Abstract

Parkinson’s disease (PD) is a common neurodegenerative condition affecting the elderly population. It is pathologically characterized by decreased dopamine levels from damage to the substantia nigra, which results in the classic motor deficits. It is less commonly known that individuals with PD are at increased risk for ocular and visual problems, including dry eyes, diplopia, contrast sensitivity loss, impairment in color vision, glaucoma-like defects, impairment of visuospatial functions, and visual hallucinations. This teaching case report incorporates a case of PD and discusses the ocular and visual manifestations, differentials, management and current research on the disease.

Key Words: Parkinson’s disease, dry eyes, diplopia, contrast sensitivity loss, visual hallucination

Background

Parkinson’s Disease (PD) is one of the most common neurodegenerative conditions, just second to Alzheimer’s. It was first documented as a neurological syndrome in 1817 by James Parkinson, though symptoms that suggested PD had been described even earlier. In 1925, Brissaud proposed that damage to the substantia nigra was seen in individuals with PD. The substantia nigra is one of the primary sites of dopamine production. Damage to the structure would then result in reduced levels of this neurotransmitter. Clinically, this presents itself as an impairment in motor control. By 1967, Hoehn and Yahr created the first staging system for PD, which was based on the level of clinical disability. Since then, there has been much advancement in understanding the condition. However, the root cause is still not known and there is no known cure for PD, only ways to treat the symptoms.

Though the motor impairments of PD are well-established, the ocular and visual manifestations are not widely recognized. With a rise in the aging population, it is of great importance that eyecare providers are aware of these findings so they can better care for patients with PD. Furthermore, greater dependence is placed on vision to guide patients in daily activities when they have motor dysfunctions.

Currently, when individuals are diagnosed with PD, they are already symptomatic with motor impairments. Some findings suggest the disease process has started years before these clinical findings present themselves. Research is now focused on several features, including identification of biomarkers that may allow for early detection of PD, an objective way to monitor for disease progression, and evaluation of novel therapies. The goal of exploring these features is to someday be able to slow the degenerative changes, if not halt them altogether. Of most interest to eyecare professionals is the retina. Within the inner retinal layer resides the cell bodies of amacrine cells, which contain dopamine. Postmortem examination of patients with PD has revealed decreased levels of dopamine within the retina. Given this finding, studies have been investigating retinal changes as a potential biomarker for PD. Though there have been many studies, there is yet to be a large-scale study with conclusive findings.

The following case involves a patient with ocular manifestations of PD whose motor impairment affected his management plan. The intended audience is third- and fourth-year optometry students, residents and current practitioners.

Case Description

A 69-year-old male presented for Humphrey visual field (HVF) 24-2 SITA Fast (SF) testing, intraocular pressure (IOP) check and gonioscopy for follow-up as a glaucoma suspect OD<OS vs. other optic neuropathy OS. The patient was first seen at the eye clinic a little over 1 year ago with an unremarkable ocular history. His medical history was significant for Parkinson’s disease and delirium in remission. Medications included carbidopa 25 mg/levodopa 100 mg (Sinemet, Merck & Co., New Jersey) 1 tablet by mouth every night at bedtime and 1.5 tablets by mouth 5x/day while awake to counteract the motor impairments, entacapone (Comtan, Orion Corporation, Finland) 200 mg 1 tablet by mouth 5x/day while awake to extend the effect of the former drug, and rasagiline mesylate (Azilect, Teva Pharmaceuticals, Israel) 1mg 1 tablet by mouth every day to stabilize movement disorders.
The patient’s best-corrected visual acuities were 20/20 OD and 20/20 OS. Extraocular muscle movements were smooth and unrestricted OU. Pupils were equally round and reactive to light with no afferent pupillary defect and stable physiological anisocoria OD<OS. Confrontation visual fields were full to finger counting OD and OS, and frequency doubling technology (FDT) screening perimetry was noted to be reliable and full OD and OS. Central corneal thickness was measured at 553 µm OD and 544 µm OS by PARK1 non-contact pachymetry.

Clinical evaluation resulted in the following pertinent findings: capped meibomian glands OU, decreased blink rate OU, cup to disc ratio of 0.35 OD and 0.45 OS with mild temporal pallor as noted during the first examination at the clinic about 1 year ago. IOP measured 13 mmHg OD and 15 mmHg OS by Goldmann applanation tonometry. Gonioscopy confirmed open angles, trace trabecular meshwork pigmentation, flat iris approach, and no angle abnormalities OU. HVF 24-2 SF was completed with an overall low reliability. There were excessive maximal gaze errors as seen on the gaze tracker indicating unreliable fixation. The patient was not able to complete visual field testing as a result of tremors, which was why only the right eye was tested at the visit (Figure 1).

The patient’s tremor from PD rapidly worsened throughout the examination to the point that it was no longer controlled. He required near complete assistance in taking his medication and getting out of the examination chair and out of the clinic. The patient was instructed to return to the clinic in 3 months for repeat FDT perimetry, dilated fundus examination and optical coherence tomography (OCT) of the optic nerve. It was recommended that he schedule the next appointment for just after taking medications to ensure better motor control, which would allow a more productive eye examination.

**Education Guidelines**

*Learning objectives*

1. Recognize that PD affects the ocular and visual system in addition to systemic motor function
2. Understand that with the loss in physical stability, those with PD are more dependent on their vision to navigate through everyday life
3. Recognize that research is being done to find a reliable biomarker for PD, and the retina is a candidate

*Key concepts*

1. Ocular and visual manifestations of PD and the eyecare provider’s role in improving the patient’s quality of life
2. Management of patients with eye findings from PD
3. Changes in retinal thickness and eye tracking as potential biomarkers for early detection of PD

*Discussion points*

1. What are the systemic motor and non-motor features of PD? What are the more common ocular disorders arising from PD?
2. What are the pathological characteristics of PD and how do they relate to the eye?
3. What is the clinical syndrome known as “parkinsonism?” What are the differential diagnoses and how would you distinguish them from PD?
4. How should dry eyes be managed in patients with PD?
5. What are possible causes of diplopia in patients with PD and how can it be managed?
6. How should glaucoma be managed in patients with PD?
7. How can contrast sensitivity loss or impairment in color vision be managed in patients with PD?
8. What should be considered if a patient with PD has visuospatial or visuoperceptual impairments?
9. How should visual hallucinations be addressed in patients with PD?

**Literature review**

PD is one of the most common neurodegenerative disorders. Both the incidence and prevalence of PD increase with age. Incidence in the general population is 14 per 100,000 people, and among those 65 years or older the incidence is 160 per 100,000 people. In a review and meta-analysis reported by Marras et al., the prevalence among North Americans age 45 years or older was 572 per 100,000 people in 2010. It was estimated that 680,000 people had PD then. This number was projected to rise to roughly 930,000 by 2020 and to 1,238,000 by 2030 due to the increasing elderly population.

A number of risk factors have been associated with PD, with increasing age being the most significant. There is a strong correlation between aging and rising prevalence of PD, with prevalence more than doubling from 60 to 80 years old. There are studies that have shown an increased risk of PD to be influenced by environment, genetics and lifestyle. Genetics is also thought to play a role, with variants in alpha-synuclein (α-syn) being a notable source.

**Discussion**

Teaching instruction: Participants should read each question and consider how they would respond. Next, they should read the information provided in the text. Participants may work alone or together in small groups, either in real time or as part of a homework assignment. Learning objectives are to be assessed by comparing participants’ responses to the information provided.

What are the systemic motor and non-motor features of PD? What are the more common ocular disorders arising from PD?

Parkinson’s disease presents with both motor and non-motor symptoms, but it is known primarily as a movement disorder. The classic presentation includes resting tremors, cogwheel rigidity (when movement is jerky rather than smooth), shuffling gait and bradykinesia (slow movement). Non-motor features include cognitive decline, constipation, sleep disturbance and hyposmia (reduced ability to smell things), some of which may precede impairment in motor control. PD also affects the ocular and visual system. The common ocular disorders that have been reported in the literature include dry eyes; abnormalities of eye movement such as pursuits, saccades and vergences; diplopia; glaucoma and glaucoma-like changes such as inner retinal thinning and retinal nerve fiber layer (RNFL) thinning on OCT (controversial); contrast sensitivity loss; impairment in color vision; visuospatial and visuoperceptual impairments; and visual hallucinations.

What are the pathological characteristics of PD and how do they relate to the eye?

Dopamine and the retina

Parkinson’s disease is characterized by reduced dopamine levels caused by destruction of neurons within the substantia nigra, specifically the pars compacta. This decrease in dopamine results in impairment of motor control. Of interest to eyecare professionals is that dopamine is produced by amacrine cells, inter-plexiform cells and retinal pigment epithelial (RPE) cells, which reside within the inner retinal layer. Postmortem examination has revealed decreased levels of dopamine within the retina. Given this finding, studies have been investigating retinal thinning, which can be readily evaluated via OCT, as a potential biomarker for PD. Tsironi et al. and Nowacka et al. found that there is no difference in RNFL thickness between patients with PD vs. a control group. Conversely, Chrysou et al. completed a meta-analysis of spectral-domain OCT studies and concluded that there is inner retinal thinning found in patients with PD, but it was similarly found in patients with glaucoma and other neurodegenerative diseases such as Alzheimer’s. In a prospective study by Kirbas et al., the retina was found to be thinner in patients with PD than in a control group. Likewise, Satue et al. found that the RNFL was remarkably thinner in PD patients than in healthy individuals. Research findings have been inconsistent with regard to which quadrant exhibits the most significant thinning. Inzelberg et al. reported the inferotemporal sector was thinnest, while Matlach et al. implicated the superior quadrant. Kirbas et al. and La Morgia et al. found the temporal quadrant to have the greatest thinning. The inconsistencies among the various results are likely
in part due to the lack of large-scale longitudinal analyses.

Alpha-synuclein and the retina

PD is also pathologically characterized by an accumulation of α-syn within Lewy bodies. This protein is of interest as studies have shown that it seems to regulate dopamine release, and overexpression is associated with decreased levels of the neurotransmitter. Aggregates of α-syn are found in those with PD. α-syn has been located in bodily fluids and peripheral tissues, including blood, cerebral spinal fluid (CSF), saliva, gut mucosa and skin. As such, it is also seen as a potential biomarker for PD. Of the aforementioned locations, CSF has shown to be the most promising though it is not as easily obtained and requires a more invasive collection technique compared with collection of other bodily fluids.

Given that α-syn is found in bodily fluids, studies have investigated its ability to cross the blood-brain barrier (BBB). Sui et al. has concluded that it not only crosses the barrier, but it can do so in both the blood-to-brain and brain-to-blood direction. Furthermore, the study showed that inflammation as triggered by lipopolysaccharide increased the uptake of α-syn by the brain. This is likely by disruption of the BBB itself, as it was confirmed in a later study that BBB leakage occurs early in the PD disease process.

α-syn is also found in the retina, specifically RPE cells, where it regulates dopamine production to some degree. Moreover, this protein is thought to function as a ferrireductase, an enzyme that reduces ferric (Fe$^{3+}$) iron to ferrous (Fe$^{2+}$). α-syn is regulated by iron and itself impacts iron levels. Iron has been found to accumulate in the substantia nigra in individuals with PD. Overabundance of iron causes the protein to accumulate and negatively impact the ability for both α-syn and dopamine to function. An imbalance in this relationship causes a reduction in neuroretinal dopamine, which is thought to contribute to the visual manifestations of PD. RPE cells have the potential to offer therapeutic benefits when transplanted to the basal ganglia by producing adequate amounts of dopamine to replace the damaged dopaminergic neurons.

PD and eye tracking

Eye tracking is now being researched as another potential biomarker of PD. Interest in this stems from the fact that eye tracking is a non-invasive way to study the cognitive and neural processing of an individual in real time. Of the various ocular events that can be measured, saccadic eye movement has the greatest relevance to PD. Latency in saccades are found to be associated with the areas of the brain that are altered by the condition. Additionally, studies have used eye tracking to assess the therapeutic effects of PD medications. As a result, saccadic metrics are being considered as an objective means to diagnosis and to monitor for progression of PD.

What is the clinical syndrome known as “parkinsonism”? What are the differential diagnoses and how would you distinguish them from PD?

The motor symptoms of PD are classic to the condition, but not solely associated with PD. Resting tremors, rigidity, shuffling gait and bradykinesia are part of the clinical syndrome known as “parkinsonism.” Other conditions can be associated with parkinsonism, including drug-induced parkinsonism, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) (Table 1). Drug-induced parkinsonism is commonly caused by antipsychotics. MSA and PSP can be differentiated from PD by how rapidly the condition progresses, with MSA and PSP known to cause a more rapid functional decline. Likewise, though falls are not uncommon in these conditions, those with PD typically do not experience falls as frequently until the middle to late stages of the disease process, whereas MSA and PSP may present with more frequent falls in the earlier stages. Another way to distinguish PD from MSA and PSP is the presence of visuoperceptual deficits, which are associated with the former rather than the latter. Additionally, dopaminergic treatment is more likely to improve symptoms from PD than from MSA and PSP. Furthermore, if the patient is noted to have dysfunction in vertical saccades, then PSP should be suspected.

How should dry eyes be managed in patients with PD?
Dry eye is a common problem in the general population, but is even more prevalent among those with PD and should be looked at differently with this group. A classical feature of PD is reduced blink rate, which leads to the characteristic “stare” in these patients and is thought to contribute to dry eyes. Dysfunction of the autonomic innervation to the lacrimal gland is also thought to contribute to reduced tear production. Individuals with PD should be evaluated for dry eyes and treated accordingly. When considering treatment with eye drops, such as artificial tears, it is important to assess the patient’s ability to instill the drops. Their motor impairment may prevent them from successfully doing so themselves. The provider should consider discussing if they have a caretaker who can help them administer the drops, or offer eye drop guides for those with relatively controlled tremoring. If they are physically unable to instill drops, punctal occlusion may be a more practical alternative. Additionally, patients should be advised to be mindful about blinking more frequently because they tend to have a reduced blink rate.

What are possible causes of diplopia in patients with PD and how can it be managed?
The prevalence of diplopia in PD is not well-studied but is thought to be relatively common reported in up to 38% of patients with PD. Both central and peripheral pathways have been proposed as potential mechanisms. It may result from dysfunctional saccades and pursuits, a limitation on upgaze or, more frequently noted, convergence insufficiency (CI), which can affect the ability to read. In terms of management of CI, base-in prism in reading glasses may help as well as convergence exercises. When considering eyeglasses, bifocals and progressive lenses should be avoided. PD patients have a higher risk for falls than the general population. Furthermore, they tend to have a stooped posture, so it may be difficult for them to locate the correct area of their bifocals or progressive lenses to view through. This may increase their already high risk for falls. It is recommended to prescribe single-vision distance and near glasses with impact resistant materials for lenses, such as polycarbonate or Trivex. Additionally, if refraction yields large amounts of astigmatism, reducing it by its spherical equivalence would be of benefit for those with tremors because glasses may not be stable on them.

How should glaucoma be managed in patients with PD?
Though the pathophysiology is not clear, a correlation is found between PD and glaucoma. Older individuals with glaucoma are at increased risk for developing PD. Likewise, those with PD are at increased risk for developing glaucoma. They may develop primary open-angle glaucoma or angle-closure glaucoma, with the latter being more likely if the individual already has shallow anterior chambers, such as in the case of a high hyperope. Because patients with PD are taking dopaminergic medication, blockage of aqueous outflow can lead to angle closure. Management of glaucoma is the same as for the general population, although it is important to consider how PD patients’ tremors may affect monitoring with OCT and HVF and the ability to instill eye drops. If reliable test results are difficult to obtain, the patient may need to be monitored structurally. Again, one must consider discussing the availability of a caretaker to help administer drops, or offering an eye drop guide for those with relatively controlled tremoring. For patients unable to use eye drops, laser or surgical treatment options should be considered.

How can contrast sensitivity loss or impairment in color vision be managed in patients with PD?
The pathophysiology for contrast sensitivity loss and impairment in color vision is not well understood, but deficiency of retinal dopamine is suspected. In terms of management, some cases have shown improvement in both contrast and color vision with dopaminergic therapy for PD. This highlights the importance of co-managing these patients with their neurologist. An adjustment in medication may alleviate the impairment. For persistent contrast sensitivity loss, yellow filters can be prescribed to increase contrast. Furthermore, the patient should be advised to read and work with sufficient ambient light. Patients who still drive should be advised to limit their driving to the daytime.

What should be considered if a patient with PD has visuospatial or visuoperceptual impairments?
Visuospatial ability involves the processing of visual information about where objects are located relative to each other and oneself in the environment. Visuoperceptual function has to do with the recognition of objects. Impairment of both visuospatial and visuoperceptual functions can occur in PD. The impairments likely result from changes within the temporo-parietal cortex. Patients who still drive can be referred for a driving assessment. They can be trained in various driving skills, such as visual scanning.

How should visual hallucinations be addressed in patients with PD?
Visual hallucinations were originally thought to be a side effect of medications because dopamine may elicit them. Many drugs for PD are dopamine promoters of some form. More recent studies show that the reduced visual input to the
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occipital lobe causes an increase in activity being released. It is said that more than half of those with PD will at some point experience visual hallucinations, though this information is generally not reported voluntarily.\(^2\)\(^3\) Therefore, it is important to directly ask patients if they are experiencing this visual phenomenon. The under-reporting is thought to occur due to fear that others will think they are mentally unstable or perhaps not take them seriously.\(^6\)\(^6\)\(^3\) Patients should be reassured that it is not uncommon for someone with PD to have visual hallucinations, as it can be a side effect of the medications and/or the lack of visual input. Co-management with the neurologist for dosage or medication changes to assist the patient may be indicated.

Conclusion

Eyecare professionals have an important role to play in caring for the visual needs of patients with PD. These individuals have a higher prevalence of ocular symptoms that frequently interfere with daily activities compared with healthy age-matched individuals, as reported by Borm et al.\(^2\)\(^3\) Vision plays an even more critical role for patients with PD because visual guidance can help compensate for loss of motor control. This highlights the importance of addressing the visual needs of patients with PD. Because ocular motor dysfunction may improve with dopaminergic treatment, the authors recommend encouraging patients to take their medications on time.

Researchers are currently looking into retinal thinning and eye tracking as potential biomarkers for monitoring PD progression, assessing the effects of treatment and helping with earlier detection, before motor symptoms appear.\(^1\)\(^6\)\(^18\)\(^27\)\(^33\)\(^41\)\(^42\) While these areas of research are inspiring, a large, rigorous study to obtain conclusive findings has not yet been conducted. In the future, eyecare professionals may play a larger role in comanaging patients with PD given what is being researched now.

References

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