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Diagnosis and Differential Diagnosis of Dementia

Richard Camicioli

Department of Medicine (Neurology), University of Alberta, Canada

Introduction

The burden of dementia, a substantial public health concern, is felt in all societies. After defining dementia, in the following chapter we discuss the diagnosis and differential diagnosis. We outline an approach to the general diagnostic work-up in this chapter, with detailed recommendations for specific situations (e.g. rapid progression, young onset, prominent depression, question of normal pressure hydrocephalus) in the chapters to follow.

Definitions

Dementia is a syndrome in which multiple-domain cognitive impairment, generally including memory impairment, is sufficiently severe to significantly affect everyday function. Memory and one additional area of cognitive impairment, including aphasia, apraxia, agnosia, and executive dysfunction, are required to be affected according to common criteria (DSM-IV). There are other generic dementia criteria, including the ICD-10 criteria,which require that several domains are affected, and newer dementia criteria are being developed (i.e. DSM-V) (Table 1.1). Some criteria have not required memory impairment as a necessary condition for dementia, since it might not be prominently impaired in non-Alzheimer's dementias, and even occasional patients with Alzheimer's disease can exceptionally have relatively preserved memory.

There are specific criteria for patients with cerebrovascular disease (vascular cognitive impairment/ vascular dementia) and Parkinson's disease (Parkinson's disease dementia - PDD), both of which have a high risk of dementia. Recently, new criteria for Alzheimer's disease (AD) have been proposed to take into account developments in biomarkers and recognition of a prodomal state, termed mild cognitive impairment, which often leads to dementia. Dementia with Lewy bodies (DLB) shares pathologies of Parkinson's disease and Alzheimer's disease. Frontotemporal dementia also has distinct features and varied pathology, and typically presents with prominent behavioral features (behavioral variant frontotemporal dementia) or language impairment (non-fluent/agrammatic/ logopenic primary progressive aphasia or semantic dementia). Some patients, particularly those with logopenic progressive aphasia, actually have Alzheimer's disease pathology. Some frontotemporal dementia patients develop co-existent motor neuron disease. Progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and Huntington's disease are other neurodegenerative disorders that usually have obvious and prominent motor features; patients with these conditions often have cognitive and behavioral problems and develop dementia. Thus, while diagnostic criteria for the dementias are in evolution, making a diagnosis and identifying the specific etiology remain critical in the clinical setting.

Distinct pathologies can be successfully identified by current clinical criteria, albeit with a rate of misdiagnosis. The recognition of unusual presentations, atypical onset, and the prodromal phase of dementias may be assisted by biomarkers (which may differ in these settings). Clinicians must

Dementia, First Edition. Edited by Joseph F. Quinn.

Table 1.1 Comparison of key guidelines for the assessment of dementia

Guideline	Mental status	Activities of daily living	Behavioral symptoms	Blood tests	Brain imaging	Other tests
AAN, 2001	Yes	No specific recommendation	Depression screen	CBC, TSH, B12, glucose, electrolytes, BUN/Cr, liver function tests	Structural imaging	Selective
Canadian Consensus, 2004	Yes	No specifc recommedation, but highlights dementia is a clinical diagnosis	No specific recommendation, but highlights dementia is a clinical diagnosis	B12, TSH, electrolytes, calcium, glucose	CT or MRI: <60, rapid onset (<2 mo), short duration (<2 yrs), head trauma, neurological signs or symptoms, urinary incontinence, gait disorder, cancer, anticoagulants, atypical cognitive features	Selective
European Federation of Neurology, 2010	Yes, and assess specific domains	Yes	Yes	B12, folate, TSH, calcium, glucose, CBC, renal and liver tests	CT or MRI may be used	Dopamine SPECT scan to differentiate AD and LBD

AD, Alzheimer's disease; BUN, blood urea nitrogen; CBC, complete blood count; CR, creatine; CT, computed tomography; LBD, Lewy body dementia; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; TSH, thyroid-stimulating hormone.

nevertheless recognize these possibilities. Also, it is important to keep in mind that overlapping pathology often occurs in older patients with cognitive impairment or dementia, which might influence the clinical picture.

Other chapters consider young-onset and rapidly progressive dementia. Here we consider dementia in people 65 years of age and older.

SCIENCE REVISITED

The clinical diagnosis of Alzheimer's diease is confirmed at brain autopsy in 90% of patients. The clinical diagnosis of vascular dementia, Lewy body dementia, and frontotemporal dementia predicts the brain autopsy diagnosis, but not as well as a clinical diagnosis of Alzheimer's.

Epidemiology

In 2010, dementia was estimated to affect 35.7 million people world-wide. Alzheimer's disease is the most common dementia in people older than age 65 years, yet Alzheimer's disease pathology is often accompanied by vascular disease or Lewy bodies. The latter two types of dementia can also occur in "pure" form. The diagnosis of dementia increases mortality risk, regardless of age or etiology of dementia. It is important to recognize that dementia may lead to a debilitated state and death in order to direct interventions appropriately, including palliative approaches. Prediction of death can be challenging in patients with dementia, which may make initiation of formal palliative care services difficult. (Chapter 9 provides a detailed discussion of the role of palliative care in dementia.)

Assessment

History

Obtaining an accurate medical history is central to the diagnosis of dementia. This should identify and qualify the nature of the symptoms as well as their onset and progression. A critical challenge to obtaining an accurate history is that patients themselves may not be able to self-monitor because of their cognitive problems, so obtaining a collateral history is necessary. Memory impairment is a central feature of many dementias and can be expected to interfere with recall of key historical events. In addition, lack of insight can occur in dementia and interfere with the acknowledgment of symptoms. It is important to interview the informant and patient separately at some point in the diagnostic process. While some standardized questionnaires are useful in identifying complaints, these do not replace a thorough history, which remains the gold standard. Instruments that can complement the clinical history include the AD8 dementia screening questionnaire, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), the Deterioration Cognitive Observation Scale (DECO), and the Alzheimer Questionnaire (AQ). The General Practitioner Assessment of Cognition (GPCog) includes both a cognitive screen and questions regarding cognitive changes and activities of daily living based on caregiver report, which improves sensitivity and specificity for the diagnosis of dementia.

While the initial focus of the history should be on cognitive complaints and their functional implications, which allow for meeting dementia criteria, psychiatric and behavioral changes need to be identified as they are often present in early dementia, and can be prominent in some patients. In many patients referred for cognitive decline, psychiatric issues may predominate and may be the cause of the so-called cognitive decline. Depression should routinely be assessed in patients with cognitive complaints. It is key to screen for depressive symptoms, and scales such as the Geriatric Depression Scale, which has 15- and 30-item versions (www.stanford.edu/~yesavage/GDS.html), and the Montgomery-Asberg Depression Scale, can be helpful in this regard, though the gold standard is a psychiatric evaluation using a standardized interview schedule. The Cornell Scale for Depression in Dementia is validated for the dementia population. Depression can be a risk factor for or coincident with the diagnosis of dementia. Moreover, it can occur *de novo* in the course of dementia. Although they are distinct symptoms, depression and anxiety often co-exist. Other mood symptoms, such as elation or euphoria, also can occur in dementia, but primary psychiatric disorders should be kept in the differential diagnosis if these are prominent.

While not absolute, the nature of cognitive deficits can help in differentiating depression from dementia. Patients with depression have long response latencies

whereas typical patients with Alzheimer's disease respond with normal latencies. Memory impairment in depression is related to retrieval problems, rather than problems with encoding, where cueing does not improve recall. Alzheimer's patients also have additional cognitive deficits, particularly in visuospatial and language domains, that would not be seen in depression. As noted, depression can coexist with dementia and it is common in Alzheimer's disease as well as vascular dementia and dementia with Lewy bodies.

Other neuropsychiatric problems that should be considered include positive symptoms such as disinhibition, irritability, agitation, aggression, or abnormal motor behavior as well as negative symptoms such as apathy. Delusions and hallucinations are also highly relevant. These symptoms can be assessed using standardized instruments such as the Neuropsychiatric Inventory (NPI). They can occur early in the course of dementia and can evolve over time. The Frontal Behavior Inventory can help with the differentiation of Alzheimer's disease from frontotemporal dementia. Patients with frontotemporal dementia often lack emotional responsiveness and can develop apathy, which can be mistaken for depression but is characterized by lack of motivation. Psychotic features, particularly visual hallucinations, are characteristic of PDD and DLB. Delusions are not as specific but can be equally disturbing to family members.

It is critical to identify functional impairment. By definition, patients with mild cognitive impairment (MCI) do not have substantial functional impairment, while patients with dementia do. Practically speaking, at the time of diagnostic evaluation, assessment of basic and instrumental activities of daily living is performed by asking the patient and their caregiver how the patient performs everyday tasks. Basic activities of daily living such as getting in and out of bed, dressing, walking, toileting, bathing, and eating are not affected early in the course of dementia. Instrumental activities of daily living (IADL) such as answering the phone, taking pills, handling money, shopping, cooking, and driving are affected early in the course.

Typically a standardized questionnaire is used to address activities of daily living. Examples include the Functional Activities Questionnaire (FAQ) which addresses IADLs, the Lawton and Brody IADL and Physical Self-Maintenance Scale and the OARS Functional Assessment Questionnaire. Assessment is not as straightforward as it seems, as there is often a mild degree of functional impairment in MCI, where such impairments may predict future cognitive decline. Moreover, a given patient's living situation might not tax their functional capacity. Conversely, a patient who is working might have some workplace impairment despite relatively well-preserved cognitive assessment. In the setting of a disorder that affects motor function, such as Parkinson's disease or after a stroke, it can be challenging to determine if a change in a patient's function is related to cognitive or motor function.

Prescribed and over-the-counter medications, as well as substances of abuse (notably alcohol), are important to identify as they might contribute to cognitive impairment. If the patient is not able to list these accurately, this suggests an important area of functional impairment that requires intervention. All co-morbid medical conditions need to be identified. Vascular risk factors such as smoking, diabetes, obesity, hyperlipidemia, hypertension, atrial fibrillation, and non-central nervous system (CNS) vascular disease (cardiac, renal, peripheral) increase the risk for cerebrovascular events, which can contribute to dementia, and can be covert. These are risk factors for dementia in the absence of identifiable stroke as well. Symptoms suggestive of cancer, especially in patients with a rapid course, raise the concern of direct or indirect central nervous system involvement.

A detailed family history is critical. While familial dementia commonly has a young onset, risk of dementia in older people is also increased in the setting of a family history. A third to half of people with frontotemporal dementia have a family history compared to roughly one in 10 patients with Alzheimer's disease. At a minimum, all first-degree relatives should be identified and the presence of neurological disorders determined. This history should not be restricted to examining dementia risk, since disorders such as Parkinson's disease and motor neuron disease may be associated with an increased risk of dementia in family members. If the family history is consistent with a hereditary dementia, testing can be offered but this should be done after appropriated counseling. At-risk family members should only be tested after genetic counseling. Huntington's disease is a relatively common cause of dementia in younger individuals,

but can occasionally be identified for the first time in older patients without an obvious family history.

Physical examination

General examination

The general examination might identify specific co-morbid conditions, such as atrial fibrillation, congestive heart failure or chronic obstructive pulmonary disease (COPD). An abdominal or rectal mass, suggesting a neoplasm, might be uncovered. These might directly or indirectly contribute to cognitive dysfunction. Some findings on general examinations, such as postural hypotension, may suggest a specific diagnosis such as dementia with Lewy bodies.

Cognitive evaluation

Cognitive assessment at the bedside is important for both differential diagnosis and rating the severity of cognitive impairment. Cognitive domains to be assessed correspond to those involved in the diagnosis, including attention, orientation, memory, executive function, language, praxis, and visuospatial abilities.

Several standardized assessment instruments have improved clinicians' abilities to assess cognition. While these are helpful, the clinician needs to be able go beyond such instruments at times, given their limitations in scope and sensitivity. The Mini-Mental Status Examination (MMSE) is the most commonly used instrument and its advantages include its widespread use and extensive validation. Disadvantages include its relative insensitivity to the diagnosis of dementia, which may be partly related to exclusion of some cognitive domains, such as executive function. Given the availability of superior instruments, its use will likely decrease over time. The MMSE may not be sensitive to memory impairment since it only relies on the immediate recall of three words. Expanded versions of the MMSE such as the 3MS might have increased sensitivity. More comprehensive standardized instruments include the Short Portable Mental Status Examination, the Montreal Cognitive Assessment (MOCA) (www.mocatest.org), and the Addenbrooke Cognitive Examination-Revised. The Frontal Assessment Battery evaluates aspects of frontal lobe function, and can be used as a complement to tools such as the MMSE that do not specifically address this cognitive domain. It can assist in the differentiation of AD from frontotemporal dementia and may be useful in assessing parkinsonian disorders.

Neuropsychological testing, which affords a comprehensive, objective, and standardized approach to quantifying cognitive impairment, is helpful for diagnosis and differential diagnosis, but is not available in all settings. It is particularly relevant in mild or questionable cases, in cases where malingering is suspected, or in subjects for whom ceiling or floor effects might obscure interpretation of results on simplified tests (for example, people with very high or very low levels of education). Patients with clear changes and obvious deficits on simpler tests may not require neuropsychological testing. Moreover, it should be borne in mind that subjects may have test scores that are abnormal based on statistical population-based comparison but that this may represent a "normal" score or minimal change for that individual. Neuropsychological tests can be helpful in following change over time. The shorter tests do not necessarily validly assess cognitive subdomains as can be done by neuropsychological batteries, which may be important in differential diagnosis.

☆ TIPS AND TRICKS

When should neuropsychological tests be used?

- In patients with worrisome history but good performance on mental status exam.
- In cases where malingering is suspected.
- To distinguish depression with cognitive symptoms from neurodegenerative disease.

Neurological examination

A complete general neurological examination is important. On cranial nerve testing, olfactory deficits are common in Lewy body dementia. Visual field defects or higher order visual defects may suggest cerebrovascular disease affecting the visual pathways or a posterior evolving dementia, such as the visual variant of AD or the Heidenhain variant of Creutzfeldt–Jakob disease (CJD). Other cranial nerve examination clues to the etiology of dementia can include vertical supranuclear gaze difficulty suggesting progressive supranuclear palsy. Nystagmus and restricted eye movement can be seen in Wernicke's encephalopathy, which can

evolve into alcoholic dementia. Gaze-evoked nystagmus is non-specific and be seen with many causes of cerebellar degeneration. Upper motor neuron facial weakness suggests pyramidal involvement. Lower motor neuron facial weakness and involvement of other lower cranial nerves may provide a clue to involvement of the subarachnoid space due to an inflammatory, neoplastic or infectious process. Bulbar difficulties are seen in processes involving the brainstem or upper motor neuron lesions.

Focal weakness with other pyramidal signs can be seen in patients with cerebrovascular disease. Pyramidal signs can also be a clue to the presence of motor neuron disease (amyotrophic lateral sclerosis – ALS), in which features of lower motor neuron dysfunction can also be found (fasciculations, atrophy). Up to 10% of frontotemporal dementia patients can develop features of ALS, which has a substantial impact on prognosis and hence on long-term planning.

Cerebellar dysfunction in dementia might indicate a specific neurodegenerative disorder such as multiple system atrophy, a paraneoplastic disorder, CJD or celiac disease.

Neuropathy can be seen in renal failure, diabetes, vitamin B12 deficiency, alcohol exposure or paraneoplastic disorders. Neuropathy can also be seen in HIV, Lyme disease or hepatitis C infections which all can be associated with cognitive impairment and dementia. In addition, some mitochondrial disorders or disorders of central white matter (leukodystrophies) can be associated with neuropathy. Mitochondrial disorders are also classically associated with myopathy, myoclonus, and seizures.

Gait assessment is critical in patients with dementia. While it is less often impaired in AD, it is commonly affected in PDD, vascular dementia, and dementia with Lewy bodies.

It is important to examine for adventitious movements. The triad of tremor (rest tremor), bradykinesia, and rigidity indicates parkinsonism, as seen in dementia with Lewy bodies or Parkinson's disease. Chorea would suggest Huntington's disease, neuroacanthocytosis or another Huntington-like disorder. Dystonia in older adults may suggest a cerebrovascular event, either in the basal ganglia or thalamus. In addition to dystonia, unilateral chorea or tremor in an older adult should lead to consideration of a cerebrovascular event or other lesion, generally involving frontostriatal circuits, which can additionally be involved in cognition.

Myoclonus can be seen in degenerative disorders, including advanced AD and DLB, and more rarely Huntington's disease and frontotemporal dementia. Focal myoclonus as well as asymmetrical apraxia, parkinsonism, and dystonia is characteristic of corticobasal ganglionic degeneration. Myoclonus is included in the diagnostic criteria of CJD, though it may not be seen early in the illness. When CJD is considered, it is important to keep alternative entities in mind. In terms of systemic illness, myoclonus is most often a manifestation of any cause of encephalopathy, including common disorders such as renal or hepatic disease (asterixis), as well as rarer autoimmune disorders such as steroid-responsive encephalopathies associated with thyroid disease or antibodies to the CNS. Rare disorders such as mitochondrial disease are characterized by myoclonus.

Laboratory studies

Blood and spinal fluid

Recommended tests for the assessment of dementia include blood work-up, including complete blood count (CBC), glucose, electrolytes (including calcium), renal and hepatic tests and thyroid function. Testing for vitamin B12 or folate deficiency is recommended. In many areas grains are supplemented with folate, making folate deficiency unlikely unless there are other reasons for malabsorption, in which case malabsorption of other B-vitamins should be considered. If indicated, based on the patient's history, assessment for chronic infections that can cause dementia, such as HIV or syphilis, is indicated.

If the presentation suggests a delirium additional testing should be done to rule out possible causes of delirium such as acute infections (cultures, chest x-ray, urinalysis). Work-up for inflammatory or autoimmune disorders should also be considered. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or more specific tests such as rheumatoid factors and antinuclear antibodies can provide clues to the presence of an autoimmune disorder. Additional work-up is indicated if specific disorders such as vasculitis, Sjögren's syndrome, sarcoidosis or a paraneoplastic or non-paraneoplastic autoimmune encephalopathies are being considered.

A complete work-up may include cerebrospinal fluid (CSF) examination, which can also be used to

seek evidence for acute or subacute infections, autoimmune or inflammatory disorders or neoplastic involvement of the central nervous system. While proteins in the CSF, such as beta-amyloid, tau and phosphorylated tau, can be used to provide evidence for AD, these tests are not currently used routinely. This may change as additional evidence accumulates for their utility in treatment decisions, and they become more readily available. The use of CSF markers in the differential diagnosis of CJD is controversial, because the markers (14-3-3, tau, S100B) are non-specific. Nevertheless, CSF examination is important in rapidly progressive dementia to rule out or rule in treatable dementia and the CSF markers may improve diagnostic certainty in the appropriate clinical context.

Imaging

Structural imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) scans can rule out structural contributions to cognitive decline (stroke, subdural hematoma, tumors) and are increasingly being used to "rule in" specific diagnoses, when atrophic or vascular changes are observed that are consistent with a particular dementia diagnosis. While MRI is more sensitive than CT, CT scans can still provide meaningful information. For example, vascular changes, subdural hematomas and many tumors, while better delineated on MRI, can be seen quite well on modern CT scans. Similarly hydrocephalus can be identified on CT in cases of suspected normal pressure hydrocephalus (NPH). In NPH and other forms of hydrocephalus, MRI allows examination of the posterior fossa to search for lesions that might lead to obstruction of CSF flow. An absence of ventricular enlargement on CT can exclude NPH and help to redirect further investigation and diagnostic considerations. A caution in interpreting ventricular enlargement is that it might be due to global atrophy.

In addition to better resolution, specific MRI approaches (such as gradient echo MRI) can identify findings such as cerebral microbleeds, which are not evident on CT. These suggest amyloid angiopathy and are often seen in association with white matter disease, which is found patients with vascular cognitive impairment or dementia. MRI imaging might help to discern an atrophy pattern consistent with degenerative syndromes such as progressive supranuclear palsy PSP, multiple system atrophy (MSA) or corticobasal ganglionic degeneration. Brain atrophy is less prominent in DLB and PDD than in AD and it is not prominent in PD until cognitive decline ensues. On the other hand, atrophy is prominent in frontotemporal lobar degenerations.

Dopamine transporter imaging (^{123}I-fluoropropyl-2-beta-carbomethoxy-3-beta(4-iodophenyl)nortropane single photon emission computed tomography: FP-CIT SPECT) is useful in differentiating DLB from dementias that do not affect the dopaminergic system. Functional studies examining perfusion (Tc-hexamethylpropyleneamine oxime [HMPAO] SPECT) or glucose metabolism (fluorodeoxyglucose [FDG] positron emission tomography [PET]) provide additional information that can be useful in the differential diagnosis of dementia. Building on previous work with the C-11 compound Pittsburgh Compound B (PIB), the availability of readily accessible ligands, such as F-18-fluorbetapir, that can bind amyloid will likely assist in differential diagnosis but, as with all imaging modalities, will have to be interpreted in the clinical context. Newer techniques are becoming available that examine brain networks and their connectivity.

Types of dementia

Specific features of the history, examination, and investigations can assist in the differential diagnosis of dementia (Figure 1.1, Table 1.2). After reversible conditions have been ruled out, the clinician should attempt to make a specific diagnosis of dementia type. The most common causes of dementia are Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia. Here some features of particular importance are discussed.

CAUTION

Be vigilant about the possibility of treatable diagnoses, even though these are quite rare with dementia. Other chapters include more detailed discussion of treatable entities like depression and NPH, or treatable encephalopathies presenting as rapidly progressive dementia or young-onset dementia.

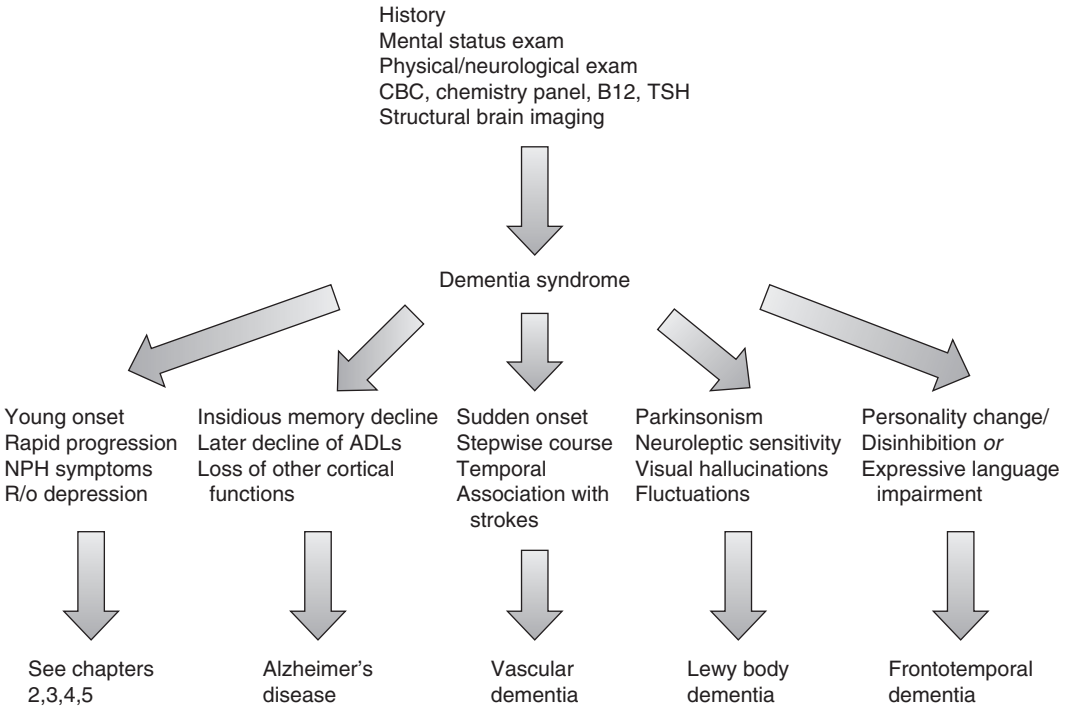

Figure 1.1 General approach to differential diagnosis of dementia.

Alzheimer's disease

Alzheimer's disease typically presents with insidiously progressive memory impairment, which eventually involves executive function and visuospatial function. Involvement of memory and at least one other cognitive domain is necessary. In addition, the cognitive deficits must be sufficient to affect function, distinguishing it from mild cognitive impairment. A key is that there should be no other specific cause of the cognitive impairment, such as a delirium or a psychiatric disorder, a principle that holds for all primary degenerative dementias. The AD criteria have been revised recently given the realization that pathological changes likely precede clinically manifest disease by years, if not decades. In addition, the new revision acknowledges that behavioral changes, in additional to cognitive changes, may interfere with function. Among developments since the 1984 criteria were published is refinement of the diagnosis of frontotemporal lobar degeneration and dementia with Lewy bodies, which now have their own criteria. It is acknowledged that rare patients might meet criteria for a specific dementia diagnosis and yet have positive biomarkers for a different one.

While AD is most commonly a memory disorder, focal cortical presentations are common, especially in younger patients. The differential diagnosis of this group of patients may be aided by biomarkers that can be used to indicate Alzheimer pathology, with the caveat that mixed pathology would not be excluded.

Some patterns are highly suggestive of Alzheimer pathology, while others suggest alternative pathology. Posterior cortical atrophy is associated with prominent visual impairment with visual agnosia and Balint syndrome (asimulagnosia, visual ataxia, and ocular apraxia) and is commonly associated with AD, though DLB pathology may also lead to impaired visuospatial function. The Heidenhain variant of CJD is also characterized by visuospatial impairment.

Vascular dementia

Vascular dementia is diagnosed when the presence of strokes is confirmed and when the clinician judges that the vascular events are responsible for

Table 1.2 Selected features allowing differential diagnosis of dementia

	Alzheimer's disease	Frontotemporal dementia	Dementia with Lewy bodies	Vascular dementia	Creutzfeldt–Jakob disease
Cognitive features	Memory predominates	Behavior and executive function and language	Relative sparing of memory, with executive and visuospatial	Localization dependent, but executive dysfunction predominates	Rapidly progressive cognitive and motor impairment
Memory impairment	+++	+	+	+/−	+/−
Executive dysfunction	+	+++	++	++	+/−
Visuospatial impairment	+	−	+++	+/−	++
Neurological signs	Absent early, may occur later	In those with motor neuron disease	Present in majority	Typically present	Defining criterion
Pyramidal	−	+ With motor neuron disease	−	+++	++
Extrapyramidal	+	+ In familial frontotemporal lobar degeneration	+++ Defining criterion	+	++
Cerebellar signs	−	−	−	+/−	++
Lower motor neuron signs	−	+	−	−	+/−

cognitive decline. The prototype of vascular dementia has an acute onset and stepwise decline, with focal neurological signs and symptoms, but this entity is rarely seen in clinical practice. It is important to note that vascular risk factors or atherosclerosis are not sufficient for a diagnosis of vascular dementia; the brain parenchyma has to be damaged by infarcts in order for this diagnosis to be appropriately applied. Diffuse white matter changes (leukoaraiosis) can also lead to vascular cognitive impairment, often gradually progressive and associated with mood changes, gait impairment and urinary frequency or incontinence.

Lewy body dementia

Lewy body dementia is distinguished by the presence of parkinsonism, neuroleptic sensitivity, fluctuations in consciousness, and spontaneous (i.e. not drug induced) visual hallucinations, although patients vary in the specific combinations of signs and symptoms. In contrast to idiopathic Parkinson's disease, the parkinsonism in Lewy body dementia tends to occur in the absence of rest tremor, is more symmetrical, and does not respond as well to dopaminergic drugs. The diagnosis of Lewy body dementia is also reserved for patients whose motor symptoms have been present for less than 1 year when dementia appears, in contrast to the 8–10 years of motor symptoms without dementia in idiopathic PD, which typically precedes PDD. Other features suggestive of Lewy body dementia include disproportionate visuospatial dysfunction and rapid eye movement (REM) behavior disorder.

Frontotemporal dementia

Frontotemporal dementia may present as either a language impairment or a behavioral variant. Progressive aphasia due to frontotemporal pathology is characterized by either progressive non-fluent speech (progressive non-fluent aphasia) or loss of knowledge of the meaning of items (semantic dementia). They typically have a young onset, and can develop behavioral features and asymmetrical focal atrophy, which suggest frontotemporal dementia but these features are insensitive. Criteria for possible behavioral variant frontotemporal dementia (bvFTD) include combinations of prominent behavioral features such as disinhibition, apathy or inertia, loss of sympathy or empathy, perseveration or compulsions, hyperorality or executive dysfunction. Relative sparing of episodic memory and visuospatial function are cognitive features of bvFTD. It should be kept in mind, however, that hippocampal pathology, distinct from AD, can be found in bvFTD. Supportive features include functional impairment sufficient to indicate dementia (which allows differentiation from primary psychiatric disorders), and imaging showing frontal or anterior temporal atrophy or hypometabolism in a pattern consistent with the diagnosis increases the likelihood of probable bvFTD.

Problems with current classifications

The current diagnostic criteria are not absolute in terms of specificity or sensitivity (see Table 1.1). Some scenarios may suggest an acute CNS disorder, yet be due to a degenerative dementia. Abrupt onset suggests delirium, which needs to be ruled out to make a diagnosis of dementia; however, delirium may be a precursor to dementia and is more common in the setting of dementia. Abrupt decline can occur in DLB, where fluctuating cognition may lead to a marked deterioration. In some, this might be precipitated by an acute infection or medications, which can lead to diagnostic confusion. Delirium increases the risk of mortality in older people. Cerebrovascular disease also can present acutely, and can lead to cognitive decline. A difficulty with the diagnosis of vascular dementia is establishing a temporal association between cerebrovascular disease and dementia, given that vascular events can be undetected without imaging in some patients, despite their contribution to cognitive decline.

A patient with incipient dementia of any kind is susceptible to delirium. In such patients, a prolonged recovery, possible to a lower level of cognitive function, may occur. While a typical patient with AD has a decline of three points on the MMSE annually, more rapid progression can be seen. When present, like acute onset, this should prompt a search for potentially treatable entities. Rapidly progressive dementias are discussed in detail in Chapter 2. Co-morbid conditions are also a reality in older populations and may influence the course of dementia but also compromise a confident diagnosis. Nevertheless, a progressive course despite medical illness should not preclude the diagnosis of degenerative dementia. Similar concerns apply in psychiatric illness, in which a late-life degenerative dementia can occur.

Focal presentations can also lead to diagnostic confusion and uncertainty. Presentation with focal symptoms is characteristic of frontotemporal dementia and corticobasal ganglionic degeneration. Focal presentations can also occur in AD, in which language impairment, characterized by paucity of speech (which needs to be differentiated from primary progressive aphasia), apraxia (which needs to be differentiated from corticobasal ganglionic degeneration) and visuospatial impairment, which is common in DLB, are not uncommon. Overlapping pathologies, including AD, vascular changes and Lewy bodies, present in a large proportion of patients with dementia, and can confound the clinical picture.

Biomarkers

While biomarkers have been available for decades, evidence is accumulating that they can be useful in the differential diagnosis of dementia. Currently most biomarkers require further validation in order to be applied clinically beyond the research setting. Beyond causal genes that are associated with autosomal dominant disease (APP, PSEN1, PSEN2), genetic risk factors exist for AD and likely for other dementias as well. Possession of an apolipoprotein E4 (APOE 4) allele is a well-established risk factor in AD. Recently identified risk alleles include alterations in complement component (3b/4b) receptor-1 (CR1), clusterin (CLU) and phosphatidylinositol binding clathrin assembly protein (PICALM), each of which may provide a hint regarding pathophysiology. For example, they may point to inflammation, lipid metabolism or trafficking of organelles. Other polymorphisms are being identified but while these may be important scientifically, they are not helpful in the clinic at present.

Blood markers are less strongly associated with the development of dementia. Since the blood–brain barrier impedes transmission of markers between the brain and blood, it is not surprising that these markers may not be as sensitive as spinal fluid markers. Nevertheless, they may be helpful in identifying potential risk factors, if not patterns related to disease. Levels of plasma amyloid, particularly beta-amyloid fragments 1-42 and 1-40, or their ratio, have been inconsistently associated with increased risk of dementia. Other markers include those for oxidative stress, inflammation, glucose metabolism, lipid metabolism, B-vitamin metabolism (i.e. homocysteine), etc. In frontotemporal dementia, low progranulin levels are found in some patients, in whom they can predict the presence of mutations. Developments in large-scale proteomic and metabolomic screening will likely identify marker patterns associated with specific dementias. These may be applicable to blood or cerebrospinal fluid but currently these approaches are not clinically available.

Cerebrospinal fluid is adjacent to the brain and might be expected to better reflect CNS pathology. As noted above, CSF examination is indicated if an inflammatory, neoplastic or infectious etiology is suspected in the evaluation of a patient. If NPH is suspected, large-volume CSF drainage may help diagnostically. CSF markers can be helpful in differentiating AD from other forms of dementia such as frontotemporal dementia or Lewy body dementia, albeit with overlap. Specifically, low CSF amyloid (1-42) concentrations are suggestive of Alzheimer pathology. Increases in total tau (t-tau) and phosphorylated-tau (p-tau) are also present in AD but these intraneuronal proteins can also reflect neuronal damage and are therefore elevated in any pathological processes that destroy brain tissue.

Current research is examining forms of beta-amyloid and tau as prognostic markers in cognitively normal individuals and people with mild cognitive impairment. Additional markers have been examined and are likely to be developed. As with the blood markers, these may provide insights into distinct pathologies and pathophysiological processes.

Imaging

As noted above, structural brain imaging is an important part of the initial evaluation of patients with suspected dementia. Assistance in differential diagnosis and use as a marker in tracking disease are also potential goals of brain imaging. MRI can identify hippocampal atrophy which correlates with the presence of AD pathology. Overall, the challenge with use of biomarkers is their relative timing in relation to clinical disease. For example, some changes, like amyloid deposition, might occur presymptomatically with little change through the disease course, whereas others, such as global brain atrophy, might be evident only after the disease is in place. These concepts apply across dementias with different markers or diagnostic signatures at play.

While positron emission tomography (PET) is not routinely used, fluorodeoxyglucose (FDG) PET scans can assist in differential diagnosis as can

technetium-HMPAO SPECT, which measures cerebral blood flow. These approaches are particularly helpful in differentiating AD, which shows posterior hypoperfusion or decreased metabolism, from frontotemporal dementia, which shows frontal changes, and vascular dementia, which shows patchy changes. Dementia with Lewy bodies is more challenging to differentiate, likely because of overlapping AD pathology in many cases. Nevertheless, the pattern of change in Lewy body dementia may be distinct, with occipital hypometabolism or decreased blood flow. In addition to assisting in the differentiation of different types of dementia, metabolic imaging may be helpful in identifying patients with early cognitive decline at risk for transitioning to dementia of the Alzheimer type. The recent advent of practical ligands that allow imaging of amyloid using PET will likely assist in identifying patients with pathological changes of AD.

Parkinsonian disorders, related to loss of striatal dopamine function, can be separated from other dementing disorders such as AD. Currently dopamine transporter imaging using SPECT or PET imaging dopamine metabolism using 18-F-dopa or presynaptic dopamine transporter using 11-C-dihydrotetrabenazine (DHTBZ) are helpful, but have been most widely used in the research setting. Readily available dopamine transporter imaging with SPECT has lead to more widespread use despite the caveat that such changes might not separate different parkinsonian disorders. Cardiac imaging using metaiodobenzylguanidine (MIBG) shows loss of uptake in Lewy body-related disorders but, like blood flow (HMPAO) and dopamine transporter imaging using SPECT, this method might not offer adequate sensitivity or specificity on its own.

Future of dementia diagnosis

The diagnosis of dementia is a clinical decision. The increased availability of imaging and other modalities will likely prove helpful, but they will not supplant clinical decision making based on key aspects of the history and physical examination.

Further reading

Carcaillon L, Berrut G, Sellal F, et al. Diagnosis of Alzheimer's disease patients with rapid cognitive decline in clinical practice: interest of the DECO questionnaire. *J Nutr Health Aging* 2011; **15**(5): 361–6.

Clark CM, Schneider JA, Bedell BJ, et al, for the AV45-A07 Study Group. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA* 2011; **305**(3): 275–83.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; **44**(12): 2308–14.

Dubois B, Burn D, Goetz CG, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the Movement Disorder Society Task Force. *Mov Disord* 2007; **22**: 2314–24.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000; **55**(11): 1621–6.

Feldman HH, Jacova C, Robillard A, et al. Diagnosis and treatment of dementia: 2. Diagnosis. *Can Med Assoc J* 2008; **178**(7): 825–36.

Galvin JE, Roe CM, Powlishta KK, et al. The AD8: a brief informant interview to detect dementia. *Neurology* 2005; **65**(4): 559–64.

Goldman JS, Hahn SE, Catania JW, et al, for the American College of Medical Genetics and the National Society of Genetic Counselors. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 2011; **13**(6): 597–605.

Hort J, O'Brien JT, Gainotti G, Pirttila T, et al, for the EFNS Scientist Panel on Dementia. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 2010; **17**(10): 1236–48.

Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimers pathological cascade. *Lancet Neurol* 2010; **9**(1): 119–28.

Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**(3): 257–62.

Kertesz A, Davidson W, Fox H. Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. *Can J Neurol Sci* 1997; **24**(1): 29–36.

Knapskog AB, Barca ML, Engedal K. A comparison of the validity of the Cornell Scale and the MADRS

in detecting depression among memory clinic patients. *Dement Geriatr Cogn Disord* 2011; **32**(4): 287–94.

McKeith IG, Dickson DW, Lowe J, et al, for the Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; **65**(12): 1863–72.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7(3): 263–9.

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011; **134**(Pt 9): 2456–77.

Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; **43**(2): 250–60.

Sabbagh MN, Malek-Ahmadi M, Kataria R, et al. The Alzheimer's questionnaire: a proof of concept study for a new informant-based dementia assessment. *J Alzheimers Dis* 2010; **22**(3): 1015–21.

Sikkes SA, van den Berg MT, Knol DL, et al. How useful is the IQCODE for discriminating between Alzheimer's disease, mild cognitive impairment and subjective memory complaints? *Dement Geriatr Cogn Disord* 2010; **30**(5): 411–16.

Teng EL, Chui HC. A Modified Mini-Mental State (3MS) Examination. *J Clin Psychiatry* 1987; **48**: 314–18.