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Clinical Note: How I Examine My Patient

The Neuro-Ophthalmological Assessment in Parkinson's Disease

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Abstract. Visual disorders like double vision, dry eyes, and visual field deficits are common but frequently missed in Parkinson's disease. Here, we aim to increase awareness for these visual disorders in Parkinson patients by discussing several common problems that can be easily diagnosed using comprehensive history taking and a basic neuro-ophthalmological examination. We offer practical guidance for the patient interview and physical exam that can facilitate a timelier recognition of visual disorders. Such recognition has immediate therapeutic relevance, because Parkinson patients are strongly dependent on an adequate vision, for example to optimally benefit from visual cueing strategies.

Keywords: Neuro-ophthalmology, Parkinson's disease, vision

INTRODUCTION

Visual disorders like double vision, dry eyes, or visual field defects are common but often unrecognized in Parkinson's disease (PD) [1]. Some visual disorders in PD are linked to retinal dopamine depletion, others to decreased dopaminergic innervation of the visual cortex [2, 3]. Dopamine plays an important role in several processes related to vision, such as adaptation to light, oculomotor control, contrast sensitivity, color vision, visuospatial construction and spatial working memory [4–6]. Lack of dopamine can therefore lead to a range of visual disturbances in PD patients, such as diplopia. PD patients also have an increased risk of eyelid apraxia and blepharospasm or dry eyes. Visual disorders are frequently seen early in the disease and may be considered as prodromal symptoms of PD as well. For example, impaired color vision may be a preclinical marker of neu-

rodegeneration [7]. Furthermore, PD patients may develop non-PD related ophthalmic diseases such as cataract or macular degeneration [4, 8–14]. Visual disorders are particularly vexing for patients with PD because of their need to compensate visually for their deficits in automatic, internally generated movements. For example, visual cues such as stripes on the floor are useful to overcome freezing of gait [4, 15, 16]. Not being able to see these visual cues adequately may therefore have an immediate impact on functioning in daily life. Indeed, visual disorders combined with postural instability and gait disability can increase the risk of falls and fall-related injuries such as hip fractures [17]. Finally, visual disorders cause difficulties in activities of daily life (e.g., driving, reading, cooking) and thus may lead to social isolation [1]. Consequently, visual disorders have a negative impact on the quality of life in PD patients [8, 9, 18]. Here, we aim to increase awareness for visual disorders in PD patients by discussing several common problems that can be detected and diagnosed easily using a comprehensive history taking and a

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basic neuro-ophthalmological examination. We offer practical guidance for the patient interview and clinical exam that can facilitate a timelier recognition. We will highlight several common visual disorders that can be readily and easily screened for in daily neurological practice. We do not aim to provide an exhaustive overview, but we rather intend to offer practical examples of what a neurologist can do for a patient with visual problems. We will not address how specific visual disorders may assist in the differential diagnosis of parkinsonism; other recent papers have addressed this [1, 19, 20].

HISTORY TAKING

Visual disorders in PD patients can be detected with a comprehensive (and specifically dedicated) set of screening questions related to visual problems. Importantly, dopaminergic medication may be one of the causes of visual problems, depending on the specific problem. Medication may either improve or worsen existing visual problems, or cause new problems as a side effect [10]. Specifically, dopamine agonists may lead to visual hallucinations, levodopa to ocular dyskinesias, MAO inhibitors to blurred vision, and anticholinergics to blurry vision or accommodation disorders. Non-parkinsonian medication—prescribed for co-morbid conditions—can also affect vision; notorious examples are tamoxifen (prescribed as hormone treatment for breast cancer) or amiodarone (prescribed for rhythm control in atrial fibrillation). Therefore, a complete medication history can give clues for visual symptoms caused by side effects or toxicity. Furthermore, asking for visual hallucinations is important, since this may be an indication of progression to more advanced disease stages, including progression to a stage with dementia. Also, hallucinations are found to be a strong predictor of nursing home admission [21]. The prevalence of hallucinations ranges from 6–87% [8, 22, 23]. When ophthalmological problems are identified, specific problems may need further attention (Table 1). We will next discuss the options for screening and treatment in several domains.

SCREENING TESTS AND RECOMMENDED TREATMENTS

We recommend starting the examination by excluding severe visual impairment. This can be done by briefly testing the near visual acuity (Box 1).

This is an excellent screening test since it is easy to administer and because only few significant disorders leave visual acuity unaffected. Above the age of 45, appropriate reading glasses are required for normal near vision. Reading acuity as well as reading speed are good predictors of everyday visual function [24]. Moderate vision impairment can be defined as $<6/24$ on the (near) visual acuity test and severe vision impairment as $<6/60$ (scores based on functioning with the best possible correction) [25]. Dopaminergic medication may influence visual acuity, causing refraction changes during the medication cycle. Therefore, some patients may need adapted glasses depending upon the medication phase. Referral to an ophthalmologist is advised in case of significant vision impairment.

Box 1

Near visual acuity

This is determined while patients wear their glasses. Each eye should be evaluated separately. The patient holds a near card at a comfortable distance, usually at about 40 cm (16 inches) and then reads until the smallest print. The test ends when the patient is unable to correctly identify three or more letters. The acuity score is recorded as Snellen distance equivalent [24, 26, 27]. (See Supplementary Material for an example of a near visual acuity chart).

Ocular surface

Patients may experience foreign body sensation, blurred vision, itching or a burning feeling as a result of dry eyes or blepharitis. The surface of the eyes and eyelids should be inspected (Box 2). Crusty eyelids, redness or inflammation of the eyelids and gritty or red eyes could be signs of blepharitis [28]. The estimated prevalence in PD is around 18%, compared to 3% in the general population [9]. Aging also contributes, so particularly elderly PD patients may be affected [18]. Due to autonomic dysfunction, seborrheic blepharitis (just like the more widely known seborrheic dermatitis) may occur, which can cause irritation and inflammation of the upper and lower eyelids. Inflammation of the ocular surface may also occur. This condition can exacerbate the symptoms of dry eyes that have an estimated prevalence as high as 60% in PD [9]. Dysfunction of the sebaceous Meibomian gland in the eyelids can contribute to increased symptoms of dry eyes and blepharitis [29].

Table 1
 Summary of several common visual problems in PD, including useful screening questions and additional tests to establish a possible diagnosis. The final column offers several recommended treatments

Domains	Specific questions for the interview	Screening tests	Possible diagnosis	Recommended treatment
Generic	Routine tests for every PD patient	Visual acuity	Visual impairment	Referral optician/optometrist, optimize refraction, optimize dopaminergic treatment; If no improvement: referral to ophthalmologist
Ocular surface	<ul style="list-style-type: none"> - Do you have sore, watery or red eyes? - Do you have a blurry vision, e.g. when reading or working with the computer for a while? - Do you have a burning or sandy feeling of the eyes? 	Eye blink rate Inspection of eyes and eyelids	Dry eyes Blepharitis, Meibomian gland dysfunction Blepharospasm	Try first artificial tears; if no improvement: referral to ophthalmologist, optimize dopaminergic treatment Eyelid hygiene, warm compresses, referral to ophthalmologist Botulinum toxin injections
Oculomotor	<ul style="list-style-type: none"> - Do you see objects twice? - During what activities do you experience double vision (e.g. do you have problems during reading, or near work?) 	Monocular/binocular diplopia Eye movement examination, cover/uncover test Near point of convergence	Intraocular pathology (e.g. cataract) Ocular misalignment Convergence insufficiency	Referral to ophthalmologist, optimize dopaminergic treatment, prisms Convergence exercises, monocular occlusion while reading, a reading stand
Optic nerve/retina	<ul style="list-style-type: none"> - Do you bump into objects or persons? - Do you see objects or traffic too late? - Do colors seem to be paler than before? 	Amsler grid, confrontation visual field exam (Donders' test) Ishihara plates, Farnswell 100 hue	Visual field deficit, glaucoma, opticopathy Structural lesion Color vision impairment	Referral to ophthalmologist Neurological work up Optimize dopaminergic treatment, Referral to ophthalmologist, selective absorption glasses
	- Can you read plain text on a colored or grey background?	Pelli-Robson (letter) charts	Contrast sensitivity impairment	Optimize dopaminergic treatment, Referral to ophthalmologist, sufficient ambient light

Explanation how to perform the tests can be found in eight boxes below.

Box 2

Eyelid inspection	Emphasis on the eyelid margin, lashes, and lid closure. Note any anatomic defects, rolling inward or outward of the eyelids, debris, and inflammation of the Meibomian glands [28, 29].
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Another factor contributing to dry eyes is the reduced eye blink rate. Regular blinking is defined as 20 to 30 blinks per minute (eye blink rate, Box 3), which can vary during reading, conversation or resting [30, 31]. Blinking rate can diminish due to medication, fatigue, illness or ageing. Dopamine controls motor control blinking, which explains why the blink rate may decrease to as little as 1 to 2 times per minute in PD [18, 32–34]. A significantly lower blink rate may lead to a less stable tear film by evaporation, again causing dry eyes. This in turn may paradoxically lead to excessive blinking, watery eyes due to reflex tearing and blepharospasm [18].

Box 3

Eye blink rate (EBR)	Count the amount of blinks for 3 minutes without any instructions to the patient [35].
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If dry eyes occur because of a reduced eye blink rate (<15/min) or signs of blepharitis, referral to an ophthalmologist is indicated [34, 36]. Artificial tears and eyelid hygiene are standard treatments in this case, but also dose increases of dopaminergic treatment may be supportive [37, 38]. In case of blepharospasm, subcutaneous botulinum toxin injections may be advantageous [39].

Ocular movements

PD is associated with abnormal ocular motility leading to blurred vision, diplopia, problems with near tasks, and restricted gaze. Three types of eye movement abnormalities may occur (Box 4): deficits of smooth pursuit, saccades and vergence movements. In PD, movement preparation and execution are impaired, with problems in initiation of pursuit. This can induce cog-wheel (jerky) movements. Abnormal saccadic and smooth pursuit movements occur in 75% of PD patients [40, 41], negatively affecting fixation and reading. Optimizing dopaminergic medications can improve ocular movements [42]. Vergence eye movements serve to move the eyes in different directions (either together, which is convergence, or apart, which is divergence), keeping

an image stable on the retina as it moves towards or away from our eyes. To test convergence, the near point of convergence test can be used (Box 5). Insufficient convergence can cause impaired accommodation, which is the eye's response to a near stimulus. Inadequacy or slowness of accommodation can result in eyestrain, headaches and diplopia when working on near tasks. Abnormal convergence contributes to diplopia in 20–30% of PD patients [11, 43–47]. Referral to the ophthalmologist or orthoptist is indicated when the patient experiences problems in daily life (as indicated during the interview) or when test results are abnormal (Box 4), with special attention to convergence insufficiency. Affected patients could be treated with prisms, that compensate for impaired convergence, or convergence exercises. Dopaminergic medication can also improve convergence insufficiency. Moreover, there is a role for physical and occupational therapists, who can use simple behavioral changes to improve visual function. Examples of simple recommendations include resorting to monocular occlusion while reading, or to using reading stands or eating from surfaces elevated to eye level if there is gaze limitation.

Box 4

Smooth pursuit	Start by observing the eyes in their primary position. Let the patient follow a moving object and observe the voluntary gaze, smoothness and pursuit in all directions (left, right, up and down) [48, 49].
Saccades	Hold two targets in front of the patient in extreme lateral positions and then ask the patient to look back and forth between the targets, while observing the latency, velocity and amplitude of movement [50]. Furthermore, the King-Devick-test (KDT) can be applied. Here the patient has to read out loud numbers of a card from left to right and from above to below. The required time and mistakes are noted [51].
Near point convergence	Assess if the patient can maintain single vision when trying to focus on an approaching subject (e.g., a written letter on a stick). Healthy individuals can avoid double vision until the object reaches about 6 cm in front of their nose [45].

Complaints of double vision, problems reading or performing near tasks should lead to test for monocular or binocular diplopia (Box 5). There are different forms of diplopia related to diverse underlying mechanisms involving deficits of peripheral and central

pathways. In PD patients, the prevalence of diplopia varies between 10–47%, compared to a maximum of 19% in healthy subjects [1, 18]. It is important to differentiate between monocular diplopia (in one eye, and usually caused by intraocular pathology), binocular diplopia (in two eyes, due to ocular misalignment) and selective double vision (a rare form of visual hallucination in PD patients) [1, 52, 53]. Binocular diplopia can occur in PD due to convergence insufficiency or decompensated latent strabismus. In latent strabismus there is a relative deviation of the visual axis compensated by the fusion mechanism of the eyes. When this mechanism is disrupted, the deviation becomes manifest, resulting in diplopia. Causes of disruption may be, e.g., decreased accommodation or fatigue. In addition, in patients with response fluctuations, diplopia may be observed as an “off” symptom, indicating an OFF phase [1, 52–54].

Box 5

Monocular or binocular diplopia	Cover one eye with the palm of the hand. Double images will disappear in binocular diplopia. Persisting diplopia indicates monocular diplopia. Perform separately for both eyes.
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Diplopia is more common in patients with pre-existent ocular misalignment, which tends to be progressive during the course of PD. This could be explained by subtle oculomotor disturbance or obvious latent strabismus (heterophoria). The cover/uncover test can be used to screen for this (Box 6). When misalignment is suspected, referral for orthoptic ophthalmologic evaluation is advised. Abnormal ocular movements can also lead to impaired depth perception (stereopsis). Stereopsis is the ability to see in three dimensions and appreciate the spatial relations between objects. In order to perceive objects accurately, a subject basically needs a normal retina, normal visual acuity and proper alignment of the eyes. Two small studies report a stereopsis prevalence of 42% in PD [55, 56].

Box 6

Cover/uncover test	Cover and uncover each eye. Observe if there is movement of the covered eye immediately after it has been uncovered and takes up fixation, this reflects heterophoria (horizontal: esophoria, exophoria or vertical: hyperphoria, hypophoria) [57].
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Optic nerve/retina

Bumping into objects or problems reading can be symptoms of a visual field defect. The visual field is the space where objects are simultaneously visible during steady fixation of gaze in one direction. In PD patients, visual field defects may occur, but the exact prevalence is unknown. Visual field defects can be caused by a broad variety of diseases (e.g., opticopathy, retinal disease, glaucoma). Two small studies suggested an increased risk of glaucoma in PD patients (16–24% compared to 7% in healthy controls) [9, 58, 59]. Central visual field defects can be screened using the Amsler grid [60]. For the more peripheral defects use the confrontational exam to exclude deep and large defects caused by optic nerve lesion or vascular lesions. However, confrontation tests have limited sensitivity to detect small, relative visual field defects. If visual field defects are suspected, specific ophthalmological examinations are required, such as automated static perimetry [61]. In addition, screening for glaucoma by assessing the risk profile is advised. Risk factors include positive family history for glaucoma, high myopia (>6 Diopters), high age (>70) and black race [62–64]. Useful questions focus on night blindness, decreased contrast vision and seeing objects too late (which may lead to traffic accidents). If there are abnormalities in any of the screening tests (Box 7), referral to an ophthalmologist is advised for extensive examination with perimetry and funduscopy.

Box 7

Amsler grid	Let patients focus at the center dot of the Amsler card with each eye separately and binocular. Ask if the patient notices if all grid lines look straight or if any lines or areas look blurry, wavy, dark or blank [60]. (See appendix 2 for an example of the Amsler card)
Confrontational exam (Donders' test)	Ask patients to cover their right eye. The examiner covers the left eye and moves a finger out of the patient's visual field. The patient must say when the finger is visible again. The same procedure is performed with each eye [61].

Color discrimination and contrast sensitivity

Decreased vision while driving in the dark or a low attention span when reading a text on a colored background can be symptoms of decreased contrast sensitivity and color discrimination. Color discrimi-

nation is the ability to distinguish differences between shades of colors and is divided into primary colors (green, red, blue and yellow) and their axis (red-green, blue-yellow). Contrast sensitivity is the ability to differentiate objects at low contrast and is needed to perform tasks such as driving, reading and navigation. Problems with color discrimination and contrast sensitivity can be present even before the diagnosis of PD and have been reported in 18–50% of patients with PD. However, the exact frequencies are not known [9, 65, 66]. Symptoms related to color and contrast vision have been associated with dopamine depletion in the retina. However, the pathophysiology of color vision deficiency in PD is complex and multifactorial [5, 67]. Several studies suggested that reduced contrast sensitivity in PD is positively associated with disease severity and cognitive impairment and that both symptoms may have prognostic or diagnostic value [2, 68, 69]. Impaired color vision is even being considered as a preclinical marker of neurodegeneration [7], but this is thus far only relevant for research settings, for example to identify candidates in the earliest possible stages of PD for inclusion in trials of potential disease-modifying therapies. Multiple tests can be performed by an ophthalmologist to screen for problems related to color vision and contrast sensitivity. The most widely used clinical tests that have good discriminative properties are shown in box 8 [70–72]. Importantly, levodopa therapy may improve both contrast sensitivity and color vision in PD patients. Furthermore, selective absorption glasses and sufficient ambient light can be supportive. Patients with decreased contrast vision may have difficulties with scotopic vision and should therefore be warned not to drive at night.

CONCLUSION

We hope that this paper will raise more awareness about the prevalence and impact of visual disorders in PD, since patients may experience a variety of visual problems during the course of their disease. We encourage clinicians to complement their patient interview with a short neuro-ophthalmological screening (basic set of ophthalmological tests). Timely recognition of visual disorders may lead to purposeful treatment and start of patient-oriented rehabilitation strategies. Simple interventions can often have immediate positive results. For example, careful refraction, separate glasses (for distance, reading and computer use), optimal dopaminergic

Box 8

Ishihara plates	Consists of a number of pseudo-isochromatic colored plates. Each contains a sphere of randomly sized and colored dots. Some of these dots form a number that can only be distinguished by individuals without a certain color vision deficiency. Ask the patient to identify the correct number [73].
Farnsworth-Munsell 100 Hue	Consists of 85 different colored caps, arranged in four boxes. The first and last reference discolors are set fixed. Ask the patient to arrange the rest of the colored discs in chromatic sequence. The total error score is measured based on the number of misplacements [74].
Pelli Robson (letter) charts	The patient sits in front of the chart at a distance of 1 meter. Letters are arranged in groups with contrast varying from high to low, in 16 triplets over 8 lines. Ask the patient to read the letters, starting with the highest contrast, until they are unable to read two or three letters in a single group. Score the patient based on the contrast of the last group in which two or three letters were correctly read [75].

treatment, prisms and convergence exercises can increase quality of life. Early identification of visual disorders might permit an earlier clinical diagnosis of PD. Indeed, some visual problems may precede the onset of the disease itself and may serve as an early marker of PD. Moreover, visual problems may also help to predict disease progression. Structural imaging of the retina can provide objective parameters that could be more reliable in the evaluation of the disease. Although many studies have assessed retinal changes in PD using Optical Coherence Tomography (OCT) [58, 76–81], to date the number of clinical trials on the use of OCT in PD that have been registered is limited. Further work remains needed to understand the association between PD and visual disorders and to develop tailored interventions and new neurorehabilitation strategies.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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