Introduction
When presented with a patient who appears to have moderate to severe cognitive impairment, differential diagnosis is often difficult. The physician may be confronted with a patient in a clinical situation that is not amenable to comprehensive or leisurely diagnostic procedures. Such patients are not typically brought to standard Memory Disorders clinics but may be found in clinical situations that require rapid assessment and management. Typical clinical scenarios for the differential diagnosis and assessment of patients with severe dementia include more complex clinical settings where patient management may be more urgent and becomes the focus of the clinical intervention. Most diagnostic criteria for the differential diagnosis of the various dementias are predicated on mild cases with a clear history of progression from an asymptomatic state. This is often lacking in the patient who presents with severe dementia for clinical ascertainment.

Typical clinical scenarios for the differential diagnosis of severe dementia might include: (1) a clinician is referred a patient who is now behaviourally agitated and/or disruptive. The patient has never been formally diagnosed with a dementia and is now severely impaired prompting admission to long-term care; (2) a patient is referred by a general practitioner who has been managing his/her care but without a formal workup ever having been performed; (3) the specialist is referred a problematic patient for whom severe behavioural disturbances have begun to develop in the community prompting the threat of institutionalisation; (4) a patient presents in the hospital with delirium – as the patient’s delirium clears it becomes evident that the patient is severely demented in addition. It is still the case that the vast majority of patients with dementia do not have specific diagnostic workups or evaluation when they are in the mild to moderate stages. Many patients will progress through their entire illness without a formal evaluation or diagnosis, necessitating a diagnostic evaluation in later stages of illness.

For a comprehensive approach to the differential diagnosis of dementia in general, the reader is referred to several excellent reviews in standard textbooks (e.g. Eastley and Wilcock, 2000). For the rapid assessment and diagnosis of severe dementia, the approach recommended here consists of examining six Axes of Evaluation (Table 1). Evaluating these axes will help the clinician get a complete picture of the patient’s illness, improve the likelihood of successful diagnosis, and to aid in treatment planning, which is the primary purpose of a diagnostic assessment at this stage of illness. The specific axes are discussed in some detail. We then review some specific features of common dementias that may be helpful in distinguishing more severe cases, and finally structured assessment instruments are reviewed with an eye toward their applicability to the severely impaired patient.
Axes of evaluation

**Axis of evaluation: historical**

Aspects of the history of the disorder, if obtainable, may provide significant clues to the patient’s underlying diagnosis or diagnoses. These include the length of illness, if known, the time from first onset of cognitive and/or behavioural impairment to the present time, and characteristics of the patient’s course of illness. Potential types of illness course include steady deterioration, step-wise deterioration with periods of stabilisation, periods of worsening and then improvement, and whether particular medical or historical events are temporally related to alterations in the severity of the disorder or specific symptomatology (Eastley and Wilcock, 2000). Families commonly underestimate the length of illness and multiple informants are best to corroborate and correct the history. Certain structured instruments discussed later in the chapter may be particularly helpful in obtaining information from multiple informants.

The course of associated features discussed below is particularly important in discerning the particular underlying illness. For example, did behaviour or memory problems begin to occur first? If motor problems developed, did they precede or follow the memory disorder? If language problems became prominent, what was the temporal relationship between the development of language difficulties and other cognitive impairments such as learning and memory deficits? For example, the development of behavioural disturbances prior to the recognition by informants of significant learning and memory or language deficits may tend to suggest a fronto-temporal dementia as the primary underlying cause (Perry and Hodges, 2000).

The history of any response to treatment may be helpful. If the patient has been exposed to an acetylcholinesterase inhibitor, whether the patient responded with stabilisation versus a relentless deterioration may be helpful in understanding whether there is an underlying cholinergic deficit. Cognitive stabilisation, particularly if confirmed by cognitive testing scores, may tend to suggest cholinergic pathology which is particularly characteristic of Alzheimer’s disease, Lewy body dementia, and/or vascular dementia. Lack of response to cholinergic agonist drugs, particularly taken together with early onset of behavioural disturbances, may suggest non-Alzheimer pathology such as Pick’s disease or other types of fronto-temporal dementia.

If behavioural symptoms and disturbances have developed as part of the patient’s course of illness, the particular characteristics and historical trajectory may be helpful in ascertaining the nature of the underlying pathology. Affective disturbances, the development of severe anxiety, impairment of insight and judgement and the development of psychosis all have specific implications for particular diagnostic entities. For example, the early development of visual hallucinations in the context of relatively mild learning and memory impairment may be particularly suggestive of Lewy body dementia (McKeith, 2000). Disinhibited behaviour, odd obsessions, and early impairment of insight and judgement all may be consistent with Pick’s disease or other fronto-temporal dementias (De Deyn, Engelborghs et al., 2005). Affective disturbances may be particularly common early in the course of vascular dementia (Reed and Goetz, 2004).

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**Table 1. Axes of Evaluation for Severe Dementia**

<table>
<thead>
<tr>
<th>Historical</th>
<th>Cognitive</th>
<th>Motor</th>
<th>Behavioural</th>
<th>Functional</th>
<th>Medical</th>
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Axis of evaluation: cognitive

Many patients who present for evaluation with severe dementia may have such severe deficits that full cognitive assessment will be difficult or impossible, at least with standard instruments. As with behaviour, the history of a cognitive deficit development may be very helpful if there is a knowledgeable informant. For example, the development of early language dysfunction may be suggestive of primary progressive aphasia (Harvey, Tyrrell et al., 2000), whereas early loss of verbal declarative memory is particularly characteristic of Alzheimer’s disease (Walker, Meares et al., 2005). It would be highly unusual for procedural memory skills to be the earliest and/or primary cognitive symptom in a patient with Alzheimer’s disease. Orientation difficulties and navigational impairments are also quite characteristic of Alzheimer’s disease and would be commonly cited as part of the patient’s history. Whether cognitive impairment developed abruptly or gradually is often useful. If the history is consistent with an abrupt onset of cognitive difficulties a particular medical event should be sought, such as the occurrence of surgery, evidence of a cerebral vascular event, etc. The particular type of course of cognitive impairment should be ascertained if possible. If the cognitive course is found to be staccato or punctuated, this may be more suggestive of underlying vascular pathology. Also characteristic of vascular impairments are periods of cognitive improvement. This may also occur following a particular event such as a hypoxic episode secondary to surgery, etc. Periods of improvement are extremely unlikely to be consistent with Alzheimer’s disease unless the improvement is secondary to medication.

Attention to particular cognitive domains is helpful in ascertaining a cognitive profile. There has been significant research focusing on the particular cognitive profiles characteristic of early dementia patients with a variety of different underlying neuropathology. There have been relatively few or no studies of the characteristics of these cognitive domains in late-stage dementia. Nonetheless, careful characterisation of impairments in a variety of domains may be very helpful.

Language impairments may be one of the most valuable features in the later-stage dementia patient to help the clinician make a diagnostic assessment. The characteristics of the particular language dysfunction, if present, can be helpful. Does the patient have an anomia or fluent aphasia versus a non-fluent aphasia? Is echolalia present, suggesting frontal lobe pathology? Stereotypic phrases, especially repetitive, are also characteristic of patients with Pick’s disease. Coarsening of the patient’s language, the use of expletives or other language not characteristic of the premorbid personality of the patient may be also seen in disorders with impaired frontal functioning. Fluent aphasias are particularly characteristic of Alzheimer’s disease (Kirshner, 1994). Loss of language functioning without prominent learning and memory impairments may suggest specific syndromes such as primary progressive aphasia (Kirshner, Tanridag et al., 1987).

Attention, learning and memory

Before considering the assessment of these cognitive domains, the clinician must ensure that the patient’s hearing and vision are optimised. Poor sensory input will make patients appear more impaired than they actually are and may contribute to the appearance of severe cognitive impairment when in fact such impairment does not exist or at least is much milder than would be the case if not for sensory loss. This can be very difficult to ascertain in the severely demented patient and may contribute significantly to the overall cognitive picture. The use of hearing aids and glasses and correction of very poor vision or hearing to the extent possible may produce significant improvements in cognitive performance.

Particular impairment of attention may be an indication of delirium, especially if it appears to be the primary cognitive symptom (Rabinowitz, Murphy et al., 2003). Delirium should be suspected as a primary problem if the patient is unable to attend to the examiner or if behavioural agitation is so severe as to preclude assessment. Large doses of psychotropic drugs will render an assessment of the patient’s particular cognitive impairments difficult or impossible owing to attentional impairment and must be accounted for in the clinical assessment. Specific defects in
spatial attention, for example, left hemi-spatial neglect, may point to lesions secondary to vascular dementia (e.g. right parietal CVA) (Erkinjuntti, 2000). Assessment of hemi-spatial neglect or spatial attentional impairments must be done only after the clinician satisfies him- or herself that the patient’s visual fields are intact.

Impairment of episodic memory is characteristic of medial temporal lobe-related dementias such as Alzheimer’s, Lewy body dementia and vascular dementia. If such impairment is not present, consider fronto-temporal dementia, Pick’s disease, and/or specific vascular lesions. Praxis and motor skill loss are generally associated with cortical dementia such as Alzheimer’s disease and frontal lobe or fronto-temporal dementias (Perry and Hodges, 2000). If these functions are not lost then this may suggest subcortical disorders such as AIDS dementia, Huntington’s disease, etc. (Eastley and Wilcock, 2000).

Loss of recognition, particularly of loved ones is a cortical sign, suggestive of Alzheimer’s or vascular dementia. Impairments of orientation to time, place or person are particularly characteristic of cortical dementias and are unlikely to be seen in subcortical dementias such as Huntington’s disease or Parkinson’s disease (Chua and Chiu, 2000).

**Axis of evaluation: motor**
The presence of a motor disorder, either hyper- or hypokinetic, particularly if it began relatively early in the course of the patient’s illness is strongly suggestive of underlying subcortical pathology (Assal and Cummings, 1994).

Hypokinetic, i.e. bradykinesia or Parkinsonian-type, symptoms suggest Parkinson’s disease, multisystem atrophy, cortical basal degeneration, depression-associated dementia, progressive supranuclear palsy or AIDS. Hyperkinetic motor problems including chorea and myoclonus are particularly suggestive of Huntington’s disease, Wilson’s disease, or rarely Creutzfeldt–Jakob disease (Assal and Cummings, 1994). Gait impairment or abnormalities may be particularly characteristic of normopressure hydrocephalus (along with other associated features). Parkinson’s disease, multisystem atrophy, cortico-basal degeneration and progressive supranuclear palsy all have characteristic gait impairments which are often associated with a history of falls relatively early in the course of the patient’s illness.

Patients with cortical dementia will develop subcortical motor symptoms in some cases. For example, from 10% to 80% of patients (depending on the study) with Alzheimer’s disease will develop some evidence of extrapyramidal system dysfunction at some point in their illness (Corey-Bloom, 2000). Stereotypic or compulsive movements or ritualistic motor behaviour may suggest fronto-temporal or frontal lobe dementia. Examples might include repetitive picking at the skin of the patient or other repetitive motor movements.

Some apparent motor dysfunction may in fact, represent difficulty in translating intention to movement. Such impairments represent an apraxia rather than a true movement disorder or impairment and may be more commonly seen in patients with cortical dementia such as Alzheimer’s disease. Development of extrapyramidal signs and symptoms early in the course of dementia may lead to a diagnosis of Lewy body dementia; conversely late-appearing extrapyramidal dysfunction may suggest the development of secondary Parkinsonism, etc., which can be unrelated to the primary underlying diagnosis of cortical dementia.

**Axis of evaluation: behavioural**
Of all the axes, behavioural manifestations of severe dementia may be the most helpful in differentiating the various illnesses. While all of the dementias can produce behavioural disturbances, some particular behavioural signs and symptoms are more characteristic of certain disorders (see Chapter 5 in this volume).
As has been suggested earlier, the development of severe behavioural pathology prior to the onset of significant learning and memory impairments is particularly characteristic of frontal lobe and/or fronto-temporal dementias (Binetti, Growdon et al., 1998; Levy, Miller et al., 1998). Such behavioural disturbances are often mistaken for other psychiatric illnesses and are often misdiagnosed, even quite late in the disease process, unless significant learning impairment has become manifest. Patients may be diagnosed as hypomanic if they exhibit poor judgement, there may be a diagnosis of obsessive-compulsive disorder entertained if the patient shows prominent obsessive-compulsive symptoms, and perhaps most commonly a misdiagnosis of major depression may be made if the patient shows increasing apathy and decline in self-care. In frontal or fronto-temporal dementias these types of behavioural abnormalities will often progress to include bizarre obsessions and compulsions, hyper-orality, counting rituals, eating and food ritualistic behaviour, etc. (Binetti, Growdon et al., 1998). The development of Klüver–Bucy type symptoms may occur late in the disorder and may be a helpful differential diagnostic feature (Levy, Miller et al., 1998), for example placing inedible objects in the mouth.

The development of psychotic symptoms is also helpful diagnostically. The most common associated psychotic symptom may be paranoid ideation or delusions, which appears to be connected to memory loss. Occasionally the patient’s course may be characterised by the apparent development of late-life delusional disorder prior to a more severe dementia becoming manifest. Such development of paranoid delusions or ideation is thought to be more characteristically associated with Alzheimer’s disease and/or vascular dementia (Mirea and Cummings, 2000).

Early onset of psychosis by history, particularly if the symptoms include visual hallucinations may indicate Lewy body dementia (McKeith, 2000; Ballard, O’Brien et al., 2001). Visual hallucinations are often of people or animate creatures. While this may be associated particularly with Lewy body dementia, such hallucinatory experiences may be seen in later or severe stages in Alzheimer’s disease and vascular dementia (Ballard, O’Brien et al., 2001). Such visual hallucinations need to be distinguished from hallucinosis without concomitant delusions which may be seen in such syndromes and such disorders as Charles Bonnet Syndrome, related to macular degeneration (Ffytche, 2005). Auditory hallucinations are somewhat rarer and may be initially musical in nature, particularly associated with hearing loss and therefore may be essentially cases of auditory Charles Bonnet Syndrome (Wengel, Burke et al., 1989).

**Affective disturbances**

While full depressive illness (e.g. major depressive disorder) is relatively rare in patients with underlying dementia, depressive symptoms are common in Alzheimer’s disease and other cortical and subcortical dementias. It is not unusual for patients with fairly severe frontal lobe syndromes to be mistaken for depression especially with patients who show decline in self-care and loss of functioning. Antidepressant treatment and even electroconvulsive therapy has been used in a generally futile attempt to improve the patient’s symptoms. Manic symptoms are perhaps less common early in the course of the patient’s illness but if they occur are particularly associated with frontal lobe dementia. Later, in severe dementia, manic-like agitation is common, particularly in Alzheimer’s disease and mixed Alzheimer’s/vascular dementias but less so in frontal lobe dementia or fronto-temporal dementia and subcortical disorders (Neary, 2000).

Apathy, or the lack of goal-directed behaviour is often mistaken for depression in patients with severe dementia but is not identical. The development of profound apathy may be one of the most common behavioural symptoms and is particularly related to the deterioration of certain frontal circuits (Cummings, 2000). The early development of profound apathy in patients may be helpful in distinguishing cortical from subcortical disorders. It is important not to mistake apathy for hypokinesia. Overall mood dysregulation may be more frequent as dementia progresses, at least through the mid stages. Late stages of dementia tend to show lesser affective disturbances.
Anxiety/agitation

The development of anxiety symptoms in the moderately to severely demented patient is generally non-specific and can occur in many types of cortical dementias (Teri, Larson et al., 1988). Anxiety tends to correlate with fear or psychosis in moderately demented patients (especially paranoia) but the correlation in severely demented patients is less clear. Motor restlessness can sometimes be mistaken for anxiety as well as the inverse. Obsessive-compulsive behaviours, particularly repetitive ritualistic behaviours, are particularly characteristic of frontal lobe dementias or fronto-temporal dementias (Snowden, Neary et al., 2002). Such ritualistic behaviour is often of a bizarre nature and includes features such as counting rituals, odd oral habits, or ritualistic oral behaviour as well as odd and bizarre eating habits. In Alzheimer’s disease, patients may develop significant apraxia associated with eating but are less likely to develop odd, obsessive, or ritualistic eating behaviours.

Axis of evaluation: functional

Changes in functional abilities may provide clues to the underlying diagnosis. Functional abilities can be assessed by a variety of instruments including ADL (Activities of Daily Living) scales, physical self-maintenance scales, and newer instruments such as the Older Adult Behavior Checklist (OABCL) (Achenbach, Newhouse et al., 2004). However the use of such instruments has not been systematically tested diagnostically in severe dementia, thus particular profiles are not yet fully characterised. In general, loss of function is closely tied to overall cognitive impairment. More specifically, cognitive deficits and apraxias will lead to particular functional impairments. Loss of functional abilities that depend on specific cognitive domains will be affected by cognitive loss and/or behavioural disturbances.

In frontal lobe dementia or fronto-temporal dementia loss of drive or motivation to perform tasks may be present even when the patient retains the ability to perform the task (Neary, 2000). Obsessive rituals may preclude task accomplishment in frontal lobe dementia. In Parkinson’s disease and other subcortical dementias executive dysfunction (probably from damage to frontal-striatal circuits) may lead to difficulty in organising and sequencing task performance (Cummings, 1988). For example, a patient with Parkinson’s disease and dementia was able to describe how to fix a door but took so long to organise the tools necessary, that his ability to actually complete the task was severely impaired.

In contrast, loss of specific motor skills, i.e. dyspraxias, are particularly characteristic of cortical dementias such as Alzheimer’s disease and mixed Alzheimer’s disease/vascular states (Sjögren, Wallin et al., 1994).

Axis of evaluation: medical

Medical evaluation will provide ancillary clues or direct confirmation of the underlying diagnosis. In patients with either cortical or subcortical dementias the presence of peripheral vascular disease, diabetes or organ-related vascular disorders such as atherosclerotic cardiovascular disease or vascular-related renal impairment will be strongly suggestive of vascular dementia or mixed Alzheimer’s disease–vascular dementia. In the younger patient rapid onset of severe dementia may suggest an infectious cause such as AIDS, Creutzfeldt–Jakob disease, a neoplastic process such as cerebral lymphoma, or unusual metabolic derangements. Head trauma and/or anoxia may initiate cognitive dysfunction that may be stable or progressive and may lead to a very severely demented patient over a relatively short period of time secondary to haematoma formation, hydrocephalus, and perhaps progressive damage (Eastley and Wilcock, 2000).

In alcoholism, Wernicke’s encephalopathy may present abruptly and may have persisting cognitive deficits especially in patients with additional cerebral pathology or continued alcohol consumption (so-called ‘alcoholic dementia’) (Joyce, 2000).
Patients who meet criteria for major depressive disorder who have a history of recurrent affective disorders appear to be at higher risk for the development of dementia. The presence of depression in the mildly demented patient may reproduce a picture of severe dementia (double disability) but may be at least partially reversible (Emery and Oxman, 1994). There continues to be controversy as to whether patients with late-onset psychosis such as late-onset schizophrenia or delusional disorder do progress to dementia, but patients with a history of schizophrenia or psychotic disorder will tend to show more severe deficits if psychotic symptoms are present (Howard and Almeida, 2000).

Schizophrenia itself produces cognitive impairment but it does not appear to be progressive. Thus severe dementia symptoms or signs in a patient with a history of schizophrenia or another chronic psychotic disorder are likely to be secondary to other underlying cerebral pathologies rather than the major psychiatric illness (Sachdev and Reutens, 1994).

Aspects of severe dementia in common dementia disorders

There are many potential causes of severe dementia (Table 2). The reader is referred to standard textbooks on dementia for a fuller discussion all of these disorders. Whether they can be accurately distinguished at late stages of severe dementia is unclear. We discuss here four major diagnostic subgroups for which substantial clinical information is available on the severe stages and for which there is evidence that remaining clinical, behavioural, and biomedical characteristics may help in diagnostic separation.

Vascular dementia/mixed vascular dementia–Alzheimer’s disease

Clinical description

Vascular dementia is usually thought to result from any combination of multiple infarcts secondary to large and small artery vessel disease, cardiac embolic events, and intracranial haemorrhages (Pirttilä, Erkinjuntti et al., 1994). Also included are arteriopathies, small vessel disease leading to ischaemic white matter disease, etc. Vascular dementia, therefore, reflects the interactions between vascular lesions, risk factors, host factors and cognition (Erkinjuntti, 2000). So-called cortical vascular dementia or traditionally called multi-infarct dementia may include classical cortical symptoms such as aphasia, apraxia, agnosia, visuospatial impairment, and executive dysfunction and can be seen in a variety of combinations and courses. The course is occasionally characterised by abrupt onset and fluctuating course with periods of stability and even occasional improvement. Associated symptoms that may aid in diagnosis include focal neurological symptoms and signs including upper motor neuron signs and gait impairment.

So-called strategic infarct dementias may be related to particular infarcts in critical areas such as the thalamus (Kirshner, 1994). Severe memory impairment, fluctuating consciousness, and confusion are observed in many patients and may be confused with delirium (Rabinowitz, Murphy et al., 2003). Apathy, perseveration and mild dysphasia may also be characteristic of strategic infarct dementia (Pirttilä, Erkinjuntti et al., 1994).

Subcortical vascular dementia represents a more homogeneous subgroup than other vascular dementia subtypes (Erkinjuntti, 1987). The cognitive syndrome of subcortical vascular dementia is characterised by a dysexecutive syndrome with slowed information processing. The memory deficit in subcortical vascular dementia is said to be different from that seen in Alzheimer’s disease with less episodic memory dysfunction (Assal and Cummings, 1994; Erkinjuntti, 2000; Schmidtke and Hülì, 2002). The course is often characterised by a slow, less abrupt onset with slow progression. In cortical vascular dementia or so-called multi-infarct dementia, the course is traditionally considered stepwise but this may be difficult to discern in practice. Periods of stabilisation and even improvement support the diagnosis of cortical vascular dementia. Patients with small vessel disease may have a more insidious course that is more gradually progressive. In combination
Table 2. Causes of severe dementias

<table>
<thead>
<tr>
<th>Potentially reversible/arrestable dementias and exacerbating states</th>
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<tbody>
<tr>
<td><strong>Psychiatric</strong></td>
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<tr>
<td>delirium</td>
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<td>depression</td>
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<td>schizophrenia</td>
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<td>cancer syndrome</td>
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<tr>
<td>malingering</td>
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<td><strong>Metabolic</strong></td>
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<tr>
<td>azotaemia</td>
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<td>hyponatraemia</td>
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<tr>
<td>volume depletion</td>
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<tr>
<td>hypo/hyperglycaemia</td>
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<td>hepatic encephalopathy</td>
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<td>hypothyroidism</td>
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<td>Addison's disease</td>
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<td>Cushing syndrome</td>
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<td>Wilson's disease</td>
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<tr>
<td>anemia</td>
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<tr>
<td>acute intermittent porphyria</td>
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<tr>
<td>metachromatic a leukodystrophy</td>
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<tr>
<td>adrenoleukodystrophy</td>
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<tr>
<td>adult polyglucosan body disease</td>
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<tr>
<td>ceroid lipofuscinosis (Kopf’s disease)</td>
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<td>Leigh’s disease</td>
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<td>Hallervorden–Spatz syndrome</td>
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<td>choreoacanthocytosis</td>
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<tr>
<td><strong>Irreversible dementias</strong></td>
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<tr>
<td>cerebrovascular dominant arteriopathy</td>
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<td>with subcortical infarcts and</td>
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<tr>
<td>leukoencephalopathy (CADASIL)</td>
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<tr>
<td>cerebral amyloid angiopathy</td>
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<tr>
<td>Binswanger’s disease</td>
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<tr>
<td>Cortical dementias</td>
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<tr>
<td>Alzheimer’s disease</td>
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<tr>
<td>Mixed dementia</td>
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<tr>
<td>Dementia with Lewy bodies</td>
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<tr>
<td>Fronto-temporal dementia (Pick’s disease)</td>
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</tbody>
</table>

Notes:
- Systemic lupus erythematosus (SLE)
- Vasculitis
- Granulomatous angiitis
- Lymphomatoid granulomatosis
- Polyarteritis nodosa
- Wagener’s granulomatosis
- Anoxic
- Anaemia
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Vitamin deficiencies (B12, folic acid, thiamine, niacin)

- Vascular
  - Ischaemic or haemorrhagic stroke
  - Ischaemic/hypoxic brain lesions

- Trauma
  - Acute or chronic subdural haematoma
  - Post-concussion syndrome
  - Dementia pugilistica

- Infecteds
  - Bacterial: meningitis, encephalitis, brain abscess
  - Viral: HIV and opportunistic infections, meningitis/encephalitis, HSV, progressive multifocal leukoencephalopathy, encephalitis lethargica (sleeping sickness), subacute sclerosing panencephalitis
  - Spirochaetal: neurosyphilis, Lyme disease
  - Fungal: meningitis, encephalitis, brain abscess
  - Prion: Subacute spongiform encephalopathy, CJD, nvCJD

- Neoplasm
  - Primary or metastatic, paraneoplastic syndromes
with the above cognitive features, other symptoms suggestive of vascular dementia include gait disturbance, unsteadiness and falls, urinary frequency, mood impairment, and personality changes (Pirttilä, Erkinjuntti et al., 1994; Erkinjuntti, 2000). While none of these signs and symptoms is specific for vascular dementia, the combination, especially with a history of associated vascular pathology in non-CNS tissues or a known specific CNS event is highly suggestive.

Neuroimaging may be helpful even in the severe patient. Bilateral lesions seen on CT or MRI, multiple lesions, deep white matter pathology, lesions located in the dominant hemisphere and limbic structures all are consistent with vascular dementia (Varma, Adams et al., 2002).

In moderate to severe dementia patients with vascular dementia, abrupt worsening of cognition, if not due to a transient disorder such as infection, may well be secondary to new-onset vascular lesions. As patients with other dementias progress, the likelihood of a vascular pathology mixed with the primary underlying disorder increases.

**Psychiatric and behavioural disturbances** Disinhibited behaviour, especially sexually disinhibited or aggressive behaviour disturbances, may be more common in vascular dementia, consistent with damaged frontal and supraorbital circuits (Erkinjuntti, 2000). Affective disturbances, including psychomotor retardation, emotional bluntness, emotional lability, and incontinence, are also generally believed to be more common in vascular dementia and may aid in the differential diagnosis even in the severely impaired patient.

**Alzheimer’s disease**

**Clinical description**

**Cognitive** In severe Alzheimer’s disease (AD), all cognitive functions are markedly impaired. At this stage, all memory systems are affected. Episodic memory, recollection of one’s past, semantic and linguistic memory, and general knowledge, are profoundly impaired. Short-term memory, the ability to store and recollect a limited number of items within a very limited time delay, is relatively preserved, although more impaired than in earlier stages of the disease. Some aspects of implicit memory, those not involved in semantic processing, may be relatively spared in severe dementia. Emotional signals may be received and reciprocated even after language function has largely been lost. Over-learned skills, habits and expression of memory are relatively spared until the very late stages of the disease (Corey-Bloom 2000).

As dementia advances, language is greatly affected with loss of fluency, echolalia, perseveration or verbal stereotypies, and nonverbal utterances. In contrast, auditory discrimination and repetition may be spared until relatively late in the course of illness. Mutism may ultimately occur, but this is less common. The language disorder of severe dementia differs from global aphasia in that demented patients are generally unable to use nonverbal communication to supplement their verbal deficits (Kirshner, 1994).

Other domains of cognition such as executive function, praxis and visuospatial behaviour are very severely impaired in later stages and are difficult to assess in most instances.

**Psychiatric and behavioural disturbances** These may be conceptualised as falling into three groups: psychomotor disturbances (pacing and agitation); psychiatric disturbances (hallucinations, delusions, depression, anxiety); behavioural disturbances (aggressiveness, inappropriate verbalisation and incontinence).

Pathological, inappropriate pacing has prevalence rates in late stage Alzheimer’s disease anywhere from 10% to 61% (Merriam, Aronson et al., 1988; Teri, Larson et al., 1988; Mirea and Cummings, 2000). Patients may be attempting to return home or wandering without a precise goal. One must consider akathisia related to side effects of medication as a possibly related factor. Studies of agitation show prevalence rates anywhere from 18% to 75% (Eastwood and Reisberg, 1996;
Verny et al., 1998). The wide variability in prevalence may be accounted for by lack of clear criteria as to what constitutes agitation. Agitation may be driven by anxiety and mild–moderate dementia and by psychosis in moderate–severe dementia (Mirea and Cummings, 2000).

Hallucinations may occur on average in 28% of cases (Wragg and Jeste, 1989). It may be difficult to assess hallucinations in more severely demented patients because of the inability to verbally report them. There may be a relationship between visual hallucinations and visual acuity. Delusions are relatively common during the course of severe dementia with frequencies reported between 13% and 73% (Binetti, Padovani et al., 1995). Delusions tend to commonly be paranoid or persecutory in nature. As with hallucinations, verbal reporting of delusions may decrease as dementia progresses (Corey-Bloom, 2000; Mirea and Cummings, 2000).

Depression prevalence ranges between 17% and 35% in severe dementia, though higher rates have been reported (Lazarus, Newton et al. 1987; Teri, Larson et al., 1988; Wragg and Jeste, 1989; Zubenko, 1994; Lebert, Pasquier et al., 1996). Depression may have an atypical presentation in the severely demented with sleep changes, aggressiveness, irritability or agitation. Scales such as the Dementia Mood Assessment Scale (Sunderland, Alterman et al., 1988) may be useful in assessing depression in severe dementia. Anxiety may also be found in patients with dementia but may be difficult to assess in severely ill people who lack verbal expression.

Aggressiveness toward others is a behaviour seen in severe Alzheimer’s disease that is poorly tolerated by family and staff members and nursing homes. Its frequency has been estimated to be between 30% and 55% (Patel and Hope, 1993). Various authors have found that a correlation exists with depression, hallucinations and delusions, loss of self-care, impaired verbal skills, and limited self-expression.

Screaming episodes are a troublesome aspect of severe dementia, and is estimated to occur in up to 25% of cases (Eastwood, 1994). Studies have shown them to be associated with the most severe cases of dementia and may be associated with pain and discomfort or hallucinations. Others have found associations with impairment in ADLs, multiple medical problems, physical restraints and taking psychotropic medications. Patients who scream have more hearing impairment, cognitive impairment, and greater dependency in daily living compared to patients who can express themselves verbally. Studies have suggested that up to a quarter of patients who scream frequently die within six months (Sloane, Davidson et al., 1999).

While incontinence is found in earlier stages in fronto-temporal dementia and dementia with Lewy bodies, approximately 25% of patients with severe Alzheimer’s suffer from incontinence.

Motor disorders and neurological signs In patients with Alzheimer’s, prevalence of extrapyramidal signs has been estimated between 23% and 65% of patients (Franssen, Kluger et al., 1993). Parkinsonism has been found to be related to greater severity of dementia and presence of primitive reflexes. Parkinsonian signs and symptoms are usually of moderate intensity with predominance of akinesia over tremor and are inversely correlated with Mini Mental State Examination (MMSE) scores.

The percentage of patients with severe dementia who are confined to bed ranges from 20% to 41% and contractures are present in 16% of cases (Auer, Selan et al., 1994). Myoclonus has been estimated to occur in 10% of cases and is believed to be related to severe dementia (Mayeux, Stern et al., 1985). Myoclonus in severe dementia must be differentiated from transient, reversible symptoms seen in conditions which affect global cerebral function such as metabolic disorders or infections. Studies have found that falls occur in 29% to 44% of patients with severe dementia (Teri, Larson et al., 1988; Ousset, Vellas et al., 1994; Vellas, Gillette-Guyonnet et al., 2000). Significant relationships between frequency of falls and severity of dementia have also been noted.
Severe dementia with Lewy bodies

Overview

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia in older people, accounting for 10–15% cases at autopsy resulting from an abnormal aggregation of the synaptic protein alpha-synuclein (McKeith, 1996). Diagnosing DLB is of clinical importance because patients with this affliction tend to respond quite well to cholinesterase inhibitors, but they are extremely sensitive to the parkinsonian side effects of neuroleptic medications (Ballard, Grace et al., 1998). DLB has been known by several names in the past and shares clinical and pathophysiological similarities with dementia associated with Parkinson's disease (PDD). A 12-month period has been arbitrarily assigned to discriminate DLB from PDD; onset of dementia within 12 months of onset of Parkinsonism qualifies for a diagnosis of DLB, after 12 months meets criteria for PDD. These criteria are arbitrary, however, and the presentations share more similarities than differences.

Clinical features

Cognitive

The cognitive presentation typically consists of recurrent, episodic confusion in the context of gradual progressive decline (McKeith, 2000). There is a combination of cortical and subcortical impairment with attentional deficits and profound fronto-subcortical and visuospatial dysfunction. These symptoms help distinguish early DLB from AD, though in later stages of DLB, more global dysfunction makes these comparisons in neuropsychological function more difficult. Levels of attention and alertness may fluctuate over minutes, hours or days in up to 75% of individuals.

Psychiatric

The common psychiatric manifestations of DLB, including visual hallucinations, delusions, apathy, depression and anxiety, tend to appear early in the course of the illness and persist into more advanced stages. The visual hallucinations (VH) are similar to those seen in PD and Charles Bonnet syndrome. They are vivid, colourful and three-dimensional, and are usually mute images of animate objects provoking emotions ranging from fear to amusement to indifference. Relative insight into the unreality of these hallucinations is usually maintained after the episode is over. Their persistence helps discriminate them from VH seen in other dementias or delirium. They occur in 46% of DLB cases during the course of illness. Of clinical note, some investigators have noted that the presence of visual hallucinations may predict a better response to cholinesterase inhibitors (Wesnes, 2002). Delusions are seen in 65% of cases at some point in their illness. The quality of delusions is usually complex and bizarre and based on hallucinatory content. This contrasts with blander and less well-formed delusions usually seen in AD. Depression is seen in up to half of DLB cases and is sufficiently more common than in AD to be considered an aid in differential diagnosis.

Neurological

Extrapyramidal signs (EPS) are present in 25–50% of DLB patients at time of diagnosis and most will develop these signs by the late stages of the illness. Parkinsonism may not be present in all cases, however, and autopsy cases confirm that up to 25% of patients with DLB had no recorded EPS (McKeith, 2000). The pattern of EPS in DLB and PDD are different from those generally seen in Parkinson's disease without dementia. In DLB, there is an axial pattern with more postural instability, gait difficulty and facial flatness with fewer tremors. This is consistent with more non-dopaminergic neuronal involvement than is seen in Parkinson's without dementia.

Sleep

Rarely seen in AD, REM sleep disorders with vivid and frightening dreams and simple or complex motor behaviour is frequently seen in DLB. Other sleep disorders seen in DLB include REM sleep behaviour disorder, daytime somnolence and cataplexy; as such this may resemble primary narcolepsy (Arnulf, 2000).
Autonomic dysfunction  Orthostatic hypotension and carotid-sinus hypersensitivity are more common in DLB than in AD. DLB often presents with symptoms of dizziness, pre-syncope, syncope and falls. Urinary incontinence is also seen earlier in the course than is seen in AD.

Differential diagnosis  Main differential diagnoses are AD, vascular dementia, PDD, atypical parkinsonian syndromes including progressive supranuclear palsy (PSP), multiple system atrophy and cortico-basal degeneration and Creutzfeldt–Jakob disease. Retrospective and prospective studies have looked at predictive accuracy of clinical criteria and found variable sensitivity but generally high specificity (McKeith, Galasko et al., 1996; McKeith, 2000).

Investigations  EEG may show early slowing, epoch-by-epoch fluctuation and transient temporal slowing. On MRI, there is generally preservation of hippocampal and medial temporal lobe volume. SPECT shows occipital hypoperfusion and dopaminergic SPECT shows transporter loss in the caudate and putamen. A sensitivity of 83% and specificity of 100% has been reported for SPECT when compared to autopsy in one study (Varma, Adams et al., 2002; Walker, 2002).

Severe fronto-temporal dementia

Clinical features  Fronto-temporal dementia is a form of primary degenerative dementia, affecting people in middle-age, accounting for up to 20% of cases. Dementia onset usually occurs between 45 and 65 years of age though some cases have been reported before age 30 as well as in the elderly. There is an equal incidence in men and women. The mean duration of illnesses is eight years, ranging from two to 20 years, and a family history of dementia is present in about half of cases (Binetti, Growdon et al., 1998; Levy, Miller et al., 1998).

While functions of perception, spatial skills, praxis and memory are relatively preserved, there is an early and profound disruption in character and social conduct. Current consensus diagnostic criteria include several behavioural features. Core features include insidious onset and gradual progression, early decline in social and personal conduct, early impairment in regulation of personal conduct, early emotional blunting and early loss of insight. Worsening social conduct includes poor interpersonal etiquette, tactlessness, and disinhibition. Impairment in regulation of personal conduct includes passivity as well as overactivity, pacing, and wandering. Emotional blunting includes difficulty in expressing primary emotions such as happiness, sadness, and fear as well as social emotions such as embarrassment and empathy. Worsening insight includes disruption in cognitive awareness of symptoms as well as emotional unawareness with lack of concern or distress even in the face of difficulty.

Supportive features of a diagnosis of fronto-temporal dementia include behavioural features, speech and language alterations, physical signs and salient investigational data. Specific patterns of deficits have been found to distinguish fronto-temporal dementia from Alzheimer’s disease, but the applicability of these criteria to severe dementia is uncertain (Perry and Hodges, 2000; Grossi, Fragassi et al., 2002; De Deyn, Engelborghs et al., 2005).

Cognitive and behavioural problems  There is a notable decline in personal hygiene and grooming noted early on in the disorder that progresses as patients become more severely demented. Frontal lobe deficits lead to mental concreteness and inflexibility as well as attentional problems, distractibility, and impersistence. Dietary changes include overeating and preference for sweet food. Perseverative and stereotyped behaviours include simple repetitive behaviours such as humming, head-rubbing, and toe-tapping as well as more complex behavioural routines. These behaviours might include compulsive behaviours such as clock-watching, adhering to fixed routines, or superstitious rituals. Visual perception is relatively spared with preserved visual recognition, naming of pictures, and use of objects. However, utilisation behaviour may be observed. This is a
term coined to represent stimulus-induced behaviour in which patients touch and utilise objects in their visual fields when such use is inappropriate, e.g. drinking from an empty cup (Levy, Miller et al., 1998). While patients have memory impairment, this impairment may be improved with more direct questioning and cues and being given multiple choices.

**Speech and language problems**  Multiple abnormalities in speech and language occur, including lack of spontaneity of speech as well as pressure of speech. Echolalia and perseveration may be featured prominently. Verbal stereotypes include repeated words, phrases or more complex themes. As dementia progresses into the more severe stages, mutism ultimately occurs. While language is severely affected later in the illness, reading aloud may be preserved, though comprehension may be diminished (Kirshner, 1994).

**Physical signs**  While primitive reflexes are usually present, other neurological signs may be relatively absent early on in the disease. Parkinsonian signs of akinesia, tremor, and rigidity develop as the disease progresses and may become severe (Neary, Snowden et al., 1998; Hodges, 2000; Neary, 2000). Hypotension and labile blood pressure may be present and, in conjunction with other neurological dysfunction, may increase risk of falls. Urinary incontinence may also be a sign of more severe illness.

**Investigations**  Routine EEG is almost always normal. Brain imaging may show abnormalities and atrophy in the fronto-temporal areas bilaterally, but sometimes asymmetrically. MRI is more sensitive than CT. Functional imaging such as SPECT scans are most sensitive to changes (Varma, Adams et al., 2002). Neuropsychological testing reveals significant impairment on frontal lobe tests without marked amnesia, aphasia or visuospatial disturbances (Slachevsky, Villalpando et al., 2004).

**Subtypes of fronto-temporal dementia**  Several subtypes have been identified that are believed to be related to regional differences in pathological involvement (Neary, 2000). Patients with prominent disinhibition, purposeless overactivity, distractibility, social inappropriateness and lack of concern have pathological changes in orbitofrontal and anterior temporal cortex. Patients on the other end of the spectrum display apathy, lack of volition, mental rigidity and perseveration. These patients tend to have pathological changes throughout the frontal lobes and the dorsolateral frontal cortex. Finally, there is a subtype characterised by stereotypical, ritualised behaviour with changes in the striatum as well as prominent temporal lobe involvement (Kirshner, 1994).

**Differential diagnosis**  The most important features in differentiating fronto-temporal dementia from other causes of dementia are the severe changes in character and behaviour noted early in the course of the illness. In comparing fronto-temporal patients with AD patients, the behavioural features of loss of social awareness, hyper-orality, stereotyped and perseverative behaviour, paucity of speech, and preserved spatial orientation best discriminate the two groups with good sensitivity and excellent specificity (Perry and Hodges, 2000). Other studies have verified that dietary changes, repetitive behaviours, generalised blunting of emotions, loss of social emotions, and disordered social behaviour are valuable in differentiating fronto-temporal patients from AD patients and vascular dementia patients.

**Assessment instruments – clinical assessment tools**  Clinical assessment instruments developed for dementia patients have generally focused on evaluation and tracking of patients in the mild to moderate stages of severity. Only recently have tools been designed or previously developed instruments have been extended to enable utilisation in the severely demented patient. We review instruments here that may be of particular applicability to the clinical assessment, staging, and/or management of patients with severe dementia.
Two tools are commonly used to stage dementia. The Clinical Dementia Rating scale (CDR) and the Global Deterioration Scale (GDS). The CDR is based on caregiver and patient interviews. Although it was not designed initially to be sensitive to severe dementia, an extended version shows correlation with increasing functional impairment, decreased independence and long-term care (Dooneief, Marder et al., 1996). A score of 0 to 5 is given in six different cognitive areas including memory, orientation, judgement and problem-solving, community affairs, home and hobbies and personal care (Heyman, Wilkinson et al., 1987). Ratings consistent with profound (Stage IV) and terminal (Stage V) have been shown to predict shortened survival (Ferris and Yan, 2003).

The GDS system consists of the GDS, the Brief Cognitive Rating Scale (BCRS), and the Functional Assessment Staging (FAST). The GDS is a seven-stage rating system based on clinical, patient, and informant interview (Reisberg, Ferris et al., 1982). The BCRS is a semi-structured clinical assessment to evaluate cognitive parameters such as concentration, recent memory, remote memory, and orientation. The FAST is informant-interview-based and examines five to 10 successive stages through which patients with dementia will pass (Selan and Reisberg, 1992). This scale may be useful for patients with more severe dementia impairment because Stages VI and VII contain several substages that describe the level of impairment in a specific way (Ferris and Yan, 2003). Usefulness of this scale diagnostically is somewhat unclear.

Cognitive evaluation
As patients with severe dementia are generally too impaired to complete the more typical instruments used at early stages such as the Alzheimer’s Disease Assessment Scale – Cognitive subscale (ADAS-Cog), MMSE or other batteries, the Severe Impairment Battery (SIB) was designed to give a way to assess patients below the level of conventional instruments (Schmitt, Ashford et al., 1997). The SIB is a clinician-rated, performance-based evaluation with 40 questions. It describes nine areas of function to assess including social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction, and orientation. Items are presented as single words or one-step commands combined with gestural cues and can be repeated. The SIB has shown utility in severe dementia patients (MMSE < 10) and has been successfully used in drug treatment trials to show treatment-related improvement (Tariot, Farlow et al., 2004).

Behavioural Disturbances
Several structured interview-based instruments are widely used for behavioural assessment including the Neuropsychiatric Inventory (NPI) and the BEHAVE-AD.

The NPI is based on a clinician interview of the caregiver (Cummings, Mega et al., 1994). The caregiver is asked to rate the frequency and severity of behavioural pathology in 10 domains including delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behaviour. In addition, caregivers are asked to assess the impact of each symptom on themselves. A frequency × severity score is then calculated and totals are obtained across all the domains. The NPI has proved to be useful in assessing development of behavioural pathology and in judging the impact of treatment on those problems. A nursing home version is available.

The BEHAVE-AD is also interview-based with the caregiver and is designed to assess behavioural pathology (Reisberg, Auer et al., 1996). Twenty-five symptoms are grouped into seven categories. Recently a frequency rating has been added to the basic scale (Monteiro, Boksay et al., 2001), similar to the NPI.

Functioning
The Alzheimer’s Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) uses information from caregivers to rate performance of 19 daily activities. Performance is rated 0–1 or 0–5 depending on the question (Galasko, Bennett et al., 1997). The scale is best utilised for
community dwelling patients as questions are not geared to nursing home residents. The Disability Assessment in Dementia (DAD scale) assesses 10 domains of instrumental and basic activities of daily living (Feldman, Gauthier et al., 2001).

**Multi-informant caregiver-based assessment**

A new approach to dementia assessment is represented by the Older Adult Self-Report (OASR) and the Older Adult Behavior Checklist (OABCL) (Achenbach, Newhouse et al., 2004). These instruments are designed for the caregiver, family members, and other informants to complete about the patient. For milder patients there is a self-completed version (OASR); however, for more severe patients it is presumed that only the informant versions will be utilised (OABCL). This 127-item scale is completed without input from the clinician and requires no clinician involvement except to ensure completion of the forms. It provides multi-informant ratings of function, psychopathology and behaviour. Self-administered in 15–20 minutes, the OABCL obtains informant reports of diverse aspects of adaptive functioning and problems. The OABCL can be utilised by a spouse, partner, family members, friends, caregivers, home health aides, residential staff, and health care providers. The OASR/OABCL are scored on profiles that make it easy to see similarities and differences between self-reports and reports by other people. The profiles display scale scores in relation to gender- and age-specific norms. Clinical staff can score profiles by hand in 5–10 minutes or by computer in about two minutes.

The OABCL produces a comprehensive picture of seven syndrome subscales including anxious/depressed, worries, somatic complaints, thought problems, functional impairment, memory/cognition problems, and irritable/disinhibited. These are factor-analytically derived syndrome subscales based on large elderly normative populations along with elders receiving treatment. Scores are plotted as t-scores allowing rapid assessment of normal and abnormal ranges for each syndrome subscale. These allow comparison of self-ratings (in mild cases) and multiple informants for more severe cases.

Preliminary data suggests that the OABCL exhibits excellent correlation with diagnosis of dementia in the Memory Clinic and high correlations with NPI subscales in patients with behavioural disturbances (Newhouse, Brigidi et al., 2004). Though no studies in severe dementia have yet been done, this instrument shows considerable promise as a tool for comprehensive assessment and tracking as well as the effects of treatment. Test/re-test reliability has been excellent and similar instruments have been shown to be sensitive to treatment effects in other populations. Extensive information regarding the utilisation of this scale is now available for research and clinical use (Achenbach, Newhouse et al., 2004).

**Conclusion**

Despite advances in the understanding of the nature of the various dementias and the availability of sophisticated diagnostic evaluation and pharmacological treatments, many patients will present for management with severe dementia having never been evaluated previously. The diagnosis of such patients can be quite challenging as many of the distinguishing clinical features of the various dementing disorders that may have been present early in the course of the illness have now disappeared and many of the neuropsychological and the biomedical distinguishing characteristics may also no longer be present. Nonetheless, careful attention to the axes of evaluation described here and armed with a knowledge of the clinical characteristics of the major dementia groups, clinicians and investigators may still be able to arrive at a differential diagnosis or a diagnostic formulation with some degree of confidence. While relatively few studies have been performed attempting to diagnose, characterise or treat severe dementia, such studies may be forthcoming in the future, particularly with the advance of increased efficacy of treatments for late stage dementing illness. As the efficacy of treatments, both pharmacological and psychosocial, enable more dementia patients
to survive longer periods of time, the challenge of managing severe dementia patients will only increase.

References


Assessment and Diagnosis of Severe Dementia


