Ophthalmological Features of Parkinson Disease

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Background: The aim of this study was to determine the type and frequency of ophthalmologic changes occurring in patients with Parkinson disease (PD).

Material/Methods: One hundred consecutive patients (196 eyes) with idiopathic PD and a control group consisting of 100 healthy patients (196 eyes) matched for age and sex underwent a complete ophthalmological examination of both eyes, including assessment of patient medical history, dry eye questionare, and visual hallucinations questionnaire, distance and near best corrected visual acuity (DBCVA, NBCVA), color vision, distance photopic contrast sensitivity, near point of convergence, slit lamp examination of the eye anterior segment, tear film osmolarity and breakup time, aqueous tear production, and intraocular pressure, as well as fundus examination and evaluation of the perimacular retinal thickness (RT) and peripapillary retinal nerve fiber layer (RNFL) thickness.

Results: In the eyes of PD patients DBCVA, NBCVA, contrast sensitivity, and color discrimination were significantly reduced. We also detected increased frequency of convergence insufficiency, seborrhoic blepharitis, meibomian gland disease (MGD), dry eye syndrome, nuclear and posterior subcapsular cataract, and glaucoma (p<0.05). However, intraocular pressure (IOP) was significantly lower in the PD group compared to controls. The frequency of visual hallucinations, age-related macular degeneration (ARMD), and other ophthalmological diseases, as well as RT and RNFL thickness, did not significantly differ between investigated groups.

Conclusions: Clinicians need to be aware of the association between PD and ophthalmological changes. Restoration of good-quality vision has a great impact on PD patients' quality of life, reduction of costs of treatment and care, and rehabilitation.

MeSH Keywords: Cataract • Dry Eye Syndromes • Glaucoma • Macular Degeneration • Parkinson Disease • Vision Disorders

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Background

Parkinson disease (PD), one of the most common neurodegenerative disorders, is characterized by progressive dopamine depletion due to dopaminergic neuron death in the substantia nigra. Visual pathway changes are also observed. In the eye, dopamine is contained in the subtype of amacrine cells A18 in the inner plexiform layer of the retina [1], while dopaminergic receptors are spread across the whole retina. The problem of ocular diseases associated with PD is not well known. It has been suggested that PD patients should be considered at increased risk of having dry eye problems [2–5], primary open-angle glaucoma [6], visual hallucinations [7–9], difficulties in oculomotor control [10,11], and deficits in contrast sensitivity and color discrimination [12–15], but, according to the WHO, there are no data about the 2 most frequent causes of blindness in the elderly, according to the WHO – cataract and age-related macular degeneration (ARMD). WHO data are cataract and ARMD, not their the frequency in PD patients.

Material and Methods

Patients

We enrolled 100 consecutive patients (196 eyes) aged 68.5±10.2 years with idiopathic PD without dementia and a control group consisting of 100 healthy patients (196 eyes) matched for age and sex with mean age of 68.6±9.8 years (p=0.95). For evaluation of RT, RNFL thickness, color vision, and contrast sensitivity, 85 PD patients (164 eyes) aged 67.4±10.3 years and 85 controls (164 eyes) aged 67.6±10.0 years, all without glaucoma, were recruited (p=0.91). We excluded all individuals with any systemic diseases, taking medications known to influence the organ of vision, or who had previous ocular surgery other than uneventful phacoemulsification. Patients with diagnosed idiopathic PD were referred for ophthalmological examination from the neurological outpatient clinics. The duration of PD and general medical history were recorded. PD staging was assessed with the modified Hoehn and Yahr (H-Y) scale. PD patients were examined in the morning without taking any antiparkinsonian drugs.

Procedures

Patients were interviewed to determine the presence and frequency of visual hallucinations and dry eye symptoms. To evaluate severity of dry eye disease, the Ocular Surface Disease Index (OSDI) questionnaire was used. To determine the distance and near best corrected visual acuity (DBCVA and NBCVA), the ETDRS logMAR chart and ETDRS near vision chart were used, respectively. A color vision examination (Farnsworth Dichotomous Test D-15) was performed separately for each eye, and contrast sensitivity (CSV-1000) was examined binocularly with and without high glare. Only subjects without glaucoma and best corrected visual acuity equal or better than 0.28 logMAR were enrolled to color vision and contrast sensitivity evaluation. The convergence insufficiency was recorded as positive when 1 or both eyes deviated out before the shown object reached 10 cm from the bridge of the nose. Examination of the anterior segment of the eye via slit-lamp biomicroscopy included evaluation of meibomian gland disease (MGD), intensity of lid-parallel conjunctival folds (LIPCOF), and presence of the other diseases. The severity of meibomian gland disease (MGD) was graded on the scale proposed by Bron et al. [16]: grade 0 – all glands clear of blockage; grade 1–1 or 2 capped (blocked) glands; grade 2–3 or 4 blocked glands with the secretions that appeared thick; grade 3 – approximately half of the glands blocked/stenosed; and grade 4 – more than half of the glands with viscous secretions. Degree of LIPCOF intensity was graded according to classification: degree 0 – no permanently present fold; degree 1 – single fold smaller than tear meniscus; degree 2 – single fold higher than tear meniscus; degree 3 – numerous folds not reaching the edges of the eyelids; and degree 4 – numerous folds reaching the edges of the eyelids. All tear film tests were performed before administration of any eye drops in the following order: non-invasive tear film break-up time (TBUT) (Tearscope), tear film osmolarity (TearLab Osmolarity System), and Shirmer's test. Intraocular pressure was measured after topical anesthesia using a PASCAL Dynamic Contour Tonometer. Assessment of lens opacity (LOCS III scale), fundus examination, and Optical Coherence Tomography (OCT) scans (fast algorithms, time domain Stratus OCT, Carl Zeiss Meditec) were obtained in all participants after pupil dilation. The diagnosis of glaucoma was based on the presence of at least 1 of the following criteria: a characteristic repeatable pattern of glaucomatous visual field loss and a cup-to-disk ratio of 0.8 or greater, with an optic nerve head appearance consistent with glaucoma. All patients from the PD and control group with glaucoma were excluded from the retinal thickness (RT) and the retinal nerve fiber layer (RNFL) thickness comparison.

All subjects participating in this study gave written informed consent. The study was approved by Ethics Committee of the Pomeranian Medical University.

Statistical analysis

The results were compared using the Mann-Whitney U test for quantitative and rank variables, or using Fisher's exact test for qualitative variables. A p-value <0.05 was considered significant. Quantitative data are presented as mean ± standard deviation (SD). Qualitative data are presented as percentages of eyes/patients and number of patients.

Table 1. Characteristics of the study groups and questionnaire data. Quantitative data are presented as mean ± standard deviation. Qualitative data are presented as number or percentage of patients.

	PD group	Control group	p-value
Number of patients	100	100	ns
Age (years)	68.5±10.2	68.6±9.8	ns
Sex (men/women)	56/44	56/44	ns
PD duration (years)	5.6±4.8	–	–
Stage of PD (H-Y)	1.8±0.7	–	–
Visual Hallucinations (%)	4.0	0.0	ns
OSDI	23.0±18.6	14.3±14.1	<0.001
	No glaucoma PD group	No glaucoma control group	p-value
Number of patients	85	85	ns
Age (years)	67.4±10.3	67.6±10.0	ns
Sex (men/women)	48/37	48/37	ns
PD duration (years)	5.5±4.6	–	–
Stage of PD (H-Y)	1.8±0.7	–	–

PD – Parkinson's disease; H-Y – Hoeh and Yahr scale; OSDI – ocular surface disease index; ns – not significant (p>0.05).

Results

Only 4 PD patients (4.0%) complained of visual hallucinations. There were no visual hallucinations in the control group (p=0.12). According to the dry eye assessment questionnaire, PD patients achieved significantly higher OSDI compared to controls (p<0.001). Patient characteristics and questionnaire results are shown in Table 1.

PD patients achieved significantly lower DBCVA than controls (0.15±0.23 *vs.* 0.07±0.15; p<0.001) and were found to more often have convergence insufficiency (24.5% *vs.* 9.7%; p<0.001). LIPCOF degree, TBUT, and tear film osmolarity did not significantly differ between groups. Schirmer's test scores was found to be significantly affected in PD patients (13.20±10.45 millimeters *vs.* 17.49±11.16 millimeters; p<0.001). When number of eyes with abnormal result ≤10mm were compared, significantly higher frequency was observed in the PD group (53% *vs.* 32%; p=0.01). Mean grade of MGD was significantly higher in PD cases compared to controls (1.23±1.36 *vs.* 0.90±1.16; p=0.02). Lens nuclear color (NC) and opalescence (NO), as well as intensity of posterior subcapsular cataract (P), were significantly more prominent in PD patients (p≤0.03). Advancement or frequency of cortical cataract (C), number of pseudoexfoliation syndrome (PEX), and number of pseudophakic eyes (IOL) did not significantly differ between investigated groups. Seborrhoic blepharitis was diagnosed in 17.86% of eyes of PD patients and only in 3.06% eyes of control cases (p<0.001). Glaucoma was found in 16.33% of eyes of patients with PD and 6.63% of eyes of controls (p=0.004). All these patients were found to have primary open-angle glaucoma. ARMD was diagnosed more frequently in eyes of PD patients than in control cases (13.27% *vs.* 8.16%). However, this difference was statistically insignificant (p=0.14). Other diseases of the anterior and posterior segment of the eye were found only in single cases in both groups. Results of the above examinations are summarized in Table 2.

In PD patients without glaucoma, DBCVA and NBCVA were significantly worse than those of controls without glaucoma (0.13±0.22 *vs.* 0.07±0.15 p=0.006 and 0.14±0.26 *vs.* 0.08±0.19 p=0.005, respectively). Impaired color vision was observed in 17.53% of eyes of PD subjects. There was 1 case of abnormal color vision in blue-yellow axis and 2 cases in red-green axis. The remaining PD patients had nonspecific abnormalities in color vision. In the control group, only 5.70% of eyes presented impaired color vision (p=0.001) and all of them was classified as nonspecific. The photopic contrast sensitivity without glare was significantly decreased in PD patients compared to controls in all 4 examined spatial frequencies when analyzed by number of correct localized gratings. The photopic contrast sensitivity with high glare was significantly more reduced in the PD group only for 2 spatial frequencies: 3 cyc/deg and 12 cyc/deg. Results of 6 cyc/deg were of borderline statistical significance (p=0.055), while 18 cyc/deg were statistically irrelevant. PD patients also demonstrated significantly lower IOP when compared to control cases (16.88±3.18 *vs.* 17.76±3.21 p=0.009). Difference of perimacular RT and peripapillary RNFL thickness in all 4 quadrants (Temporal, Superior, Nasal, and Inferior) were not significant. Results of these examinations are summarized in Table 3.

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Table 2. Results of ophthalmological examination of 100 PD patients and 100 control cases. Quantitative data presented as mean±standard deviation Qualitative data are presented as percentages.

	PD group	Control group	p-value
Number of eyes	196	196	–
DBCVA	0.15±0.23	0.07±0.15	**<0.001**
Convergence insufficiency	24.5%	9.7%	**<0.001**
Tear film evaluation:			
LICOF	1.89±1.23	1.72±1.12	ns
TBUT (sec)	16.29±13.19	14.92±11.94	ns
Schirmer's test (mm)	13.20±10.45	17.49±11.16	**<0.001**
MGD	1.23±1.36	0.90±1.16	**0.02**
Osmolarity (mOs/L)	298.11±11.20	302.20±12.66	ns
Bleharitis	17.86%	3.06%	**<0.001**
Lens opacity (LOCS III scale):			
NO	2.84±1.14	2.39±0.91	**<0.001**
NC	2.59±1.38	2.24±1.12	**0.003**
C	0.29±0.79	0.37±0.99	ns
P	0.14±0.59	0.08±0.51	**0.03**
PEX	1.70%	1.63%	ns
IOL	10.20%	6.12%	ns
Glaucoma	16.33%	6.63%	**0.004**
ARMD	13.27%	8.16%	ns

PD – Parkinson's disease; DBCVA – distance best corrected visual acuity; LIPCOF – degree of lid-parallel conjunctival folds; TBUT – tear film break-up time; MGD – meibomian gland disease grade; NO – nuclear opalescence; NC – nuclear color; C – cortical cataract; P – posterior subcapsular cataract; PEX – pseudoexfoliation syndrome; IOL – intraocular lens; ARMD – age-related macular degeneration; ns – not significant (p>0.05).

Discussion

Dopamine plays multiple roles in the eye. The results of previous studies indicate that it takes part in light adaptation [1,17], spatial contrast sensitivity, color discrimination [7,14,15], visuospatial problem solving, spatial working memory, oculomotor control [13], promotion of the photoreceptor renewal process, and reduction of its waste products accumulation [18], as well as probably being involved in the cyclic regulation of intraocular pressure [19]. Dopamine also seems to have an anti-apoptotic role [20]. According to our best knowledge, this is the first study to comprehensively describe ophthalmological changes in the course of PD.

PD causes visual dysfunction manifested by decreased visual acuity, contrast sensitivity, and color discrimination. Results of this study are consistent with previous research [12–14,21]. Poor visual function may be caused by lack of dopamine in the retina, abnormal eye movements, or poor blinking [22]. However, for the first time, we also observed significantly

higher frequency of nuclear and posterior subcapsular cataract in the PD group, which may deteriorate visual functions. Oxidative stress has a great impact on cataract formation due to prevalent oxidation of lens DNA, proteins, and lipids [23]. One of the mechanisms in PD neurodegeneration is excessive oxidative stress, which may explain the higher frequency of cataract in PD patients. It is important to note that despite higher prevalence of cataract in the PD group, the frequency of pseudophakic eyes did not significantly differ between the 2 investigated groups, which suggests that PD patients are less frequently referred for cataract surgery. We also observed that PD patients more often had convergence insufficiency, which is consistent with previous studies [2,24]. This may lead to complaints of difficulties in reading, even with a restoration of normal near visual acuity.

In the literature, the prevalence of visual hallucinations in PD patients is estimated at up to 37% [7]. In this study, only 4 PD patients (4.0%) complained of visual hallucinations. There are many risk factors of visual hallucinations associated with PD,

Table 3. Results of ophthalmological examination of 85 PD patients and 85 control cases without glaucoma. Quantitative data presented as mean ±standard deviation. Qualitative data are presented as percentages.

	PD group	Control group	p-value
Number of eyes	164	164	–
DBCVA	0.13±0.22	0.07±0.15	**0.006**
NBCVA	0.14±0.26	0.08±0.19	**0.005**
Abnormalities in color vision	17.53%	5.70%	**0.005**
IOP	16.88±3.18	17.76±3.21	**0.009**
RT	215.31±21.80	213.14±21.44	ns
RNFL thickness:			
Temporal	63.05±16.62	62.62±15.42	ns
Superior	119.41±20.20	117.03±20.99	ns
Nasal	77.15±18.70	77.23±20.11	ns
Inferior	123.93±22.57	120.04±20.92	ns
Number of patients	85	85	–
CSV-1000 without glare			
A (3cyc/deg)	5.38±1.87	6.31±1.29	**0.001**
B (6cyc/deg)	4.81±2.01	5.61±1.83	**0.01**
C (12cyc/dg)	4.23±2.36	5.11±2.32	**0.02**
D (18cyc/deg)	4.01±2.25	4.78±2.18	**0.03**
CSV-1000 with high glare			
A (3cyc/deg)	4.33±2.18	5.43±1.68	**<0.001**
B (6cyc/deg)	4.04±1.99	4.54±1.99	ns
C (12cyc/dg)	3.38±2.20	4.08±2.45	**0.04**
D (18cyc/deg)	3.77±2.34	4.06±2.42	ns

PD – Parkinson's disease; DBCVA – distance best corrected visual acuity; NBCVA – near best corrected visual acuity; CSV-100 – contrast sensitivity test; IOP – intraocular pressure; RT – retinal thickness; RNFL thickness – retinal nerve fiber layer thickness; ns – not significant (p>0.05).

including cognitive impairment [12], decreased dopamine level before the next dose of levodopa, REM sleep dysfunction [25], longer disease duration and higher severity of disease, higher levodopa dosage and longer duration of treatment [26], impaired color discrimination and contrast sensitivity [27], and decreased visual acuity. In the present study, only patients without dementia were enrolled. Meanwhile, cognitive impairment seems to be one of the strongest risk factors for visual hallucinations [12]. Mean disease duration was quite short (5.6±4.8 years) and stage of PD according to the H-Y scale was relatively low (1.8±0.7). Although DBCVA was significantly worse in PD cases compared to controls, most of them had useful visual acuity. In summary, the PD patients who participated in

this study did not have many risk factors for development of visual hallucinations, which may explain their low frequency.

Results of this study indicate that PD patients should be considered at increased risk of having dry eye problems. Schirmer's test scores and meibomian glands are significantly affected in comparison to control cases. These results agree with previous research [3–5] and suggest that aqueous tear production is the most affected feature in PD. Some study results [2,3] suggest that PD patients have also deficits in the tear film mucin layer. In our study, TBUT did not significantly differ between PD patients and controls. Moreover, the percentage of eyes with abnormal TBUT, defined as no greater than

5 seconds, was exactly the same in our 2 investigated groups (12.2%). Also, tear film osmolarity did not significantly differ between PD and control subjects. To the best of our knowledge, no other study has investigated tear film osmolarity in PD patients; therefore, further research is needed to verify these results. All abnormalities in tear film production lead to more common ocular complaints of dry eyes (higher OSDI index) in PD patients. Moreover, symptoms of dry eye syndrome can be aggravated by seborrhoic blepharitis, which is most likely secondary to seborrhea. Researchers hypothesize that abnormalities of the tear film may be the result of autonomic dysfunction due to presence of Lewy bodies at sympathetic ganglia, substantia nigra, and peripheral parasympathetic ganglia [28], as well as decreased androgen levels [29].

We found a greater risk of primary open-angle glaucoma (16.33%) in PD patients. To date, only 1 study has reported an increased rate of glaucoma in patients with PD (23.7%) – mostly normal tension glaucoma [6]. Glaucoma in PD may be a result of decreased level of reduced glutathione (GSH), a prominent antioxidant found in the eye [30,31]. GSH protects ocular tissue from damage caused by oxidative stress, which is implicated in the pathogenesis of primary open-angle glaucoma, especially with normal IOP [32]. When compared to without glaucoma who participated in the present study, IOP turned out to be significantly lower in the PD group and the mean was within normal limits. Studies concerned with visual field changes in PD patients reported more frequent occurrence of glaucoma-like visual field defects, without any other clinical signs of glaucoma [33,34]. Tsironi et al. [33] suggested that the functional deficit observed in PD patients can be explained by intra-retinal, subcortical, and cortical neuronal disorganization or injury related to PD. Prospective longitudinal investigations of these patients would be valuable to determine repeatability or progression of glaucoma-like visual field defects. In present study, OCT examinations of peripapillary RNFL thickness did not reveal significant differences between PD patients and control cases without glaucoma. The results of previous OCT studies are inconclusive. Some studies reported RNFL thinning in PD cases [36–39], while other did not support this [21,33,40,41]. Perimacular RT also did not significantly differ between the 2 examined groups. Results of OCT studies are also inconclusive [21,36,37,40]. Also in this matter, results of OCT seems to be not useful in the PD diagnosis.

We believe the present study is the first to analyze the frequency of ARMD in PD. The neurodegenerative mechanisms of ARMD and PD were found to be quite similar and include impairment of the autophagy system, chronic inflammation, oxidative stress, and aging [42]. Moreover, dopamine seems to be involved in reduction of photoreceptor waste product accumulation [18]. However, we did not observe a significantly higher frequency of ARMD in the PD group compared to controls.

Among patients with ARMD, all PD subjects had dry form, while in the control group 1 patient had neovascular form and the rest had dry form. In the literature, only 1 study [42] reported some relationship between ARMD and PD, observing that subjects with neovascular ARMD were at a significant risk of PD during a 3-year follow-up period after diagnosis. Further studies are needed to confirm these findings and explore the underlying pathomechanism.

Conclusions

Clinical examination of PD patients by general ophthalmologists requires knowledge of the common, but often underdiagnosed, ocular features of PD. Simple interventions can often significantly improve patient quality of life. PD patients should have a proper refraction to facilitate their daily activities and prevent falls. When prescribing glasses, the spherical equivalent may be preferable to significant astigmatic correction, as glasses tend not to be stable on patients with tremor or dyskinesias [2]. Early management of cataract also is important in preservation of good vision. It is important to note that chances for successful cataract surgery are better in early stages of PD when involuntary head and body movements are less advanced. Because many PD patients have decreased contrast sensitivity and color vision, good ambient light while reading is required. Convergence insufficiency should be detected and treated with reading glasses with base-in prism or monocular occlusion while reading, when required [2]. Because PD patients often complain of dry eye symptoms, artificial tears should be prescribed to provide adequate corneal lubrication. However, ophthalmologists must remember the possibility of seborrhoic blepharitis and MGD, which may require daily eyelid hygiene. PD patients should be considered as being at increased risk of primary open-angle glaucoma. The attribution of glaucomatous visual field defects with definite glaucoma, especially with the absence of elevated IOP, can be clinically challenging. In such cases, careful attention to the matching patterns of structural and functional damage is critical for assessment of possible glaucomatous damage [33]. Clinicians need to be aware of the association between PD and coexistence of ophthalmological changes, especially that restoration of good quality of vision has a great impact on the PD patients' quality of life, and reduction of costs of treatment and care, as well as rehabilitation.

Statement

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