Section 1
Chapter 1

Introduction

Basic clinical approaches to diagnosis

Bruce L. Miller

There are few areas in all of medicine that are more difficult, yet gratifying, than the assessment, diagnosis and treatment of patients with cognitive complaints. Since the mid 1990s there have been dramatic changes in the accuracy of dementia diagnosis with improvements seen not only for Alzheimer's disease (AD), but also many of the other non-AD conditions including frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), vascular dementia and Jakob–Creutzfeldt disease (CJD). Simultaneously, better detection and differential diagnosis of mild cognitive impairment (MCI), a condition that often represents an early stage of a specific degenerative or cerebrovascular condition, is now possible. One of the major reasons for these improvements is that research is helping to reveal specific roadmaps for the detection of each of these conditions, while simultaneously devising systematic approaches to rule out potentially treatable non-degenerative etiologies for cognitive impairment.

In this chapter, a simple approach to dementia at the bedside is described and clinical diagnosis is outlined with regards to the following categories:

- the history
- the examination including cognitive, behavioral, medical and neurological findings
- laboratory testing including genetic testing and

Additionally, a simple approach to treatment of the varied dementing conditions is described. With the approaches outlined in this chapter, a clinician can make highly accurate diagnoses for all of the major degenerative and vascular dementias and MCI, while simultaneously generating appropriate treatments once a diagnosis has been made. Although the features of all of these neurodegenerative disorders is described in a more comprehensive fashion throughout the book, this chapter is meant to serve as an introduction to dementia, emphasizing a simple approach to diagnosis and treatment.

The history

No component of the diagnostic process is more important than is the history. Beyond its value for diagnosis, the historical features of the illness allow the clinician to quantify the burden of the disorder upon the caregiver, and define an approach to the treatment of both the dementia and the associated medical and psychiatric conditions. Additionally, the history offers important insights into whether or not non-standard laboratory testing such as genetic testing will be needed. For the primary care physician, the history is the primary guide as to whether or not a referral to a specialist will be necessary.

The history begins with determination of the first symptoms and with tracking of symptom progression. When a history is precisely taken, the clinician should be able to describe in vivid detail specific episodes that show a change from prior levels of function, and define a linear picture of how the disorder has progressed and fluctuated. The greater the specificity in the history, the greater is the likelihood that the clinician will be able to derive an accurate diagnosis. Ideally, the patient's history should be recorded like a script in a documentary movie, with a detailed story-line that is agreed upon by the patient

conditions are unable to track the symptoms of their illness accurately and, therefore, primary and collateral sources should always be sought. Defining the first symptoms and those that follow the initial complaints will help to determine where in the brain the dementia begins and to where it has spread. Often, in the more advanced stages of dementia, whatever the etiology, the pathology has spread diffusely making diagnosis difficult based upon current symptoms or findings. Therefore, even in advanced cases, focusing upon first symptoms will be the key to diagnosis.

The Behavioral Neurology of Dementia, eds. Bruce L. Miller and Bradley F. Boeve. Published by Cambridge University Press.

Patients with AD usually begin with forgetfulness because in this disorder pathology typically starts in the hippocampus. If progressive problems with speech or language are the first symptoms, an FTD-related condition such as non-fluent aphasia or semantic dementia is the major consideration. Prominent behavioral or personality changes such as disinhibition, apathy, compulsions, overeating, loss of sympathy and empathy for others suggest FTD, while visual deficits as an early feature suggest posterior cortical atrophy. Visual hallucinations or delusional misidentification syndromes as early features of a dementia usually point to DLB. The presence of motor symptoms should be queried. Frequent falls are characteristic of progressive supranuclear palsy (PSP), or sometimes vascular dementia. Early movement abnormalities suggest the possibility of parkinsonian-dementia syndromes, such as DLB, PSP or corticobasal degeneration (CBD). Vascular dementia and CBD can begin with asymmetric motor findings.

Most of the degenerative dementias follow a slowly progressive and non-fluctuating course. In patients in whom symptoms vary from moment to moment or day to day, DLB and vascular dementia should be considered. Conversely, in patients who progress rapidly, an entirely different set of disorders must be considered including CJD, paraneoplastic syndromes, encephalitis, vasculitis, and metabolic disorders. Because patients with DLB are delirium prone, this disorder sometimes begins in an acute or subacute fashion.

A functional assessment of the patient is critical for the determination of the level of cognitive impairment and for helping to guide the family on management and outcome. Patients with mild cognitive impairment should have relatively normal day-to-day function, while completely normal day-to-day activities are more typical of individuals in whom cognition is normal.

The psychiatric history is not only critically important for differential diagnosis but also helps the clinician to target symptoms and behaviors with specific medications. Symptoms suggestive of depression, psychosis or anxiety should be sought and are typical of subcortical disorders but occur to a limited degree with all neurodegenerative conditions. Simple statements that a patient is depressed should not be accepted at face value. Apathy is common in dementia and does not necessarily represent depression. Pseudo-dementia due to depression is relatively rare in AD but the co-occurrence of dementia and depression is common. REM sleep-behavior syndrome is a characteristic of synuclein-related disorders including DLB, Parkinson's disease (PD) and multisystem atrophy, while sleep apnea can greatly exacerbate cognitive deficits. Understanding the nature and severity of psychiatric disturbances can be facilitated with questionnaires like the Neuropsychiatric Inventory or Geriatric Depression Scale. One of the major responsibilities of the clinician is to make sure that the caregiver is coping with the illness, and referrals of the caregiver for psychiatric care should always be considered.

Past illnesses and medications are a key component of the history. Anxiolytics, anticholinergic and antipsychotic compounds can have profoundly negative influences upon the behavioral and cognitive status of patients, and current and past medications need to be reviewed carefully. Similarly, an acute change in cognitive status should trigger the search for toxic, metabolic or infectious diseases.

Mental status testing

Mental status testing is helpful for staging the dementia, for differentiating one dementia from another and for understanding how the cognitive deficits influence day-to-day behaviors. A variety of screening tools are available to help the clinician to search for cognitive deficits, but it is critically important that the strengths and limitations of these screening tools are understood. The Mini-Mental State Examination (MMSE) is an excellent tool for following AD, FTD, DLB and many other dementias once a diagnosis has been made. Additionally, the dementing conditions tend to show somewhat distinctive patterns on the MMSE. Patients with AD tend to fail on orientation, recall and sometimes the intersecting pentagons; patients with FTD often have trouble with "world" backwards and patients with DLB have particular difficulty correctly drawing the intersecting pentagons and spelling "world" backwards. A shaky tremulous drawing or micrographia on the sentence or the copy of the pentagons suggest a parkinsonian disorder. Similarly, the copy should be analyzed for evidence of neglect, a sign of vascular dementia or CBD. It is important to realize that the MMSE is not sensitive to early dementing conditions of any kind, and tends to underestimate the severity of dementia in patients with frontosubcortical disorders such as FTD, PSP or Huntington's disease.

More extensive neuropsychological testing than the MMSE is necessary for patients with mild disease and to help with differential diagnosis. At the University of California at San Francisco (UCSF), we have constructed a bedside cognitive battery that probes working and episodic memory, animal and "d" word generation, alternating sequences, inhibition, drawing, language fluency, comprehension, naming, repetition and emotion recognition. The numbers generated from this battery prove valuable for determining whether or not there are longitudinal changes in cognition, either positive or negative. Also, this battery helps to define patterns of deficits, data that are critically valuable in differential diagnosis. Typical AD patients show problems with episodic visual and verbal memory, animal generation and sometimes drawing, with relative sparing of language and emotion recognition. There is a very different pattern in FTD, with poor performance in executive functions including working memory, "d" generation, alternating sequences and emotion recognition, with relative sparing of drawing and episodic memory. In progressive non-fluent aphasia (PNFA), cognitive performance is remarkably normal with the exception of word fluency, "d" generation and sometimes alternating sequence speed. Patients with semantic dementia show profound deficits in naming that are not improved by clues, along with deficits with episodic verbal memory and animal generation, while DLB is characterized by abnormalities in drawing and sometimes executive function.

The quality of cognitive testing and interpretation is extremely variable and the clinician should be able to perform their own cognitive testing and interpret reports from others. Normal performance on difficult mental status tasks is reassuring but when patients have persistent complaints, repeat testing may be indicated. Having a quantitative measure is particularly helpful in determining whether or not a patient has progressed over time.

Psychiatric and behavioral observations

Good clinicians understand the importance of bedside observations for differential diagnosis of dementia. Most patients with MCI, AD and PNFA are well behaved and socially correct. In contrast, in FTD, patients may come to their appointments inappropriately dressed, poorly groomed or exhibit inappropriate behaviors including grandiose comments, undue familiarity, repetitive motor behaviors, inappropriate staring or aversion of eye gaze. The absence of a smile, averted eye gaze, a soft voice that trails off and crying are features of a major depression. Similarly, paranoia, psychosis and hallucinations are often apparent in the interview with the patient. Not only are these symptoms helpful for differential diagnosis but they also aid in the targeting of specific behaviors with medications.

The medical and neurological examination

The general examination should be performed to search for evidence of hypertension, cardiac arrhythmias, heart failure, skin infections or bruises, pulmonary disease, anemia, jaundice or other evidence for systemic illness. Medical illnesses can cause cognitive impairment and can exacerbate or worsen subtle cognitive disorders caused by an underlying degenerative disorder. It should be noted that cerebrovascular risk factors predispose to both vascular dementia and to AD. As the degenerative disorders worsen, patients become less able to describe symptoms of medical illnesses, including pain. This makes it particularly important for the clinician to look carefully for medical conditions that might be exacerbating cognitive or behavioral symptoms.

The neurological examination is central to differential diagnosis. With classical AD, the neurological examination remains normal until the late stages of the illness. Therefore, features of parkinsonism in patients with mild dementia should suggest other disorders such as DLB, PSP or CBD. The DLB parkinsonian features are often slightly atypical but can include facial bradykinesia, a soft festinating voice, cogwheel rigidity, tremor, slowing of movement, micrographia and stooped posture with a festinating gait; these should suggest DLB. Axial rigidity, a stare, vertical gaze disturbance, square wave jerks of the eyes and frequent falls typify PSP, and asymmetric parkinsonism, ocular apraxia, dystonia and alien limb occur with CBD. Prominent autonomic symptoms such as orthostatic hypotension can occur with DLB but reflect multisystem atrophy. Pseudobulbar affect, uncontrollable laughter and crying associated with a brisk jaw jerk, is seen with amyotrophic lateral sclerosis (ALS), PSP and vascular dementia. Asymmetric pyramidal deficits are seen with cerebrovascular disease. Rapidly progressive dementia with parkinsonism brings up the possibility of CJD.

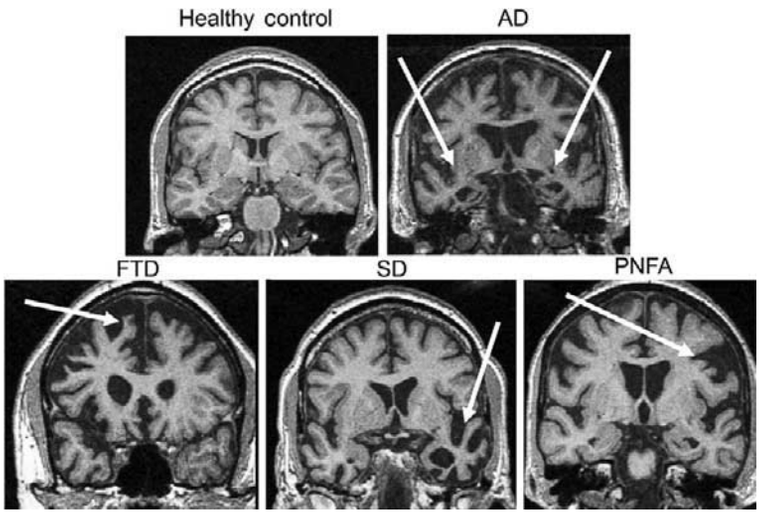

Fig. 1.1. Atrophy patterns in dementia. Patients showing different patterns of atrophy in T_1-weighted MRI images of healthy age-matched control. AD, Alzheimer's disease; FTD, frontotemporal dementia; SD, semantic dementia; PNFA, progressive non-fluent aphasia.

Laboratory testing and neuroimaging

The American Academy of Neurology has recommended a complete blood count, electrolytes, blood urea nitrogen (BUN) and serum glucose as part of the work-up for patients with memory complaints. Beyond these simple measures the clinician should remain flexible and adapt the evaluation to the conditions that are suggested by the patient's clinical syndrome. Elevations of serum calcium and phosphorus should be sought if there is a history of cancer, somnolence or bone pain. Liver failure should be considered in patients with dementia in whom chronic hepatitis or alcoholism is present. Neurosyphilis is exceedingly rare, and false positives are common with current screening techniques. For this reason, the rapid plasma reagin (RPR) test is no longer recommended for routine measurement. An electroencephalograph (EEG) is important in patients with spells, or fluctuating alertness. Lumbar puncture should be considered in patients with chronic headache, rapidly progressive changes or exposure to Lyme disease, human immunodeficiency virus (HIV) or syphilis.

Genetic testing should be considered in patients with autosomal dominant patterns of dementia. When genetic testing is performed, it should be done in conjunction with formal genetic counseling so that the patient is truly informed regarding the potential good and harm that can accompany this process. Presenilin 1 is the most common mutation for early-age-of-onset AD, while tau and progranulin mutations account for the vast majority of mutations linked to FTD. It is generally accepted that apolipoprotein polymorphisms should not be tested as their presence does not rule in or rule out AD.

Some sort of structural image should be performed in all patients with suspected dementia. Magnetic resonance imaging (MRI) is almost always preferable to computed tomography (CT) owing to its better resolution of tissue contrast. The presence of stroke, subdural hematoma, tumor, small bleeds caused by amyloid angiopathy, or excessive basal ganglia mineralization should be sought. Use of MRI is valuable for differential diagnosis of dementing conditions. Patients with AD show hippocampal and posterior parietal atrophy, white FTD is associated with anterior cingulate, orbitofrontal, insular and usually dorsolateral prefrontal atrophy (Fig. 1.1). In addition, the caudate and putamen often show atrophy. In CBD, frontally predominant and basal ganglia atrophy is common, while in PSP the frontal lobes tend to be spared but the midbrain is often atrophied. Changes in DLB are more variable but atrophy tends to be more posterior than in AD. CJD is associated with cortical ribboning and basal ganglia hyperintensities on fluid-attenuated inversion recovery (FLAIR) MRI, which demonstrate decrease diffusion of water molecules on diffusion-weighted imaging (DWI). This pattern reliably differentiates CJD from the other degenerative disorders. Often it is difficult to decide whether or not the vascular changes on an MRI are responsible for the cognitive syndrome. There is no hard rule to follow but the larger number of basal ganglia infarctions and white matter hyperintensities, the greater the likelihood that vascular disease accounts

Table 1.1. Clinical features of the major dementing conditions

Dementia	First symptom	Cognitive pattern	Neurology examination	Neuroimaging	Treatment
AD	Memory loss	Amnesia, word fluency	Normal till late	Posterior temporal/ parietal, PIB positive	Cholinesterase inhibition, NMDA antagonist
FTD	Behavior-apathy, disinhibition, overeating	Loss of executive control	Normal (look for PSP, CBD, ALS)	Anterior frontotemporal insular, basal ganglia	SSRI, NMDA antagonist?
PNFA	Speech, word finding	Non-fluent, dysarthric, apractic speech	Sometimes asymmetric parkinsonism, axial rigidity	Left frontoinsular, basal ganglia	Speech therapy, treat parkinsonism, depression
DLB	Hallucinations, parkinsonism, delirium	Visuospatial, attentional	PD (can be normal at first)	Posterior inferior, Some are PIB positive	Cholinesterase inhibition, carbidopa-levodopa
SD	Word finding, loss of word meaning	Semantic loss, anomia	Normal till later	Anterior temporal	Consider cholinesterase inhibition
Vascular	Variable	Variable, subcortical lesions cause frontal syndrome	Variable, asymmetric, pyramidal deficits	Multiple strokes and/or subcortical white matter lesions	Stroke prevention, consider cholinesterase inhibition
CBD	Asymmetric parkinsonism, PNFA or behavioral	Like FTD or PNFA, sometimes parietal	Asymmetric PD, dystonia, ocular apraxia; alien hand	Frontal, basal ganglia, sometimes parietal	Exercise, treat parkinsonism, treat depression
PSP	Falls, PNFA, behavior	Loss of executive control	Supranuclear gaze palsy, axial rigidity	Midbrain atrophy (variable)	Exercise, treat PD
CJD	Rapid dementia, parkinsonism	Variable	PD, variable	Cortical ribbon, basal ganglia hyperintensity	None

Notes:
SSRI, selective serotonin-reuptake inhibitor; NMDA, *N*-methyl-D-aspartate; other abbreviations as in text.

Table 1.2. Underlying biology of the dementias

Dementia	Histology	Genes for	Molecules	Topography
AD	Amyloid plaques, neurofibrillary tangles	Causal: APP, PS1, PS2 Susceptibility: ApoE4, SIRT-1	Aβ-42, tau	Posterior temporal/parietal
FTD	Gliosis, spongiosus, Pick bodies, ubiquitin-TDP-43	Causal: progranulin, tau VCP, CHMP2B	Tau or TDP-43	Anterior frontotemporal insular, basal ganglia
PNFA	Gliosis, CBD or PSP pathology (see below)	Causal: progranulin, rarely tau, often sporadic	Tau	Left frontoinsular, basal ganglia
DLB	Lewy bodies, nigral loss, often amyloid plaques	Causal: rarely α-synuclein, often sporadic	α-Synuclein, often comorbid; Aβ-42	Posterior parietal, amygdala, basal ganglia, brainstem
SD	Gliosis, ubiquitin-TDP-43	Causal: rarely progranulin, tau, often sporadic	TDP-43	Anterior temporal, amygdala, eventually basal ganglia
Vascular	Infarctions, hyalinization of blood vessels	No specific causal genes	No	Subcortical white matter vulnerable with aging
CBD	Gliosis (cortical, subcortical) coiled tangles, astrocytic plaques	Progranulin, tau, susceptibility polymorphism is H1/H1 tau	Tau	Frontal, basal ganglia, sometimes parietal
PSP	Globose tangles, tufted astrocytes, neurofibrillary tangles	Rarely tau susceptibility polymorphism is H1/H1 tau	Tau	Midbrain, caudate, putamen, brainstem, cerebellum, some frontal
CJD	Astrocytosis, spongiosus	Prion gene mutations	Prion	Cortical, basal ganglia, cerebellum

Notes:
APP, amyloid precursor protein; Aβ-42, amyloid β-42; ApoE, apoprotein E; TDP-43, *TAR DNA*-binding protein 43; PSI, presenilin; CHMP2B, charged multivesicular body protein 2B; VCP, valosin-containing protein; other abbreviations as in text.

for at least some of the patient's cognitive symptoms. These lesions are cumulative and tend to cause deficits in frontal executive control as well as cognitive and motor slowing.

The role of nuclear imaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) is debated. Although some suggest that SPECT and PET improve differentiation between AD and FTD, these techniques may not offer much beyond careful inspection of the atrophy patterns of MRI. Molecular imaging is emerging as an exciting adjunct to differential diagnosis. Amyloid imaging, particularly the Pittsburgh compound B (PIB), is already proving valuable in the differential diagnosis of AD from FTD. It is still too early to know what role that new MRI techniques including perfusion, diffusion tensor and functional MRI (fMRI) will play in dementia detection and differential diagnosis.

Summary

The diagnosis of degenerative disorders remains a clinical exercise that is largely determined after the taking of a careful history. Table 1.1 emphasizes the clinical features that differentiate the major dementing conditions. Fig. 1.1 shows the typical MRI patterns of the major dementias, while Table 1.2 emphasizes the underlying biology of the various dementias.

Chapter 2

Dementia with Lewy bodies

Caroline A. Racine

Introduction

Dementia with Lewy bodies (DLB) is clinical syndrome characterized by progressive dementia, parkinsonism and neuropsychiatric symptoms (McKeith *et al.*, 2004a). Pathologically, DLB is a synuclein disorder with widespread Lewy body pathology in the brainstem and cerebral cortex. Research has suggested that in individuals over 75 years, DLB is the second most common type of neurodegenerative dementia after Alzheimer's disease (AD). Although prevalent, our understanding of this complex disorder is in its relative infancy. The accurate diagnosis of DLB can be difficult owing to its frequent co-occurrence with AD and perceived similarity to other motor disorders such as Parkinson's disease (PD). However, the identification of individuals with DLB is extremely important because of the potential for life-threatening reactions to neuroleptic medications, and more encouraging, their ability to benefit greatly from treatment with anticholinesterase (AChEI) therapies.

Epidemiology

Epidemiological estimates have suggested that after AD, DLB is the second most common dementia in individuals over 75, with a prevalence rate of approximately 22% (Rahkonen *et al.*, 2003). Similarly, estimates of prevalence based on pathological data have suggested that DLB may represent between 15–35% of all dementia cases (Zaccai *et al.*, 2005), while population-based studies have estimated that DLB accounts for 5% of the population (Rahkonen *et al.*, 2003). In a pathologically confirmed sample, Williams *et al.* (2006) found that DLB was associated with increased mortality rates compared with AD (hazard ratio = 1.88), with a median survival of 78 years in DLB and 85 years in AD. However, rates of institutionalization and survival in long-term care facilities did not differ significantly. A study from Sweden found that patients with DLB utilized twice the monetary resources needed for AD patients, which is strongly linked to a higher need for assistance with activities of daily living and subsequent assisted living placement (Bostrom *et al.*, 2006). Interestingly, in this study, increased monetary resources in DLB were not correlated with cognition (i.e. Mini-Mental Scale Examination [MMSE]) or level of neuropsychiatric symptoms (i.e. Neuropsychiatric Inventory [NPI]), which is more suggestive of placement secondary to motor difficulties. Indeed, other studies have found that motor impairment in DLB is a strong predictor of decreased functional abilities (Murman *et al.*, 2003.) Rapidity of progression has been found to be similar to that of AD (Stavitsky *et al.*, 2006). In summary, DLB is the second-most common form of dementia in individuals older than 75 and, relative to AD, is associated with increased functional impairment owing to motor deficits and a higher risk of mortality.

Clinical features

Diagnostic criteria

Diagnostic criteria for DLB were originally developed by a consensus workgroup (McKeith *et al.*, 1996) and have undergone subsequent revisions, with the most recent criteria being published in 2005 (McKeith *et al.*, 2005). As can be seen in Table 2.1, a central required feature for the diagnosis of DLB is the presence of dementia. 'Core' features of DLB include fluctuations in attention, visual hallucinations and parkinsonism. Additional supportive features include falls, syncope, neuroleptic sensitivity, REM sleep-behavior disorder (RBD), depression and delusions, amongst others. When dementia occurs in the context of well-established parkinsonism (> 1 year), a diagnosis of PD with dementia (PDD) is made. Exclusive of the temporal difference in symptom onset, DLB and PDD have overlapping clinical and pathological features and

The Behavioral Neurology of Dementia, eds. Bruce L. Miller and Bradley F. Boeve. Published by Cambridge University Press.

Table 2.1. Research criteria for the diagnosis of dementia with Lewy bodies[a]

Features	Specific symptoms
Central feature	Presence of dementia (cognitive decline substantial enough to interfere with daily function)
Core features	Fluctuations in attention, recurrent visual hallucinations, parkinsonism
Suggestive features	REM sleep-behavior disorder, severe neuroleptic sensitivity, low dopamine transporter uptake in basal ganglia on SPECT/PET
Supportive features	Repeated falls/syncope, transient unexplained loss of consciousness, severe autonomic dysfunction, hallucinations in other modalities, delusions, depression, relative preservation of medial temporal lobe structure on CT/MRI, occipital hypoperfusion on SPECT/PET, abnormal MIBG myocardial scintigraphy, prominent slow-wave activity on EEG with temporal lobe transient sharp waves

Notes:
SPECT, single-photon emission computed tomography; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; MIBG, *meta*-iodobenzylguanidine.
[a]A diagnosis of dementia with Lewy bodies (DLB) requires the presence of the core feature of dementia. A diagnosis of probable DLB requires the presence of 2/3 core features, or the presence of one core and one suggestive feature. A diagnosis of possible DLB can be made with one core feature, and/or one or more suggestive features in the absence of any core features. Supportive features are frequently associated with DLB but are not part of the diagnostic criteria.
Source: From McKeith *et al.* (2005).

are largely felt to reflect the same underlying disorder (Galvin *et al.*, 2006; Lippa *et al.*, 2007).

Although the diagnosis of DLB has certainly become more standardized through the development of specific diagnostic criteria (e.g. McKeith *et al.*, 1996, 2000a, 2005), studies suggest that the accuracy of a clinical diagnosis of DLB ranges between 34 and 65% (Litvan *et al.*, 1998; Lopez *et al.*, 2002; Merdes *et al.*, 2003) although some studies have found accuracy rates as high as 83% (McKeith *et al.*, 2000a). As will be discussed below, the clinical correlates of DLB are often altered by concomitant AD pathology, which can make accurate diagnosis particularly difficult. Specific clinical features typically associated with DLB are described in more detail below.

Fluctuations in attention

Caregivers frequently report that patients with dementia experience fluctuations in cognitive abilities (e.g. "good days and bad days"). However, research has suggested that, in comparison to other diagnostic groups, patients with DLB show marked differences in attention and awareness, which may fluctuate over the course of minutes or hours. These transient episodes are often associated with altered levels of alertness (e.g. drowsiness) and may take on a confabulatory or delusional quality at times. Although fluctuations in attention are one of the core criteria for the diagnosis of DLB, no operational definition of "fluctuation" has been developed, making it difficult for clinicians to accurately use this feature for diagnosis.

Two measures have been developed to assess fluctuations in cognition via informant interview, the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale (Walker *et al.*, 2000a). Increased scores on these scales were correlated with increased fluctuations in awareness as measured by neuropsychological testing and electroencephalography (EEG) (i.e. variability in theta rhythm). In addition, the scales were found to be effective in the differential diagnosis of DLB from both AD and vascular disease (DLB versus AD: sensitivity 81%, specificity 92%; DLB versus vascular disease: sensitivity 81%, specificity 82%) (Walker *et al.*, 2000b). A study by Ferman *et al.* (2004) examined normal elderly, patients with DLB and patients with AD and compared informants' responses on a 19-item questionnaire about fluctuations symptoms. They found that four symptoms reliably distinguished DLB from AD: daytime drowsiness and lethargy, daytime sleep of >2 hours, staring into space for long periods of time, and episodes of disorganized speech. A study by Bradshaw *et al.* (2004), suggested that the qualitative features of fluctuations may be particularly helpful in the differential diagnosis of DLB. An examination of caregiver responses' on the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale found that patients with DLB tend to show spontaneous transient fluctuations in awareness, with return to near-normal levels of cognition. These fluctuations tend to be independent of the environment and often have no discernible triggers. Most notably, the degree of variation in awareness can be extreme (e.g. can balance

the checkbook one day but not hold a conversation other days). Consequently, one of the most sensitive clinical measures of fluctuation in DLB may be the amplitude of change between best and worst performance (McKeith, 2002). In contrast, patients with AD tend to show contextually dependent periods of increased confusion (e.g. conditions with high memory requirements, novel environments).

Quantitative measures have also shown significant abnormalities in attention in DLB. For example, a study by Ballard *et al.* (2002) found that on a battery of continuous performance tasks, patients with DLB or PDD showed similar levels of impairment in vigilance, reaction time and fluctuating choice reaction times. In contrast, patients with PD demonstrated decreased reaction times, but no fluctuations in attention, while patients with AD showed an intermediate pattern of increased reaction times and fluctuations (Ballard *et al.*, 2002). Measures of brain activity have also shown abnormalities in attention. Using auditory-evoked potentials, DLB patients have been found to have deficits in prepulse inhibition, suggesting decreased ability to filter out irrelevant sensory information (Perriol *et al.*, 2005). Studies with EEG have also demonstrated significant abnormalities in DLB, including diffuse slow-wave theta activity and periodic spike-wave complexes (Yamamoto and Imai, 1988; Doran *et al.*, 2004). A study of EEG in 14 pathologically confirmed cases of DLB found loss of alpha activity and slow-wave transient activity in the temporal lobes (Briel *et al.*, 1999). Thus, in addition to clinically observed features of fluctuating awareness, patients with DLB also show marked abnormalities on quantitative measures of attention abilities.

Overall, although fluctuations in attention may be difficult to define, a significant amount of research suggests that patients with DLB exhibit spontaneous transient alterations in consciousness. These fluctuations have been hypothesized to reflect a decline in acetylcholine (ACh) and/or brainstem dysfunction; however, additional research is needed to further understand this complex symptom and its underlying etiology.

Parkinsonism

Another key feature of DLB is the presence of parkinsonism. In contrast to classic PD, patients with, DLB/PDD tend to have a slightly different constellation of motor symptoms, with greater rigidity, less-frequent resting tremor and more symmetric presentation (Gnanalingham *et al.*, 1997; Del Ser *et al.*, 2000). Additionally, patients with DLB/PDD tend to fall into the postural instability-gait difficulty (PIGD) subtype of extrapyramidal dysfunction, as compared with the tremor dominant (TD) subtype associated with classic PD. In a study by Burn *et al.* (2003), patients with DLB and PDD were found to be more likely to have the PIGD subtype (PDD, 88%; DLB, 69%), while PD subjects were more evenly distributed between PIGD (38%) and TD (62%). A follow-up study by this group found that 25% of the PD patients with PIGD subtype developed dementia over 2 years, compared with none of the TD subtype. Therefore, the presence of PIGD motor subtype may be associated with an increased risk of developing dementia in the context of parkinsonism. Additionally, the PIGD subtype is thought to be less dopamine-dependent than TD and may be linked with cholinergic deficits observed in DLB/PDD (Jankovic *et al.*, 1990). The presence of a gait disturbance may also assist with the differentiation of AD from non-AD dementias, including DLB/PDD. In particular, Allan *et al.* (2005) found that the presence of a parkinsonian gait was found in 93% of patients with PDD and 75% of patients with DLB and that these individuals were at a greater risk for falls (odds risk = 2.3). The presence of parkinsonian gait was able to identify patients with DLB/PDD from those with AD with 87% sensitivity and 84% specificity. Motor symptoms in DLB tend to be less responsive to treatment with levodopa compared with PD and PDD (Molloy *et al.*, 2006; see Treatment/Management section for additional information).

In summary, parkinsonism is a key feature of DLB/PDD; however, the constellation of symptoms differs from classic PD, with increased gait difficulty and rigidity, symmetry of presentation and less-frequent resting tremor. These symptoms are less responsive to dopaminergic agonists and may reflect underlying cholinergic deficits in addition to alterations in dopamine.

REM sleep-behavior disorder

The REM sleep-behavior disorder is a parasomnia characterized by loss of muscle atonia during REM sleep, with resultant complex motor activity during dreaming (Schenck and Mahowald, 2002). Patients with RBD are at an increased risk for injuring themselves and their bed partners during these events, as they tend to "act out" dreams of being chased and/or

attacked, and thus may punch, kick or perform other harmful behaviors during sleep. The condition is more prevalent in men and has a mean age of onset in the mid sixties (Olson *et al.*, 2000). It also appears to be a risk factor for developing a synuclein disorder (Boeve *et al.*, 1998, 2001), with some studies suggesting that up to 65% of individuals with RBD develop parkinsonism and/or dementia when followed longitudinally (Boeve *et al.*, 2003). The presence of RBD may herald the onset of a neurodegenerative condition by 10 or more years before the development of clinical symptoms (Tan *et al.*, 1996; Ferman *et al.*, 1999; Schenck *et al.*, 2002). Frequency estimates suggest that as many as 50% of patients with DLB exhibit RBD at some point, with the presence and severity of the RBD fluctuating over the clinical course (Boeve *et al.*, 2004). Occurrence of RBD is known to affect sleep quality, with qualitative ratings suggesting greater overall sleep disturbance in DLB and increased daytime sleepiness relative to AD (Grace *et al.*, 2000; Boddy *et al.*, 2007); however, the daytime sleepiness finding likely overlaps in part with the fluctuations in attention and awareness seen in DLB.

Pathologically, RBD has been associated with Lewy bodies in the brainstem (see Boeve *et al.*, 2004). Specifically, RBD has been associated with pathology in the pedunculopontine nucleus (PPN) and the locus coeruleus (LC), which involve both cholinergic and noradrenergic neurons. Consistent with RBD being one of the earliest symptoms of a potential underlying synuclein disorder, there is evidence for early Lewy body pathology in the lower brainstem nuclei in DLB (Braak *et al.*, 2003; see Boeve *et al.* [2007] for review). In summary, RBD is a frequently observed symptom in DLB that reflects a complex interaction between Lewy body pathology in the brainstem and neurotransmitter deficits, particularly in ACh. Occurrence of RBD often precedes DLB by 10 or more years, and thus may serve as one of the earliest hallmarks of the disorder.

Autonomic function

Autonomic dysfunction is also a prevalent feature of DLB (Horimoto *et al.*, 2003). When compared with other synuclein disorders, the degree of autonomic dysfunction in DLB is moderate, falling between the severe autonomic dysfunction seen in multisystem atrophy and the mild autonomic dysfunction observed in PD (Thaisetthawatkul *et al.*, 2004). Thaisetthawatkul *et al.* (2004) examined a sample of 20 patients with DLB and found that 95% had autonomic symptoms, with the most common symptoms being orthostatic intolerance (85%), orthostatic hypotension (50%), adrenergic dysfunction (85%), distal anhidrosis (54%) and urinary symptoms (35%). Another study found that lower urinary tract dysfunction was found in all DLB patients studied (11/11), with the most common symptoms being urinary incontinence (91%), increased night-time frequency (82%), urgency (73%), increased daytime frequency (55%) and difficulty voiding (55%) (Sakakibara *et al.*, 2005). Urinary symptoms in particular are thought to be caused by an altered spino-bulbospinal micturition reflex that is dependent on both the cholinergic and dopaminergic pathways, as well as alterations at the level of the autonomic ganglia.

Although orthostatic hypotension and urinary incontinence are common in DLB, these symptoms typically do not appear within the first year of disease onset (Wenning *et al.*, 1999); however, case studies with autonomic symptoms as a presenting feature have been described (Kaufmann *et al.*, 2004). The appearance of autonomic dysfunction can occur prior to, concurrent with or after the onset of parkinsonism and cognitive difficulties (Sakakibara *et al.*, 2005). The presence of autonomic symptoms can assist with differential diagnosis, as patients with DLB and PDD have been found to show greater autonomic dysfunction than those with AD or vascular dementia, with some suggestion of greater dysfunction in PDD relative to DLB (Allan *et al.*, 2007). Importantly, the autonomic features observed in DLB/PDD are associated with poorer outcomes on measures of physical activity, activities of daily living, depression and quality of life (Allan *et al.*, 2006).

In particular, research using *meta*-iodoenzylguanidine (MIBG) cardiac scintigraphy has suggested early autonomic dysfunction in DLB. This compound is a physiologic analogue of norepinephrine and MIBG cardiac scintigraphy is a non-invasive tool for estimating local myocardial sympathetic nerve damage. In a sample of 37 patients with DLB and 42 patients with AD, Yoshita *et al.* (2006) found that reduced MIBG uptake was 100% specific and 100% sensitive to the diagnosis of DLB, irrespective of the presence of parkinsonism. Additional research has found that MIBG is significantly reduced in DLB relative to both controls and patients with PD (Suzuki *et al.*, 2006; Oka *et al.*, 2007). This research suggests that autonomic postganglionic neurons may be one of the earliest regions of Lewy body pathology in DLB, and it suggests the possibility of using autonomic markers as a measure of preclinical disease.

Overall, autonomic symptoms may be an underrecognized feature of DLB, with severity falling