

## **A comparison of visual problems in the Parkinsonian syndromes**

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## **Abstract**

Five disorders currently comprise the ‘Parkinsonian syndromes’, viz. Parkinson’s disease (PD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and corticobasal degeneration (CBD). Differential diagnosis of these disorders can be challenging but if ocular signs and symptoms are present they may aid clinical diagnosis. Visual problems in the Parkinsonism syndromes may involve visual acuity (VA), contrast sensitivity (CS), color vision, pupil reactivity, and eye movements; more complex aspects of vision such as reading ability, visuo-spatial orientation, the identification and naming of objects, and visual hallucinations. No single visual feature can definitively diagnose a specific Parkinsonism syndrome. Nevertheless, the presence of visual hallucinations and color vision problems may be more characteristic of DLB and PD than CBD or PSP and vertical supranuclear gaze palsy may be a significant feature of PSP. In addition, variation in saccadic eye movement (SEM) problems may help to distinguish PD and CBD from PSP. A multidisciplinary approach is often necessary to manage the visual problems of patients with a Parkinsonism syndrome.

**Key words:** Parkinsonian syndrome; Visual problems; Diagnosis; Saccadic eye movements (SEM); Visual hallucinations; Patient management

## List of abbreviations

AD	Alzheimer's disease
AON	Abnormal optokinetic nystagmus
CBD	Corticobasal degeneration
CS	Contrast sensitivity
DLB	Dementia with Lewy bodies
EEG	Electroencephalogram
ERG	Electroretinogram
EOG	Electrooculography
ERP	Event-related potential
FSW	Focal slow waves
GCI	Glial cytoplasmic inclusion
GFS	Global field synchronization
REM	Rapid eye movement sleep disorder
LB	Lewy body
MAP	Microtubule-associated protein
MSA	Multiple system atrophy
NFT	Neurofibrillary tangle
PD	Parkinson's disease
PERG	Pattern electroretinogram
PHF	Paired helical filament
PSP	Progressive supranuclear palsy
rCBF	Regional cerebral blood flow
QOL	Quality of life
SEM	Saccadic eye movements
SPM	Smooth pursuit movements
SN	Substantia nigra
VA	Visual acuity
VEP	Visual evoked potential
VOR	Vestibulo-ocular reflex

VSP      Vertical supranuclear gaze palsy

## **1. Introduction**

There are five disorders currently included within the ‘Parkinsonism syndromes’, viz., Parkinson’s disease (PD),<sup>1</sup> dementia with Lewy bodies (DLB),<sup>2</sup> progressive supranuclear palsy (PSP),<sup>3</sup> multiple system atrophy (MSA),<sup>4</sup> and corticobasal degeneration (CBD).<sup>5</sup> Patients with a Parkinsonism syndrome exhibit a variety of motor and, non-motor symptoms, the latter including loss of motivation, decreased activity, poverty of behavior, depression, sleep problems, cognitive impairment, dementia, and autonomic, gastrointestinal, and sensory dysfunction.<sup>1,6</sup> Sensory dysfunction can affect several modalities including visual, auditory and olfactory problems<sup>7</sup> and ‘restless legs’ syndrome.<sup>8</sup>

Although criteria have been developed for differential diagnosis within the Parkinsonism syndromes,<sup>9</sup> identification of individual disorders can be challenging.<sup>7</sup> Nevertheless, a variety of visual problems may be present including defects in eye movement, pupillary function, and in more complex visual tasks involving the ability to judge distance or the shape of an object. If visual problems are present, they may provide useful additional features to aid clinical diagnosis. In addition, management of the complex variety of visual problems will be necessary to maximize the vision of individual patients and improve their quality of life (QOL). Hence, this review describes: (1) the clinical and pathological features of each syndrome, (2) the visual problems associated with the different syndromes, (3) the usefulness of visual signs and symptoms in differential diagnosis, and (4) management and visual care of the patient.

## **2. Clinical and pathological features of the syndromes**

The various Parkinsonism syndromes together with the criteria currently used for their diagnosis are listed in Table 1.

**Table 1.** Clinical diagnostic criteria for the Parkinsonism syndromes (CDLB = Consortium on dementia with Lewy bodies, NINDS-SPSP = National Institute of Neurological Disorders and Stroke and the Society of progressive supranuclear palsy, NIH-ORD = National Institute of Health-Office of rare disorders, PD = Parkinson’s disease, UK = United Kingdom).

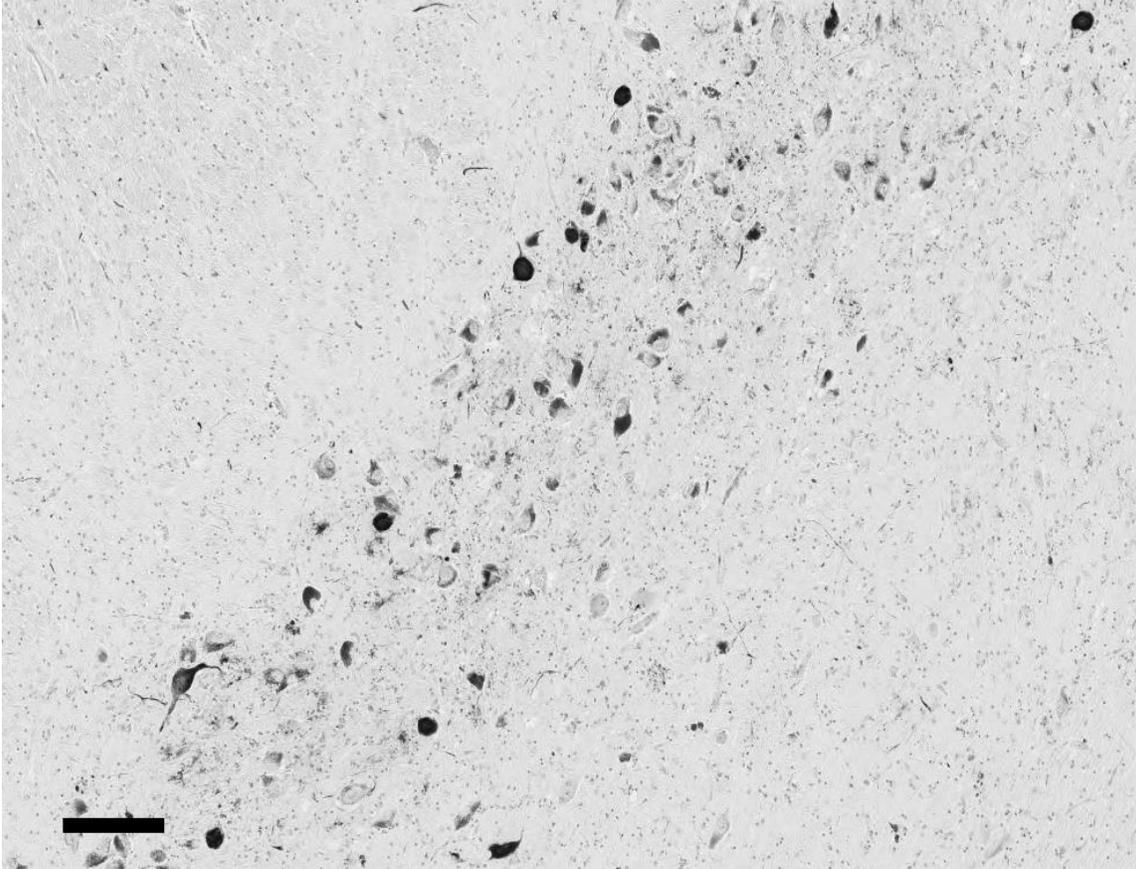
<u>Disorder</u>	<u>Diagnostic Criteria</u>	<u>Reference</u>
Parkinson’s disease	Modified UK PD Society Clinical Diagnostic Criteria	Hughes et al. <sup>10</sup>
Dementia with Lewy bodies	CDLB	McKeith et al. <sup>11</sup>
Progressive supranuclear palsy	NINDS-SPSP	Litvan et al. <sup>12,13</sup>
Multiple system atrophy	Minneapolis Consensus Criteria	Gilman et al. <sup>14</sup>
Corticobasal degeneration	NIH-ORD	Dickson et al. <sup>15</sup>

### *2.1 Parkinson’s disease (PD)*

PD is the most common of the Parkinsonism syndromes throughout the world with the possible exception of some oriental countries and in the black population.<sup>16</sup> The three cardinal signs of PD are akinesia, rigidity, and tremor.<sup>17</sup> Akinesia describes the characteristic slowness of movement, the initiation of a movement being especially affected. Rigidity describes the increase in muscle tone which results in stiffness of the limbs and is often manifest as ‘lead-pipe’ or ‘cog-wheel’ rigidity. Lead-pipe rigidity

refers to the general stiffness of a limb which changes little as the arm is moved whereas in cog-wheel rigidity, the arm 'catches' as it moves, as if it were controlled by a cog-wheel. The patient may also have a 'blank' facial expression with loss of emotional content. Moreover, increased flexion of muscles in the upper back may cause the spine to bend forward leading to a characteristic 'stooped' appearance. Tremor primarily affects the fingers, hands, and head, is most severe while the limb is at rest, and is often increased by anxiety but disappears during sleep. In addition, patients treated with *levodopa* (*L-dopa*) may exhibit 'dyskinesia' or 'dystonia'; in the former the patient may fidget, twitch, or be generally restless while the latter describes a spasm of one set of muscles deforming a limb into an abnormal posture.

Neuropathologically, the substantia nigra (SN) in the midbrain is particularly affected in PD, often being reduced in size as a result of the death of most of its pigmented neurons. Cells in the SN project to the striatum via the striatonigral pathway which uses dopamine as neurotransmitter. As a consequence, there is decreased connectivity between the SN, the globus pallidus, and the subthalamic nucleus.<sup>18</sup> This pathway has a general inhibitory influence on the striatum and the consequent increased activity of these regions may be responsible for the observed tremor and rigidity. In addition, surviving neurons of the SN frequently contain inclusions known as 'Lewy bodies' (LB) (Fig 1) which are found in the cytoplasm of the cell and may be derived from the breakdown products of cytoskeletal filaments. LB contain significant amounts of  $\alpha$ -synuclein,<sup>19</sup> a small pre-synaptic protein which ensures the normal functioning of dopamine transporter and tyrosine hydroxylase.<sup>20</sup> It normally exists in a relatively unfolded state and is highly soluble, but in PD, undergoes a conformational change to insoluble amyloid fibrils.



**Fig 1.** Neuropathology of the substantia nigra in a case of Parkinson's disease (PD) showing the presence of darkly stained Lewy bodies (LB) in many of the surviving neurons, ( $\alpha$ -synuclein immunohistochemistry, haematoxylin stain, magnification bar = 25  $\mu$ m)

## *2.2 Dementia with Lewy bodies (DLB)*

In DLB<sup>11,21</sup> a progressive mental impairment is characteristic, typical features including fluctuating cognition, visual hallucinations, and Parkinsonism.<sup>11</sup> A prominent and persistent memory impairment may not occur in the early stages, but is evident at some stage of the disease. Problems of attention and in visuo-spatial ability are common, the latter causing difficulties in drawing the shapes of common objects. The majority of patients with DLB exhibit at least two of the following features<sup>11</sup>: (1) fluctuating cognitive ability with variation in attention and alertness, (2) frequent visual

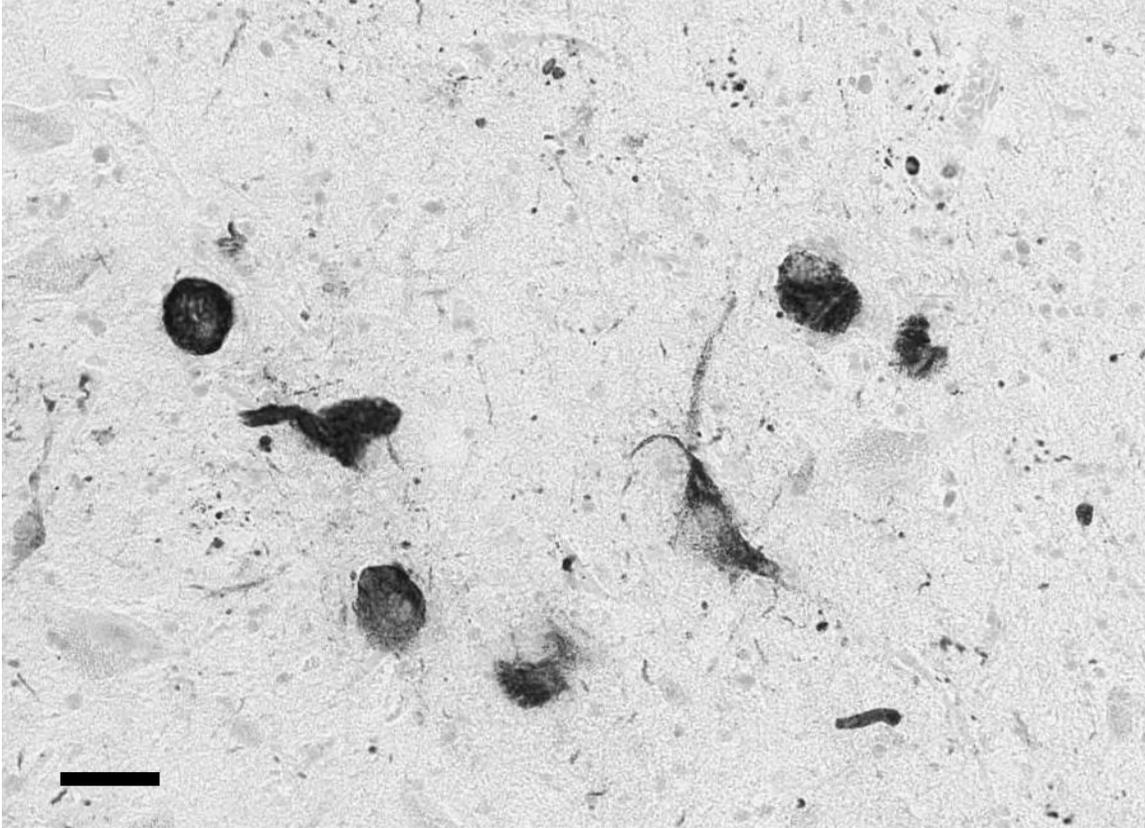
hallucinations, and (3) the motor features of PD.<sup>22</sup> Hence, typical PD features of DLB include shuffling gait, reduced arm-swinging while walking, blank expression, rigidity, ‘ratchet-like’ cogwheeling movements, low speech volume, and difficulties in swallowing. There may be two distinct clinical DLB syndromes: (1) DLB and dementia accompanied by Parkinsonism with prominent hallucinations and rapid eye movement (REM) sleep behavioral disorder, and (2) DLB with ‘Parkinsonism dementia syndrome’ in which the symptoms of parkinsonism and dementia predominate.<sup>23</sup>

Neuropathologically, brain atrophy in DLB resembles that of Alzheimer’s disease (AD)<sup>24</sup> but the size of the parietal, frontal, and temporal lobes is often intermediate between those of AD and control brain.<sup>25</sup> In the cerebral cortex, areas of temporal lobe such as the superior temporal gyrus and parahippocampal gyrus are affected together with the limbic system including the hippocampus and amygdala. Other cortical regions involved include the cingulate gyrus, insula, claustrum, superior frontal cortex, and occipital cortex. Within the basal ganglia, the putamen and caudate nucleus are affected but the globus pallidus appears to be relatively unimpaired.<sup>26,27</sup> The essential feature necessary for a neuropathological diagnosis of DLB is the presence of LB which have a different distribution in the brain in DLB compared with PD. Hence, in DLB, there are significant numbers of LB in the cerebral cortex whereas in PD, they are largely confined to the SN unless a significant dementia is present. LB are also frequent in the insula while fewer have been recorded in the frontal, parietal, and occipital regions.<sup>28</sup>

### *2.3 Progressive supranuclear palsy (PSP)*

PSP, first described in 1964, is significantly rarer than PD, and was originally referred to as ‘Steele-Richardson-Olszewski’ syndrome.<sup>29</sup> PSP is a complex disorder in which clinical progression can vary markedly among patients.<sup>30</sup> The most characteristic symptoms include gait and balance problems, the patient walking clumsily, and often falling backwards. There may also be changes in personality and loss of interest in the ordinary activities of life, the patient tiring easily, becoming forgetful, and often losing emotional control. With time, controlling the movement of the eyes and eyelids may

become difficult, speech may become slurred, and the patient may find it increasingly difficult to swallow solid food or liquid. A small number of patients develop dementia which is often associated with the spread of pathological changes to affect the cerebral cortex.<sup>31</sup>



**Fig 2.** Neuropathology of the oculomotor nucleus in a case of progressive supranuclear palsy (PSP) showing the presence of darkly stained neurofibrillary tangles (NFT) in many of the surviving neurons, Tau immunohistochemistry, haematoxylin stain, magnification bar =10  $\mu$ m)

Neuropathologically, the brain of a patient with PSP may show only minor abnormalities and is often normal in appearance. Nevertheless, brain weight may be reduced to some extent and the midbrain may appear shrunken and atrophic. When the midbrain is sectioned, the SN and red nuclei may appear discolored. The volume of the right head of the caudate nucleus may be lower in PSP<sup>32</sup> and there is often a marked atrophy of the globus pallidus.<sup>33</sup> In the cerebellum, the superior peduncles and the dentate nuclei may be

reduced in size and the nucleus discolored. Histologically, there is loss of neurons, proliferation of glial cells, the presence of inclusions in the cytoplasm of neurons termed neurofibrillary tangles (NFT) (Fig 2), the appearance of intracellular vacuoles, and loss of myelin, the globus pallidus, subthalamic nucleus, and SN being particularly affected.<sup>34</sup> The most significant molecular constituent of the NFT is the microtubule associated protein (MAP) tau which is involved in the assembly and stabilization of microtubules. In normal neurons, tau is soluble and binds reversibly to microtubules with a rapid turnover.<sup>35</sup> In disorders such as PSP, however, tau does not bind to the microtubules but collects as insoluble aggregates as paired helical filaments (PHF) which resist proteolysis and ultimately accumulate as NFT.

#### *2.4 Multiple system atrophy (MSA)*

MSA is derived from three previously described syndromes: (1) olivo-pontocerebellar atrophy, (2) striato-nigral degeneration, and (3) Shy-Drager syndrome.<sup>36</sup> A variety of signs and symptoms are present including autonomic failure, Parkinsonism, cerebellar ataxia, and pyramidal signs such as paralysis, muscle weakness, loss of muscle control, and tremor. The most consistent clinical syndrome, however, is Parkinsonism, followed by autonomic dysfunction, cerebellar ataxia, and pyramidal tract signs.<sup>37</sup> Urinary dysfunction is the most common autonomic symptom and an earlier manifestation of the disease than postural low blood pressure. Patients with either cerebellar signs or Parkinsonism may be distinct subtypes of the disease, viz. MSA-C and MSA-P respectively. MSA-C patients have marginally increased survival times but the prognosis is poor for the majority. In addition, patients with MSA-P may have abnormal movements of the hands and fingers referred to as a 'jerky' tremor or myoclonus, no abnormal movements being present at rest but when holding a posture, small amplitude, non-rhythmic movements of one or a few fingers may occur. There is a moderate intellectual impairment in some patients but overt dementia is relatively rare.<sup>37</sup>

Neuropathologically, the cerebral cortex in MSA is smaller than in controls, the degree of atrophy reflecting disease duration rather than the age of the patient.<sup>38</sup> In addition, there

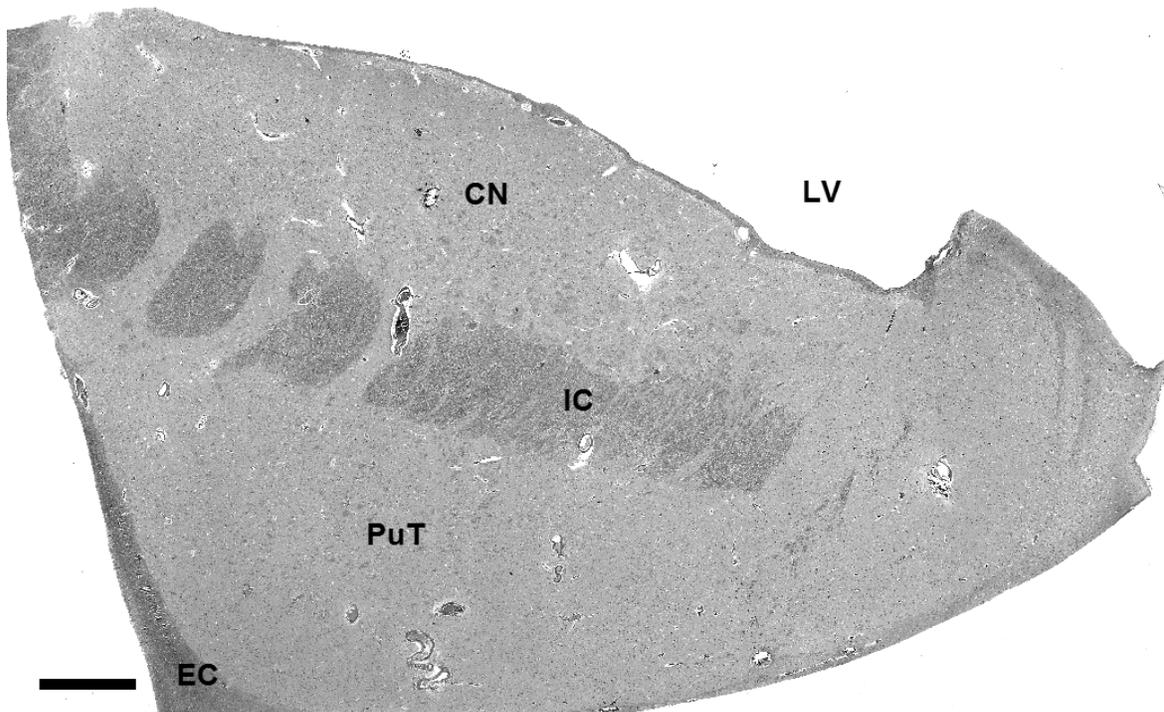
may be a progressive cerebral atrophy affecting the frontal lobes<sup>39</sup> and the motor/premotor areas. In the cerebellum, a more severe pathology affects the vermis than the hemispheres.<sup>40</sup> Within the basal ganglia, the SN is often pale due to loss of pigment and there may be atrophy and discoloration of the striatum, specifically affecting the putamen. Histologically, MSA is characterized by neuronal loss, gliosis, and myelin pathology in the putamen, caudate nucleus, external pallidum, substantia nigra, locus caeruleus, inferior olive, pontine nuclei, Purkinje cells of the cerebellum, and the intermediate cell columns of the spinal cord.<sup>37,41</sup> The most characteristic pathological change is the presence of glial cytoplasmic inclusions (GCI) in oligodendrocytes, a pathology first described in 1989.<sup>42</sup> This change often affects the SN, striatum, inferior olivary nucleus, pontine nuclei, and cerebellum.<sup>42</sup> Inclusions have also been observed in the nuclei, cytoplasm, and cell processes of neurons in MSA.<sup>43</sup>

### *2.5 Corticobasal degeneration (CBD)*

CBD is a rare, progressive disorder with a disease onset usually after 60 years of age, death following within approximately eight years. Clinical diagnosis can be complex as symptoms may resemble other types of neurodegenerative disorder. The most characteristic clinical features are limb dysfunction<sup>44,45</sup>, parkinsonism,<sup>46</sup> apraxia,<sup>45</sup> and dementia.<sup>46</sup> Onset of symptoms can be sudden,<sup>47</sup> patients exhibiting problems related to cortical processing and motor dysfunction, the most common initial symptom being limb clumsiness affecting one side of the body with or without accompanying rigidity or tremor.<sup>44,48</sup> Subsequently, the disease may progress to affect gait and there is a slow progression to affect the ipsilateral arms and legs.<sup>44</sup> Apraxia and cortical dementia are the most common cortical signs.<sup>48</sup>

Neuropathologically, CBD is characterized by a progressive and often asymmetric cortical atrophy which affects the anterior cerebral cortex,<sup>49</sup> the fronto-parietal region,<sup>50</sup> and the superior temporal cortex.<sup>50</sup> Atrophy of the basal ganglia, including the caudate nucleus<sup>51</sup> and SN is common<sup>52</sup> accompanied by a mild to moderate gliosis and neuronal loss in the putamen, globus pallidus and subthalamic nucleus.<sup>53</sup> The typical gross features

of the brain include enlarged lateral ventricles and atrophy of the head of the caudate nucleus, while the internal capsule, insula, putamen, and globus pallidus are more normal (Fig 3). Histologically, there is a widespread neuronal and glial pathology including abnormally enlarged neurons,<sup>54</sup> neuropil threads<sup>55</sup> NFT,<sup>50</sup> and glial pathology. The glial pathology includes oligodendroglial inclusions<sup>56</sup> and astrocytic plaques which largely affect the caudate nucleus.<sup>57</sup> In the cortex, these lesions are particularly severe in the posterior frontal area anterior to the precentral gyrus but are less severe in the primary motor area.<sup>49</sup>



**Fig 3.** Coronal section of the striatum of the brain from a pathologically confirmed case of corticobasal degeneration (CBD). The figure shows enlarged lateral ventricles (LV), atrophy of the head of the caudate nucleus (CN), but more normal internal capsule (IC), external capsule (EC), claustrum (Cl), and putamen (PuT) (bar = 4 mm).

### **3. Visual problems in the Parkinsonism syndromes**

For the purpose of this discussion, aspects of visual function in the Parkinsonism syndromes have been divided into various categories based largely on those used to characterize vision in the dementias<sup>58</sup> and are summarized in Table 2. Although these aspects of vision are discussed individually, many patients exhibit multiple visual defects. In addition, a number of factors need to be taken into account in interpreting these observations. First, some aspects of visual function have been little studied making a comparison problematical. Second, most studies rely on a clinical diagnosis of a syndrome and therefore, on the criteria used and should be viewed with caution if the most rigorous consensus criteria have not been applied. Third, visual testing may be carried out using a variety of different objective and subjective methods and the effectiveness of some of these methods in testing participants, especially if dementia is present, should be taken into account. Fourth, participants may have been visually assessed without having had an eye examination, and thus, without knowing if the optimal refraction has been used or if an ocular pathology was present.<sup>58</sup>

#### *4.1 Visual acuity (VA)*

Patients with a Parkinsonism syndrome frequently exhibit poor vision, especially in PD as the disease progresses and if dementia is present.<sup>59,60</sup> Poor VA is particularly evident if low contrast stimuli are used.<sup>61,62</sup> In addition, poor VA may be associated with the development of chronic hallucinations which are especially frequent in PD and DLB.<sup>63</sup> Primary aspects of vision have been less well studied in the other Parkinsonism syndromes but defects in VA are likely to occur in DLB and PSP.<sup>59</sup> In CBD, in which difficulties involving visuospatial tasks or in reading ability have been reported, the patients denied that they had a significant visual loss.<sup>64</sup>

**Table 2.** Comparison of visual problems among Parkinsonism syndromes.

<u>Feature</u>	<u>Syndrome</u>				
	<u>PD</u>	<u>DLB</u>	<u>PSP</u>	<u>MSA</u>	<u>CBD</u>
Visual acuity	++	+	+	?	?
Color vision	+	+	-	+	-
Stereopsis	+	?	?	?	?
Contrast sensitivity	+	?	+	-	?
Visual fields	+ <sup>g,s</sup>	+	?	?	++
Eyelid mobility	?	?	+	?	+
Pupil response to mydriatics	+	+	+	?	?
Abnormal pupils	?	?	+	+	?
Blink frequency	+	?	?	?	?
Blink reflex	+	+	?	+	+
Blepharospasm	?	?	++	++	+
Fixation	-	?	+	+	+
SEM	+	+ <sup>c</sup>	+	+	+
SPM	+	?	+	+	+
VSP	-	?	++	-	-
Nystagmus	?	?	+	?	+
VOR	-	?	+	+	-
EEG	+ <sup>θ</sup>	?	+ <sup>δ</sup>	?	+ <sup>δ,fs</sup>
ERG	+ <sup>f</sup>	+ <sup>f</sup>	+	-	?
VEP	+	?	-	V	?
ERP	?	+	+	+ <sup>ch</sup>	+
Discrimination	?	++	?	?	?
Visuo-spatial function	+	+	?	?	++
Speech, Language	+	?	+	+	?
Visual hallucinations	++	++	-	?	-



#### 4.4 Contrast sensitivity (CS)

Contrast sensitivity (CS) is a measure of visual performance across a wide range of spatial frequencies and contrasts. In PD, for example, CS is affected in some patients,<sup>73,74</sup> performance at high or intermediate frequencies being the most reduced thus providing one possible explanation for their poor vision. A substantial decrease in CS may also occur with disease progression. Abnormalities of CS in PD may be related to dopamine dysfunction in the retina but are also orientation specific which suggests cortical involvement.<sup>75</sup> Furthermore, treatment with *L-dopa* may improve CS performance in PD close to that of controls.<sup>76</sup> There have been few psychophysical studies carried out on other types of Parkinsonism but patients with PSP have been shown to exhibit impaired CS, an effect that may be less apparent in MSA.<sup>77</sup>

#### 4.5 Visual fields

Relatively few detailed studies of visual fields have been carried out to date in any Parkinsonism syndrome.<sup>78</sup> Nevertheless, there may be an increased frequency of visual field defects in PD if glaucoma is present.<sup>79</sup> Visual fields have also been investigated in PD patients undergoing posterior pallidotomy, a surgical procedure which may damage the optic tract.<sup>80</sup> Forty such patients were studied, three having visual field defects which could have been attributable to the surgery, viz., contralateral superior quadrantanopia, associated in two patients with small paracentral scotomas. In DLB, a 66 year-old patient developed a left homonymous hemianopia early in the disease and had large numbers of LB in the visual cortex.<sup>81</sup> In addition, studies of regional cerebral blood flow (rCBF) in DLB indicated hypoperfusion in occipital cortical areas which could result in visual field loss.<sup>82</sup> The highly lateralized pathology often present in CBD suggests that a hemianopia may be more common in this disorder than in other syndromes. A rare case of MSA has also been reported with enlarged blind spots but with no central scotoma.<sup>83</sup>

#### 4.6 Eyelids

A disorder of eyelid mobility has been observed in approximately a third of PSP patients<sup>84</sup> with both spontaneous and voluntary eye movements affected.<sup>85</sup> Since ocular and eyelid movements are highly coordinated mainly in the vertical plane, vertical supranuclear gaze palsy (VSP) is often regarded as a cardinal feature of PSP.<sup>84</sup> Eyelid reflexes are generally preserved with the exception of the ‘acoustic startle reflex’, which is a response to a sudden and unexpected sound involving a brief closing of the eye. Eyelid problems in PSP can also seriously impair vision as a result of difficulties in opening the eyes after voluntary closure (‘apraxia of eye opening’). This problem is likely to be attributable to a loss of the reciprocal relationship between the levator palpebrae and the pretarsal portion of the orbicularis oculi muscles both of which contract together rather than exhibiting a normal opponent action.<sup>86</sup> Apraxia of eyelid opening has also been observed in CBD.<sup>86</sup>

#### *4.7 Blinking and the blink reflex*

Patients with PD exhibit a reduced frequency of blinking leading to a staring appearance.<sup>87</sup> Reduced blink rates can cause an abnormal tear film, dry eye, and reduced vision. In addition, blink duration may be increased in PD reflecting the loss of dopamine neurons.<sup>88</sup>

The blink reflex is elicited by a light tap on the glabella, successive taps in normal individuals producing less and less response as the reflex habituates. In PD, for example, the blink reflex may not disappear on repeated tapping. The blink reflex to electrical stimulation of the supraorbital nerve has been studied in the Parkinsonism syndromes including patients with DLB.<sup>89</sup> The reflex was significantly delayed in DLB compared with controls and the other syndromes, with a bilateral delay in the latency of the R2 response. In a proportion of DLB, patients, the latency delay was greater than two standard deviations of the control mean. There was also a significant correlation between the delay in the R2 response and the degree of cognitive fluctuation of the patient. In addition, the blink reflex was studied in DLB patients treated with cholinesterase inhibitors.<sup>90</sup> Treatment with *donepezil* was not associated with a change in cognitive or

motor performance but after two weeks of treatment, the latency of the R2 response was significantly decreased. In a 65-year-old female patient with MSA, blink reflexes were poor with an impaired R2 response and enhanced recovery cycle which could be attributable to increased excitability of brain stem interneurons.<sup>91</sup> In a single case diagnosed as severe CBD, the blink reflex was completely absent.<sup>92</sup>

‘Blepharospasm’, an abnormal contraction or twitch of an eyelid, is a common symptom and when observed early in untreated patients with Parkinsonism should raise a suspicion of the presence of MSA, PSP, or CBD.<sup>93</sup> In addition, blepharospasm may be more prevalent in PSP and MSA than in the other Parkinsonism syndromes.<sup>94,95</sup>

#### *4.8 Pupillary function*

Abnormal pupillary responses have been reported to the mydriatic muscarinic receptor antagonist tropicamide in a variety of disorders but remain controversial. The earliest reports suggest some patients with AD, for example, displayed a specific response to a low dose (0.01%) of tropicamide, pupils dilating by approximately 13% or more compared with controls.<sup>96</sup> Later studies, however, suggested there were no difference in the pupillary responses of AD patients when compared with several other disorders including PD.<sup>97</sup> In PSP, studies suggest that the results of the tropicamide test may also be similar to those observed in patients with AD.<sup>98</sup> Enhanced pupillary responses have also been reported using dilute solutions of phenylephrine (a sympathetic agonist) and pilocarpine (a cholinergic agonist).<sup>99</sup> Hence, response to a 0.065% solution of pilocarpine was studied in DLB, pupil responses being significantly greater in DLB than in AD.

Some authors report decreased pupil diameters in the dark in PSP compared with controls.<sup>100</sup> In MSA, about a quarter of patients tested had abnormal pupils and in the majority, the defects were bilateral and symmetrical. Pupil defects were not usually apparent to the patients themselves or to their physicians. In addition, in normal subjects, pupil size often increases in response to stress but no such change is apparent in MSA.<sup>101</sup>

‘Horner’s syndrome’ (abnormally small pupil diameter) has rarely been observed, although such a change has been reported in one case of MSA.<sup>102</sup>

#### *4.9 Fixation*

Normally the eyes will turn inwards when fixating a near target (‘convergence’). Abnormal ocular fixation, however, has been shown in a study of seven out of eight patients with PSP,<sup>103</sup> individuals demonstrating a ‘fixation instability’ accompanied by small side to side movements of the head (‘square wave jerks’).<sup>104</sup> This type of response is relatively rare in PD.<sup>103</sup> In addition, patients with PSP exhibit ‘heterophoria’, i.e., a tendency for the eyes not to line up properly when one eye is covered.<sup>105</sup> As a result, patients often exhibit difficulties in making eye contact and develop a ‘staring appearance’ similar to that in PD. Abnormal ocular fixation may also occur in a significant proportion of MSA patients.<sup>36</sup> Convergence problems can be associated with a relatively large exophoria (deviation of an eye outwards), and the result is often diplopia.<sup>106</sup>

#### *4.10 Eye movement*

Abnormal saccadic (SEM) and smooth pursuit eye movements (SPM), usually studied by clinical examination in combination with electrooculography (EOG), have been reported in about 75% of patients with PD.<sup>107</sup> Both reaction time and the maximum saccadic velocity of horizontal gaze are slower in PD,<sup>107</sup> but the response of PD and controls frequently overlap.<sup>108</sup> In addition, SEM may exhibit hypometria (‘under reaching of task’)<sup>109</sup> while SPM may be interrupted by small saccades.<sup>106</sup> The amplitude of SEM is often increased in normal subjects when there is a change from externally cued saccades to self-paced saccades and this effect may be enhanced in PD.<sup>110</sup> In addition, patients with PD often have difficulty in sustaining repetitive actions and hence, SPM may exhibit reduced amplitudes and a progressive decline as the stimulus is repeated.<sup>111</sup> Abnormal optokinetic nystagmus (AON)<sup>107</sup> and problems in convergence<sup>112</sup> have also been reported

in PD. Further abnormalities include 'jerkiness', 'cogwheeling', and limitation of eye movement. Vertical eye movements are often more impaired than horizontal movements.

A comparison of SEM in DLB and in PD with dementia suggests that DLB patients were impaired in both reflexive and saccadic execution and in the performance of more complex SEM tasks.<sup>113</sup> In addition, problems in convergence were often followed by akinesia and rigidity.<sup>114</sup> Some cases of DLB can also present with a vertical and horizontal gaze palsy and these could be easily confused with PSP<sup>115</sup> and caution is therefore necessary in distinguishing the two disorders.<sup>116</sup>

VSP is often regarded as a 'cardinal' sign of PSP.<sup>84,117</sup> As the disease progresses, however, upgaze may also be affected and eventually, a complete gaze palsy may occur resulting in diplopia.<sup>118</sup> In addition, PSP patients exhibit slow SEM,<sup>117</sup> a significantly decreased ability to carry out vertical saccades, and an early slowing of horizontal saccades.<sup>119</sup> A reduction in the generation of motor commands by midbrain 'burst' neurons may be the most likely explanation for slower saccades in PSP.<sup>120</sup> As a consequence, additional SEM are often necessary for PSP patients to achieve fixation especially in the vertical plane.<sup>121</sup> SPM may also be affected in PSP,<sup>117</sup> the median gain of the movements being less than in controls<sup>122</sup> and small corrective saccades may be necessary for the eyes to fixate their target. SPM involve several brain areas including the parietal and occipital cortices, the frontal eye-fields, the cerebellum, as well as nuclei in the basal area of the pons.<sup>123</sup> AON has also been reported in PSP, vertical responses including an impaired slow phase response while the rapid phase is combined with the appearance of square-wave jerks.<sup>124</sup>

In a patient with MSA, in which a combination of olivopontocerebellar atrophy and striato-nigral degeneration was present, the typical eye movement impairments characteristic of PD were observed, in combination with AON in the vertical plane.<sup>125</sup> SEM and SPM in the vertical direction, however, were only slightly affected. In a study of oculomotor function in thirty MSA patients, excessive square-wave jerks, a mild supranuclear gaze palsy, a gaze-evoked nystagmus, a positioning down-beat nystagmus,

mild-moderate saccadic hypometria, impaired SPM, and reduced vestibulo-ocular reflex (VOR) suppression were all present in a significant number of the patients.<sup>126</sup>

In CBD, an increase in saccadic latency may be a characteristic feature.<sup>119,127,128</sup> Hence, in a study of 36 well-characterized CBD patients, SPM were commonly affected, a significant number of patients presenting with ‘jerky’ movements, and in a small number of these patients, the range of movement was also restricted.<sup>44</sup> Decreased gain of SPM has also been observed in CBD<sup>129</sup> as well as square-wave jerks<sup>44,130</sup> while AON may also be common.<sup>64</sup>

#### *4.11 Vestibulo-ocular reflex (VOR)*

The vestibulo-ocular reflex (VOR) is a reflex eye movement that stabilizes images on the retina during movements of the head. The ‘gain’ of the VOR is the ratio of the change in eye angle to head angle during a head turn. If the gain is impaired (ratio not equal to unity), head movements result in image motion on the retina and blurred vision. The gain of the VOR in the dark may be cancelled by fixation. Both MSA and PSP patients show this cancellation compared with control cases and PD,<sup>77</sup> a response which could be related to cerebellar dysfunction. In CBD, in which there is a less significant cerebellar pathology, there is little evidence for an effect on VOR.

#### *4.12 Electroencephalogram (EEG)*

Electroencephalography (EEG) has been performed in response to eye opening and to 12-Hz photic stimulation in PD using global field synchronization (GFS), which assesses the degree of correlation between waves of different frequency.<sup>131</sup> However, closing the eyes resulted in an increase in theta-GFS while using 12-Hz intermittent photic stimulation, reactivity of posterior electrodes was decreased indicating a general disruption of posterior brain activity.<sup>131</sup> In addition, a slowing of general background activity and the appearance of focal slow waves (FSW) has been reported in CBD.<sup>132</sup> Intermittent delta

activity has also been recorded in both CBD and PSP, but FSW may be characteristic only of CBD.<sup>132</sup>

#### *4.13 Electroretinogram (ERG)*

ERG using a flash stimulus has been studied in PD and DLB compared with controls,<sup>133</sup> abnormalities being recorded in both disorders and attributed to pathology affecting photoreceptor cells and the inner plexiform layer. In PSP, the amplitude of the ERG may be reduced<sup>134</sup> as well as that of the electromyogram (EMG) recorded from the orbicularis oculi muscle. The pattern reversal ERG (PERG) to a colored stimulus was recorded in both PD and MSA.<sup>135</sup> Although reduced amplitude and increased latency of evoked components were observed in PD, especially when a blue-yellow horizontal grating was used as a stimulus, no significant effects were present in MSA.<sup>135</sup>

#### *4.14 Visual evoked potentials (VEP)*

Longer latencies of VEP components have been observed in PD, the extent of the delay being correlated with the severity of motor symptoms.<sup>136</sup> Latencies are often longer when colored stimuli are used especially with a blue-yellow grating.<sup>135</sup> Early signal components of the VEP, such as the P100, are usually not affected in PSP.<sup>137</sup> In MSA, VEP responses are more variable with significantly less impairment to a full-field flash stimulus than in PD or PSP.<sup>134</sup> Moreover, using a horizontal sinusoidal grating, no effects on the VEP in MSA were reported although such effects were recorded in PD.<sup>138</sup>

#### *4.15 Event-related potentials (ERP)*

Event-related potentials (ERP) elicit the 'P3' (P300) evoked response which reflects orientation, attention, stimulus evaluation, and memory. Mean latency of the visual P200 and P300 ERP responses are greater in DLB than in controls suggesting that visual cognitive function may be selectively impaired. The latency and amplitude of the P300 signal, however, are also affected in PSP.<sup>138-142</sup> In MSA, the visual P300 component can

be successfully recorded even when a severe motor disability was present.<sup>141</sup> Reaction times to rare target stimuli were also significantly decreased in both PD and MSA compared with PSP.<sup>142</sup> In addition, ERP has been studied in MSA-C and MSA-P, no significant differences being observed between subtypes in the latency of the N1 or N2 components suggesting early stages of visual processing were preserved.<sup>143</sup> Nevertheless, the P3a peak was less easy to identify and there were some reductions in amplitude of this response in both MSA subtypes. By contrast, the P3b component appeared to be affected only in the MSA-C subtype and exhibited both increased latency and reduced amplitude. In a further study of selective attention to color in MSA,<sup>144</sup> the N2 component was significantly delayed suggesting that the color discrimination process may be impaired during selective attention in MSA. In CBD, the latency of the visual P300 was increased and mean reaction times were greater in both CBD and in PSP compared with PD, the degree of the response being correlated with the extent of motor disability.<sup>142</sup>

#### *4.16 Complex visual functions*

More complex visual problems are frequent in the Parkinsonism syndromes and may involve reading ability, visuo-spatial function, and in the identification and naming of objects. In DLB, for example, impairments have been identified in object size discrimination, form discrimination, overlapping figure identification, in drawing common objects, and in tasks involving visual counting.<sup>145</sup> By comparison, performance on line orientation, color integration, and rotated object comparison tasks appeared less affected.<sup>146</sup> A significant defect in the ‘trail-making task’, a test of visual attention in which the subject is asked to ‘connect the dots’ on paper or computer screen, has also been reported in DLB.<sup>147</sup>

Deficits in visuo-spatial function including difficulty in judging verticals and the position of body parts, and in carrying out a route-walking task have been reported in both PD and DLB.<sup>148,149</sup> Hence, inability to copy the shape of a pentagon may be more evident in DLB than in AD suggesting a greater visuospatial deficit.<sup>150</sup> Moreover, PD and DLB patients may have a problem in memory tasks which involve spatial orientation, PD patients in

particular exhibiting an impairment of orientation and motion discrimination.<sup>151</sup> Problems involving the perception and imagining of faces has also been reported in PD,<sup>152</sup> most frequently in untreated patients.<sup>153</sup> Moreover, controls often contract their facial muscles while imaging faces, a process which can be impaired in PD, and which may be related to pathological changes affecting the basal ganglia.<sup>154</sup>

Patients with a Parkinsonism syndrome often exhibit problems with speech, language, and reading especially in PD, PSP, and MSA,<sup>155,156</sup> similar reductions in reading speed being present in all three syndromes. In addition, PSP patients may exhibit dysarthria, reading difficulties, and problems with handwriting.<sup>155</sup> Some PSP patients also exhibit visual dyslexia, constructional dysgraphia, and an increased rate of self-correction. Visual misperception was a major cause of problems in naming objects in these patients.

In a case of ‘atypical CBD’, a patient exhibited a decline in spatial orientation and visual function which included fixation, optic ataxia, agraphia, acalculia, ideomotor apraxia, but color matching ability was preserved.<sup>157</sup> CBD patients may also exhibit difficulties in locating objects within visual space,<sup>64</sup> visuo-spatial problems in CBD appearing to be more severe when spatial rather than object-based tasks are involved.<sup>158</sup> These problems could be related to pathology affecting the frontal region of the brain<sup>159</sup> and the visual association areas in CBD.<sup>160</sup>

#### *4.17 Visual hallucinations*

Visual hallucinations are commonly reported in the Parkinsonism syndromes, especially in those individuals with impaired VA or who have more severe cognitive impairments.<sup>161</sup> Nevertheless, hallucinations are generally more common in DLB and PD<sup>162</sup> than in PSP or CBD.<sup>163</sup> Visual hallucinations in DLB are frequently recurrent, well-formed and detailed.<sup>164</sup> They most typically involve people or animals invading the patient’s home, but may also include inanimate objects, such as the appearance of writing on walls or ceilings. The hallucinations do not appear to trouble the majority of patients but can evoke considerable fear in some.<sup>164</sup> Visual hallucinations also occur as a

complication in about 30 - 60% of PD patients treated with L-dopa and dopamine agonists.<sup>165</sup> These hallucinations may be particularly complex with flickering lights and illusionary misconceptions followed by colorful images. Poor VA and reduced activity of the primary visual cortex (area V1) may be risk factors the development of visual hallucinations.

#### *4.18 REM sleep behavioral disorder*

Various disorders involving sleep, including excessive daytime sleeping, have been reported in the Parkinsonism syndromes.<sup>166</sup> However, REM sleep behavior disorder appears to be the most characteristic symptom having been observed in many of the disorders and characterized by abnormal behavior during sleep accompanied by REM.<sup>167</sup> So common is REM in Parkinsonism that it is often regarded as a strong indicator of the presence of such a syndrome. Nevertheless, REM sleep behavior disorder appears to be rarer in CBD, recent estimates suggesting an incidence of only 5%, and its absence could be a useful additional diagnostic feature.<sup>168</sup>

### **5. Discussion and conclusions**

#### *5.1 Visual features of the Parkinsonism syndromes*

Visual problems in the Parkinsonism syndromes can be highly variable with some patients being visually asymptomatic whereas others exhibit one or more visual problems. Visual dysfunction may involve a variety of ocular structures and affect many functions including VA, CS, color discrimination, pupil reactivity, eye movements, visual field defects, and visual processing speeds. In addition, disturbance of visuo-spatial orientation, facial recognition problems, REM sleep behavior disorder, and chronic visual hallucinations may occur. Some of these visual features may be characteristic of the early stages of a Parkinsonism syndrome including problems in pupil reactivity<sup>169</sup> SPM,<sup>170</sup> visuo-motor adaptation,<sup>171</sup> and sleep behavior disorder. The presence of any of these features in undiagnosed individuals may raise a concern of a possible Parkinsonism

syndrome, and since early diagnosis may enable intervention and possible neuroprotection,<sup>172</sup> further visual studies of early-stage symptoms in the Parkinsonism syndromes are indicated.

### *5.2 Differential diagnosis of Parkinsonism syndromes*

Some of the visual features described in the Parkinsonism syndromes have been little investigated, e.g. stereopsis and CS whereas others may occur in all disorders and have little diagnostic value, e.g., VA and some aspects of eye movement. In addition, there are few visual features that will affect all patients with a specific syndrome. Nevertheless, there are some visual features which in combination with other signs and symptoms may be useful in a differential diagnosis (Table 3). Two features in particular may enable an initial separation of the Parkinsonism syndromes into two groups. First, the presence of visual hallucinations may indicate an underlying  $\alpha$ -synuclein-type pathology in some disorders, i.e., supporting a diagnosis of PD or DLB rather than PSP or CBD.<sup>173</sup> However, MSA which is also has  $\alpha$ -synuclein pathology may be an exception to this rule. Second, color vision problems may be more characteristic of the  $\alpha$ -synuclein than the tau-based disorders.<sup>69</sup>

In addition, there may be combinations of visual features which may be helpful in separating specific pairs of disorders. Hence, distinguishing PD and PSP can be especially difficult especially early in the disease. 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.<sup>174</sup> Especially useful in separating PSP from other disorders is the presence in the former of vertical supranuclear gaze palsy, fixation instability, lid retraction, blepharospasm, and apraxia of eyelid opening and closing.<sup>104</sup> Vertical supranuclear palsy is probably the single most useful diagnostic clinical sign of PSP<sup>84</sup>]although such signs do occur more rarely in other disorders.<sup>115,116</sup>

**Table 3.** Potentially useful visual motor and non-motor features that may help in distinguishing the Parkinsonism syndromes.

<u>Visual features</u>		
<u>Disorder</u>	<u>Motor</u>	<u>Non-motor</u>
PD	Slower reaction time and velocity of saccades, hypometria, SPM affected early	Color vision deficits, visual hallucinations, PERG affected
DLB	Impaired performance of more complex eye movement tasks	Color vision deficits, visual hallucinations
PSP	Vertical supranuclear gaze palsy, fixation instability, lid retraction, blepharospasm, apraxia of eyelid opening and closing	Contrast perception affected, P300 ERP affected
MSA	Abnormal fixation, square wave jerks, mild supranuclear gaze palsy, gaze evoked nystagmus, saccadic hypometria, down-beat nystagmus, impaired SPM, reduced VOR suppression	Color vision deficits less frequent, PERG less affected
CBD	Increase in saccadic latency. 'jerky' SPM, square-wave jerks, optokinetic nystagmus	Visual field defects likely, visuo-spatial problems, P300 ERP

affected, REM sleep  
less affected

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Abbreviations: *Disorders*: PD = Parkinson's disease without dementia, DLB = Dementia with Lewy bodies, PSP = Progressive supranuclear palsy, CBD = Corticobasal degeneration; MSA = Multiple system atrophy, *Visual features*: ERP = Event-related potential, SPM = smooth pursuit eye movements, PERG = Color electroretinogram, REM = Rapid eye movement, VOR = Vestibulo-ocular reflex

Separating PD from DLB can be difficult especially if dementia is present. Nevertheless, the distinction is important because patients with visual hallucinations may be treated with antipsychotic drugs, a hazardous treatment in DLB.<sup>175</sup> DLB and PD generally exhibit similarities on SEM tasks. Nevertheless, a newly developed portable saccadometer, has been used to compare Parkinsonism syndromes<sup>176</sup> and suggests that a combination of saccadic parameters may enable PD and DLB to be separated. In addition, deficits in orientation, 'trail-making', and reading the names of colors ('Stroop test') may indicate DLB rather than PD.<sup>147</sup>

A number of visual symptoms may be suggestive of MSA including excessive square-wave jerks, mild to moderate hypometria of saccades, impaired VOR, and the presence of nystagmus.<sup>126</sup> Visual hallucinations, unrelated to medication, are also rare in MSA compared with PD.<sup>177</sup> Moreover, the color VEP is affected in PD but not in MSA.<sup>135</sup> An additional feature which may be useful in separating PD and MSA is an ability to fixate an object, which is abnormal in a significant proportion of patients with MSA but less so in PD.<sup>103</sup> In addition, eye movements recorded during sinusoidal tracking by EOG show that in MSA, saccades may correct for position errors ('catch-up saccades') while in PD, saccades are directed towards future target positions ('anticipatory saccades').<sup>178</sup>

CBD is a particularly complex disorder and distinguishing it from other Parkinsonism syndromes can be challenging.<sup>45,48</sup> Nevertheless, a combination of increased latency of SEM,<sup>119,127,128</sup> impaired SPM,<sup>44</sup> and visuo-spatial problems especially involving object-

based tasks<sup>145</sup> may be more typical of CBD while vertical gaze palsy, visual hallucinations, sleep disturbance, and an impaired ERG are relatively rare.

### *5.3 Visual Management of the patient*

Visual symptoms in the Parkinsonism syndromes when present are important in influencing overall motor function and can be markedly debilitating when a combination of visual deficits are present.<sup>64</sup> Hence, identifying and correcting visual problems as far as possible can reduce the chances that a patient may have a serious fall and can be important in improving QOL. A multidisciplinary approach is often necessary to manage the problems of the patient including pharmacological intervention and rehabilitation.<sup>179</sup>

Collaboration between the patient, eye-care practitioners, and various health care providers is important in identifying and managing specific visual problems. First, a decline in VA is fairly typical of the Parkinsonism syndromes in general. Appropriate refractive correction can improve overall motor performance and associated procedures such as cataract surgery may help to maximize vision. Second, visual fields should be tested as the pathology may be lateralized resulting in a hemianopia, especially in CBD or in PD if there is associated glaucoma.<sup>180,181</sup> Third, the external eye should be examined as blepharospasm and/or dry eye may be present and are essentially treatable visual features.<sup>86,93,95</sup> Artificial tears can be used to help dry eyes while blepharospasm has been treated successfully with botulinum toxin A injected at the junction of the preseptal and pretarsal parts of the levator palpebrae and orbicularis oculi muscles.<sup>86</sup> Fourth, patients with difficulties in opening their eyelids can have ‘lid crutches’ fitted to spectacle frames that can hold the lids open. Fifth, patients may have deficits in gaze control which may influence ‘stepping behavior’ thus increasing the risk of trips or falls.<sup>182</sup> In addition, impaired postural control is common and a significant contributor to falls.<sup>183</sup> Balance training combined with eye movement and visual awareness exercises may improve gaze control in both PSP and may also help in PD. Sixth, patients may have problems locating objects in visual space<sup>158</sup> and strategies to improve object recognition in the home could be beneficial. Seventh there may be a potential problems involving driving in the

Parkinsonism syndromes because of low contrast VA deficits, as in PD.<sup>184</sup> It is also possible that some pharmacological interventions could produce effects on fitness to drive.<sup>185</sup>

In conclusion, visual problems in the Parkinsonism syndromes can involve a variety of functions including VA, CS, color discrimination, pupil reactivity, SEM, SPM, visual fields, and visual processing speeds. In addition, disturbance of visuo-spatial orientation, facial recognition problems, REM sleep behavior disorder, and chronic visual hallucinations may be present. Visual dysfunction may provide some useful diagnostic features helpful in differentiating the different syndromes, the presence of visual hallucinations, color vision problems, visuo-spatial deficits, and variations in eye movement problems being possible discriminating features.

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