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Ocular Motor and Sensory Function in Parkinson Disease

Zina Almer, MD, **Kathyrn S. Klein, MD, MPH**, **Laura Marsh, MD**, **Melissa Gerstenhaber, RNC, MSN**, and **Michael X. Repka, MD, MBA**
Wilmer Ophthalmological Institute, Department of Pediatrics, and Morris K. Udall Parkinson Disease Center of Excellence. Johns Hopkins Medical Institutions, Baltimore, Maryland Dr. Almer is currently with the Ophthalmology Department, Assaf Harofe Medical Center, Zeriffin, Israel. Dr. Marsh is currently with the Mental Health Care Line, Michael E. DeBakey Veterans Affairs Medical Center and Departments of Psychiatry and Neurology, Baylor College of Medicine, Houston, Texas

Abstract

Purpose—To evaluate the effect of dopaminergic medication and deep brain stimulation on ocular function in Parkinson disease (PD) and to measure vision-related quality of life in subjects with PD.

Design—Prospective comparative case series.

Participants and Controls—Twenty-seven PD and 16 control subjects were recruited.

Methods—We measured visual acuity, ocular motor function, convergence, and vision-related quality of life using the Visual Function Questionnaire–25 (VFQ-25). Visual sensory and motor measurements were made during the “on” and “off” states of PD dopaminergic treatment.

Main Outcome Measures—Convergence ability and vision related quality of life.

Results—The PD subjects had a mean age of 58.8 years; 30% were female. Their mean duration of PD was 10.9 ± 6.8 years. The control subjects had a mean age of 61.6 years; 56% were female. There was no difference in visual acuity, contrast sensitivity or color vision of the PD subjects in their “on” state compared with controls. Convergence amplitudes measured with base-out prism were significantly poorer in PD subjects compared with controls (24.1 ± 8 Δ vs 14.8 ±10.3 Δ; P=0.003). The mean composite VFQ-25 score was significantly worse in the PD subjects compared with the controls (87.1 ± 8.69 vs 96.6 ± 3.05; P=0.0001).

Comparing the PD subjects in their “on” with their “off” states, there was no difference in distance exodeviation, near exodeviation or ocular ductions. Mean convergence amplitudes and near point of convergence were better in the “on” state compared with the “off” state, 14.8±10.3 Δ vs 10.7±9.0 Δ, (P=0.0006), and 13.1±9.1 cm vs 18.1±12.2, (P=0.002), respectively.

Conclusions—Convergence ability is significantly poorer in PD subjects in both their “on” and “off” states compared with controls, but significantly improves with systemic dopaminergic treatment. Ocular motor function in PD subjects fluctuates in response to treatment, which

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Correspondence to: Dr. Michael X. Repka, Wilmer 233, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287-9028, 1-410-955-8314, 1-410-955-0809, mrepka@jhmi.edu.

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complicates ophthalmic management. PD subjects have a significant reduction in vision-related quality of life, especially near activities, that is not associated with visual acuity.

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by disruption of dopaminergic pathways involving the basal ganglia. PD, defined by its motor features, is associated with many non-motor and neuropsychiatric disturbances.[1] Ocular signs and symptoms in PD include blepharospasm, apraxia of eyelid opening, dry eye, reduced blink rate, visual hallucinations, decreased visual acuity, color vision and contrast sensitivity, abnormal saccades and pursuit, diplopia, up-gaze limitation and convergence insufficiency.[2-4] Reduced convergence creates difficulty for reading and other visual tasks at near. Symptoms of visual dysfunction would likely contribute to the overall disability of individuals with PD.[5]

Dopamine replacement is the mainstay of therapy in PD. Hour to hour fluctuations of signs and symptoms are common with dopaminergic treatment. This phenomenon is referred to as ‘wearing off’ or ‘on-off’ fluctuations. While on-off fluctuations are characterized by overt manifestations such as freezing of gait and bradykinesia, ocular movements may also be affected. If there is fluctuation of visual abilities, this could contribute to visual dysfunction. In a case report, dopamine improved ocular signs and symptoms.[6]

Implantation of a deep brain stimulator is a more recent intervention offered to individuals with advanced PD who have severe tremor that responds inadequately to medical therapy or experience unacceptable medication side effects, namely, severe motor fluctuations and dyskinesias.[7,8] While deep brain stimulation has been shown to increase visual evoked potential amplitudes (VEP),[9] the impact of this treatment on convergence ability has not been studied.

Our purpose was to determine prospectively whether dopaminergic medication alone or in combination with deep brain stimulation improved visual and ocular motor function in subjects with PD during the “on” state. A secondary objective was to assess the vision related quality of life in PD subjects using the composite and subscales of the National Eye Institute Visual Function-25 Questionnaire.[10]

Methods

Subjects with PD were recruited prospectively from the Morris K. Udall Parkinson Disease Research Center of Excellence at the Johns Hopkins Hospital. The study protocol and consent forms were approved by the Johns Hopkins Hospital/Johns Hopkins University institutional review board. Written informed consent was obtained from each subject in accordance with the Health Information Portability and Accountability Act of 1996.

Eligible subjects were 18 years of age or older with at least moderate stage PD, had responded clinically to either levodopa/carbidopa or DBS treatment, and had reached a steady state in their treatment regimen. We excluded individuals with atypical PD, dementia, other neurological diseases, best corrected distance visual acuity less than 20/40 in either eye, any eye disease that might affect vision and/or ocular motility, or who were taking anticholinergic medications as part of their PD treatment. A control group was recruited from healthy individuals, aged 18 years or older, with no known neurological disease. In some cases these subjects were accompanying the PD patient.

Duration of the disease, use of medications and ocular complaints (visual disturbances, diplopia, difficulty or headache when reading) were recorded for all subjects. Study specific

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procedures included PD severity assessments, comprehensive ophthalmological examinations, and administration of the VFQ-25.[10]

PD severity was assessed using the Hoehn and Yahr (H&Y) Scale[11] and the Motor Subscale (Part 3) of the Unified Parkinson Disease Rating Scale (UPDRS).[12] These assessments were made without knowledge of the ophthalmological findings.

The ophthalmological examination was performed by an examiner masked to the "on" or "off" treatment state of the PD subjects. The examination elements were:

- Best-corrected visual acuity (BCVA) at distance and near with the electronic ETDRS surrounded letter chart for distance (recorded as logarithm of the minimum angle of resolution)[13] and the Rosenbaum near vision chart at 30 cm for near
- Color vision (CV) with the Ishihara plates
- Contrast sensitivity (CS) with low contrast letter charts (Pelli-Robson) at one meter [14] (Richmond Products, Albuquerque, New Mexico 87108)
- Simultaneous Prism Cover Test (SPCT) at distance and near
- Prism and Alternate Cover Test (PACT) at distance and near
- Convergence amplitudes measured with base-out prism until the recognition of diplopia or exotropia developed
- Near point of convergence (NPC) measured with a Prince rule
- Ocular ductions assessed using a four-point scale (−4 = no movement past the midline, and 0 = full ductions).
- Convergence insufficiency = difference between distance and near PACT measurements

Visual acuity and ocular motility assessments were performed on PD subjects twice during a single visit. Subjects were examined once in the "off" state (just before their regular levodopa/carbidopa dose and/or 30 minutes after turning off their deep brain stimulator and once in the "on" state (90 minutes after their regular dose and 15 minutes after turning on the deep brain stimulator). They were randomly assigned to be examined first in the "on" or "off" state, waiting several hours to repeat the visual acuity and ocular motility measurements in the alternative treatment state. Before each ocular motility assessment, the subjects in the study group were asked to grade their global motor status on a 10-step Likert scale, 1 being the worst "off" state and 10 the best "on" state. Control subjects underwent a single ophthalmologic exam.

The VFQ-25 was administered to each subject. The quality of life questionnaire consists of 25 items in 12 subscales. The composite and subscales range from 0 to 100, with higher numbers better. Subscales were calculated as has been described.[10] Four PD patients did not drive, and that subscale did not include responses for those subjects.

Statistics

The control subjects were compared with the PD subjects in the "on" state. Primary analyses compared best-corrected visual acuity, color vision, contrast sensitivity, ocular ductions, strabismus, convergence amplitudes, convergence insufficiency, and NPC. In addition, to evaluate the impact of dopaminergic treatment, we compared the PD subjects in the "on" with the "off" state. A paired t-test was used to compare continuous variables between groups. Secondary analyses calculated the Pearson correlation coefficients for the

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relationships between PD duration or PD severity assessments (UPDRS and H&Y) and VFQ-25 (composite and subscales), ocular alignment, and convergence ability. 95% confidence intervals (95% CI) were calculated for these relationships.

Results

Twenty-seven PD subjects and 16 control subjects were recruited. All subjects were Caucasian. The PD subjects had a mean age of 58.8±8.6 years (range 42-73), and 29.6% were female. The control subjects had a mean age of 61.6±13.9 years (range 33-80), and 56% were female. Other demographic and clinical characteristics of the participants are listed in Table 1. The controls were similar in age to the PD subjects (P=0.42) but were more often female (P< 0.05). Nineteen PD subjects (70.3%) were being treated only with levodopa/carbidopa, while eight (29.6%) were being treated with levodopa/carbidopa and deep brain stimulation. No patient in the study group was treated solely with deep brain stimulation.

Ophthalmological findings – PD subjects in the “on” state compared with controls (Table 2)

There was no clinically significant difference in BCVA, contrast sensitivity or color vision between the PD subjects in the “on” state and the controls. Ductions were normal or minimally limited in elevation for the PD subjects. No subject or control had a heterotropia at distance.

Convergence amplitudes measured with base-out prism were significantly worse in PD subjects in the “on” state compared with controls (P=0.005) and in PD subjects in the “off” state compared with the “on” state (P=0.0007). Similarly, the near point of convergence was significantly worse, or more remote, in PD subjects in the “on” state compared with controls (P=0.08)..

Ophthalmological findings - Comparison of PD subjects in the “on” with the “off” state (Table 2)

The PD subjects graded their global motor status as significantly better during the “on” state compared with the “off” state, 8.0 ±1.7 vs 5.5±2.1, respectively (P=0.000007). There was no difference in BCVA, CS, color vision, ocular ductions or mean exodeviation between the “on” and “off” states.

Convergence amplitudes measured with base-out prism were significantly worse in PD subjects in the “off” state compared with the “on” state (P=0.0007). Similarly, the near point of convergence was significantly worse, or more remote, in PD subjects in the “off” state compared with the “on” state (P=0.002)

Quality of life (Table 3)

The mean composite VFQ-25 composite score was significantly better in the control group than in the study group (96.6±3.05 vs. 87.1±8.69; P=0.0001). Subscales for general health, general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific role difficulties, vision-specific mental health, vision-specific dependency, driving, and peripheral vision were each significantly worse in PD subjects than controls (Table 3).

Further analysis of the quality of life data was undertaken to determine whether the general health status from the VFQ-25 as a measure of PD severity correlated with vision. The data failed to show a correlation between the general health subscale (question) and the subscale

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for general vision in either the control or the PD groups. However, general health and near activities functions were modestly correlated in the PD subjects (r = 0.40, 95% confidence interval (CI): 0.20 to 0.68), but not among the controls (r = 0.12, 95% CI: −0.40 to 0.58). These analyses suggest that the PD has a greater effect on near activities than other aspects of visual function as assessed using this vision-related quality of life questionnaire, consistent with the clinical measurements.

Impact of PD duration and severity

There was no correlation between duration or severity of PD (UPDRS or H&Y scales) and the size of the exodeviation or the convergence insufficiency. There was a modest correlation between the VFQ-25 composite scores and one of the PD severity indices [UPDRS (r = −0.58, 95% CI:−0.79 to −0.26), H & Y (−0.58, 95% CI: −0.79 to −0.26).

Discussion

We studied a group of patients with PD for a mean duration of 11 years. Our study confirms the presence of substantial convergence insufficiency in subjects with PD as compared with control subjects. Furthermore, the severity of this deficit fluctuates throughout the day in association with the dosing schedule of anti-Parkinson medications. Whereas our data show that duration and severity of the PD do not affect the size of the convergence insufficiency, severity of PD adversely affects vision-related quality of life. This appeared to be greater for near activities, rather than all vision tasks.

In our subjects with known ‘wearing-off’ symptoms, convergence ability improved substantially after a discrete dose of dopamine, although convergence did not normalize. Anti-Parkinsonian treatment typically involves taking multiple doses of dopaminergic medications throughout the day, with more frequent dosing as the disease progresses (for example, up to six to seven times daily). Therefore, convergence ability is likely to be in nearly constant flux during waking hours as dopamine levels in the central nervous system rise and fall. Consequently, there is nearly constant but varying reading difficulty and double vision at near.

Ophthalmologic management of individuals with PD requires an understanding of typical PD-related ocular motor dysfunction and cognitive dysfunction as well as the impact of PD treatments. Most subjects had no exodeviation at distance, yet a substantial exodeviation at near. Thus, a custom-fabricated split lens with base-in prism only in the lower segment or single vision readers with prism would be necessary. The clinical situation is aggravated, however, by the sizeable fluctuation of convergence amplitudes in response to dopaminergic therapy. Fluctuating convergence insufficiency compounds the difficulty of prescribing a single satisfactory prism correction even for a single fixation distance. In addition, the reduced convergence ability, even when optimally treated with dopamine, increases the difficulty of alleviating the symptoms.

Our findings suggest that optical correction be prescribed after consideration of the timing of the eye exam relative to dopaminergic treatment. Orthoptic measurements during the “on” and “off” states may be useful in selecting a suitable prism correction, but the effectiveness of this approach remains to be studied. In addition, the typical timing for use of the near spectacle correction by the patient relative to dosing seems essential. Patients with PD should also be queried about on-off fluctuations and wearing-off with respect to their visual complaints. Collaboration with the treating neurologist to ensure that the anti-Parkinsonian regimen is optimized to minimize motor fluctuations may be an appropriate step before prescribing the visual correction. Referral to a program specializing in PD may be appropriate for patients with unmanaged motor fluctuations.[15]

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Afferent visual system function including visual acuity, contrast sensitivity, and color vision in PD subjects did not differ from those observed in controls and did not fluctuate with dopaminergic treatment state. CS measured in the PD subjects (1.63) was similar to normal values described among individuals 50 years of age and older for the Pelli-Robson chart.[16,17]

Vision-related quality of life was much worse in PD subjects compared to controls using the VFQ-25. This finding seems most likely related to ocular motor function since acuity, color vision, and contrast sensitivity did not appear to vary significantly from controls. However, impaired vision-related quality of life was evident for nearly all of the VFQ-25 subscales, including those specific for near visual activities, driving, and peripheral vision. Although the vision-specific questions in the VFQ-25 specifically direct the respondent to answer only with respect to vision, there could in theory be a generalized impact of PD on the vision-related quality of life assessments. To address that issue, we reviewed the questionnaire results for a correlation between the general health question and the subscale for general vision. There was no correlation for either the controls or the PD subjects suggesting that the subjects were able to separate these two issues. In addition, reviewing the data for general health and near activities, there was no correlation for controls (0.12), but a modest correlation for PD subjects (0.40). This suggests that the effect of PD on vision quality of life is mostly for near activities. This is consistent with the clinical ocular motor measurements made in this study. Lastly, our small sample size prevented a comparison of oral medication alone to oral medication plus deep brain stimulation.

Our study has several strengths. It utilized prospective data collection including functional neurological status to examine the impact of dopaminergic treatment on ocular sensory and motor findings. The examiners were masked to the PD severity and the “on/off” state of the subjects they were assessing. We are limited by a relatively small sample size and the potential for unmasking of the examiners by the presence of the tremor, mobility difficulty, and other features of PD. The PD group included fewer females than the controls because of our use of a convenience sample for controls. We are uncertain of any bias in ocular function that may have been introduced. Lastly, all of our patients were white so we cannot generalize to other races or ethnic groups without further study.

Future study among patients with PD should investigate the effectiveness of optical interventions such as base-in prism or single vision reading glasses for improvement in the visual function of PD patients. Single vision reading glasses may allow the necessary refractive correction and prism to allow restoration of more comfortable reading vision. In addition, attention to the timing of the determination of prism power and medication adjustments that limit ocular motor fluctuations, in cooperation with the treating neurologist, may have an important impact on success of such therapy. Lastly, given the difficulty of finding a single prism correction that is suitable for the varying convergence insufficiency experienced by these patients, evaluation of the effectiveness of vergence exercises to improve convergence as well as varied strength prism correction seems warranted.

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Table 1

Characteristics of subjects

	Controls (N= 16)	Parkinson disease subjects (N=27)	P value
Age - years	61.6±13.9	58.8±8.6	0.42
Females - %	56.2	29.6	<0.05
Parkinson disease duration -years	…	10.9±6.84	…
UPDRS rating	…	20.2±8.72	…
H&Y rating	…	2.3±0.65	…
NEI VFQ-25 Composite Score	96.6±3.05	87.1±8.69	<0.00001

Mean ± Standard Deviation

H&Y = Hoehn and Yahr Rating Scale[11]

UPDRS - Motor Section (part 3) of the Unified Parkinson Disease Rating Scale[12]

NEI VFQ-25 – National Eye Institute Visual Function Questionnaire.[10] Maximum score is 100.

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Table 2

Ocular Sensory and Motor Findings

	Controls	PD subjects during "on" state	PD subjects during "off" state	95% CI of difference - controls minus PD subjects in "on" state	P value (control vs PD "on" state)	P value (PD - "on" state vs "off" state)
Global self-assessment	…	8.27±1.14	5.25±2.16	…	…	0.000007
Mean Best Corrected Visual Acuity (logMAR)	0.15±0.09	0.20±0.14	0.21±0.15	−0.13, 0.03	…	1
Color Vision (mean number of plates correct – tested 13)	12.5±0.6	12.7±0.8	12.5±0.9	−0.67, 0.27	0.64	0.23
Mean log contrast sensitivity of lowest contrast Pelli-Robson triplet correctly identified[14]	1.69±0.2	1.63±1.76	1.62±0.16	−0.35, 0.47	0.37	0.6
Mean heterotropia by SPCT at distance (prism diopters)	0	0	0	0	…	…
Mean heterotropia by SPCT at near (prism diopters)	0.6±1.4	0.7±2.3	1.3±3.0	−0.15, −0.05	0.82	0.08
Mean deviation by PACT at distance (prism diopters)	−0.8+3.0	1.5±2.5	1.9±3.3	−4.02, −0.58	0.01	0.46
Mean total deviation by PACT at near (prism diopters)	1.2±3.5	6.0±7.7	7.2±9.04	−8.97, −0.67	0.02	0.12
Convergence amplitude (prism diopters)	24.1±8	14.8±10.3	10.7±9.0	3.23, 15.37	0.003	0.0007
Near point of convergence (cm)	8.7±4.5	13.1±9.1	18.1±12.2	−9.33, 0.53	0.079	0.002

Mean ± Standard Deviation

logMAR - logarithm of minimal angle of resolution

PD - Parkinson disease

Global Self-Assessment – PD subjects' subjective self-grading of their overall function during their on or off state on a 1-10 Likert scale (1 – worst, 10 – best)

SPCT = simultaneous prism and cover test

PACT = prism and alternate cover test

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Table 3
Vision Related Quality of Life with NEI VFQ-25: Composite and Subscale Scores

	Controls (N = 16)	Parkinson disease subjects (N = 27)	P value
NEI VFQ-25 Composite (mean± standard deviation)	**96.6±3.05**	**87.1±8.69**	**<0.00001**
General Health	82.8	61.1	.001
General vision	87.5	80.7	.05
Ocular pain	95.3	89.8	.04
Near activities	93.8	81.0	.002
Distance activities	97.4	85.8	.003
Vision-specific social functioning	100.0	95.4	.02
Vision-specific role difficulties	97.3	87.7	.005
Vision-specific mental health	98.4	80.6	.003
Vision-specific dependency	100.0	96.6	.05
Driving*	92.7	82.8	.01
Color vision	98.4	92.6	.06
Peripheral vision	100.0	90.7	.002

NEI VFQ-25 – National Eye Institute Visual Function Questionnaire.[10] Maximum score is 100.

*4 subjects with Parkinson disease do not drive and are excluded from the driving subscale.