

Review article

VISUAL SIGNS AND SYMPTOMS OF DEMENTIA WITH LEWY BODIES

Richard A. Armstrong BSc., DPhil.

Vision Sciences, Aston University, Birmingham B4 7ET, UK

Corresponding author: Dr R.A. Armstrong, Vision Sciences, Aston University,
Birmingham B4 7ET, UK (Tel: 0121-204-4102; Fax: 0121-204-4048; Email:

R.A.Armstrong@aston.ac.uk

Abstract

Dementia with Lewy bodies ('Lewy body dementia' or 'diffuse Lewy body disease') (DLB) is the second commonest form of dementia to affect elderly people after Alzheimer's disease. A combination of the clinical symptoms of Alzheimer's disease and Parkinson's disease is present in DLB and the disorder is classified as a 'parkinsonian syndrome', a group of diseases which also includes Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy. Characteristic of DLB are: (1) fluctuating cognitive ability with pronounced variations in attention and alertness, (2) recurrent visual hallucinations, and (3) spontaneous motor features including akinesia, rigidity, and tremor. In addition, DLB patients may exhibit visual signs and symptoms including defects in eye movement, pupillary function, and in complex visual functions. Visual symptoms may aid the differential diagnosis of the parkinsonian syndromes. Hence, the presence of visual hallucinations supports a diagnosis of Parkinson's disease or DLB rather than progressive supranuclear palsy. DLB and Parkinson's disease may exhibit similar impairments on a variety of saccadic and visual perception tasks (visual discrimination, space-motion, and object-form recognition). Nevertheless, deficits in orientation, trail-making, and in reading the names of colours are often significantly greater in DLB than in Parkinson's disease. As primary eye-care practitioners, optometrists should be able to identify work with patients with DLB and their carers to manage their visual welfare.

Key words: Dementia with Lewy bodies (DLB), Progressive supranuclear palsy, Parkinson's disease, visual hallucinations, dementia, Alzheimer's disease

Introduction

Previous reviews have described the visual signs and symptoms of two ‘parkinsonian syndromes’, viz., Parkinson’s disease (Parkinson’s disease)¹ and progressive supranuclear palsy (progressive supranuclear palsy).² Patients with Parkinson’s disease and progressive supranuclear palsy may exhibit defects in primary vision, eye movement, pupillary function, and in complex visual functions involving the ability to judge distances or to make out the shape of an object.^{1,2} Differential diagnosis of the parkinsonian syndromes, however, can be difficult owing to overlapping clinical features and visual signs and symptoms may help to distinguish the various disorders. Particularly useful in separating progressive supranuclear palsy from Parkinson’s disease, for example, is the presence in the former of vertical supranuclear gaze palsy, fixation instability, lid retraction, blepharospasm, and apraxia of eyelid opening and closing.^{1,2}

Dementia with Lewy bodies (DLB) (also known as 'Lewy body dementia' or ‘diffuse Lewy body disease’) is the second most common form of dementia after Alzheimer’s disease (Alzheimer’s disease)^{3,4} and may account for up to a quarter of all cases of dementia in elderly people. It is characterised by a progressive disabling mental impairment and includes fluctuating cognition, visual hallucinations, and parkinsonism as typical features. Hence, DLB is also classified as a parkinsonian syndrome and may be associated with a variety of visual problems which, although they may overlap with those of progressive supranuclear palsy and Parkinson’s disease, can aid clinical diagnosis. Therefore, the main objectives of this review are: (1) to describe the general features of DLB, (2) to evaluate the visual signs and symptoms reported in the disorder, (3) to discuss those visual features which may help in the differential diagnosis of DLB, and (4) to consider the role of the optometrist in managing DLB.

General features

Incidence and prevalence

There have been relatively few studies of the incidence and prevalence of DLB. Between 1999 and 2001, the incidence of a diagnosis of DLB among patients attending the Santa Caterina Hospital in Girona, Spain was 26/100,000 cases per year.⁵ In addition, incidence increased with age and there was a preponderance of males (63%) in the sample. This study, however, does not provide an unbiased estimate of the incidence of DLB as patients were referred from primary health centres. A review of all studies reporting the prevalence of DLB⁶, suggested estimates in the range 0 – 5% of the general population and up to 30.5% of all dementia cases. Incidence was estimated to be 0.1% a year for the general population and 3.2% for all new dementias. The most recent estimates of incidence of DLB relate to an elderly French population assessed over 15 years.⁷ Incidence was estimated to be 112/100,000 person-years and increased continuously with age even in the oldest individuals.

Signs and symptoms

The original ‘concept’ of DLB was based on the clinical description of patients exhibiting ‘paralysis agitans’ associated with a typical brain pathology, viz., the intracellular ‘inclusions’ known as Lewy bodies (LB).⁸ The most important general feature of DLB is a progressive decline in the mental ability of the patient of sufficient magnitude to interfere with normal social or occupational function (Table 1).⁴ Prominent and persistent memory impairments may not necessarily occur in the early stages of DLB, but are usually evident at some stage of the disease. Problems of attention and in visuo-spatial ability are common, the latter including difficulties in drawing the shapes of common objects such as a clock or in copying figures. The majority of patients with DLB exhibit at least two of the following ‘core’ features:⁴ (1) fluctuating cognitive ability with pronounced variations in attention and alertness, (2) recurrent visual hallucinations that are typically well-formed and detailed, and (3) the spontaneous motor features characteristic of parkinsonian syndromes in general.^{10,11} Hence, typical Parkinson’s disease features which may be present in 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 syndromes: (1) DLB in which there is a combination of dementia and parkinsonism characterised by prominent

hallucinations, and rapid eye movement (REM) sleep behavioural disorder, and 2) DLB with ‘parkinsonian dementia syndrome’ in which the symptoms of parkinsonism predominate.¹²

Dementia is defined as a deterioration of intellectual capacity often affecting memory, concentration, cognitive ability, and judgement. In DLB, dementia either precedes the symptoms of parkinsonism or the two symptoms appear together. About a third of Parkinson’s disease patients also develop a progressive dementia and may exhibit the characteristic neuropathology of DLB after death further blurring the distinction between the two disorders.¹¹ In DLB, these symptoms are associated with impaired psychomotor speed, visuo-spatial, and executive functions, i.e., an inability to carry out the normal and familiar tasks of life, but with the relative preservation of language.

In addition, several features, although not in themselves diagnostic of DLB, would support such a diagnosis, viz., repeated falls, syncope (fainting due to a sudden fall in blood pressure), transient loss of consciousness, sensitivity to neuroleptic drugs, delusions, and other types of sensory hallucination.¹³ Rapid eye movement (REM) sleep behavioural disorder is often regarded as a sign of impending DLB.¹⁴ By contrast, features less suggestive of DLB include any evidence of vascular disease, such as stroke, or the presence of other types of brain disorder which could account for the clinical symptoms. Males may be more susceptible than females and often have a worse prognosis.¹⁵

Functional imaging

A number of functional imaging studies have been carried out on patients with DLB and the results compared with Alzheimer’s disease. Within the temporal lobe, for example, the volume of the hippocampus (HC) and parahippocampal gyrus (PHG) is usually greater in DLB than in Alzheimer’s disease and may be responsible for the relative preservation of memory function in DLB.¹⁶ In addition, relative cerebral blood flow is usually lower in the occipital cortex and higher in the medial temporal lobe in DLB compared with Alzheimer’s disease.¹⁷ Moreover, both DLB and Alzheimer’s disease show significant reductions in metabolism in the parietal and

temporal cortex, the posterior cingulate gyrus (CG), and frontal association areas,¹⁸ but only in DLB is there a significant reduction in the occipital cortex and especially in the primary visual area (V1). Occipital hypometabolism may be a useful potential marker to distinguish DLB from Alzheimer's disease. In common with Alzheimer's disease and vascular dementia, periventricular and white matter hyperintensities are more extensive in DLB compared with elderly control patients.¹⁹

Neuropathology

Confirmation of the presence of DLB is often only possible after death and subsequent post-mortem. The degree of gross brain atrophy has been described as broadly similar in DLB and Alzheimer's disease²⁰ but in other studies, the size of parietal, frontal, and temporal lobes was reported to be intermediate between those of Alzheimer's disease and elderly control brains.²¹ In addition, little evidence of atrophy of the occipital lobes has been observed despite the reported hypometabolism. The major brain areas affected by the pathology of DLB, based on neuropathological and functional imaging data, are shown in Fig 1. In the cerebral cortex, areas of the temporal lobe such as the superior temporal gyrus (STG) and PHG are affected together with limbic system areas including the HC and amygdala (A). Other cortical regions involved include the CG, the insula and claustrum (I/C), the superior frontal cortex (SFC), and the occipital cortex (OC). The basal ganglia are also affected, including the putamen and caudate nucleus, but the globus pallidus appears to be spared.^{22,23} The pigmented nuclei of the brain stem, such as the substantia nigra and the locus caeruleus, are also likely to exhibit pathological changes.

The essential feature necessary for a neuropathological diagnosis of DLB is the presence of the characteristic LB (Fig 2).¹ Lewy bodies have also been observed in Parkinson's disease, but have a different distribution in the brain than in DLB. In DLB, there are significant numbers of LB in the cerebral cortex whereas in Parkinson's disease, LB are largely confined to the substantia nigra in the midbrain.¹ The density of LB in various brain areas were studied in 12 cases of DLB and are shown in Fig 3.²⁴ The greatest densities of LB were recorded in the temporal lobe and in limbic regions, especially the PHG, amygdala, and STG. Significant numbers of

LB are also observed in the substantia nigra, as in Parkinson's disease, and in the insula while fewer LB have been recorded in the frontal, parietal, and occipital regions.²⁵

Lewy bodies themselves (Fig 2) are spherical structures found in the cytoplasm of affected cells and can be visualised in histological sections by a variety of staining and immunolabelling techniques including haemotoxylin and eosin, alpha-B-crystallin, ubiquitin, and most significantly, α -synuclein. α -Synuclein is also found in LB in the brains of cases of Parkinson's disease and in the rare parkinsonian syndrome multiple system atrophy (MSA) and thus, unites these disorders as a major molecular group of neurodegenerative disorders, the 'synucleinopathies'.²⁶ The synucleins themselves are small proteins (123-143 amino acids), localized to presynaptic terminals, and may be involved in neurotransmission and/or synaptic organisation.²⁷

Pathological changes may also occur in DLB which resemble those of Alzheimer's disease⁹ including the presence of inclusions termed neurofibrillary tangles (NFT) and extracellular protein deposits known as senile plaques (SP).⁹ The density of these pathological changes is significant enough in some DLB cases to conclude that they have a combined or 'mixed' disease, i.e., DLB in association with Alzheimer's disease.²⁴ Hence, cases which combine the features of DLB and Alzheimer's disease, as well as overlap with parkinsonian syndromes,²⁸ can make the clinical and pathological diagnosis of DLB especially difficult.

Aetiology

There is no evidence that DLB is an infectious disease or that it can spread from one individual to another. The majority of cases occur sporadically but genetic factors, previously thought to be unimportant, may be involved to some extent. Hence, missense mutations in exons 3 and 4 of the α -synuclein gene have been observed in rare cases of familial DLB²⁹ but in other studies no such associations have been found.³⁰ In addition, cases of DLB in three generations of a Belgian family have been linked to a region of chromosome 2 (2q35-q36) adjacent to the previously described *PARK11* gene.³¹ As in Alzheimer's disease, allelic variations in the apolipoprotein E

(*Apo E*) gene have been identified as a risk factor for DLB.^{32,33} Hence, individuals with DLB have an increased frequency of *Apo E* allele $\epsilon 4$ compared with non-demented elderly controls. The presence of the $\epsilon 4$ allele may accelerate the development of Alzheimer's disease-type pathology within the aged brain and hence, is often associated with an earlier onset of the disease.

Treatment

There is no effective cure for DLB and existing treatments usually confer small benefits to the patient and are essentially palliative. The observation that DLB, Alzheimer's disease, and Parkinson's disease share overlapping clinical and pathological features suggests that treatments used in Alzheimer's disease and Parkinson's disease could also be effective in DLB. For example, a more severe neurotransmitter deficit involving the cholinergic system is often seen in DLB compared with Alzheimer's disease suggesting that cholinergic therapy may be more effective. The cholinergic deficit in DLB is often associated with less prominent cerebral atrophy and neuronal damage than is observed in Alzheimer's disease and hence, encouraging results have been obtained when DLB patients have been treated with cholinesterase inhibitors such as *rivastigmine*, *donepezil*, and *galatamine*.³⁴ Nevertheless, parkinsonian motor signs in DLB, such as rigidity and bradykinesia, may be less amenable to conventional dopamine therapies than in Parkinson's disease³⁵, e.g., *sinemet* may help movement problems but in some cases may aggravate psychosis in DLB. In addition, DLB is more sensitive than Alzheimer's disease to the adverse effects of antipsychotic agents, and especially the older 'typical' antipsychotic drugs such as *haloperidol*, which can cause the extrapyramidal signs and symptoms typical of Parkinson's disease, and may even lead to an early death.³⁴ Hence, caution is needed in the treatment of visual hallucinations and other psychotic symptoms in DLB. In addition, medications used to treat urinary incontinence, and antihistamines such as *benadry*, may exacerbate the symptoms of dementia. *Clonazepam* may be useful in the treatment of REM sleep behavioural disorder.

Visual signs and symptoms

A summary of the visual signs and symptoms that have been reported in DLB to date is given in Table 2. For the purpose of this article, they will be divided into those affecting: (1) visual acuity, (2) visual fields, (3) eye movement, (4) blink reflex and pupil reactivity, (5) electrophysiology, (6) complex visual functions, (7) visual hallucinations, and (8) REM sleep behaviour disorder.

Visual acuity

Visual acuity in DLB is essentially similar to that seen in control patients of similar age³⁶ suggesting that the visual pathway from eye to brain is relatively preserved. Hence, it is the higher level visual areas involved in more complex visual functions which are more likely to be impaired in DLB.³⁶

Visual fields

There have been relatively few studies to date on the visual field defects in any parkinsonian syndrome including DLB.^{1,2} A 66 year-old patient diagnosed with DLB, however, developed a left homonymous hemianopia early in the disease process.³⁷ Large numbers of NFT were observed in the right striate, peristriate, and inferior temporal cortex of this patient. In addition, studies of regional cerebral blood flow have suggested significant hypoperfusion in occipital areas in DLB and this could also lead to the development of significant visual field problems.³⁸ As a consequence, studies of the incidence and type of visual field problem in DLB are urgently needed.

Eye movement

A variety of eye movement problems have been reported in patients with Parkinson's disease¹ and in progressive supranuclear palsy² including abnormal saccadic and smooth pursuit eye movements, abnormal optokinetic nystagmus ('train nystagmus'), and convergence.³⁹ DLB patients specifically have been shown to be impaired in both reflexive and saccadic execution and in the performance of more complex saccadic eye movement tasks.⁴⁰ In addition, problems in convergence⁴⁰ are often followed by akinesia and rigidity.⁴¹ There have also been cases of DLB presenting with a vertical and horizontal gaze palsy and these could easily be confused with progressive

supranuclear palsy.^{2,42} Hence, caution is required in the interpretation of deficits in vertical gaze palsy when distinguishing the various parkinsonian syndromes.⁴³

Blink reflex

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 Parkinson's disease, for example, the blink reflex may not disappear on repeated tapping. This affect has, to date, not been studied in DLB but is likely to be present in patients exhibiting a significant degree of parkinsonian-type symptoms. The blink reflex to electrical stimulation of the supraorbital nerve, however, has been studied in parkinsonian patients including those with DLB.⁴⁴ Blink reflex was significantly delayed in the DLB group compared with controls and other parkinsonian groups, with a bilateral delay in the latency of the R2 response. There was also a significant correlation between the delay in the R2 response and the degree of cognitive fluctuation of the patient. Blink reflex has also been studied in DLB patients treated with cholinesterase inhibitors.⁴⁵ Treatment with *donepezil*, for example, was not associated with a change in cognitive or motor performance but after treatment for two weeks, the latency of the R2 response was significantly decreased.

Pupil reactivity

Pupillary responses using dilute *phenylephrine*, a sympathetic agonist and dilute *pilocarpine*, a cholinergic agonist, have been studied in DLB. The mydriatic response to 0.5% *phenylephrine* is greater in DLB than in Alzheimer's disease while the miotic response to 0.0625% *pilocarpine* is similar in DLB and Alzheimer's disease, both being greater than in control subjects.⁴⁶ Hence, pupil reactivity tests using *phenylephrine* and *pilocarpine* may prove useful in the differential diagnosis of patients with DLB and Alzheimer's disease.

Electrophysiology

The electroencephalogram (EEG) to eyes opening and to 12-Hz photic stimulation was studied in various groups of patients, including DLB, using global field

synchronization (GFS).⁴⁷ When the eyes were closed, theta-GFS was increased in Parkinson's disease and alpha-1 GFS was decreased in DLB. In addition, using 12-Hz intermittent photic stimulation, reactivity of posterior electrodes was also decreased in Parkinson's disease and DLB suggesting disruption of posterior anatomical pathways.⁴⁷ The electroretinogram (ERG) to a flash stimulus has been used to demonstrate dysfunction of the photopic and scotopic systems of the retina in DLB patients exhibiting visual hallucinations, DLB patients not exhibiting hallucinations, Parkinson's disease, and control patients.⁴⁸ Retinal dysfunction in the DLB and Parkinson's disease groups was attributed to pathological alterations in the photoreceptor cells which were accompanied by an increase of 'pale inclusions' in the inner plexiform layer. Event related potentials (ERP) have also been studied in DLB using a facial discrimination task.⁴⁹ The mean latency of the visual P3 response was greater in DLB than in Alzheimer's disease and mean latency of the P2 response was greater than in controls. The results suggested that visual cognitive functions were selectively impaired in DLB and that the impairment may occur at a relatively early stage of visual processing.

Complex Visual Functions

Deficits in complex visual function tasks are particularly characteristic of DLB.^{36,50,51} Impairments have been identified in object size discrimination, form discrimination, overlapping figure identification, drawing common objects such as a clock, and on visual counting tasks.⁵¹ Patients that develop visual hallucinations are often the worst performers on overlapping figure tasks. However, performance on line orientation, colour integration, and rotated object comparison tasks were often similar in DLB compared with control patients.³⁶ 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 been observed in DLB.⁵²

Visual hallucinations

Hallucinations may occur in a significant proportion of cases of both DLB and Parkinson's disease but are much less common in other parkinsonian syndromes such

as progressive supranuclear palsy.⁵³ In addition, less frequent auditory hallucinations have been observed in DLB.

In the study of Hely et al.,⁵⁴ hallucinations were present in six out of nine DLB patients studied and were the presenting feature in one patient. The visual hallucinations were recurrent, well formed and detailed. The presence of visual hallucinations may be the only psychotic symptom which reliably discriminates between DLB and Alzheimer's disease. There is considerable overlap between the visual hallucinations seen in DLB, however, and those in other types of disorder such as the 'misidentification syndromes' and the 'visual agnosias'. In addition, they are similar to those described in association with 'delerium' but differ from those produced by hallucinogenic drugs such as LSD. Patients with DLB may see faces emerging out of the patterns of chair cushions or curtains or hidden amongst trees or flowers and, at the same time, figures may be seen as if they were observed against a blank background. Most typically the hallucinations involve people or animals invading the patient's home but may also involve inanimate objects and the appearance of writing on walls or ceilings. The hallucinations are often seen in great detail and although they may not trouble the patient can evoke considerable fear.

Various factors may be involved in the production of visual hallucinations in DLB (Fig 4). Although there may be pathology in some areas of the thalamus,²³ visual hallucinations in DLB are more likely to be caused by pathology affecting the cerebral cortex. Hence, hallucinations are often abolished by eye closure which indicates a primary cortical pathology.⁵⁵ Hypometabolism in area V1 of the visual cortex, and relatively preserved metabolism in the temporal and parietal lobes may be associated with the development of these symptoms. Well-formed visual hallucinations are also evident in patients with extensive development of LB in the temporal lobe²⁵ and are rarely reported in parkinsonian syndromes without LB.⁵³ Furthermore, cholinergic activity is reduced in the cerebral cortex of patients with DLB. More extensive cholinergic abnormalities are believed to be associated with an increased risk of visual hallucinations. Hence, hallucinations in DLB could result from a change in the balance of neurotransmitter activity between the cholinergic and monoaminergic systems as a consequence of LB pathology in brain stem nuclei.⁵⁶ Nevertheless, ocular and retinal pathology may also contribute to hallucinations by

reducing occipital stimulation.⁵⁷⁻⁵⁹ Pale inclusions were observed in the inner plexiform layer of the retina in a patient with DLB. The inclusions were related to disorganisation of the cytoskeleton of the cone cells and a modification of the distribution of synuclein proteins in the retina.⁴⁸ As a consequence, downstream ventral association areas may increase their activity as a result of cortical disinhibition resulting in the hallucinations.

REM sleep behavioural disorder

REM sleep is a normal stage of sleep associated with random movements of the eyes. Characteristic of REM sleep behaviour disorder are vivid and frightening dreams associated with a simple or complex motor disturbance taking place during REM sleep. Patients essentially 'act out their dreams' and the condition may have clinical, diagnostic, and pathophysiological significance.⁶⁰ The pathological basis of the disorder may be the loss of neurons in the pigmented monoaminergic nuclei such as the locus caeruleus and substantia nigra, and which project to the pontine nuclei responsible for mediating 'atonia' (the inhibition of motor neurons) during REM sleep.¹⁴

DLB and the optometrist

Detecting the visual problems of the patient

As primary eye-care practitioners, optometrists should be able to identify the visual problems of patients with DLB and be expected to work with them and their carers to manage their visual welfare. The optometrist has a role in helping a patient with DLB if it is believed that signs and symptoms of the disease are present. As in Parkinson's disease, visual symptoms of DLB are highly variable, patients exhibiting various combinations of such symptoms.¹ In addition, the literature regarding the visual changes in DLB is limited compared with that in Parkinson's disease¹ and progressive supranuclear palsy.² Existing data are also controversial, different studies often giving conflicting results. A number of tests and procedures may be useful in identifying the visual problems of patients with a parkinsonian syndrome including DLB. It is particularly important to carry out the full examination including ocular

health assessment. Subsequently, several additional tests may be helpful and these have been described in detail in a previous review of progressive supranuclear palsy² and are equally applicable to DLB.

Differential diagnosis

The clinical symptoms of DLB overlap with those of both Alzheimer's disease and Parkinson's disease which can make differential diagnosis difficult especially in the early stages of the disease. In addition, the exact presentation of DLB will vary and some patients will not exhibit any overt visual symptoms. It is not the role of the optometrist to attempt a diagnosis of DLB or to be able to separate the condition from other parkinsonian syndromes and from Alzheimer's disease. Nevertheless, optometrists may provide useful additional information regarding the visual problems of the patient that may be helpful subsequently in a differential diagnosis. One of the main difficulties is distinguishing DLB from Parkinson's disease, especially early in the disease. A correct diagnosis is important because patients with visual hallucinations may be treated with antipsychotic drugs, a hazardous treatment in DLB.³⁴

Many of the parkinsonian syndromes have overlapping clinical features and it can be difficult to diagnose an individual case. In patients with unclassifiable or with indeterminate parkinsonian symptoms, the presence of visual hallucinations should be regarded as a 'red flag' symptom indicating underlying LB pathology⁶¹ and therefore, supporting a diagnosis of Parkinson's disease or DLB rather than progressive supranuclear palsy or MSA. Generally, DLB patients exhibit fewer tremors, more asymmetry of motor symptoms, more falls, and respond less to dopamine treatment than Parkinson's disease.⁶² DLB and Parkinson's disease show similar impairments on a variety of saccadic eye movement tasks. A newly developed portable saccadometer has been used to compare saccadic latency distribution in several parkinsonian syndromes⁶³ and a combination of saccadic parameters may give greater discrimination between Parkinson's disease and DLB than a single parameter such as median latency. There are also similarities in general cognitive performance in Parkinson's disease and DLB but there are some subtle differences. For example, deficits in orientation, 'trail-making', and reading the names of colours ('Stroop test')

would support a diagnosis of DLB rather than Parkinson's disease.⁵² Visual perception tasks (visual discrimination, space-motion and object-form recognition), however, are usually equally impaired in DLB and Parkinson's disease, especially in patients with visual hallucinations.⁶⁴ In addition, cognitive/psychiatric symptoms are generally less frequent in Parkinson's disease than in DLB.⁶⁵

Many of the clinical signs and symptoms of DLB can also be seen in patients with Alzheimer's disease⁶⁶⁻⁶⁹ but there may be a specific pattern of cognitive/psychiatric symptoms of dementia which can be used to differentiate DLB from Alzheimer's disease.⁷⁰ The presenting symptoms of DLB vary considerable but a clinical diagnosis of the disorder may be suspected when certain features are present. For example, although visual hallucinations may be present in Alzheimer's disease⁶⁹ they are much more pronounced and vivid in DLB.¹⁰ In addition, functional brain imaging reveals hypometabolism in the visual cortex in DLB, a feature not so frequently present in Alzheimer's disease.⁷¹ Other prominent features of DLB include fluctuating cognitive impairment, episodes of confusion and parkinsonism together with many of the visual signs and symptoms of Parkinson's disease.¹ Impairment of short-term memory, myoclonus (involuntary limb jerking), disturbances of gait and posture, and varying degrees of depression may also be present in DLB. In addition, pupil reactivity tests using *phenylephrine* and *pilocarpine* and electrophysiology may prove useful in the differential diagnosis of patients with DLB and Alzheimer's disease.

Practical ways the optometrist can help

As in Alzheimer's disease⁶⁹ and other parkinsonian syndromes,^{1,2} patients with DLB are likely to have visual problems that may not have been detected due to the developing disease. Patients with neurodegenerative disease are also less likely to be able to describe their visual problems effectively and are more likely to experience and tolerate visual deficits.⁷² Optometrists can refer patients to other health-care professionals for treatment and evaluation. For example, patients with visual hallucinations can be referred to clinical psychologists for counseling.

Care giving is particularly important in DLB as the disease gradually reduces the ability of an individual to look after themselves. One factor in improving the quality of life of DLB patients and as a consequence, reducing the burden on those that care for them, is for the patient to be able to see as clearly as possible. This is particularly important in DLB because visual hallucinations are exacerbated by other visual impairments and may be temporally relieved by environmental stimulation. Hence, it is important that the visual problems present should be investigated and detected and those due to ocular factors corrected as far as possible. In addition, various procedures may help the patient cope with the visual symptoms of DLB. DLB patients fall more readily resulting in a sedentary life style and if vertical gaze palsy is present, the patient may develop reading problems and eating difficulties. New devices are being tested in which refraction-positive moveable prism glasses are placed in front of the eyes to help patients with these problems.⁷³ In addition, it is important to bring to the attention of carers those visual problems of the patient that cannot be easily corrected such as oculomotor apraxia or possible visual field defects. As a consequence, carers may be able to make some provision for these problems, e.g., by simplifying the visual environment of the patient or by careful positioning of objects.

Conclusion

DLB is a common neurodegenerative syndrome of elderly people characterized by symptoms that can resemble those seen in other parkinsonian syndromes such as Parkinson's disease and progressive supranuclear palsy. The signs and symptoms of DLB can also resemble those of Alzheimer's disease. Where visual signs and symptoms are present, they may help in a differential diagnosis of DLB and especially in separating the disorder from Parkinson's disease. A diagnosis of probable DLB is important to prevent the prescribing of specific antipsychotic medications. Diagnosis may also benefit the patient because there may be visual problems present that need to be recognized and which can be subsequently managed by the eye-care practitioner.

References

1. Armstrong RA. Visual signs and symptoms of Parkinson's disease. *Clin Exp Opt* 2008; 91: 129-138.
2. Armstrong RA. Visual signs and symptoms of progressive supranuclear palsy. *Clin Exp Opt* 2010; 94: 150-160.
3. Lippa CF, Smith TW, Swearer JM. Alzheimer's disease and Lewy body disease: A comparative clinicopathological study. *Ann Neurol* 1994; 35: 81-88.
4. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen ENH, Ballard C, de Vos RAI, Wilcock GK, Jellinger KA, Perry RH. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113-1124.
5. Lopez-Pousa S, Garre-Olmo J, Turon-Estrada A, Gelada-Badale E, Lozano-Gallego M, Hernandez-Ferrandiz M, Morante-Munoz V, Petalita-Rodriguez J, Cruz-Reina MM. Clinical incidence of Dementia with Lewy bodies. *Rev de Neurol* 2003; 36: 715-720.
6. Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidence studies of dementia with Lewy bodies. *Age & Ageing* 2005; 34: 561-566.
7. Perez F, Helmer C, Dartigues JF, Auriacombe S, Tison F. A 15-year population-based cohort study of the incidence of Parkinson's disease and dementia with Lewy bodies in an elderly French cohort. *J Neurol Neurosurg Psychiatr* 2010; 81: 742-746.
8. Lewy FH. ‚Paralysis agitans‘. I. Pathologische Anatomie. In: *Handbuch der Neurologie* (Ed M. Lewandowsky), Julius Springer, Berlin 1912; 3: 920-933.
9. Armstrong RA. Plaques and tangles and the pathogenesis of Alzheimer's disease. *Folia Neuropathol* 2006; 44: 1-11.

10. Galasko D, Katzman R, Salmon DP, Hansen I. Clinical and neuropathological findings in Lewy body dementias. *Brain and Cog* 1996; 31: 166-175.
11. Galasko D. A clinical approach to dementia with Lewy bodies. *Neurology* 1999; 5: 247-257.
12. Cummings JL. Dementia with Lewy bodies: Molecular pathogenesis and implications for classification. *J Ger Psych Neurol* 2004; 17: 112-119.
13. Lauterbach EC. (2004) The neuropsychiatry of Parkinson's disease and related disorders. *Psych Clin N A* 2004; 27: 801-825.
14. Turner RS. Idiopathic rapid eye movement sleep behavioural disorder is a harbinger of dementia with Lewy bodies. *J Ger Psych Neurol* 2002; 15: 195-199.
15. Kosaka K. Diffuse Lewy body disease in Japan. *J Neurol* 1990; 237: 197-204.
16. Barber R, McKeith IG, Ballard C, Gholkov A, O'Brien JT. A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study. *Dement Ger Cogn Dis* 2001; 12: 198-205.
17. Ishii K, Yamazi S, Kitagaki H, Imamura T, Hirono N, Mori E. Regional cerebral blood flow difference between dementia with Lewy bodies and Alzheimer's disease. *Neurology* 1999; 53: 413-416.
18. Minoshima S, Foster NL, Sima AAF, Frey KA, Abin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol* 2001; 50: 358-365.
19. Barber R, Schettens F, Gholkov A, Ballard C, McKeith I, Ince P, Perry R, O'Brien J. White matter lesions on MRI in dementia with Lewy bodies, Alzheimer's disease, vascular dementia and normal aging. *J Neurol Neursurg Psychiatr* 1999; 67: 66-72.

20. Mann DMA, Snowden JS. The topographic distribution of brain atrophy in cortical Lewy body Disease – comparison with Alzheimer’s disease. *Acta Neuropathol* 1995; 89: 178-183.
21. Robles A, Cacabelos P. Dementia with Lewy Bodies: New data for the understanding of neuroimaging. *Rev de Neurol* 1999; 29: 993-998.
22. Jellinger KA, Attems J. Does striatal pathology distinguish Parkinson’s disease with dementia from dementia with Lewy bodies? *Acta Neuropathol* 2006; 112: 253-260.
23. Perneczky R, Haussermann P, Diehl-Schmid J, Boecker H, Forstl H, Drzezga A, Kurz A. Metabolic correlates of brain reserve power in dementia with Lewy bodies: An FDG PET study. *Dem Ger Cog Disord* 2007; 23: 416-422.
24. Armstrong RA, Cairns NJ and Lantos PL. The spatial patterns of Lewy bodies, senile plaques and neurofibrillary tangles in dementia with Lewy bodies. *Exp Neurol* 1998; 150: 122-127.
25. Harding AJ, Broe GA and Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain* 2002; 125: 391-403.
26. Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M. Filamentous α -synuclein inclusions link multiple system atrophy with Parkinson’s disease and dementia with Lewy bodies. *Neurosci Lett* 1998; 251: 205-208.
27. Iwai A, Masliah E, Yoshimoto M, Ge N, Flanagan L, Rohan de Silva HA, Kittel A, Sa T. The precursor protein of non-A β component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron* 1995; 14: 467-475.
28. Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. *Neuropathol* 2005; 25: 111-124.

29. El-Aguaf OMA, Curran MD, Wallace A, Middleton D, Murgatroyd C, Curtis A, Perry R, Jaros E. Mutation screening in exons 3 and 4 of alpha-synuclein in sporadic Parkinson's and sporadic familial dementia with Lewy body cases. *NeuroReport* 1998; 9: 3925-3927.
30. Higuchi S, Arai H, Matsushiba S, Matsui T, Kimpara T, Takeda A, Shirakura K. Mutation in the α -synuclein gene and sporadic Parkinson's disease, Alzheimer's disease, and dementia with Lewy bodies. *Exp Neurol* 1998; 153: 164-166.
31. Bogaerts V, Engelborghs S, Kumar-Singh S, Goosens D, Pickut B, van der Zee J, Sleegen K, Peeters K, Martin JJ, Del-Favero J, Gasser T, Dickson DW, Wszolek ZK, de Deyn PP, Theuns J, van Broeckhoven C. A novel locus for dementia with Lewy bodies: a clinically and genetically heterogeneous disorder. *Brain* 2007; 130: 2277-2291.
32. Benjamin R, Leake A, Ince PG, Perry RH, McKeith IG, Edwardson JA, Morris CM. Effects of Apo E genotype on cortical neuropathology in senile dementia of the Lewy body type and Alzheimer's disease. *Neurodegeneration* 1995; 4: 443-448.
33. Galasko D, Saitoh T, Xia Y, Thal IJ, Katzman R, Hill IR, Hansen I. The apolipoprotein E allele epsilon 4 is overexpressed in patients with the Lewy body variant of Alzheimer's disease. *Neurology* 1994; 44: 1950-1951.
34. Kaufer DI. Pharmacologic treatment expectations in the management of dementia with Lewy bodies. *Dem Ger Cog Disord* 2004; 17: 32-39.
35. Kaufer DI. Pharmacologic therapy of dementia with Lewy bodies. *J Ger Psych Neurol* 2002; 15: 224-232.
36. Metzler-Baddeley C, Baddeley RJ, Lovell PG, Laffan A, Jones RW. Visual impairment in dementia with Lewy bodies and posterior cortical atrophy. *Neuropsych* 2010; 24: 35-48.

37. Bashir K, Elbe RJ, Ghabrial M, Struble RG. Hemianopsia in dementia with Lewy bodies. *Arch Neurol* 1998; 55: 1132-1135.
38. Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Balard C, McKeith IG and O'Brien JT. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not Alzheimer's disease. *Neurology* 2001; 56: 643-649.
39. Corin MS, Elizan TS, Bender MB. Oculomotor function in patients with Parkinson's disease. *J Neurol Sci* 1971; 15: 251-265.
40. Mosimann UP, Muri RM, Burn DJ, Felblinger J, O'Brien JT, McKeith IG. Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies. *Brain* 2005; 128: 1267-1276.
41. Debruin VM, Lees AJ, Daniel SE. Diffuse Lewy body disease presenting with supranuclear gaze palsy, Parkinsonism and dementia: a case report. *Move Disord* 1992; 7: 355-358.
42. Fearnley JM, Revesz T, Brooks DJ, Frackowiak RS, Lees AJ. Diffuse Lewy body disease presenting with a supranuclear gaze palsy. *J Neurol Neurosurg Psych* 1991; 54: 159-161.
43. Brett FM, Henson C, Staunton H. Familial diffuse Lewy body disease, eye movements, eye movement abnormalities and distribution of pathology. *Arch Neurol* 2002; 59: 464-467.
44. Bonanni L, Anzelli F, Varanese S, Thomas A, Manzoli L, Onofri M. Delayed blink reflex in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatr* 2007; 78: 1137-1139.
45. Anzelli F, Bonanni L, Iorio E, Di Baldassarre F, D'Andreagiovanni A, Monaco D, Thomas A, Onofri M. Delayed blink reflex in dementia with Lewy bodies is sensitive to cholinergic stimulation. *Clin Neuropharmacol* 2008; 31: 231-237.

46. Hanyu H, Hirao K, Shimizu S, Kanetaka H, Sakurai H, Iwamoto T. Phenylephrine and pilocarpine eye drop test for dementia with Lewy bodies and Alzheimer's disease. *Neurosci Lett* 2007; 414: 174-177.
47. Pugnetti L, Baglio F, Farina E, Alberoni M, Calabrese E, Gambini A, Di Bella E, Garagnani M, Deleonaedis L, Nemni R. EEG evidence of posterior cortical disconnection in Parkinson's disease and related dementias. *Int J Neurosci* 2010; 120: 88-98.
48. Devos P, Tir M, Maurage CA, Waucquier N, Defebvre L, Defoort-Dhellmmes S, Destee A. ERG and anatomical abnormalities suggesting retinopathy in dementia with Lewy bodies. *Neurology* 2005; 65: 1107-1110.
49. Kurita A, Murakami M, Takagi S, Matsushima M, Suzuki M. Visual hallucinations and altered visual information processing in Parkinson disease and dementia with Lewy bodies. *Move Disord* 2010; 25: 167-171.
50. Salmon DP, Galasko D, Hansen LA, Masliah E, Butters N, Thal LJ, Katzman R. Neuropsychological deficits associated with diffuse Lewy body disease. *Brain Cog* 1996; 31: 148-165.
51. Mori E, Shimomura T, Fujimori M, Hirono N, Imamura T, Hashimoto M, Tanimukai S, Kazin H, Hanihara T. Visuoperceptual impairment in dementia with Lewy bodies. *Arch Neurol* 2000; 57: 489-493.
52. Mondon K, Gochard A, Margue A, Armand A, Beauchamp D, Prunier C, Jacobi D, de Toffol B, Autret A, Camus V, Hommet C. Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia. *J Neurol Neurosurg Psych* 2007; 78: 738-741.
53. Ebersbach G. Hallucinations and psychosis in Parkinson's disease: consequences for diagnosis and management. *Nervenheilkunde* 2008; 27: 709.

54. Hely MA, Reid WG, Halliday GM, McRitchie DA, Leicester J, Joffe R, Brooks W, Brae GA, Morris JGL. Diffuse Lewy body disease: clinical features in nine cases without coexistent Alzheimer's disease. *J Neurol Neurosurg Psych* 1996; 60: 531-538.
55. Collerton D, Perry E. Thalamocortical dysfunction and complex visual hallucinations in brain disease: are the primary disturbances in the cerebral cortex? *Behav and Brain Sci* 2004; 27: 789.
56. Fenelon G, Mahieux F. (2004) Hallucinations and dementia: prevalence, clinical presentation and pathophysiology. *Rev Neurol* 2004; 160: 531-543.
57. Manford M, Andermann F. Complex visual hallucinations: clinical and neurobiological insights. *Brain* 1998; 121: 1819-1840.
58. Santhouse AM, Howard RJ, ffytche DH. Visual hallucinatory syndromes and the anatomy of the visual brain. *Brain* 2000; 123: 2055-2064.
59. Maurage CA, Ruchoux MM, de Vos R, Surguchov A, Destee A. Retinal involvement in dementia with Lewy bodies: A clue to hallucinations? *Ann Neurol* 2003; 54: 542-547.
60. Boeve BF, Silber MH, Ferman TJ. REM sleep behavioural disorder in Parkinson's disease and dementia with Lewy bodies. *J Ger Psych Neurol* 2004; 17: 146-157.
61. Williams DR, Warren JD, Lees AJ. Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism. *J Neurol Neurosurg Psychiatr* 2008; 79: 652-655.
62. Ransmayer G. Dementia with Lewy bodies: prevalence, clinical spectrum and natural history. In Riederer P, Calne DB, Horowski R, Mizuno Y, Olanow CW, Poewe W, Youdim MBH eds. *Advances in research on Neurodegeneration* 2000; 8: 303-314.

63. Antoniadou CA, Bak TH, Carpenter RHS, Hodges JR, Barker RA. Diagnostic potential of saccadometry in progressive supranuclear palsy. *Biom in Med* 2007; 1: 487-490.
64. Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson's disease dementia and dementia with Lewy bodies. *Neurology* 2004; 63: 2091-2096.
65. Loins ED, Goldman JE, Powers JM, Fahn S. Parkinsonian features of eight pathologically diagnosed cases of diffuse Lewy Body Disease. *Move Disord* 1995; 10: 188-194.
66. Mendez MF, Tomsak RL, Remler B. Disorders of the visual system in Alzheimer's disease. *Neurology* 1990; 40: 439-443.
67. Armstrong RA, Syed AB. Alzheimer's disease and the eye. *Ophthalm Physiol Opt* 1996; 16: S2-S8.
68. Sadun AA, Borchert M, DeVita E, Hinton DR, Bassi CJ. Assessment of visual impairment in patients with Alzheimer's disease. *Am J Ophthalmol* 1987; 104: 113-120.
69. Armstrong RA. Alzheimer's disease and the eye. *J Optom* 2009; 2: 103-111.
70. Devos RAI, Jansen ENH, Stain FC, Ravid R, Swaab DF. Lewy Body Disease – clinicopathological correlations in 18 consecutive cases of Parkinson's disease with and without dementia. *Clin Neurol & Neurosurg* 1995; 97: 13-22.
71. Albin RL, Minoshima S, Damato CJ, Frey KA, Kuhl DA, Sima AAF. Fluorodeoxyglucose positron emission tomography in diffuse Lewy body disease. *Neurology* 1996; 47: 462-466.

72. Koch JM, Datta G, Makdoom S, Grossberg, GT. Unmet visual needs of Alzheimer's disease patients in long-term care facilities. *J Am Med Dir Assoc* 2005; 6: 233-237.

73. Di Fabio RP, Zampieri C, Tuite P. Gaze control and foot kinematics during stair climbing: Characteristics leading to fall risk in progressive supranuclear palsy. *Phys Ther* 2008; 88: 240-250.

Table 1. Criteria for the diagnosis of dementia with Lewy bodies (DLB) (McKeith et al., 1996).

1. Progressive cognitive decline which interferes with social or occupational function. Memory deficit apparent at some stage. Deficits on tests of attention and visuo-spatial tasks prominent.
 2. Two of the following features:
 - a) Fluctuating cognition
 - b) Recurrent visual hallucinations
 - c) Motor features of Parkinson's disease
 3. Additional features which support diagnosis:
 - a) Repeated falls
 - b) Syncope
 - c) Transient loss of consciousness
 - d) Neuroleptic sensitivity
 - e) Systematised delusions
 - f) Non-visual hallucinations
 4. A diagnosis of DLB is less likely if there is evidence of vascular disease of the brain.
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Table 2. Visual signs and symptoms of dementia with Lewy bodies (DLB). (Alzheimer's disease = Alzheimer's disease, Parkinson's disease = Parkinson's disease)

<u>Ocular aspect</u>	<u>Change in DLB</u>	<u>References</u>
Visual fields	Homonymous hemianopia may occur early in disease process	Bashir et al., 1998
Eye movements	Impaired reflexive and saccadic execution	Mosimann et al., 2005
	Convergence problems followed by akinesia and rigidity	Debruin et al., 1992
	Vertical and horizontal gaze palsy	Fearnley et al., 1991
Blink reflex	R2 response significantly delayed to stimulation of supraorbital nerve	Bonnani et al., 2007
	R2 decreased after <i>donepezil</i> Treatment	Anzelloti et al., 2008
Pupillary reactivity	Mydriatic response to <i>pilocarpine</i> and <i>phenylephrine</i>	Hanyu et al., 2007
Electrophysiology	EEG: alpha-1 GFS decreased	Pugnetti et al., 2010
	ERG: dysfunction in patients with hallucinations	Devos et al., 2005
	ERP: P3 latency increased	Kurita et al., 2010

Complex visual tasks	Abnormalities in object size discrimination, form discrimination, overlapping figure identification, visual counting tasks, drawing simple objects, copying figures	Mori et al., 2000
Visual hallucinations	More frequent in DLB than Alzheimer's disease and may be presenting feature in a proportion of patients	Galasko et al., 1996 Hely et al., 1996

Legends to Figures

Fig 1. The areas of the brain affected by the pathology of dementia with Lewy bodies (DLB) (shown in bold in large font) (SFC = superior frontal cortex, OC = Occipital cortex, STG = Superior temporal gyrus, PHG = Parahippocampal gyrus, HC = Hippocampus, CG = Cingulate gyrus, I/C = Insula/clastrum, A = Amygdala, nB = Nucleus basalis of Meynert, Put = Putamen, CN = caudate nucleus, P = Pulvinar of thalamus, SN = Substantia nigra, R = Raphe nuclei, LC = Locus careuleus, Other areas identified (in normal text and small font) (OG = orbital gyrus, GR = Gyrus rectus, PC = Parietal cortex, DG = Dentate gyrus, Th = Thalamus, LGN = lateral geniculate nucleus, Hy = Hypothalamus, VT = Ventral tegmentum, Ce = Cerebellum, MB = Mamillary bodies, GP = Globus pallidus) superimposed on a two-dimensional model of the brain based on that of WJH Nauta and M Feirtag (1986) *Fundamental Neuroanatomy*. WH Freeman & Co. Hence the cerebral cortex is represented at the right of the diagram with the striatum (ST) and thalamus (Th) below. Midbrain and brain stem nuclei are at the left of the diagram.

Fig 2. Section through the cerebral cortex of a patient with dementia with Lewy bodies (DLB) showing the presence of Lewy bodies (LB) (arrow) within the neurons. These structures probably represent abnormalities of the neuronal cytoskeleton resulting from degeneration (Section immunolabelled with antibodies against α -synuclein).

Fig 3. Density of Lewy bodies (LB) in various brain areas, averaged over 12 cases of DLB. The greatest densities of LB are seen in the temporal lobe and in limbic regions, especially the parahippocampal gyrus (PHG), amygdala (AM), superior temporal gyrus (STG) and middle temporal gyrus (MTG). Significant numbers of LB are also seen in the substantia nigra (SN) as in Parkinson's disease, the cingulate gyrus (CG), and the insular cortex (IC) while fewer LB have been recorded in the frontal (SFG), sector CA1 of the hippocampus, parietal cortex (PC), and occipital regions (OC).

Fig 4. Factors involved in the production of visual hallucinations in dementia with Lewy bodies (DLB). Abbreviations: LB = Lewy bodies LB, TL = Temporal lobe,

CHOL = Cholinergic neurotransmitter system, NA = Noradrenergic neurotransmitter system.