CLINICAL AND EXPERIMENTAL
OPTOMETRY

REVIEW

Visual signs and symptoms of Parkinson's disease

Clin Exp Optom 2008; 91: 2: 129–138 DOI:10.1111/j.1444-0938.2007.00211.x

Richard A Armstrong DPhil
Vision Sciences, Aston University, Birmingham, UK
E-mail: R.A.Armstrong@aston.ac.uk

Parkinson's disease (PD) is a common disorder of middle-aged and elderly people, in which there is degeneration of the extra-pyramidal motor system. In some patients, the disease is associated with a range of visual signs and symptoms, including defects in visual acuity, colour vision, the blink reflex, pupil reactivity, saccadic and smooth pursuit movements and visual evoked potentials. In addition, there may be psychophysical changes, disturbances of complex visual functions such as visuospatial orientation and facial recognition, and chronic visual hallucinations. Some of the treatments associated with PD may have adverse ocular reactions. If visual problems are present, they can have an important effect on overall motor function, and quality of life of patients can be improved by accurate diagnosis and correction of such defects. Moreover, visual testing is useful in separating PD from other movement disorders with visual symptoms, such as dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Although not central to PD, visual signs and symptoms can be an important though obscure aspect of the disease and should not be overlooked.

Submitted: 27 February 2007
Revised: 21 June 2007
Accepted for publication: 15 July 2007

Key words: adverse ocular reactions, differential diagnosis, dopamine pathways, Parkinsons's disease, visual signs and symptoms

Parkinson's disease (PD) is a common neurodegenerative disorder affecting middle-aged and elderly people. It was named after the physician James Parkinson who described the first known cases in 1817. Parkinson called the disease 'paralysis agitans' but the physician Charcot suggested that the disorder should be named after Parkinson. PD is a disease characterised by deficiency of dopamine in areas of the mid-brain causing akinesia, rigidity and tremor. Although many patients may be visually asymptomatic, the disease can be associated with visual signs and symptoms including defects in eye movement and pupillary function. and in more complex visual tasks involving the ability to judge distance or the shape of an object. The symptoms of PD can be treated successfully using drug therapy or surgery and these treatments may have ocular side-effects. This article reviews:

1. the general features of PD, including its prevalence, signs and symptoms, diagnosis, pathology, and possible causes
2. the visual signs and symptoms
3. the pathological changes in the eye and visual system, which may explain these symptoms
4. the ocular reactions to treatment.

GENERAL FEATURES OF PARKINSON'S DISEASE

Prevalence

PD is a common disorder throughout the world, although it is less frequent in China and Japan, and in the black population.[1] A study in Wellington, New Zealand, reported a prevalence of 106 per 100,000 and in Queensland, Australia, 146 per 100,000.[2] On average, the disease is believed to affect 1 per 750 of the population. Prevalence of PD increases with age, reaching a peak in the seventh decade,

after which the disease declines. Under 40 years of age, the prevalence in males (28 per 100,000) is greater than that in females (15 per 100,000) but this trend is reversed in the seventh and eighth decades (females 645 to 830 per 100,000; males 465 to 736 per 100,000). The risk of an individual developing PD at some stage in their life is approximately 1 in 40.

Signs and symptoms

The symptoms of PD are caused by problems in the co-ordination of the muscle groups involved in movement and therefore it is referred to as a 'movement disorder', a group of diseases which also includes corticobasal degeneration (CBD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and Lewy body dementia (LBD).

The three most characteristic signs of PD are akinesia, rigidity and tremor.[3] Akinesia describes the 'slowness of movement', the initiation of a movement being especially affected. Rigidity describes the increase in muscle tone resulting in stiffness of the limbs and manifests as 'lead-pipe' and 'cog-wheel' rigidity. Lead-pipe rigidity refers to the general stiffness of a limb, which changes little as the limb, usually the arm, is moved. In cog-wheel rigidity, the arm 'catches' as it moves, rather as if it were controlled by a cog-wheel. In addition, the patient may have a 'dead-pan' facial expression with loss of blinking and emotional content. Moreover, increased flexion of muscles in the upper back may cause the spine to bend forward, leading to a characteristic stooped appearance. Stooping may also be due to decreased postural reflexes, which usually function to prevent a fall. Tremor, which occurs at a frequency of four to eight hertz, primarily affects the fingers, hands and head. Tremor is most acute while the limb is at rest but improves as it is used. Tremor is often increased by fear and anxiety and disappears during sleep. In addition, patients treated with levodopa (L-dopa) may exhibit dyskinesia or dystonia. Dyskinesia is a state in which the patient fidgets, twitches or is generally restless, while dystonia is a spasm of one set of muscles often deforming a limb into an abnormal posture.

Some patients with PD develop memory problems and mood changes and a few individuals may develop dementia similar to that found in Alzheimer's disease (AD).[4] Depression is also common, a condition which can occur either early or late in the disease. A variety of additional problems is often experienced by PD patients. These include constipation, urinary difficulties, sexual dysfunction, sweating, salivation, dizziness and ankle swelling. Many of these symptoms may be related to the disease process, for example, urinary difficulties result from problems in co-ordinating the muscles, which control the opening and closing of the bladder.

The rate of progression of PD varies considerably. About 10 per cent of patients may show little progression of the symptoms and the disease can be controlled successfully by minor adjustments in treatment. In patients with mild symptoms, the medication can lose efficacy with time and may need to be replaced. Greater problems usually develop after about eight to 10 years, although this depends on the age of the patient. Younger patients have a better prognosis. Patients rarely die of the disease, as chest infections and general disability are the commonest causes of death. On average, PD shortens the life span and the risk of death at any particular age is about two to three times greater than normal.

Differential diagnosis

There is no single test that is able to definitively diagnose PD and up to 25 per cent of cases may have been misdiagnosed.[5] The greatest difficulty in diagnosis is often separating PD from PSP early in the disease process. A brain scan employing positron emission tomography (PET) may be helpful in separating these two disorders. In addition, if the patient is given the drug L-dopa notable improvements in symptoms can be seen in PD but the drug is less beneficial in PSP.

There is a variety of conditions and disorders that can result in symptoms similar to those of PD. These include viral infection ('post-encephalitic' parkinsonism), adverse reactions to drugs, poisoning, genetic disorders, head trauma, normal pressure hydrocephalus and thyroid disease. The term 'parkinsonism' is often used to describe PD-like symptoms resulting from these causes. The diagnosis of true 'idiopathic' PD is based on the presence of the characteristic movement problems and elimination of the conditions that closely resemble it. A brain scan using magnetic resonance imaging (MRI) and other laboratory tests are often used to distinguish between parkinsonism and idiopathic PD.

Pathology

Several brain regions contribute to the initiation and control of movement (Figure 1). These involve areas of the cerebral cortex, including the pre-motor and motor cortex and areas deeper in the brain collectively known as the basal ganglia. The basal ganglia (which constitute the extra-pyramidal system) are important in the co-ordination of a movement. This system functions as follows.

1. The decision to make a movement is made in the cortex and this information is transferred to the basal ganglia.
2. The basal ganglia co-ordinate the information necessary for the movement to take place and this is transferred to the thalamus.
3. The thalamus passes the processed data back to the motor cortex, which then initiates the movement via the descending pyramidal tract.

In PD, the substantia nigra, an area with extensive connections with the basal ganglia, appears to be particularly affected. In a patient with PD, this region is reduced in size as a result of the death of most of the pigmented neurons.[6] Cells in the substantia nigra (cell group A9) project to the basal ganglia via the striatonigral pathway (Figure 2), a projection that uses dopamine as neurotransmitter. This pathway has an inhibitory influence on the activity of cells of the basal ganglia and the resulting increased activity of these cells may be responsible for the tremor and rigidity.

There are six central nervous system pathways that use dopamine as neu-

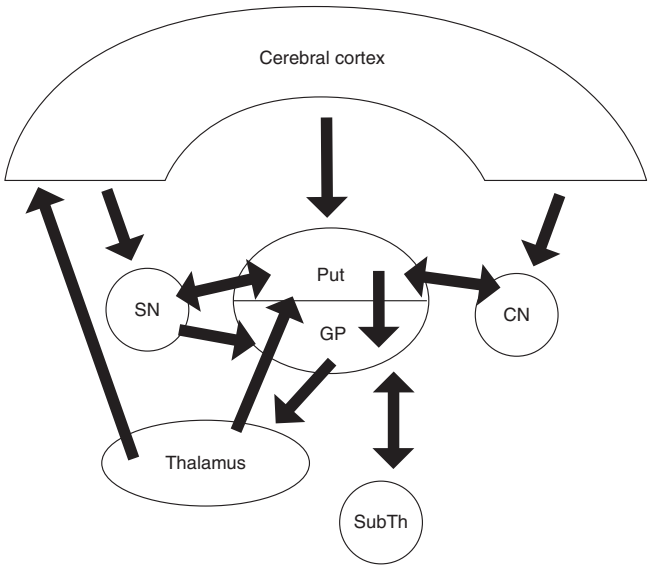

Figure 1. The extrapyramidal system showing the anatomical connections between various areas of the basal ganglia (SN = substantia nigra, PT = putamen, CN = caudate nucleus, GP = globus pallidus, SubTh = subthalamic nucleus)

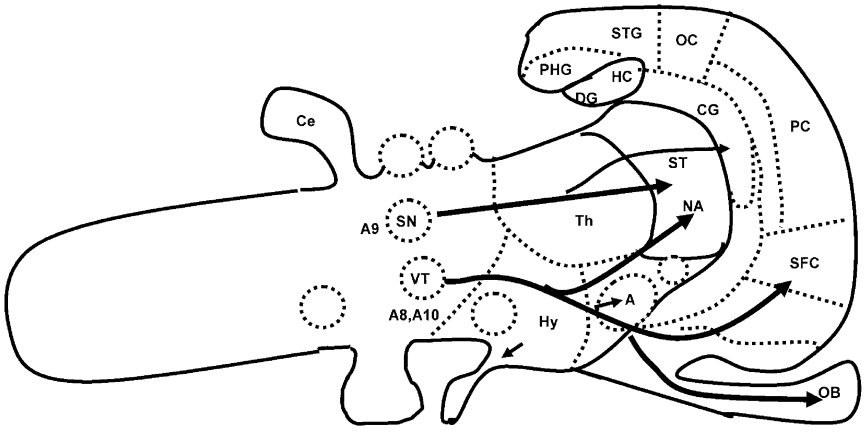

Figure 2. The dopamine projections of the central nervous (OB = olfactory bulb, SFC = superior frontal cortex, PC = parietal cortex, OC = occipital cortex, STG = superior temporal gyrus, PHG = parahippocampal gyrus, HC = hippocampus, DG = dentate gyrus, CG = cingulate gyrus, ST = striatum, NA = nucleus accumbens, Th = thalamus, A = amygdala, Hy = hypothalamus, VT = ventral tegmentum, SN = substantia nigra, Ce = cerebellum) system superimposed on a two-dimensional map of the brain. Based on the map of WJH Nauta and M Feirtag. *Fundamental Neuroanatomy*, WH Freeman & Co, 1986.

rotransmitter (Figure 2). In addition to the striatonigral pathway, there are dopamine neurons in the inner plexiform layer of the retina. A major pathway originates in the ventral tegmentum (cell groups A8, A10) and projects to the amygdala, septum, nucleus accumbens, olfactory tubercle and frontal cortex. There are also two small dopamine pathways within the hypothalamus. All the dopamine pathways are affected to some extent in PD.

The surviving neurons of the substantia nigra and cerebral cortex often contain structures called Lewy bodies (LB) in PD (Figure 3). LB are found in the cytoplasm of the cell and may be derived from cytoskeletal filaments. Recent research suggests that LB differ significantly from other neurofibrillary pathologies in neurodegenerative disease, for example, the neurofibrillary tangles (NFT) found in AD,[4] in that they contain significant amounts of the protein α-synuclein.[7] α-synuclein is a small pre-synaptic protein without a well-defined function and the entire molecule undergoes a conformational change to result in the insoluble protein that forms a major component of the LB.

Causes

Very few 'risk factors' have been unequivocally identified in PD. The disease does not appear to be associated with stress, overwork, pregnancy, smoking, alcohol or social class. PD has not been shown to be linked to diet. Some occupations appear to be associated with an increased incidence of PD, including farmers, forestry workers, gardeners, teachers and welders.[8]

Some cases of PD are familial with about one in 10 of all patients coming from families with a history of the disease. Recent research suggests that mutations in the PARK7 gene *DJ-1* are associated with autosomal recessive PD.[9] Moreover, mutations of the *LRRK2* gene are associated with PD with dopaminergic neuronal degeneration and accumulation of either α-synuclein or tau within the cells.[10] Some forms of parkinsonism have been linked to a heterozygous missense mutation together with a heterozygous deletion in the 'parkin' gene (*PARK2*).[11] This results

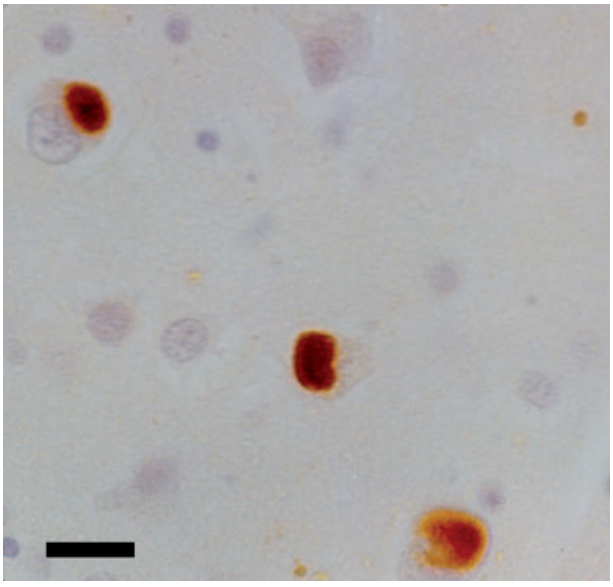

Figure 3. Highly magnified cells from the cerebral cortex of a patient with Parkinson's disease showing the presence of Lewy bodies (α-synuclein immunohistochemistry, haematoxylin stain, bar = 25 μm)

in a parkinsonism with a mild gait ataxia, spinocerebellar syndrome and tau pathology but without the presence of distinct LB or NFT.

The majority of cases of PD cannot be attributable directly to defective genes. There is no convincing evidence either that idiopathic PD is caused by a virus or other infectious agent. Evidence supporting an environmental cause comes from three sources. First, the substance MPTP, a contaminant of certain street drugs, can produce signs very similar to PD,[12] symptoms that can be relieved by L-dopa. Second, workers exposed to dust rich in manganese develop some of the symptoms of PD. Third, the Chamorro Indians on the island of Guam develop a disease that combines the symptoms of PD with dementia. Exposure to the seed of a cycad plant, used by the Indians for food, may be the cause of this condition.[13] A toxic amino acid (L-BMAA) has been isolated from the cycad and this substance administered to monkeys can produce some of the signs of PD. Hence, although it is not probable that idiopathic PD results from any of these specific causes, the evidence does implicate environmental factors.

VISUAL SIGNS AND SYMPTOMS IN PARKINSON'S DISEASE

PD is associated with a variety of visual signs and symptoms that are summarised in Table 1.

Visual acuity

There is little detailed information about changes in visual acuity in PD. PD patients often complain of poor vision, especially as the disease progresses, resulting, in part, from poor visual acuity,[14] with low contrast acuity being especially affected.[15,16] Impaired visual acuity appears to be a risk factor for the development of chronic hallucinations in PD.[17] Poor visual acuity is only marginally improved by drug therapy.[16] Poor visual acuity may be caused by lack of dopamine in the retina, abnormal eye movements or poor blinking. Many diseases can produce poor visual acuity in older patients and it is not known whether PD patients are specifically aware of their reduction in acuity when no other disease is present.

Colour vision

Vision has been reported to be blurred for coloured stimuli[18] with reduced colour fusion times,[19] which indicates the acuity of perception of monochromatic contours. A progressive deterioration of colour discrimination is also evident and is often associated with impairments of higher motor function.[20] Using the Farnsworth-Munsell 100-hue test, colour visual discrimination is not consistently impaired in the early stages of PD.[21]

Visual fields

There have been few studies of visual field defects in patients with PD, probably due to the difficulties when testing patients with severe movement disorders. Retrospective analysis of PD ophthalmic charts using a cup-to-disc ratio of 0.8 or greater to define glaucoma revealed glaucomatous visual field defects in approximately 24 per cent of patients, suggesting an increased rate of glaucoma in PD.[22] In addition, intraocular pressure (IOP) was slightly higher in PD patients with compared with without glaucoma (mean 18.9 compared with 16.0). Of the eight PD patients with glaucoma, five were considered to have low tension glaucoma. In one study, visual fields were investigated in patients undergoing posterior pallidotomy, a procedure that risks damaging structures such as the optic tract.[23] Of 40 patients studied, three had visual field defects likely to be attributable to the surgery, namely, contralateral superior quadrantanopias associated in two patients with small paracentral scotomata.

Eye movement

Eye movement problems are a particularly important aspect of PD. Assessment of oculomotor function can be made clinically or by using electro-oculography (EOG). EOG responses are often normal in PD patients, when the eyes are in the primary position or when resting, however, abnormal saccadic and smooth pursuit eye movements have been reported in about 75 per cent of patients.[24] Both reaction times and the

Ocular aspect	Change in Parkinson's disease	References
PRIMARY FUNCTION		
Visual acuity	Poor, especially at low contrast	Jones et al, 1992; Repka et al, 1996
Visual fields	Increase in glaucomatous visual field defects	Bayer et al, 2002
Colour vision	Vision blurred for coloured stimuli Shortened colour fusion time Progressive deterioration	Price et al, 1992 Buttner et al, 1993 Diederich et al, 2002
EYE MOVEMENT		
Reaction time	Slower than normal	Shibasaki et al, 1979
Saccadic gaze	Slower than normal	Shibasaki et al, 1979
Saccadic eye movement	Hypometria	Crawford et al, 1989
Smooth pursuit movement	Affected early in disease process Superimposed saccades Reduction in response magnitude	Bares et al, 2003 Shibasaki et al, 1979 Lekwiewa et al, 1999
Optokinetic nystagmus	Abnormal in some patients	Shibasaki et al, 1979
Convergence	Impaired in about 80% of cases	Corin et al, 1971
BLINK REFLEX		
Blink frequency	Reduced, but increased blink duration and excitability	Garland, 1952 Peshori et al, 2001 Biousse et al, 2004
Habituation	Habituation not observed	Garland, 1952
PUPIL REACTIVITY		
Pupil diameter	Larger after light adaptation with anisocoria	Micieli et al, 1991
Light reflex	Longer latency	Micieli et al, 1991
Constriction time	Increased	
Contraction amplitude	Reduced	Biousse et al, 2004
PSYCHOPHYSICS		
Contrast sensitivity	Abnormal in 60% of cases	Hutton et al, 1993
Temporal sensitivity	Reduced	
VISUAL EVOKED POTENTIALS		
Flash ERG	Reduced amplitude of 'b' wave using photopic and scotopic stimuli	Gottlob et al, 1987
Pattern ERG	Reduced amplitude Delayed P50	Gottlob et al, 1987 Peppe et al, 1995
Cortical VEP	Delayed P100, changing to normal with L-dopa	Bodis-Wollner & Yahr, 1978; Bodis-Wollner et al, 1982
Chromatic VEP	Increased latency and reduced Amplitude (esp. blue-yellow)	Sartucci et al, 2006
COMPLEX VISUAL FUNCTIONS		
Visuo-spatial	Severe impairment in some cases	Levin et al, 1990 Davidsdottir et al, 2005
Orientation and motion discrimination	Impaired	Trick et al, 1994
Facial perception	Impaired ability to perceive and imagine emotional faces	Lang, 1979
Visual hallucinations	Chronic in 30–60% treated cases	Diederich et al, 2005

Table 1. Visual changes in Parkinson's disease

maximum saccadic velocity of horizontal gaze are slower in PD and probably a consequence of akinesia,[24] although there is often overlap between PD patients and controls.[25] Saccadic eye movements may exhibit hypometria, that is, 'under-reaching of task',[26] while smooth pursuit movements may be interrupted by small saccades.[24] In addition, the amplitude of saccadic eye movements is increased in normal subjects, when there is a change from externally cued saccades to self-paced saccades and this effect is often greater in PD.[27] EOG recordings have been made before and after apomorphine treatment in patients in the early stages of PD and have confirmed that smooth pursuit movements are affected during the initial stages of the disease and are under dopaminergic control.[28] Patients with PD often have difficulty in sustaining repetitive actions and hence, smooth pursuit movements exhibit a reduction in response magnitude and a progressive decline of response with stimulus repetition.[29]

Abnormal optokinetic nystagmus ('train nystagmus')[24] and convergence[30] have been reported in PD patients, although the former has not been confirmed by all studies. Further abnormalities that have been observed include 'jerkiness', 'cogwheeling' and limitation of eye movement. Vertical eye movements are often more impaired than horizontal movements. Convergence can be associated with relatively large exophoria and the result is often diplopia.[31]

Blink reflex

Patients with PD exhibit a reduced frequency of blinking leading to a staring appearance.[32] Reduced blink rate can cause an abnormal tear film, dry eye and reduced vision. A characteristic ocular sign may be the blink reflex, elicited by a light tap on the glabella above the bridge of the nose, successive taps in normal individuals producing less and less response as the reflex habituates.[33] In PD, the blink reflex may not disappear on repeated tapping and this reaction may be present in a high proportion of patients. Habituation may improve after treatment with L-dopa or amantadine. Eye blink rate does

not appear to be significantly different in PD and controls and therefore may not be a good indicator of bradykinesia.[34] Blink duration and excitability appear to be increased in PD and may reflect loss of dopamine neurons.[35]

Pupil reactivity

Significantly larger pupil diameters with anisocoria after light adaptation have been reported in PD,[36] with no differences being observed after dark adaptation. In addition, longer light reflex latencies and constriction times have been observed, while contraction amplitudes may be reduced.[32] These results suggest that there is an autonomic imbalance in PD patients involving the parasympathetic system.

Psychophysics

Contrast sensitivity is affected in PD, at least in a proportion of patients.[37,38] Where contrast sensitivity is affected, it is performance at the high or intermediate frequencies that is reduced. Whether the abnormality is related to the severity of the disease is controversial. In some individuals, a substantial decrease in contrast sensitivity can be demonstrated as the disease progresses. Deficits in contrast sensitivity could be one explanation for the reports of poor vision often made by PD patients. Abnormalities in visual contrast sensitivity are likely to be related to dopamine dysfunction but are often orientation specific, suggesting cortical involvement.[39] L-dopa therapy generally improves contrast sensitivity performance to close to that of normal patients. In addition, apomorphine significantly improves achromatic spatial contrast sensitivity at all spatial frequencies but appears to have minimal effects on colour vision.[40] There may be decreased sensitivity to temporally changing stimuli, suggesting a deficit in motion perception in PD.

Visual evoked potentials

Significant effects on the electroretinogram (ERG) and visual evoked potential (VEP) have been found in PD. Increased latency of the VEP P100 peak to a checkerboard stimulus has been reported in a proportion of patients, suggesting a delay in visual processing at one or more stages of the visual system.[41,42] This delay could be retinal in origin as dopamine neurons are rare in the visual system other than in the retina. Consistent with this suggestion, studies show that the amplitude of the ERG 'b'-wave may be reduced in PD patients under a variety of light conditions.[43] As the amplitude of the 'b' wave may be a diagnostic indicator of the functioning of the inner nuclear layer, the reduction may reflect defects in visual processing involving dopamine neurons. In addition, the amplitude of the ERG to a checkerboard stimulus is decreased[43] and the latency of the P50 component delayed[44] in PD patients. The latter observation may be particularly significant because of the assumed involvement of dopamine neurons in the P50 response. Evoked responses to coloured stimuli are also affected,[45] supporting the hypothesis that dopamine modulates the retinal colour system. In idiopathic PD, amplitude is decreased and latency increased for all chromatic stimuli and especially for those using blue-yellow (B-Y) horizontal gratings[46] and this test may be a simple tool for separating MSA from PD.

Complex visual functions

PD patients may exhibit a variety of deficits in visuospatial orientation,[47,48] including difficulty in judging verticals and the position of body parts and in carrying out a route-walking task. Patients may have problems with memory tasks involving spatial orientation. PD patients often show an impairment of orientation and motion discrimination.[49] This suggests that the visual pathway beyond the retina may be affected as these tasks are most likely to involve the visual cortex. In addition, impairment in the ability to perceive and imagine faces has been reported in PD.[50] Medicated and unmedicated patients exhibit facial recognition problems but they are most frequently present in the unmedicated group.[51] Normal subjects contract their facial muscles while imaging faces, a process that is often impaired in PD patients. Pathological changes affecting the basal ganglia could be the cause of this problem.[52] Complex visuospatial deficits are also seen in AD[4] and there could be a degree of overlap in these symptoms with PD.

Visual hallucinations

Visual hallucinations are a chronic complication in about 30 to 60 per cent of treated PD patients[53] and especially those treated with L-dopa and dopamine agonists. Hallucinations are complex with flickering lights and illusionary misconceptions often preceding the most common manifestation, namely, stereotypical colourful images. Visual hallucinations may involve a disturbance in the regulation of the gating and filtering of external perception and internally generated visual images. Risk factors for hallucinations in PD patients include poor primary vision and reduced activity of the primary visual cortex (area V1).

PATHOLOGICAL CHANGES AFFECTING THE VISUAL SYSTEM

Ocular pathology

Few pathological changes have been reported in the eye in PD with the exception of the retina.[54] The maximum contraction of the iris muscle measured *in vitro* is greater in PD than in controls, suggesting that the muscle may acquire adaptive sensitivity changes.[55]

Dopamine is an important neurotransmitter in the retina. Its precursor, tyrosine hydroxylase, has been detected in the majority of animal retinas that have been studied. In the human retina, dopamine is present in amacrine cells and along the inner border of the inner nuclear layer.[56] In addition, dopamine may be accumulated by interplexiform cells.[57] Two types of amacrine cells appear to be involved (Figure 4). Type 1 cells send ascending processes to the inner plexiform layer where they synapse with γ-aminobutyric acid (GABA) interplexiform cells in stratum 1, whereas type 2 cells have their dendrites stratifying above those of the type 1 cells of the inner plexiform layer. Dopamine may be involved in the organisation of the ganglion cell and bipolar cell receptive fields, and appears to modulate

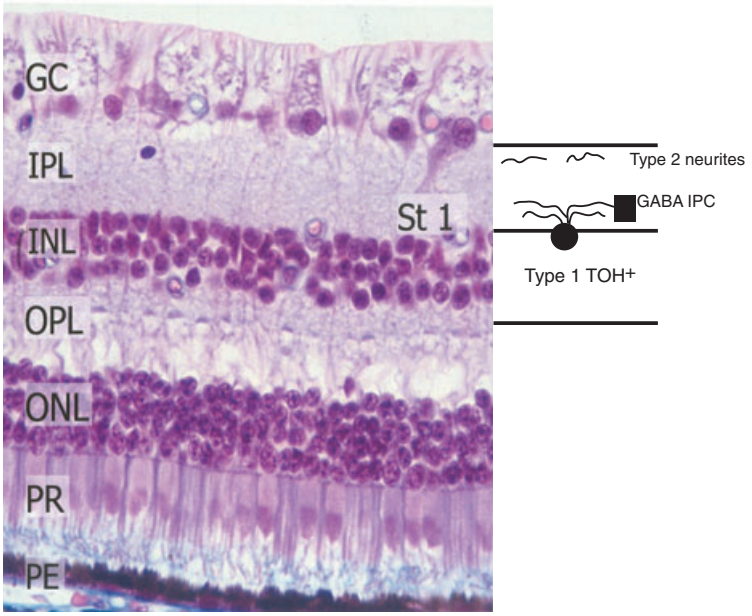

Figure 4. The layers of the retina (PE = pigment epithelium, PR = visual receptors, ONL = outer nuclear layer, OPL = outer plexiform layer, INL = internal nuclear layer, IPL = internal plexiform layer, GC = ganglion cell layer, St1 = stratum 1 of IPL). Dopamine neurons (TOH+ = Tyrosine hydroxylase positive neurons, Type 1 cells and Type 2 amacrine cells) are primarily concentrated in the INL and dopamine positive neurites (Type 1 in stratum 1 and Type 2 ramify above stratum 1) in the IPL. Type 1 cells may synapse onto to GABA IPC. Some dopamine activity may also be observed in the ganglion cell layer.

the physical activity of the photoreceptors.[58] In addition, dopamine is involved in the coupling of the horizontal and amacrine lateral system.[59]

Pathological changes that have been observed in the PD retina include cell losses, which often affect the peripheral segments of the retina most severely and reductions in retinal dopamine.[60] In addition, in normal subjects, the foveola contains no dopamine neurons, innervation being achieved by processes originating in the avascular zone. In PD, swelling and loss of these processes have been observed. These observations are consistent with the ERG data and support the hypothesis that at least some of the cortical VEP changes could be retinal in origin.

Brain pathology

Significant dopamine activity is limited to the frontal and limbic areas of the cerebral cortex with significantly less activity in the visual cortex, however, cerebral metabolic rates for glucose are reduced by up to 23 per cent in the primary visual cortex of PD patients.[61] Reductions in dopamine levels in the basal ganglia and frontal cortex may also deplete levels in the superior colliculus and thus be a factor in the production of defective saccades.[26] Within the cerebral cortex, functional MRI (fMRI) and EEG studies have both revealed the essential role of the occipital cortex in producing saccadic eye movements, while PET studies have revealed occipital hypometabolism in these areas in PD. Within the basal ganglia, the substantia nigra pars reticulata, the subthalamic nucleus and the caudate nucleus are all involved in saccadic eye movements.[62] There is an overlap in the anatomical pathways involved in saccadic and smooth pursuit movements, which may explain why both are affected in PD. Dopamine also has a peripheral role in sympathetic ganglia, visceral ganglia and in mesenteric and renal artery walls. Hence, reductions in dopamine in some of these areas could be a factor contributing to eye movement problems and defects in pupil reactivity.

ADVERSE OCULAR REACTIONS TO TREATMENT

Several drugs alone or in combination are used to treat PD (Table 2). With the possible exception of selegiline and rasagiline, the majority do not appear to slow the progression of the disease but control its symptoms. Most act on the brain either by reducing cholinergic activity or by encouraging dopamine activity in the basal ganglia.[63]

Anticholinergic drugs

Anticholinergic drugs such as benzhexol and diphenydrine were some of the first preparations used to treat PD. They act to decrease acetylcholine levels, the effect of which is enhanced by the lack of dopamine. As a group they are regarded as particularly beneficial in treating tremor. Benzhexol may have a significant mydriatic effect and therefore, should not be given to patients with angle-closure glaucoma and should be used with caution in those with a narrow anterior chamber angles. In a few patients, prolonged exposure to this drug may cause an angle-closure of gradual onset but without acute symptoms. Optometrists may be the only practitioners aware of this risk, therefore, it is always important to assess anterior chamber depth in PD patients. In addition, photophobia and decreased accommodation can occur resulting in blurred vision.[64]

Dopamine agonists

Dopamine agonists are another early treatment for PD and act by enhancing the effect of dopamine by directly stimulating dopamine receptors. These drugs may cause less motor complications and dyskinesia than L-dopa but are often given in combination with the latter. Use of

Treatment	Examples	Ocular side-effects
Anticholinergic	Benzhexol, Diphenydrine	Mydriasis, photophobia, dry eyes, decreased accommodation, anisocoria, blurred vision, anterior angle closure
Dopamine agonists	Bromocriptine	May exacerbate hallucinations
L-dopa	L-dopa/carbidopa	Mydriasis, miosis, blepharospasm eyelid ptosis, diplopia, reduced vision
MAO inhibitors	Selegiline Rasagiline	May cause loss of visual acuity and blurred vision
Antiviral	Amantadine	Mydriasis, superficial keratitis, hallucinations
Antidepressant	Imipramine	Mydriasis, cycloplegia, dry eyes, ocular muscle paresis, nystagmus
Surgery	Pallidotomy	Saccadic eye movements affected, visual field defects

Table 2. Adverse ocular reactions to treatment for Parkinson's disease

dopamine agonists may exacerbate visual hallucinations in PD.

L-dopa

L-dopa itself has been one of the most successful therapies in PD. It is a precursor of dopamine and can penetrate the blood-brain barrier more successfully than dopamine itself. It is often given with a peripheral decarboxylase inhibitor, for example, carbidopa or benserazide, to reduce the breakdown of L-dopa outside the brain. Mydriasis may occur at first and this may be followed by miosis. Lid ptosis and blepharospasm have been reported in a few patients.[65] In addition, L-dopa may also prolong the latency of saccades, although the magnitude of this effect varies greatly among patients.[25]

MAO inhibitors

Monoamine oxidase B (MAO-B) inhibitors, such as seliginine and rasagiline, slow the breakdown of dopamine at the synapse. In a PD patient treated with MAO-B inhibitors and multiple ergotene-derived dopamine agonists, there was blurring of vision.[66] This effect was attributable to inhibition of dopamine receptors in the retina and/or excessive stimulation of post-synaptic dopamine receptors resulting in faulty retinal information processing.

Amantadine and Imipramine

The anti-viral drug amantadine is also used to treat PD. The mode of action of amantadine is uncertain but it does appear to have a beneficial effect on many of the symptoms of the disease. A few adverse reactions have been reported including a superficial keratitis, mydriasis and reduced accommodation while in some patients visual hallucinations may occur.[67] By contrast, imipramine has anti-depressant and anticholinergic properties and acts by inhibiting the reuptake of dopamine. Ocular side effects include mydriasis, cycloplegia, dry eyes, nystagmus and the paresis of ocular muscles.

Surgery

The globus pallidus (Figure 1) is overactive in PD and hence pallidotomy, a treatment in which a small part of the globus pallidus is destroyed surgically, may help to relieve movement problems such as tremor and rigidity in more advanced patients. Patients have been monitored before and after pallidotomy and the data suggest that after surgery, peak saccadic velocity of internally mediated saccades decreased but that visually guided saccades were unaffected.[68]

DISCUSSION AND CONCLUSIONS

Middle-aged to elderly patients who have not been diagnosed with PD may exhibit visual signs and symptoms suggestive of a diagnosis of PD. The most important of these signs involve oculomotor function and pupil reactivity. Hence, a patient with unexplained symptoms or signs of this type should be referred for neurological examination. Nevertheless, the exact presentation of PD is highly variable and many patients with PD will be visually asymptomatic. It may also be difficult to separate PD from other disorders with parkinsonism such as progressive supranuclear palsy, especially before visual symptoms become apparent. When ocular signs and symptoms appear, the separation between PD and PSP becomes more straightforward. Atypical features of PSP include slowing of upward saccades, moderate slowing of downward saccades, the presence of a full range of voluntary vertical eye movements, a curved trajectory of oblique saccades and absence of square-wave jerks.[69] Particularly useful in separating PSP from PD is the presence in the former of vertical supranuclear gaze palsy, fixation instability, lid retraction, blepharospasm and apraxia of eyelid opening and closing.[70] Downgaze palsy is probably the most useful diagnostic clinical symptom of PSP. Deficits in colour vision appear to be more important in PD and directly related to the dopamine system, however, in early untreated PD, no consistent deficits in colour vision could be demonstrated, making this alone an unreliable indicator of PD.[21] Some of the saccadic eye movement problems will be evident only with the benefit of sophisticated technology not readily available to ophthalmic practitioners in the practice.

Patients who have been diagnosed with PD may develop a range of visual problems during the course of the disease. Visual deficits in PD are important in influencing overall motor function[20] and are a risk factor for developing hallucinations.[17] Hence, identifying and correcting the visual problems of a PD patient as far as possible can significantly benefit quality of life. Clinical examination of the patient

requires sensitivity to both the physical disability and mental state of the patient and the problems involved have been described in detail by Naylor.[63] In addition, some of the visual problems may be adverse reactions to treatment. Side effects may occur relatively rapidly at the beginning or after a change in drug treatment but can also occur after a long latent period. It is important that those symptoms due to adverse reactions are distinguished from those due to the disease. If ocular side effects are identified and become severe, then it is essential that these are monitored and the patient be referred back to the physician for further clinical assessment.

REFERENCES

1. Sagar H. Parkinson's Disease. Optima Health Guides. London: Macdonald & Co, 1991.
2. Peters CM, Gartner CE, Silburn PA, Mellick GD. Prevalence of Parkinson's disease in metropolitan and rural Queensland: A general practice survey. *J Clin Neurosci* 2006; 13: 243–348.
3. Walton Sir J. Brain's Diseases of the Nervous System. Oxford UK: Oxford University Press, 1985. p 322–336
4. Armstrong RA, Syed AB. Alzheimer's disease and the eye. *Ophthalmic Physiol Opt* 1996; 16, suppl 1: S2–S8.
5. Tolosa ES. Early signs of Parkinson's disease: Can they be used in diagnosis? *Eur J Neurol* 2006; 13 (Suppl 2): 324–325.
6. Armstrong RA. Parkinson's disease and the eye. *Ophthalmic Physiol Opt* 1997; 17 (suppl): S9–S16.
7. Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M. Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. *Neurosci Lett* 1998; 251: 205–208.
8. de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006; 5: 525–535.
9. Neumann M, Muller V, Gorner K, Kretzschmar HA, Haass C, Kahle PJ. Pathological properties of the Parkinson's disease-associated protein DJ-1 in alpha-synucleinopathies and tauopathies: relevance for multiple system atrophy and Parkinson's disease. *Acta Neuropathol* 2004; 107: 489–496.
10. Galpern WR, Lang AE. Interface between tauopathies and synucleinopathies: A tale of two proteins. *Ann Neurol* 2006; 59: 449–458.
11. Van de Warrenburg BPC, Lammens M, Lucking CB, Denefle P, Wesseling P, Booij J, Praamstra P, Quinn N, Brice A, Horstink MWIM. Clinical and pathologic abnormalities in a family with parkinsonism and parkin gene mutations. *Neurology* 2001; 56: 555–557.
12. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analogue synthesis. *Science* 1983; 219: 979–980.
13. Spencer PS, Nunn PB, Hugon J, Ludolph AC, Ross SM, Roy DN, Robertson RC. Guam amylotrophic lateral sclerosis: Parkinsonism dementia linked to a plant excitant neurotoxin. *Science* 1987; 237: 517–522.
14. Repka MX, Claro MC, Loupe DN, Reich SG. Ocular motility in Parkinson's disease. *J Pediatr Ophthalmol Strabismus* 1996; 33: 144–147.
15. Jones RD, Donaldson IM. Fractionation of visuo-perceptual dysfunction in Parkinson's disease. *J Neurol Sci* 1995; 131: 43–50.
16. Jones RD, Donaldson IM, Timmings PL. Impairment of high-contrast visual activity in Parkinson's disease. *Movement Disord* 1992; 7: 232–238.
17. Matsui H, Udaka F, Tamura A, Oda M, Kubori T, Nishinaka K, Kameyama M. Impaired visual acuity as a risk factor for visual hallucinations in Parkinsons's disease. *J Geriatr Psychiatry Neurol* 2006; 19: 36–40.
18. Price MJ, Feldman RG, Adelberg D, Kayne H. Abnormalities in colour vision and contrast sensitivity in Parkinson's disease. *Neurology* 1992; 42: 887–890.
19. Buttner T, Kuhn W, Klotz P, Steinberg R, Voss L, Bulgaru D, Przuntek H. Disturbance of colour perception in Parkinson's disease. *J Neural Transm Park Dis dement Sect* 1993; 6: 11–15.
20. Diederich NJ, Raman R, Leurgans S, Goetz CG. Progressive worsening of spatial and chromatic processing deficits in Parkinson's disease. *Arch Neurol* 2002; 59: 1249–1252.
21. Vesela O, Ruzicka E, Jech R, Roth J, Stepankova K, Mecir P, Solano Z, Preclikova E. Colour discrimination is not a reliable early marker of Parkinson's disease. *J Neurol* 2001; 248: 975–978.
22. Bayer AU, Keller ON, Ferrari F, Maag KP. Association of glaucoma with neurodegenerative diseases with apoptotic cell death.: Alzheimer's disease and Parkinson's disease. *Am J Ophthalmol* 2002; 133: 135–137.
23. Biousse V, Newman NJ, Carroll C, Mewes K, Vitek JL, Bakay RAE, Baron MS, DeLong MR. Visual fields in patients with posterior GPi pallidotomy. *Neurology* 1998; 50: 258–265.
24. Shibasaki H, Tsuji S, Kuroiwa Y. Oculomotor abnormalities in Parkinson's disease. *Arch Neurol* 1979; 36: 360–364.
25. Mitchell AW, Xu Z, Lewis SJG, Foltynie T, Williams-Gray CH, Robbins TW, Carpenter RHS, Barker RA. Saccadic latency distribution in Parkinson's disease and the effects of L-dopa. *Exp Brain Res* 2006; 174: 7–18.
26. Crawford TJ, Goodrich S, Henderson L, Kennard C. Predictive responses in Parkinson's disease: manual keypresses and saccadic eye movements to regular stimulus events. *J Neurol Neurosurg Psych* 1989; 52: 1033–1042.
27. Winograd-Gurvich C, Georgiou-Karistianis N, Fitzgerald PB, Millist L, White OB. Self-paced saccades and saccades to oddball targets in Parkinson's disease. *Brain Res* 2006; 1106: 134–141.
28. Bares M, Brazdil M, Kanovsky P, Jurak P, Daniel P, Kukleta M, Rector I. The effect of apomorphine administration on smooth pursuit ocular movements in early Parkinson's disease. *Parkinsonism Rel Disord* 2003; 9: 139–144.
29. Lekwuwa GU, Barnes GR, Collins CJS, Limousin P. Progressive bradykinesia and hypokinesia of ocular pursuit in Parkinsons's disease. *J Neurol Neurosurg Psychiatr* 1999; 66: 746–753.
30. Corin MS, Bender MB, Elizan TS. Oculomotor function in patients with Parkinson's disease. *J Neurol Sci* 1971; 15: 251–265.
31. Lepore FE. Parkinson's disease and diplopia. *Neuro-ophthalmol* 2006; 30: 37–40.
32. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. *Neurology* 2004; 62: 177–180.
33. Garland HG. Refresher course for general practitioners. Parkinsonism. *Br Med J* 1952; 1:153–155.
34. Chen WH, Chiang TJ, Hsu MC, Liu JS. The validity of eye blink rate in Chinese adults for the diagnosis of Parkinson's disease. *Clin Neurol Neurosurg* 2003; 105: 90–92.
35. Peshori KR, Schicatano EJ, Gopalaswamy R, Sahay E, Evinger C. Aging of the trigeminal blink system. *Exp Brain Res* 2001; 136: 351–363.
36. Micieli G, Tassorelli C, Martignoni E, Pachetti C, Bruggi P, Magri M, Nappi G. Disordered pupil reactivity in Parkinson's disease. *Clin Auto Res* 1991; 1: 55–58.
37. Bulens C, Meerwaldt JD, Van der Wildt GJ, Van Deursen JBP. Effect of levodopa treatment on contrast sensitivity in Parkinson's disease. *Ann Neurol* 1987; 22: 365–369.
38. Hutton JT, Morris JL, Elias JW. Levodopa improves spatial contrast sensitivity in Parkinson's disease. *Arch Neurol* 1993; 50, 721–724.
39. Rodnitzky RL. Visual dysfunction in Parkinson's disease. *Clin Neurosci* 1998; 5: 102–106.

40. Buttner T, Muller T, Kuhn W. Effects of apomorphine on visual functions in Parkinson's disease. *J Neural Transm* 2000; 107: 87–94.
41. Bodis-Wollner I, Yahr M. Measurement of visual evoked potentials in Parkinson's disease. *Brain* 1978; 101: 661–671.
42. Bodis-Wollner I, Marx MC, Mitra S, Bobak P, Mylin L, Yahr M. Visual dysfunction in Parkinson's disease: Loss in spatiotemporal contrast sensitivity. *Brain* 1987; 110: 1675–1698.
43. Gottlob I, Schneider E, Heider W, Skrandies W. Alteration of visual evoked potentials and electroretinograms in Parkinson's disease. *Electroencephalogr clin Neurophysiol* 1987; 66: 349–357.
44. Peppe A, Stanzione P, Pierelli F, De Angelis D, Pierantozzi M, Bernardi G. Visual alterations in de novo Parkinson's disease: Pattern electroretinogram latencies are more delayed and more reversible by levodopa than are visual evoked potentials. *Neurology* 1995; 45: 1144–1148.
45. Barbato L, Rinalduzzi S, Laurenti M, Ruggieri S, Accornero N. Color visual evoked potentials in Parkinson's disease. *Electroencephalogr Clin Neurophysiol* 1994; 92: 169–172.
46. Sartucci F, Orlandi G, Bonuccelli U, Borghetti D, Murri L, Orsini C, Domenica L, Porciatti V. Chromatic pattern-reversal electroretinogram (ChPERG) are spared in multiple system atrophy compared with Parkinson's disease. *Neurol Sci* 2006; 26: 395–401.
47. Levin BE, Llabre MM, Reisman S, Weiner WJ, Sanchez-Ramos J, Singer C, Brown MC. Visuospatial impairments in Parkinson's disease. *Neurology* 1991; 41: 365–369.
48. Davidsdottir S, Cronin-Golomb A, Lee A. Visual and spatial symptoms in Parkinsons's disease. *Vision Res* 2005; 45: 1285–1296.
49. Trick GL, Kaski B, Steinman SB. Visual impairment in Parkinson's disease: Deficits in orientation and motion discrimination. *Optom Vis Sci* 1994; 71: 242–245.
50. Lang PJ. A bio-informational theory of emotional imagery. *Psychophysiology* 1979; 16: 495–512.
51. Sprengelmeyer R, Young AW, Mahn K, Schroeder U, Woitalla D, Buttner T, Kuhn W, Przuntek H. Facial expression recognition in people with medicated and unmedicated Parkinson's disease. *Neuropsychol* 2003; 41: 1047–1057.
52. Jacobs DH, Shuren J, Bowers D, Heilman KM. Emotional facial imagery, perception and expression in Parkinson's disease. *Neurology* 1995; 45: 1696–1702.
53. Diederich NJ, Goetz CG, Stebbins GT. Repeated visual hallucinations in Parkinsons's disease as disturbed external/internal perceptions: Focussed review and a new integrative model. *Move Disord* 2005; 20: 130–140.
54. Hunt LA, Sadun AA, Bassi CJ. Review of the visual system in Parkinson's disease. *Optom Vis Sci* 1995; 92: 92–99.
55. Patil PN, Mauger TF. Cholinergic sensitivity of irides from donors with various pathological conditions and lens implants. Nauryn-Schmiedebergs *Arch Pharmacol* 1992; 346: 620–628.
56. Dowling JE, Ehinger B, Hedden WL. Interplexiform cell: New type of retinal neuron. *Invest Ophthalmol Vis Sci* 1976; 15, 916–926.
57. Frederick JM, Rayborn ME, Laties AM, Lam DMK, Hollyfield JG. Dopaminergic neurones in the human retina. *J Comp Neurol* 1982; 210: 65–79.
58. Masson G, Mestre D, Blin O. Dopaminergic modulation of visual sensitivity in man. *Fundam Clin Pharmacol* 1993; 7: 449–463.
59. Djamgoz MBA, Hankins MW, Hirano J, Archer SN. Neurobiology or retinal dopamine in relation to degenerative states of the tissue. *Vision Res* 1997; 37: 3509–3529.
60. Nguyen-Legros J, Harnois C, Di Paolo T, Simon A. The retinal dopamine system in Parkinson's disease. *Clin Vis Sci* 1993; 8, 1–12.
61. Eberling JL, Richardson BC, Reed BR, Wolfe N, Jagust WJ. Cortical glucose metabolism in Parkinson's disease without dementia. *Neurobiol Aging* 1994; 15: 329–335.
62. Basso MA, Pokorny JJ, Lui P. Activity of substantia nigra pars reticulata neurons during smooth pursuit eye movements in monkeys. *Eur J Neurosci* 2005; 22: 448–464.
63. Naylor RJ. The ocular effects of parkinsonism and its treatment. *Optom Pract* 2005, 6: 19–31.
64. Friedman Z, Neumann E. Benhexol-induced blindness in Parkinson's disease. *Br Med J* 1972; 1: 605.
65. Spiers ASD, Calne DB, Fayers PM. Miosis during L-dopa therapy. *Br Med J* 1970; 2: 639–640.
66. Peters S, Schweibold G, Przuntek H, Muller T. Loss of visual acuity under dopamine substitution therapy. *Neuro-ophthalmol* 2000; 24: 273–277.
67. Pearlman JT, Kadish AH, Ramseyer JC. Vision loss associated with amantadine hydrochloride use. *JAMA* 1977; 237: 1200.
68. Blekher T, Siemers E, Abel LA, Yee RD. Eye movements in Parkinson's disease: before and after pallidotomy. *Invest Ophthalmol Vis Sci* 2000; 41: 2177–2183.
69. Averbach-Heller L, Paulson GW, Davoff RB, Leigh RJ. Whipple's disease mimicking progressive supranuclear palsy, the diagnostic value of eye movement recording. *J Neurol Neurosurg Psychiatr* 1999; 66: 532–535.
70. Friedman DI, Jankovic J, McCrary JA. Neuro-ophthalmic findings in progressive supranuclear palsy. *J Clin Neuro-ophthalmol* 1992; 12: 104–109.

Corresponding author:
Dr Richard A Armstrong
Vision Sciences
Aston University
Birmingham B4 7ET
UNITED KINGDOM
E-mail: R.A.Armstrong@aston.ac.uk