

VISUAL DISTURBANCES IN PARKINSON'S DISEASE PATIENTS

Nicoleta Tohanean¹, Lucia Muntean^{1,2}, Horea Demea³, Lacramioara Perju-Dumbrava¹

¹Neurology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

²Department of Clinical Neurophysiology, University of Göttingen, Göttingen, Germany

³Ofta Review Clinic Cluj-Napoca, Romania

ABSTRACT

Along with the motor symptoms, Parkinson's disease (PD) patients experience a wide range of non-motor problems including visual disturbances. These are multifaceted, but often underreported as such. In a visual survey questionnaire, 78% PD patients reported at least one problem related to vision or visuospatial functioning.

The most frequent encountered problems are impaired contrast sensitivity, color discrimination, visuospatial processing, ocular or eyelid movements and diplopia followed by visual misperceptions and hallucinations. Some patients report dry eyes, ocular pain or photophobia.

The pathophysiological basis of the visual disturbances is not completely understood. Changes in the visual cortex were detected with functional MRI before the visual symptoms were clinically evident. Further studies are necessary to determine how these changes will contribute to development of visual symptoms in PD patients. Other authors consider a dopaminergic deficit in the retina to be responsible for some of these symptoms, being known that dopamine is the major neurotransmitter in the amacrine and interplexiform cells in the retina. Visual hallucinations are likely to be a result of disruption across related yet diverse neural circuitry.

The therapy is only symptomatic and not always satisfactory. It includes ophthalmological treatment and specific treatment for hallucinations.

Optical Coherence Tomography (OCT) is a new investigation method who offers quantitative morphology of gross retinal histology. The thinning of the peripapillary retinal nerve fiber layer was observed in PD. Some studies mentioned that macular thickness measured by the OCT could be a promising biomarker of PD.

This work shows how complex the visual problems in PD patients can be and the importance of a thorough and multidisciplinary approach.

Keywords: visual disturbances, amacrine cells, dopamine deficit, Optical Coherence Tomography

INTRODUCTION

The nonmotor symptoms (NMS) of PD have received a lot of attention in the last few years. Immense advances have been made in the treatment of motor symptoms of PD but the nonmotor symptoms have lagged behind. Nonmotor symptoms, first described by James Parkinson in the 19th century may play a significant role in determining the general quality of life of the patient. Despite this fact, they have still been underrecognized and undertreated (1).

NMS may include a wide range of symptoms like cognitive problems, apathy, depression, anxiety, hallucinations, and psychosis as well as sleep disorders, fatigue, autonomic dysfunction, sensory problems, and pain (1). Sensory problems may include visual loss, loss of smell, auditory problems, and restless legs syndrome (RLS) (2).

In the context of PD sensitive symptoms one can distinguish visual disturbances. They frequently do not receive enough attention during the consultation neither from the physician, nor from the patient.

Author for correspondence:

Nicoleta Tohanean, "Iuliu Hatieganu" University of Medicine and Pharmacy, 6 Pasteur Street, Cluj-Napoca

Visual symptoms are underreported and multifaceted with various origin from the disturbed ocular motility to a retinal dysfunction or malfunction of attentional control networks in the brain (3,4).

The major visual problems in PD are impairment of contrast sensitivity, colour discrimination, visuospatial processing and ocular movements (4). Visual hallucinations may occur in absence of dementia and the presence of this feature represents a major risk for nursing home placement (4). Ocular motor function in PD subjects fluctuates in response to treatment, which complicates ophthalmic management (2,4).

PREVALENCE OF VISUAL SYMPTOMS

In 2005, in a survey that used a visual questionnaire, the prevalence of all visual symptoms in PD has reached about 78% (5). These PD patients reported at least one problem related to vision or visuospatial functioning (5).

The NMS-Quest – a 30-item screening tool – was developed in 2006 by Chaudhuri to evaluate the nonmotor symptoms in current clinical practice (6).

Diplopia is one of visual symptoms that is included in the questionnaire. 21.9% of patients with PD reported diplopia to the questionnaire compared to 4.2% in the control group and most patients had not declared prior diplopia to the physicians (6). Another study in Europe using NMS-Quest reported a prevalence of diplopia in PD patients of 18.2% and one study in China using the same questionnaire has found diplopia in 16.7% of PD patients (7).

Color discrimination and contrast sensitivity is more prevalent in PD patients than controls (2,4).

Visual misperception and hallucinations occur in more than 50% of PD patients with advanced disease (2,4).

PATHOLOGICAL CHANGES IN PD AFFECTING VISUAL SYSTEM

Retinal pathology

Dopamine is the major neurotransmitter in the retina and is present in the subtype of amacrine cells A18 and along the inner plexiform layer of the retina (2,4,8,9) while dopaminergic receptors are spread across the whole retina (8).

In the PD it has been described some pathological changes in the retina: cell losses, which often affect the peripheral segments more severely and reductions in retinal dopamine (2). Dopaminergic cells in the retina are *amacrine A18 cells* with D1

and D2 receptors and *interplexiform cells* with role in light adaptation. (2,4)

Dopamine is essential for light adaptation, by modulating visual signal transmission in rod and cone circuits at the photoreceptor level: during daylight switches the active visual pathway from being rod-to cone-mediated (via D2 receptors) and during dim-light (via D1 receptors) (4,10,11).

Also dopamine has multiple trophic effects in retinal cells (10). Studies in autopsy cases of PD revealed loss of the dopaminergic innervation around the macula and dopamine deficiency in the retina despite the preservation of retinal dopaminergic neurons (10). There are no reports on the presence or absence of α -synuclein aggregates in the retina (9).

Brain pathology

Dopamine activity is limited to the frontal area of the cerebral cortex with significantly less activity in the visual cortex (2) and cerebral metabolic rate for glucose is reduced by up to 23% in the primary visual cortex of PD patients (2). Positron emission tomography (PET) studies of PD patients have revealed occipital hypometabolism. The Occipital and Frontal Eye Field (FEF) cortex has an essential role in producing saccadic eye movements (2).

Dopamine also has a peripheral role in sympathetic system and reductions in dopamine in some of these areas can contribute to eye movement problems and defects in pupil reactivity (2).

Visual symptoms

In PD, the patients described a variety of ophthalmological problems with two principal origins: retinal or ocular. These visual symptoms are summarised in Table 1.

TABLE 1. Visual symptoms in Parkinson's disease (2,4)

Retinal origin	Decreased visual acuity	
	Colour vision impairment	
	Visual contrast insensitivity	
	Dyskinesia related visual contrast supersensitivity	
Ocular origin	Ocular motility related	Low and reduced blink rate
		Blepharospasm
		Hypometric saccades
		Cogwheel pursuit
	Diplopia	
	Sensory	
	Pupillary	
	Open-angle glaucoma – visual field defects	
	Cataract	
	Visual hallucination	
Symptoms in the context of adverse reactions to anti-Parkinsonian therapy		

VISUAL PROBLEMS WITH RETINAL ORIGIN

Decreased visual acuity

PD patients often complain of low vision especially as the disease progresses resulting, in part, from poor visual acuity (2) and low contrast acuity is especially affected (2).

Poor visual acuity may be caused by lack of dopamine in the retina, abnormal eye movements, or poor blinking and is only partially improved by drug therapy (2).

Colour vision impairment

Impairment of color discrimination and contrast sensitivity are established signs of PD (8). In PD the vision of colored stimuli has been reported to be blurred (2,12) with reduced color fusion times which indicate the accuracy of perception of monochromatic contours (2,12). The most significant deficits were reported by studies in the blue-green axis and the red-green axis (4). The exact mechanism is unknown but this impaired color discrimination may be predictor for the dopamine deficit in the retina (4).

There are some reports of abnormalities of color vision in PD with REM Sleep Behavior Disorder (RBD), which could suggest that color vision impairment may be a preclinical marker of neurodegeneration (4).

In PD patients with genetic mutation, only patients with LRKK2 MC (manifesting mutation carriers) showed poor color discrimination compared to controls. Patients with LRKK2 NMC (non-manifesting mutation carriers) showed average performance (13).

In another study, using the Farnsworth-Munsell 100-hue test, colour visual discrimination does not appear to be significantly impaired in the early stages of PD and is not a reliable early marker of PD (2,14).

A progressive deterioration of color discrimination is also present in PD and is often associated with impairments of higher motor function (2).

Visual contrast insensitivity

The domain of contrast sensitivity is also affected at PD patients especially at the high or intermediate frequencies (2). Some patients developed a substantial decrease in contrast sensitivity as the disease progresses and that may contribute to poor vision in PD. (2)

Some studies reported that in untreated PD patients, the dopamine content in the retina and the

dopaminergic innervation around the macula are decreased (4) and so, contrast insensitivity seems to be correlated to retinal dopamine deficiency (2,4).

Dopaminergic deficit may reduce the ability of retinal network to differentiate spatially distinct stimuli accurately, which contribute to decrease in contrast sensitivity (2,4).

Contrast insensitivity usually responds to L-dopa therapy (2,4). Apo-morphine also improves contrast sensitivity at all spatial frequencies but appears to have minimal effects on color vision (2). Other solutions in order to improve the contrast sensitivity are increasing room lighting and using a magnifying glass (4).

During L-dopa induced dyskinesias, contrast sensitivity can fluctuate rapidly leading to blurred vision (4).

VISUAL PROBLEMS WITH OCULAR ORIGIN

Symptoms related to ocular motility

Bradykinesia in PD is the cardinal sign of the disease and hypomimia is characterized by **low and reduced blink rate**. The studies show that during the voluntary blinking there is an extended pause between the closing and opening phase. Also, spontaneous blinking is characterized by lower amplitude and reduced velocity of the blinking rate (4). Reduced blink rate can cause dry eyes and reduced vision (2).

Blepharospasm and **apraxia** of eyelid opening are others visual signs described in PD (4-6). For therapy of blepharospasm, botulinum toxin A or B are effective, well tolerated and improve the severity and functional impairment even with varying doses and injection intervals (4).

Clinically assessment of ocular motricity in extrapyramidal syndromes is an important step to the diagnosis. Abnormal **hypometric saccadic** and **smooth pursuit eye movement** has been reported in 75% of PD patient (4). Hypometric saccades affect more vertical movements (2).

Cogwheel pursuit is defined like a reduced smooth pursuit eye movements derived from the need to catch-up saccades to compensate. This visual problem is more probably related to cortical-non-dopaminergic damage or to impaired frontal cortical circuitry (2).

Diplopia

Diplopia occurs often in PD patients with normal visual acuity (2) and is more frequent in moderate to severe PD than early stage disease (2).

The studies found that there are some predisposing factors for diplopia like ocular factors: ocular misalignment and ocular motility and also disease factors such as progression of PD, worsening of cognition.

When only duplication of single objects occurs it is called “selective diplopia” which is probably related to development of visual hallucinations.

In the therapy of symptomatic diplopia specific prismatic lenses or adjustment of glasses can be used but optical correction has to be prescribed in consideration with dopaminergic treatment (*on* or *off* periods) (2,4).

Sauerbier et al. described 5 patterns of diplopia in PD (Table 2) (2,15).

TABLE 2. Types of diplopia (2,15)

Type 1	Fleeting transient diplopia, “words jumping during reading”
Type 2	A relatively constant pattern of diplopia often related to convergence dysfunction
Type 3	Diplopia linked to motor fluctuations
Type 4	Diplopia linked to visual hallucinations (perceptory diplopia)
Type 5	Drug induced diplopia

Sensory symptoms

Xerofthalmia (dry eyes) is caused mainly by reduced spontaneous blink rate but also by aqueous tear production who is affected. Xerofthalmia is a frequent symptom in PD, associated with blurred vision, ocular discomfort and reading difficulty (4). Shirmer’s test scores is significantly affected in PD, which suggests the impairment of aqueous tear production (8).

Blepharitis may occur in PD patients and a study reported that in conjunctival flora, Staphylococcus aureus was more often found in PD patients than in controls (4,16).

Another’s encountered symptoms are **ocular pain, ocular fatigue, photophobia or excessive tearing** (4).

Pupil reactivity

Different varieties of pupillary abnormalities have been described in PD disease: these have been attributed to either the disease itself or to its pharmacological treatment.

At PD patient it have been reported: anisocoria or miosis after light adaptation, tonooptic reactions (characterized by long latency, normal or slightly reduced amplitude and fast recovery of pupil diameter after light exposure) and prolonged edge light pupil cycle time (2,17,18).

All of this are determined by alteration of both systems: sympathetic (by diencephalic lesions) and parasympathetic (by changes at Edinger Westphal nucleus) with autonomic imbalance (2).

Open-angle glaucoma

Retrospective analysis of ophthalmic charts from PD patients revealed **glaucomatous visual field defects** in 23.7% of patients (2,19). Studies reported more frequent occurrence of glaucoma-like visual field defects, without any other clinical signs of glaucoma (8,10).

The study of Nowacka in 2014 reported a greater risk of **primary open-angle glaucoma** in PD patients (16.33%) (8).

Glaucoma in PD may be a result of decreased level of reduced glutathione (GSH), an important antioxidant found in the eye (8). GSH protects ocular tissue from damage caused by oxidative stress, which is implicated in the pathogenesis of primary open-angle glaucoma, especially with normal intra-ocular pressure (8,20).

Nuclear and posterior subcapsular cataract

Nowacka reported also in her study a higher frequency in the PD group, compared to controls, which may deteriorate visual functions (8). In PD there is excessive oxidative stress and oxidative stress has a great impact on cataract formation due to prevalent oxidation of lens DNA, proteins, and lipids (8).

It was observed also that PD patients are less frequently referred for cataract surgery (8).

VISUAL HALLUCINATIONS

Visual misperception and hallucinations (VH) are typical features of psychosis and represent a major problem in advanced PD because represents an important reason for the transition to institutional care (21). Currently available treatments offer only limited symptomatic benefit (21).

About 37% in all patients with PD experienced VH (22) and their prevalence increases with disease progression, in over half of PD patients with advanced disease (21).

Visual misperception represents the failure to successfully integrate stimuli that have been physically presented (3,21).

Visual hallucinations occur in the absence of a stimulus (3, 21) and may be induced by dopaminergic drugs but also may develop as a natural history of PD (22). Symptoms typically progress from **vivid**

dreams, visual misperception, and hallucinations to frank *psychosis* (commonly associated dementia) (3). The hallucinations associated with PD possess a common set of characteristics: typically occurs while alert with the eyes open and in dim light, the image appears without any known trigger or voluntary effort, it takes a few seconds or minutes and most often were complex, usually containing animate or inanimate objects or persons (23).

Visual hallucinations in PD patients are similar to the *Charles Bonnet Syndrome* (CBS), which occurs in elderly persons with visual deficits. PD patients suffer from visual deficits of contrast and color discrimination, so a similar pathogenesis to CBS could be hypothesized (21,23).

Visual hallucinations in PD are often comorbid with RBD, where patients act out their dreams during sleep (3,21). The prevalence of visual hallucinations is of 42% at PD patients with RBD versus 19% in patients without (4,24). This association has led to the proposal that symptoms may be caused by the intrusion of REM-like sleep imagery into waking consciousness (3,21,25).

TABLE 3. Factors associated with the development of visual hallucinations in PD (21)

✓ Decreased visual acuity
✓ Cognitive decline
✓ Decrease level of levo-dopa related to end-of-dose phenomena
✓ Longer disease duration and higher severity of disease
✓ Higher levodopa dosage and longer duration of treatment
✓ Intrusion of REM-like sleep imagery into wakefulness state (polysomnographic studies failed to show such REM intrusions)
✓ Nerve cell loss and Lewy Body pathology in the ventral temporal regions of the brain
✓ Side effect of the anti-Parkinson medication (L-Dopa, dopamine agonists)
✓ Dysfunction within the attentional control network

The pathophysiology is not yet completely understood with limited test for their assessment (21) but seems to be multifactorial and there are some factors involved in the occurrence of visual hallucinations (Table 3) (4,12,21).

Different models are proposed and both – peripheral (retinal) and central (association cortex) changes can be involved (22).

Impairment of object and space perception in PD patients with visual hallucinations, possibly in association with a decreased sustained visual attention, might play a role in pathogenesis (12,21). Recognition of objects is intact in PD patients with hallucinations, but slower than in PD patients without hallucinations (12,21). Impaired visual acuity

also appears to be a risk factor for the development of chronic hallucinations in PD (2,7).

Functional MRI studies showed that in PD patients with visual hallucinations there is a lower level of frontal lobe activation, when performing tasks that test their visual recognition system (12). Reduced visual information processing and retinal pathology may also have a role (12).

The study of Ballanger in 2010 provides the first evidence suggesting a role for serotonin 2A receptors in mediating visual hallucinations via the ventral visual pathway in PD (26). PD patients with visual hallucinations demonstrate increased serotonin 2A receptor binding in the ventral visual pathway (26). Treatment strategies should use selective serotonin 2A receptor antagonists, and this may have important implications for the clinical management of VHS and psychosis in PD (26).

The actual treatment of VH depends on origin. When VH represent side-effects of medication, the doctor must adjust medication and add clozapine or quetiapine (27,28). Evidence based studies support the use of clozapine in PD patients with dementia (27,28). Quetiapine has been proved to be more efficient than placebo in reducing visual hallucinations in PD, but no through normalizing sleep architecture (27,28). Cholinesterase inhibitors potentially improve hallucinatory experiences. Patient-initiated coping strategies may be useful (27,28).

SYMPTOMS IN THE CONTEXT OF ADVERSE REACTIONS TO ANTI-PARKINSONIAN THERAPY

Most antiparkinsonian medications act in the brain either by reducing cholinergic activity or by encouraging dopamine activity in the basal ganglia (2). The anticholinergic drugs have the most ocular adverse effects of which the most important is anterior angle closure (2).

Principal side effects of dopaminergic medication are summarized in Table 4.

TABLE 4. Adverse ocular reactions to treatment for Parkinson's disease (2)

Treatment	Ocular side effects
Anticholinergic	Mydriasis, photophobia, dry eyes, decreased accommodation, anisocoria, blurred vision, anterior angle closure
Dopamine agonists	May exacerbate visual hallucinations
L-Dopa	Mydriasis, miosis, blepharospasm eyelid ptosis, may prolong latency of saccades
MAO-inhibitors	Loss of visual acuity and blurred vision
Amantadine	Mydriasis, superficial keratitis, reduced accommodation, hallucinations

Ophthalmological evaluation

In PD, the studies have shown disturbances of retina with low content of dopamine. Consequently, morphological changes of multiple cell layers in retina may occur (22).

Optical Coherence Tomography (OCT) is a new investigation method who offer quantitative morphology of gross retinal histology (29). OCT scans have been used to investigate the structural changes in the retina in vivo and segmental measures of the vertical retinal layers and OCT provide structural evidence for retinal dopamine loss and macular dysfunction in PD (30).

TABLE 5. The advantages of OCT in PD (29)

Evaluates:
• Peripapillary retinal nerve fiber layer (RNFL)
• Macula volume
• Macular thickness
– Noninvasive, noncontact, reproducible procedure
– Quantitative and qualitative analysis of retinal morphology
– Widely available
– Fast

OCT is most useful in making a diagnosis because it measures the thickness of the circumpapillary retinal nerve fiber layer (2), is performed very quickly, is a non invasive and objective method and makes histological section in vivo of the biological tissues with high resolution for about 10 microns (31).

Ophthalmological examination should take into account the dopaminergic status of the patient: on or off state (29).

In PD patients was observed the **thinning of the peripapillary retinal nerve fiber layer (RNFL)**, which represent axons of the ganglion cells and is consistent with dopaminergic deficit in the retina and structural changes in PD (29,31).

The inferior quadrant layer, and especially the inferior temporal region, was significantly thinner in PD than in controls (2,31). Mean inferior and temporal quadrant RNFL thickness was reported to be significantly lower in PD patients without visual

impairments than in control subjects (31). OCT may be able to detect early subclinical PD-associated visual impairment (30).

The studies showed a significant inverse correlations between RNFL thickness and UPDRS scores (32).

Some studies show that the macula in PD patients is thinner than in ET patients or controls and show a interocular macular asymmetry in PD and ET, but not in controls (29,33). The usefulness of measuring **macular thickness** by OCT as a diagnostic tool to differentiate PD from other tremor disease, such as essential tremor (ET) is discuss but unclear yet (29,33).

Some authors consider that macular thickness measured by the OCT could be a promising, feasible biomarker of PD, by quantifying the morphological changes of retinal dopaminergic neurons. It may be used to follow disease progression and efficacy of the neuroprotective treatment (29,30,33,34).

Thinning of the photoreceptor layer was also detected, but the pathophysiological mechanisms remain to be elucidated (29,33).

CONCLUSION

Visual disturbances occur frequently in PD patients but are still underrecognized as part of the PD non-motor symptomatology, therefore not always asked for by the neurologist.

Their clinical manifestation is as diverse as their pathophysiology, and thus an intriguing medical problem.

Evaluation includes detailed and targeted anamnesis, neurological and ophthalmological examination. Optical coherence tomography may be useful already from the early stages of the disease. The management is complex and the treatment most of the time only symptomatic.

The cooperation between neurologist and an ophthalmologist with knowledge of the specific visual symptomatology in PD is the key for improving patients' vision-related quality of life.

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