerative condition, the vascular components have been shown to play a key pathological feature and a possible contributing factor to disease progress [15]. However, there is very little

Table 1 Retinal artery diameter measurements (mean ± SD in μm) of subjects with Parkinson's disease and controls

Measurement points	Parkinson's disease	Control	*p*
Superior nasal artery	68.40 ± 18.88	73.94 ± 13.26	0.151
Inferior nasal artery	64.46 ± 14.27	67.83 ± 14.99	0.320
Superior temporal artery	93.54 ± 21.46	97.54 ± 16.21	0.088
Inferior temporal artery	95.26 ± 16.49	96.77 ± 21.70	0.733
Mean retinal artery	80.17 ± 12.92	84.02 ± 9.51	0.143

Table 2 Retinal vein diameter measurements (mean ± SD in μm) of subjects with Parkinson's disease and controls

Measurement points	Parkinson's disease	Control	*p*
Superior nasal vein	90.58 ± 18.94	93.57 ± 17.60	0.482
Inferior nasal vein	84.41 ± 18.19	85.69 ± 19.36	0.855
Superior temporal vein	132.17 ± 29.42	126.20 ± 16.53	0.750
Inferior temporal vein	128.05 ± 19.26	126.60 ± 21.96	0.770
Mean retinal vein	108.80 ± 15.17	108.01 ± 11.42	0.801

Table 3 Retinal vessel diameter measurements (mean ± SD in μm) of subjects with Parkinson's disease with levodopa treatment and without levodopa treatment

Measurement points	With levodopa	Without levodopa	*p*
Superior nasal artery	63.50 ± 12.50	51.00 ± 16.87	0.197
Inferior nasal artery	64.09 ± 14.14	66.00 ± 15.68	0.739
Superior temporal artery	90.00 ± 10.50	100.50 ± 15.32	0.022*
Inferior temporal artery	92.66 ± 16.52	91.62 ± 11.04	0.867
Mean retinal artery	78.55 ± 12.19	77.06 ± 8.61	0.747
Superior nasal vein	98.00 ± 21.14	88.48 ± 18.78	0.277
Inferior nasal vein	87.45 ± 19.21	85.42 ± 19.36	0.961
Superior temporal vein	126.00 ± 19.50	114.20 ± 23.51	0.155
Inferior temporal vein	127.04 ± 17.32	124.60 ± 21.48	0.910
Mean retinal vein	108.57 ± 16.32	113.03 ± 13.54	0.480

*Statistical significance

known about the vascular changes in PD, and the contribution of possible vascular degeneration to the neuronal degeneration.

Optical coherence tomography is a noninvasive and reproducible tool for evaluating the retinal and optic disc anatomy in central nervous system diseases. It uses low-coherence interferometry to obtain detailed images of the retinal architecture. Modern high-speed spectral-domain (SD) OCT devices can obtain high-resolution images of the retina. Retinal involvement and thus OCT changes such as total or segmental RNFL thinning, retinal thickness, and volume changes have been shown in the literature in Parkinson's disease (PD) [7, 16, 17]. Retinal blood vessels are the only part of the central circulation system that can be directly and noninvasively visualized *in vivo*. The diameters of retinal blood vessels are considered as an important indicator of cerebrovascular and cardiovascular diseases, and the diameter measurement with OCT has become a subject of extensive research in various conditions [12, 18, 19]. In this study, our primary aim was to find out whether there were any differences in the retinal vessel diameters in patients with PD compared to controls.

Cerebral small vessel disease (SVD) has been shown to play a role in the etiology of parkinsonism [20]. Yet there are conflicting data concerning the issue. In a study, the prevalence of vascular risk factors and SVD pathology was found lower in autopsy-proven PD compared with controls [21]. In the literature, there are various studies pointing to a relationship between SVD and the use of levodopa by causing hyperhomocysteinemia [22]. Hyperhomocysteinemia causes various ocular diseases including retinal vascular atherosclerosis by causing impaired vascular endothelial dysfunction [23]. In Kromer

et al.'s study, the authors stated that the patients in their study had relatively long disease duration and most of their patients were on levodopa, which might be the cause of their reduced grey value ratios in PD. So based on the findings of their study, they could not conclude whether their results were the impact of the disease solely or because of the levodopa treatment all the patients in their group were on. We had the opportunity to compare the levodopa users with nonusers, since our patients had relatively shorter disease duration compared to the latter study (median 4 years vs 8 years) and some of the patients were not on levodopa regimen, and we found that superior temporal artery diameter was significantly reduced in patients on levodopa. Since we did not find a significant relationship between the disease duration and retinal vessel diameters, we think that this finding is suggestive of the levodopa use of these patients rather than their longer duration of the disease. We also observed that even though the differences did not reach statistical significance, superior temporal vein and superior nasal vein had larger diameters (both have a difference of about 10 micron) in the levodopa group compared to nonusers. Small vessel disease in PD likely is related to the arteries more than to veins, and in the literature, there is some argument that SVD in PD is potentially related to chronic levodopa therapy. However, it is well known that arteriosclerotic diseases such as arterial hypertension, diabetes mellitus, or hyperlipidemia result in venous retinal pathology in patients with retinal vein occlusions [24]. It is generally accepted that arterial rigidity and turbulent flows affect the retinal veins which share the adventitial sheath [22]. We suspect that this could be the case in our patients in the levodopa group. Also in their study, Kromer and his colleagues detected lower grey vessel value contrast in retinal veins but no changes in arteries which they thought was unexpected [22]. They also discussed that this venous pathology might be reflecting the arteriosclerotic changes and the rationale of their findings could be either they were able to detect more veins per PD patient or control in the OCT scan or easier detection of the veins because of their wider lumens compared to arteries or veins were even more sensitive parameter than arterial retinal pathology in PD [22]. It is also shown that in patients with hypertension, the central OCT-based retinal artery equivalent (CORAE) was decreased while the central OCT-based retinal venous equivalent was increased (CORVE), which resulted in a decrease in the A/V ratio when compared with normotensive controls [12]. This is also consistent with our findings.

The mean value of pRNFL in levodopa group was 97.68 ± 8.58, while it was 92.25 ± 8.38 ($p = 0.118$). Even though the difference did not reach a statistical significance, it is consistent with previous reports that show neuroprotective effects of levodopa treatment in PD. Rim area, rim volume, and retinal nerve fiber layer were significantly greater in the group treated with levodopa while it was the thinnest in the group receiving dopamine agonists in a study recruited by Yavas et al, and they stated that levodopa could play a neuroprotective effect on RNFL in cases with PD [25]. In a recent study conducted by Lyttle et al., it was observed that treatment with levodopa significantly improved central visual acuity compared to untreated group in nonarteritic anterior ischemic optic neuropathy [26]. The authors concluded that levodopa may promote neuroprotection of the maculopapular retinal ganglion cell fibers in NAION. However, the smaller sample size of the patients without levodopa treatment, 19% of the patients, is one of the limitations of our study and limits the interpretations. Yet further studies assessing a possible relationship between cumulative levodopa doses, homocysteine levels, and retinal vessel diameters can provide a further insight into these possible correlations.

In a study examining the vascular morphology of human brain tissue of PD patients, the authors revealed that the capillaries were less in number, shorter in length, larger in diameter, and had fewer branches, suggesting that the vascular degeneration could be an additional contributing factor to the progression of PD [27]. In their study, their data suggested that the vessel degeneration was primarily at the level of the capillaries, with a cut of line of 10 μm for measuring, than small arteries and veins. In our study, we did not find any difference in the diameters, but we did not evaluate the other factors such as the length and branching that might have shown differences. Also we did not evaluate the peripheral retinal capillary diameters, and our data included larger vessels at the border of the optic disc, which might be the underlying reason for our conflicting results.

There is only one study in the literature evaluating retinal vessel diameters with OCT [22]. They revealed lower contrast of retinal veins in PD patients compared

to controls and also on the contralateral side of the clinically predominant and first affected side compared to the ipsilateral side. Similar to the findings of our study, they did not find a difference in vessel diameter between subject groups although in our study the patients had a relatively shorter disease duration (median 4 years) compared to the latter study (median 8 years).

Our study has some limitations. First, we could only measure the diameters of retinal vessels and could not reveal the other morphological prospects, and secondly our data give information on larger vessels than the impaired smaller vessels (< 10 microns in diameter) previously shown to be deteriorated in PD in the literature [27]. Our study also has a relatively small sample size, the differences in the retinal artery diameter measurements between PD and controls could have reached statistical significance if the sample size was larger. The strength of our study is that it is the first study in the literature studying the relationship between average pRNFL thickness and retinal vessel diameters and also contributes to the literature studying retinal vessel in PD, yet as far as we know, there has been only one study published in the literature up-to-date concerning this subject [22].

Our study reveals that retinal vessel diameters are not impaired in the course of PD, and average pRNFL thickness is decreased compared to age- and sex-matched controls. Further studies should be performed on patients with longer duration of the disease and higher cumulative levodopa usage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. We confirm that we had full access to all data and we took final responsibility for decision to submit.

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