Ophthalmological Symptoms, Evaluation and Diagnoses in Parkinson's Disease

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Abstract

Objective: To evaluate ophthalmologic symptoms in Parkinson's Disease patients, the frequency of referral to ophthalmology for these symptoms and the variability in ophthalmologic assessment and diagnosis.

Design: Retrospective case series from January 2016 to December 2018.

Setting: Northwell affiliated primary care and referral centers.

Participants: Parkinson's Disease patients with a documented ophthalmologic complaint between January 2016 and December 2018.

Exposures: Clinical ophthalmologic assessment for referred patients.

Main Outcomes and Measures: Rate of ophthalmology referral in Parkinson's patients with eye related complaints, most common ocular symptoms and diagnosis. We also examined the frequency of ophthalmologic testing including manifest refraction, near vision assessment, oculomotor exam and optical coherence tomography.

Results: 123 of the 345 Parkinson's Disease patients with documented ocular or visual complaint were subsequently seen by ophthalmology, 64 males and 59 females with a mean age of 76.1 +/- 7.78. The most common symptoms included blurry vision (72%), difficulty reading (72%), ocular discomfort (51%) and double vision (31%). The most common ophthalmological diagnoses included glaucoma (30%), dry eye (28%), and strabismus (22%). There was substantial variability in components of the ophthalmology evaluation, specifically the inclusion of optical coherence tomography (OCT) of the retinal nerve fiber layer (33%), and ganglion cell layer- inner plexiform layer (10%), testing of near vision (37%) and manifest refraction (31%).

Conclusion and Relevance: PD patients with visual complaints are under referred to ophthalmology. Furthermore, once patients are referred, they undergo ophthalmological evaluations that are inconsistent and often not comprehensive. Standards for both referral structure to ophthalmology and ophthalmological assessment are integral for optimal patient care.

Keywords: Parkinson's Disease; Ocular Complaint; Ophthalmology; Visual Dysfunction; Optical Coherence Tomography

Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that over time leads to loss of motor function and significant motor disability. Non-motor manifestations are integral part of the disease, and include sensory abnormalities, cognitive and neuropsychiatric disorders, and autonomic dysfunction [1-5].

Visual changes are among the most common sensory abnormalities experienced by patients with PD. They often present in early stages of the disease with a variety of symptoms, which increase in severity and complexity as the disease progresses [6].

Visual symptoms in Parkinson's disease, contribute to difficulty in performing activities of daily living (ADLs), since they adversely affect fine motor activities in addition to gait and balance [7-9].

Visual dysfunction in the later stages of disease can worsen cognitive impairment and lead to visual hallucinations, affecting the ability of patients to remain functionally independent and avoid institutionalization [10].

Despite the frequency of visual dysfunction in PD and its detrimental impact on both patient prognosis and quality of life, there is great variability in the evaluation and management of visual and ocular symptoms in PD patients [6-9].

Methods

Study subjects

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Feinstein Institute for Medical Research, Northwell Health. The patient's written informed consent was waived for this retrospective study. We reviewed the charts of 345 PD patients with visual complaints who were examined by a neurologist at a Northwell Health facility. The inclusion criteria for this study were: (1) a diagnosis of Parkinson's disease and (2) an ophthalmological complaint documented by their neurologist between January 2016 and December 2018. Of the 345 reviewed patient charts, 123 had documented an ophthalmologic evaluation.

The duration of disease was based on the clinical documentation from available physician encounters. When there was no clear documentation of the date of disease onset, but there was a verified point of initiation of anti-parkinsonian medication, we estimated the disease onset at the time when anti-Parkinson treatment was first instituted. In patients who had multiple ophthalmologic visits during the specified time frame, clinical data abstraction was obtained from the first available exam. In patients with multiple OCT scans within the time frame, we used the scan with the highest reliability based on patient fixation and signal strength.

Ophthalmic complaints

We assessed the frequency of the following ocular/visual symptoms: a) Blurry vision, described by complaints of blurring of images, difficulty focusing, difficulty with depth perception, or driving at night. b) Ocular discomfort, described by complaints of grittiness, burning, pain, dryness and light sensitivity. c) Double vision (diplopia) described by complaints of either intermittent or constant monocular or binocular double vision at distance or at near.

Ophthalmologic exam

We then reviewed the frequency of the following ophthalmological exam components: a) Manifest refraction was defined by subjectively testing a patient's need for lens correction in order to achieve best Snellen visual acuity at 20 meters. b) Near vision assessment was performed at approximately 33 cm using a Jaeger reading card. c) Sensorimotor exam was performed by measuring ocular deviation by prism neutralization in multiple fields of gaze. d) Spectral Domain Optical Coherence Tomography (SD-OCT) to analyze of the retinal nerve fiber layer (RNFL) and macula, using either the Cirrus SD-OCT (Carl Zeiss Meditec, Dublin CA) optic disc cube or macular cube protocol with automated segmentation software or the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg Germany) peripapillary retinal nerve fiber layer (pRNFL) or macular protocol. SD-OCT of the ganglion cell layer-inner plexiform layer (GCL-IPL) was performed using automated segmentation software of the Cirrus macular scan.

Diagnoses

We then evaluated the frequency of the most common diagnosis (based on clinical provider documentation) and their association to patient complaints and ophthalmologic testing. These diagnosis included glaucoma, dry eye, strabismus, maculopathy (such as age related macular degeneration, macular edema, or epiretinal membrane) and blepharitis.

Results

Of the 345 PD charts reviewed, 123 had documented ophthalmologic evaluations. The demographics were fairly distributed as there were 64 males, 59 females ranging in age from 48-95 with the average as 76.1, standard deviation 7.78 years, and median 76 years. The average duration of PD was 6.8 years, standard deviation 0.71 years with a range from 1 to 39 years.

Ophthalmic complaints

The most common patient complaints were blurry vision (72.4%) and difficulty reading (72.4%). Nearly a third (30.9%) complained of double vision. Less frequent complaints included ocular discomfort (51.2%), dryness (47.2%), redness (10.6%), light sensitivity (9.8%) and visual hallucinations (6.5%) (See figure 1).
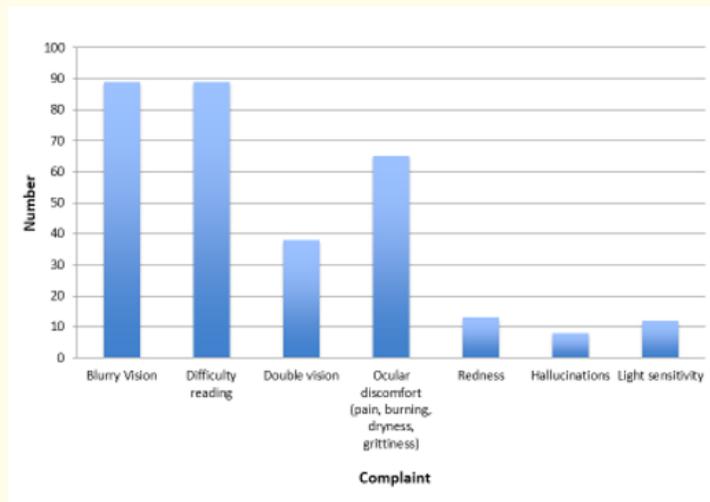

Figure 1: Ophthalmological complaints in PD patients.

Clinical exam

Thirty-eight patients received refractions (30.9%) and 27 (71.1%) of these patients had improvement in their vision with the updated refraction. Of the 89 patients with blurry vision, 26 (29.2%) received refractions.

Near vision was assessed in 46 patients (37.4%). Of the 63 patients complaining of difficulty reading, 20 (31.7%) had their near vision assessed. Binocular diplopia was experienced by 38 patients (30.9%), 5 of whom were diagnosed with convergence insufficiency, 21 with strabismus, and 14 patients remained undiagnosed.

We found no correlation between duration of disease (DOD) and best corrected visual acuity.

OCT results

Overall, 37 (30.1%) patients underwent OCT testing to screen for RNFL thinning. Of those 37 screened, 20 (54.1%) had a diagnosis of glaucoma. Seventeen PD patients without glaucoma had RNFL screening, and 6 of these 17 showed RNFL thinning. Macular OCT was performed on 42 patients (34.1%), 20 of whom (47.6%) showed pathology in one or both eyes. Twelve patients underwent OCT of the GCL-IPL and 10 of the 12 showed GCL-IPL thinning in one or both eyes. Using a linear regression model, there was a moderate correlation (r^2 = 0.57789) between DOD and RNFL thickness (See figure 2).
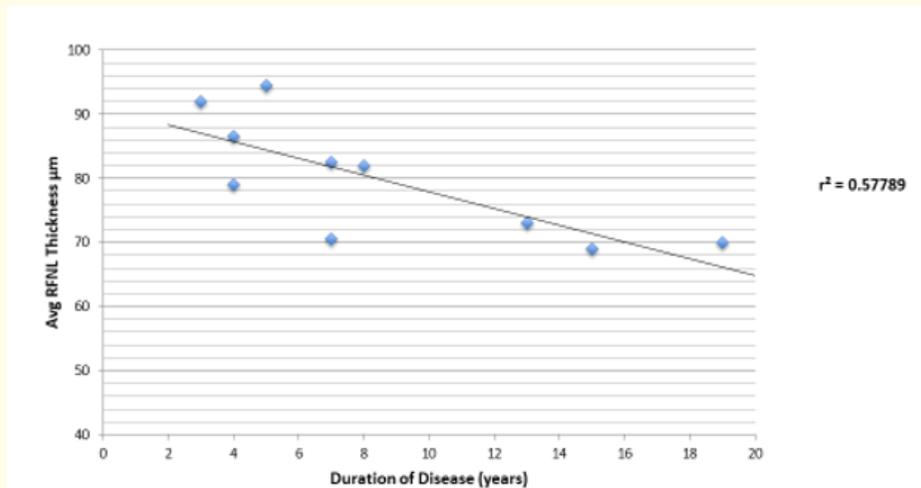

Figure 2: Average RNFL thickness vs. duration of PD.

Diagnosis

The most common diagnosis overall was glaucoma (n = 37, 30.1%), followed by dry eye (n = 34, 27.6%), and strabismus (n = 27, 22%). Other common diagnoses included macular degeneration, seen in twenty patients (16.3%) and blepharitis which was diagnosed in 12 patients (9.76%). Overall 49 patients (39.8%) had multiple ophthalmologic diagnosis (See figure 3).
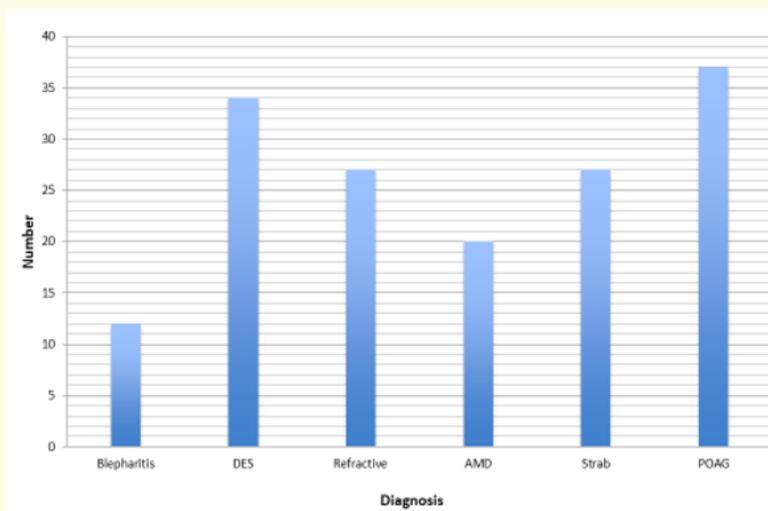

Figure 3: Diagnosis associated with complaint of blurry vision.

Discussion

PD patients not under referred to ophthalmology

The most important finding of the study is that although visual symptoms are very common in PD, with blurry vision and difficulty reading as the two most common visual complaints, only 35.7% of patients with visual complaints were referred for an ophthalmological evaluation. Furthermore, many PD patients had multiple ophthalmologic diagnosis, yet received only a limited or focused ophthalmologic evaluation.

Despite the known high prevalence of ocular pathology in PD, we found that less than 50% of PD patients reporting visual/ocular complaints to their neurologist had a documented ophthalmologic evaluation between 2016 and 2018. We suspect two primary reasons for the poor referral:

a) First, there is a lack of established guidelines and standard of care regarding the timing and necessity of ophthalmologic referral in PD patients. Many systemic and neurologic diseases associated with significant ocular pathology have clear and specific guidelines for ophthalmology referral. For example, the American Academy of Ophthalmology preferred practice pattern guidelines recommend that patients with type 2 diabetes mellitus are referred to ophthalmology upon diagnosis with annual follow up. There are also specific guidelines regarding ophthalmology referral in patients with MS or HIV [11]. However, there are no similar recommendations for ophthalmology referral in PD patients. Therefore, current referral patterns are inconsistent and tend to be based on patient's vocalizing visual or ocular complaints.

b) A possible second reason for low ophthalmology referrals in PD patients is that many ophthalmologists are not familiar with the extent of ophthalmic complications associated with PD. This results in limited exams that insufficiently address the concerns of the patient and referring physician. For example, many PD patients have difficulty reading due to convergence insufficiency, but this condition is usually not assessed during a routine eye exam. Therefore, the patient may be told their exam is "normal" and the cause of their symptom remains undiagnosed. Similarly, a complaint of "blurry vision" is not always associated with a decrease in objectively measured visual acuity. Notably, in our study 42.7% of patients complaining of blurry vision had Snellen visual acuities measuring 20/40 or better in both eyes. Conditions such as dry eye, blepharitis, eyelid apraxia, and oculomotor abnormalities can cause subjective decrease in visual quality that is not always reflected in standard visual acuity testing. Addressing these complaints requires a more comprehensive evaluation rather than a problem-focused approach.

c) Finally, other potential reasons for low referral rates in PD patients could be due to poor patient follow up or lack of communication between care providers

PD associated with multiple ocular pathologies

Our study further highlighted the need for comprehensive ophthalmic evaluation of PD patients because of the wide variety of associated visual symptoms and ocular disease [5,6,7,9].

Dry eye

Dry eye is one of the most common documented ocular pathologies associated wit PD. This it thought to be due to several factors including, decreased blink rate, decreased tear break up time, and decreased tear production secondary to autonomic dysfunction [12]. We found 27.6% of PD patients had a documented diagnosis of dry eyes disease. This is in contrast with previous studies that have estimated anywhere from 53 - 87.5% prevalence of dry eye disease in PD patients versus 20.5% of controls [6,12]. We suspect this underrepresenta-

tion in our review is due to bias in subspecialist documentation at a tertiary care center. For example, PD patients were frequently referred to neuro-ophthalmology specialists whose exam may focus on neurologic aspects of the disease, such as oculomotor dysfunction, as opposed to ocular surface abnormalities.

Refractive error

Refractive error is a frequent and easily treated cause of decreased visual acuity. 71% of the patients in our study who received refractions had improved vision with the updated prescription. Despite the high rate of improved vision with refraction in our study, only 31% of patients received refractions as part of their exam. This is especially surprising, considering that 71% of patients had blurry vision as one of their presenting complaints. This suggests that including manifest refraction as part of the exam in all PD patients is an efficient straightforward way to improve patient care.

Macular pathology

We found that 20/123 (16.3%) PD patients had a diagnosis of age-related macular degeneration (ARMD). This is similar to the prevalence of ARMD in the general aged population according to the National Eye Institute, which reports a range of 1.5 - 15%, increasing with patient age. The neurodegenerative mechanisms of ARMD and PD both involve impairment of metabolic waste removal. This leads to accumulation of lipofuscin in the retinal pigment epithelium in ARMD and the accumulation of neuronal alpha synuclein in PD [13]. Chronic inflammation, and oxidative stress also exacerbate both retinal and neuronal degeneration in ARMD and PD [13]. However, most studies have failed to demonstrate an increased incidence of ARMD in PD patients as compared to controls [9,14]. Therefore, despite the similarities in neurodegenerative mechanism, PD patients do not appear to be at higher risk for developing ARMD.

Glaucoma

In contrast to ARMD, there does appear to be an increased incidence of glaucoma and glaucomatous retinal changes in PD patients. Glaucoma is a chronic, progressive optic neuropathy in patients > 18 years of age in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons [15]. We found that nearly 30% of PD patients had a diagnosis of glaucoma. This is even higher than previous studies, which have shown a 16 - 24% prevalence of glaucoma in PD patients, as compared 7% in controls [6,16]. Overall 41 of the patients in our study underwent RNFL OCT and 23 of those patients showed significant RNFL thinning. Only 12 patients were screened with OCT of the GCL-IPL, and 10 out of the 12 had GCL-IPL thinning.

We did not evaluate visual fields, but prior studies have shown visual field changes in PD [17,18]. Therefore, PD patients have been shown to not only have an increased incidence of glaucoma diagnosis, but also increased incidence of visual field defects, as well as RNFL and GCL-IPL thinning. Despite this evidence, only 30% of PD patients in our study underwent RNFL screening and less than 10% underwent GCL-IPL OCT, suggesting that many PD patients with glaucoma may remain undiagnosed.

Neuro-ophthalmological findings

Previous meta-analysis demonstrated that PD patients have significant thinning of the RNFL compared to controls [19,20]. We had similar findings, where 30% of the PD patients without glaucoma who underwent RNFL OCT screening showed RNFL thinning. This suggests that PD patients are at increased risk for non-glaucomatous optic atrophy. Interestingly, the pattern of RNFL thinning in PD tends to show a relative sparring of the nasal quadrant, similar to the pattern of RNFL thinning seen in glaucoma. Thus, there may be a common underlying mechanism of inner retinal degeneration in PD and glaucoma [21].

Prior studies have demonstrated increased GCL-IPL thinning in PD [21,22]. Sari., *et al*. further showed that the degree of GCL-IPL thinning was associated with PD severity and duration [16]. We found GCL-IPL thinning in almost all of the PD patients who underwent OCT

of the GCL-IPL. A reasonable explanation for this is that dopamine is found in the amacrine cells of the inner plexiform layer and thus lack of dopamine leads to the retinal thinning in PD patients. But similar inner retinal layer thinning is also seen in other neuro-degenerative diseases such as Alzheimer's disease and multiple sclerosis raising the question of whether there is an unidentified common mechanism of retinal thinning in neurodegenerative disease [23,24].

Oculomotor abnormalities

The prevalence of diplopia in PD varies from 10 - 30% [6]. This is frequently due to convergence insufficiency, which can be seen in 24.5% of PD patients [9] and leads to blurred or double vision when reading [25]. 30.1% of patients in our study had complaints of double vision and 27.6% of patients were diagnosed with strabismus. Interestingly, we found only 8.1% of patients had documented convergence insufficiency.

This low estimate may be due to inconsistencies in of physician documentation in our retrospective chart review. Other common oculomotor abnormalities in PD include hypometric saccades [26], saccadic smooth pursuit [5] up-gaze limitation, blepharospasm and apraxia of lid opening [6].

Limitations of the Study

There ware several limitations to our study related to its retrospective design which presumes complete and consistent documentation of patient symptoms and exam findings. We suspect that practitioners tend to focus more on the symptoms and findings related to their subspecialty (for example a neuro-ophthalmologist may focus more on symptoms of double vision than on dry eye symptoms, and vice versa for a cornea specialist). Furthermore, there is no standardized approach for ophthalmologic evaluation of PD patients, so evaluation and workup is left to the practitioner's discretion.

Some of our statistical analyses were limited due to the small number of patients who received certain tests such as OCT. For many patients we were unable to determine a precise date of PD onset and disease duration due to lack of, or inconsistent documentation in the medical record.

Finally, OCT images were obtained by multiple different photographers and technicians, and variability in their experience and skill could potentially affect the imaging results.

Conclusion

Clinicians in ophthalmology and neurology should be aware of the association between PD and ophthalmological disease. Given the high frequency of ophthalmological complaints in PD, there is a clear need for consistent and timely ophthalmology referral and evaluation. The cause of visual dysfunction is often not easily determined and may be multifactorial. Thus, we recommend a standardized approach to patient referral, potentially based on duration of disease, stage of disease or, initiation of dopaminergic therapy.

We also recommend a standardized approach for ophthalmologists to follow in both their history and exam of PD patients. We suggest including the following in all PD patient ophthalmological exams:

1. Evaluation of near vision

2. Accurate refraction for distance and near

3. Dry eye assessment

4.   Oculomotor exam, including testing for strabismus and convergence insufficiency.

5.   Complete dilated exam

6.   Baseline OCT of the RNFL and retina

Furthermore, we recommend always prescribing separate distance and reading glasses rather than progressive lenses or bifocals.

Future prospective clinical studies are needed in order to more accurately establish the frequency of ocular and visual disorders in PD. Further research is also needed to determine the mechanism and relevance of inner retinal thinning in PD and to clarify the role of OCT as a potential biomarker in PD.

Acknowledgements

Bibliography

1.   Jankovic J. "Parkinson's disease: clinical features and diagnosis". *Journal of Neurology, Neurosurgery, and Psychiatry* 79.4 (2008): 368-376.

2.   Obeso JA., *et al.* "Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy". *Journal of Movement Disorders* 32.9 (2017): 1264-1310.

3.   Goldman JG and Postuma R. "Premotor and nonmotor features of Parkinson's disease". *Current Opinion in Neurology* 27.4 (2014): 434-441.

4.   Chaudhuri KR., *et al.* "Parkinson's disease: the non-motor issues". *Parkinsonism and Related Disorders* 17.10 (2011): 717-723.

5.   Armstrong RA. "Visual symptoms in Parkinson's disease". *Parkinson's Disease* (2011): 908306.

6.   Ekker MS., *et al.* "Ocular and visual disorders in Parkinson's disease: Common but frequently overlooked". *Parkinsonism and Related Disorders* 40 (2017): 1-10.

7.   Biousse V., *et al.* "Ophthalmologic features of Parkinson's disease". *Neurology* 62.2 (2004): 177-180.

8.   Lawrence BJ., *et al.* "Activities of daily living, depression, and quality of life in Parkinson's disease". *PLoS One* 9.7 (2014): e102294.

9.   Nowacka B., *et al.* "Ophthalmological features of Parkinson disease". *Medical Science Monitor* 20 (2014): 2243-2249.

10. Aarsland D., *et al.* "Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study". *Journal of the American Geriatrics Society* 48.8 (2000): 938-942.

11. Nishijima T., *et al.* "Routine Eye Screening by an Ophthalmologist Is Clinically Useful for HIV-1-Infected Patients with CD4 Count Less than 200 /μL". *PLoS One* 10.9 (2015): e0136747.

12. Tamer C., *et al.* "Tear film tests in Parkinson's disease patients". *Ophthalmology* 112.10 (2005): 1795.

13. Chung SD., *et al.* "Increased risk of Parkinson disease following a diagnosis of neovascular age-related macular degeneration: a retrospective cohort study". *American Journal of Ophthalmology* 157.2 (2014): 464-469.e1.

14. Matlach J., *et al.* "Retinal changes in Parkinson's disease and glaucoma". *Parkinsonism and Related Disorders* 56 (2018): 41-46.

15. Weinreb RN., *et al.* "The pathophysiology and treatment of glaucoma: a review". *The Journal of the American Medical Association* 311.18 (2014): 1901-1911.

16. AU Bayer., *et al.* "Association of glaucoma with neurodegenerative diseases with apoptotic cell death: Alzheimer's disease and Parkinson's disease". *American Journal of Ophthalmology* 133 (2002): 135e137.

17. Yenice O., *et al.* "Visual field analysis in patients with Parkinson's disease". *Parkinsonism and Related Disorders* 14.3 (2008): 193-198.

18. Tsironi Evangelia., *et al.* "Perimetric and retinal nerve fiber layer findings in patients with Parkinson's disease". *BMC Ophthalmology* 12 (2012): 54.

19. Yu J-g., *et al.* "Retinal Nerve Fiber Layer Thickness Changes in Parkinson Disease: A Meta-Analysis". *PLoS ONE* 9.1 (2014): e85718.

20. Chrysou A., *et al.* "Retinal layers in Parkinson's disease: A meta-analysis of spectral-domain optical coherence tomography studies". *Parkinsonism and Related Disorders* 64 (2019): 40-49.

21. Sari ES., *et al.* "Ganglion cell-inner plexiform layer thickness in patients with Parkinson disease and association with disease severity and duration". *Journal of Neuro-Ophthalmology* 35.2 (2015): 117-121.

22. Ucak T., *et al.* "Analysis of the retinal neve fiber and ganglion cell-Inner plexiform layer by optical coherence tomography in Parkinson's patients". *Parkinsonism and Related Disorders* (2016): 59-64.

23. Doustar J., *et al.* "Optical Coherence Tomography in Alzheimer's Disease and Other Neurodegenerative Diseases". *Frontiers in Neurology* 8 (2017): 701.

24. Satue M., *et al.* "Optical Coherence Tomography as a Biomarker for Diagnosis, Progression, and Prognosis of Neurodegenerative Diseases". *Journal of Ophthalmology* (2016): 8503859.

25. Lepore FE. "Parkinsons disease and diplopia". *Neuro-Ophthalmology* 30 (2006): 37-40.

26. Shibasaki H., *et al.* "Oculomotor Absnormalities in Parkinson's Disease". *Archives of Neurology* 36.6 (1979): 360-364.