Evaluation of cognitive impairment and dementia

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Literature review current through: **Jan 2024.**
This topic last updated: **Nov 02, 2022.**

INTRODUCTION AND DEFINITIONS

Dementia is an acquired disorder that is characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) [1,2]. While traditional definitions of dementia required a decline in at least two cognitive domains, the definition of major neurocognitive disorder as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) only requires a substantial decline in a single cognitive area [1]. The deficits must represent a decline from previous level of function and be severe enough to interfere with daily function and independence. The most common form of dementia in older adults is Alzheimer disease (AD), accounting for 60 to 80 percent of cases.

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia in which there are objective cognitive impairments but no decline in overall level of function. While specific subtle changes in cognition can occur in normal aging, MCI can also be a precursor to dementia [1]. At the same time, MCI may also represent a reversible condition in the setting of depression, as a complication of certain medications, or during the recovery from an acute illness.

As the population ages, the overall burden of dementia is increasing worldwide. With an aging population and growing awareness of AD and other late-life dementias, clinicians should be equipped to test for cognitive impairment and ask about functional decline to avoid failure to

recognize cases of AD and related dementias. Clinicians will need to accurately diagnose and manage the early cognitive manifestations of AD and other dementias.

This topic will discuss the evaluation of patients with cognitive impairment and dementia. Recommendations for the evaluation of cognitive impairment and dementia are derived from our clinical experience as well as from the American Academy of Neurology (AAN) practice guidelines [3,4].

The clinical, diagnostic, and pathologic aspects of specific dementia syndromes are discussed separately:

- (See "Clinical features and diagnosis of Alzheimer disease".)
- (See "Etiology, clinical manifestations, and diagnosis of vascular dementia".)
- (See "Clinical features and diagnosis of dementia with Lewy bodies".)
- (See "Frontotemporal dementia: Clinical features and diagnosis".)
- (See "Mild cognitive impairment: Epidemiology, pathology, and clinical assessment".)

CAUSES

Most dementia is caused by a neurodegenerative disease; these produce broadly overlapping clinical syndromes, albeit with some distinctive features. (See 'Dementia syndromes' below.)

The most common neurodegenerative conditions causing dementia are [5-7]:

- Alzheimer disease (AD) (see "Clinical features and diagnosis of Alzheimer disease")
- Dementia with Lewy bodies (DLB) (see "Clinical features and diagnosis of dementia with Lewy bodies")
- Frontotemporal dementia (FTD) (see "Frontotemporal dementia: Clinical features and diagnosis")
- Parkinson disease dementia (PDD) (see "Cognitive impairment and dementia in Parkinson disease")

Less common neurodegenerative disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multisystem atrophy, and Huntington disease can also be associated with dementia. (See "Progressive supranuclear palsy (PSP): Clinical features and

diagnosis" and "Corticobasal degeneration" and "Multiple system atrophy: Clinical features and diagnosis" and "Huntington disease: Clinical features and diagnosis".)

Non-neurodegenerative dementias may be reversible, or progression slowed or halted, if the underlying cause can be identified and adequately treated [8]. The most common of these is:

- Vascular dementia (see "Etiology, clinical manifestations, and diagnosis of vascular dementia")

Most older adult patients with chronic dementia have AD (approximately 60 to 80 percent), and many of these patients also have concomitant cerebrovascular disease. The prevalence of vascular dementia and vascular cognitive impairment (VCI) is relatively high in patients who are Black and/or have hypertension or diabetes. Some of the reversible dementias (eg, metabolic dementias) tend to occur in younger individuals. DLB may be as prevalent as vascular dementia in older cohorts of patients [9]. FTD, which has its usual age of onset before age 65 years, is less common than AD or vascular dementia.

Dementia may have more than one cause, particularly as the condition progresses and especially in older persons. In addition, medical illnesses and comorbidities exacerbating poor cognition are common in older adult patients with dementia; examples include chronic diseases such as congestive heart failure and renal insufficiency, as well as the effects of antihistaminergic and anticholinergic medications.

- Mixed dementia refers to the coexistence of more than one dementia-producing pathology, most commonly AD and vascular dementia.

Less common etiologies include alcohol-related dementia, chronic traumatic encephalopathy, normal pressure hydrocephalus (NPH), chronic subdural hematoma, and other central nervous system (CNS) illnesses (eg, prion diseases, human immunodeficiency virus [HIV] infection):

- (See "Overview of the chronic neurologic complications of alcohol".)
- (See "Sequelae of mild traumatic brain injury", section on 'Chronic traumatic encephalopathy'.)
- (See "Creutzfeldt-Jakob disease".)
- (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)
- (See "Normal pressure hydrocephalus".)

- (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency".)
- (See "Subdural hematoma in adults: Etiology, clinical features, and diagnosis", section on 'Chronic subdural hematoma'.)

CLINICAL PRESENTATION

Dementia syndromes — Most patients with dementia do not present with a self-complaint of memory loss; it is often a spouse or other informant who brings the problem to the clinician's attention. Self-reported memory loss does not appear to correlate with the subsequent development of dementia, while informant-reported memory loss is a much better predictor of the current presence and future development of dementia [10,11]. Nevertheless, family members are often delayed in recognizing the signs of dementia, many of which are inaccurately ascribed to aging.

An essential aspect of dementia is that the cognitive impairment represents a change from baseline. With most of the dementia syndromes, the change is gradual and progresses over time; however, that aspect may not be appreciated by family members. By the time the patient has stopped driving or managing finances, subtle but worsening clinical manifestations have often been present for at least a few years.

Memory difficulty is the most common chief complaint; in addition, patients with dementia also have difficulty with one or more of the following [12]:

- Retaining new information (eg, trouble remembering events)
- Handling complex tasks (eg, balancing a checkbook)
- Reasoning (eg, unable to cope with unexpected events)
- Spatial ability and orientation (eg, getting lost in familiar places)
- Language (eg, word finding)
- Behavior

Alzheimer disease (AD) and vascular dementia comprise the majority of cases such that in the absence of other compelling anomalies, these are often diagnosed presumptively (see 'Making a presumptive diagnosis' below). Their clinical syndromes, however, are somewhat nonspecific:

- Alzheimer disease most commonly occurs in older adults, typically older than 65 years and with increasing incidence and prevalence over the next two decades, with memory impairment as the most common initial symptom. Other common early features are impaired executive function and reduced insight. Behavioral and psychologic symptoms,

apraxia, and sleep disturbance become more common as the disease progresses. (See "Clinical features and diagnosis of Alzheimer disease".)

- Vascular dementia or vascular cognitive impairment (VCI), particularly that associated with arteriolosclerotic small vessel disease, has a cognitive profile that is characterized by prominent impairments in executive function and processing speed. A step-wise progression in association with recognized or unrecognized strokes is characteristic, but a more gradual progression is also reported, not infrequently with concomitant AD. In many cases, a clinically diagnosed stroke appears to initiate the onset of what has been called poststroke dementia. Signs and symptoms related to diagnosed or undiagnosed stroke may also be present. Brain magnetic resonance imaging (MRI) will show evidence of vascular disease; however, the extent of changes does not clearly correlate with the severity of dementia and its poststroke progressive course. (See "Etiology, clinical manifestations, and diagnosis of vascular dementia".)

Different causes of dementia present with different patterns of cognitive impairment in association with other neurologic manifestations. These differences are not always easy to distinguish, particularly in the very early stages of illness. Very late in the disease course, when patients are very disabled, the syndromes are also not easily distinguishable.

Conditions that include parkinsonism (tremor, bradykinesia, rigidity, and/or postural instability) along with dementia include:

- Lewy body diseases (eg, Parkinson disease, dementia with Lewy bodies [DLB]) produce a gradual, progressive decline in cognitive abilities with motor parkinsonism. The presence of rapid eye movement (REM) sleep behavior disorder, visual hallucinations, fluctuations in level of alertness, and prominent visuospatial dysfunction favor DLB as the cause of or contributor to the dementia. Notably, the dementia of Parkinson disease emerges five to eight years after the onset of the movement disorder, whereas DLB manifests parkinsonism and cognitive decline contemporaneously. (See "Clinical features and diagnosis of dementia with Lewy bodies" and "Cognitive impairment and dementia in Parkinson disease".)

- Progressive supranuclear palsy (PSP) is a rare disease that includes dementia and parkinsonism. Distinctive early features of this disorder include vertical supranuclear gaze palsy, especially diminished downgaze, and prominent postural instability with falls. Behavioral changes including apathy, disinhibition, dysphoria, and anxiety are common. (See "Progressive supranuclear palsy (PSP): Clinical features and diagnosis".)

- Multiple system atrophy (MSA) is an umbrella term for olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome, and commonly presents with parkinsonism. Other features can include dysautonomia, cerebellar ataxia, and corticospinal tract deficits. (See "Multiple system atrophy: Clinical features and diagnosis".)

- Corticobasal degeneration (CBD) can manifest with asymmetric parkinsonism along with cognitive impairment. More distinctive features can include ideomotor apraxia, alien limb phenomenon, aphasia, and loss of cortical sensory function. Absence of tremor is typical for CBD. (See "Corticobasal degeneration".)

Less common clinical syndromes with relatively distinctive clinical features include:

- Normal pressure hydrocephalus (NPH) produces decline in cognition, slowed gait, and urinary incontinence. The classic gait sign in NPH is an apraxic, wide-based "magnetic" gait. (See "Normal pressure hydrocephalus" and "Normal pressure hydrocephalus", section on 'Clinical features'.)

- Creutzfeldt-Jakob disease (CJD) is a rare but rapidly progressive dementia that produces prominent behavioral and sleep abnormalities early on. Myoclonus and cerebellar deficits are also common features. (See "Creutzfeldt-Jakob disease", section on 'Clinical features'.)

  Other rapidly progressive dementia syndromes are discussed separately. (See "Creutzfeldt-Jakob disease", section on 'Differential diagnosis'.)

Dementia mimics — The normal cognitive decline associated with aging consists primarily of mild changes in memory and rate of information processing. Features that distinguish normal aging from dementia include that deficits are generally not very progressive and usually do not affect daily function. In a study of 161 community-dwelling, cognitively normal individuals ages 62 to 100 years, learning or acquisition performance declined uniformly with increasing age [13]. By contrast, delayed recall or forgetting remained relatively stable. Similarly, a second report found that aging was associated with decline in learning of new information but not in memory retention [14].

Mild cognitive impairment (MCI) is an intermediate category in which the severity of cognitive change appears worse than expected for normal aging but does not meet criteria for dementia. Its presence indicates a greater risk of progression to dementia, but it may also be stable and not progress or even revert to normal. (See 'Mild cognitive impairment' below and "Mild cognitive impairment: Epidemiology, pathology, and clinical assessment".)

Cognitive impairment related to dementia must be distinguished from delirium and depression (table 1) [15].

- Delirium is usually acute or subacute in onset and is associated with prominent deficits in attention; patients have fluctuations in their level of consciousness and have difficulty maintaining concentration (table 2).

  The distinction between delirium and dementia can be difficult and sometimes impossible in acute presentations. Dementia is a significant risk factor for delirium, and thus, delirium and dementia can co-occur. In addition, some dementia syndromes such as DLB have overlapping features with delirium. (See "Diagnosis of delirium and confusional states".)

- Patients with depression are often more likely to complain about memory loss than those with dementia; the latter are frequently brought to clinicians by their families or caregivers, while depressed patients may present by themselves. The presentation of depression as dementia has been called "pseudodementia" or, more recently, "dementia of depression." Patients with depression may have signs of psychomotor slowing and give poor effort on testing ("I just can't do this"), while those with dementia often try hard but respond with incorrect answers. It is important for the clinician and/or test administrator to estimate the effort given by the patient. It is also important to realize that depression and dementia can occur in the same patient and that patients with dementia present with depression as a presenting complaint. (See "Diagnosis and management of late-life unipolar depression" and "Unipolar depression in adults: Clinical features", section on 'Symptoms'.)

EVALUATION

A full dementia evaluation probably cannot be completed in a routine 30-minute visit; adequate time should be arranged in a follow-up appointment or an initial longer evaluation. A family member or close friend familiar with the patient should accompany them to the visits to present symptoms they have seen and remember what the patient is told. The initial step at the follow-up visit is an assessment of cognitive function. This should be followed by a complete physical examination, including neurologic examination. The subsequent work-up may include laboratory and imaging studies [16,17]. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and Fifth Edition (DSM-5) criteria for the diagnosis of dementia (major neurocognitive disorder) are shown in the table (table 3).

Screening for dementia — The US Preventive Services Task Force (USPSTF) has concluded that there is insufficient evidence to recommend for or against routine screening for dementia in older adults [18,19]. Similarly, the American Academy of Neurology (AAN) and the Canadian Task Force on Preventive Health Care either do not endorse screening or recommend against it in asymptomatic adults.

We do not routinely screen asymptomatic older adults for cognitive impairment. However, observed cognitive difficulty in a patient encounter and family or patient concerns for memory and cognition require thorough evaluation.

History — Family members or someone who knows the patient well must be available to give an adequate history of cognitive and behavioral changes [6]. A drug history is particularly important; use of drugs (including nonprescription) that impair cognition (eg, analgesics, anticholinergics, psychotropic medications, and sedative-hypnotics) should be sought (table 4) [20,21]. The customary medical, psychiatric, and social histories also provide relevant information.

Patients and informants are often uncertain about the onset of symptoms since the appearance of dementia is insidious. Useful questions for the patient and informant are, "When did you first notice the memory loss?" and "How has the memory loss progressed since then?" By the time the patient has stopped driving or managing finances, the disease has often been present for a few years.

An assessment of daily activities also provides evidence of impairment, particularly in the context of what the patient had done previously, at their baseline. Work and education history help establish baseline; their current participation in handling finances, community and social activities, driving, and other household tasks helps assess current performance.

The clinical interview also allows the examiner to establish rapport with the patient. The comfort level established during the interview may lessen the frequency and severity of any subsequent test and performance anxiety that may be engendered by explicit testing. Family members should be present at both examination and follow-up. When explaining findings, it is important to make eye contact with and speak directly to the patient, and avoid speaking to the family directly. Asking the family members to "please listen carefully while I talk to [the patient]" will let them know that the information is for them as well.

Questions guided by the differential diagnosis are also helpful, including loss of vision or motor function, tremor, poor balance, falls, difficulty walking, urinary incontinence, prominent personality changes, behavioral disturbances, visual hallucinations, abnormal sleep, and

excessive alcohol use. (See 'Dementia mimics' above and 'Identifying the underlying disease' below.)

Cognitive testing — Patients with cognitive complaints should undergo a careful mental status examination. Cognitive and behavioral assessments are designed to distinguish normal and abnormal performance arising across a range of different conditions. They can be divided into three levels of rigor: screening tools such as the Mini-Mental State Examination (MMSE), an extended mental status examination, and formal neuropsychological testing. The scope of the evaluation should be guided by the complaints brought forward by the patient or family member.

The MMSE, Montreal Cognitive Assessment (MoCA), and other brief screening tests for dementia have a pooled sensitivity of 75 to 92 percent and a specificity of 81 to 91 percent [22]. Typically, these assess a broad range of cognitive domains but do not include an assessment of mood or thought content. These assessments are discussed in detail separately. (See "Mental status scales to evaluate cognition".)

More detailed mental status testing is often warranted, for example, when the results from a screening assessment appear at odds with the history and when observed deficits are uncertain because of a language barrier, physical handicap, or level of education. An extended bedside evaluation of mental status is described separately. (See "The mental status examination in adults".)

Both altered mood and abnormal thought content have a strong impact on cognitive function; thus, such an assessment should always accompany a brief screening evaluation for dementia. (See "The mental status examination in adults", section on 'Mood and thought content' and 'Screening for depression' below.)

The diagnosis of dementia cannot be made solely on the basis of a low score on one of these assessments; these tests help to quantify the types and severity of impairment, but the most important part of the diagnostic evaluation is a detailed history including the perspective of an informant (eg, spouse or adult child), interviewed separately from the patient if possible. Agreement between the history and the mental status examination is strongly suggestive of the diagnosis of dementia. When the history suggests cognitive impairment but the mental status examination is normal, possible explanations include mild dementia, high intelligence or education, depression, or, rarely, misrepresentation on the part of the informants [23]. Conversely, when the mental status examination suggests cognitive impairment but the family and patient deny any problems, possible explanations include an acute confusional state, very low intelligence or education, or inadequate recognition by the family [23]. For some, the

diagnosis of dementia is regarded as shameful, and reluctance to recognize or acknowledge the problem must be addressed.

Neuropsychological assessment (psychometric testing) may be useful in difficult situations; repeated clinical assessments over time (eg, 9 to 12 months) are often the most helpful tool.

Screening for depression — All patients being evaluated for cognitive impairment or dementia should be screened for depression. Cognitive impairment may be the chief complaint in a patient with depression. Depression can mimic dementia and can also worsen cognitive impairment in patients with dementia or mild cognitive impairment (MCI). It is not uncommon for a depressed person to literally elicit a depressed feeling in the clinician examining that patient. (See 'Dementia mimics' above.)

Several screening tools have been validated in this setting. One, the Patient Health Questionnaire 2, consists of just two questions (table 5). This and other screening tools are described in detail separately. (See "Diagnosis and management of late-life unipolar depression", section on 'Screening instruments'.)

Physical examination — A thorough general physical examination to rule out an atypical presentation of a medical illness should be combined with a neurologic examination. The latter should focus upon focal neurologic deficits that may be consistent with prior strokes, parkinsonism (eg, cogwheel rigidity and/or tremors), gait abnormalities or slowing, and eye movements. In comparison, patients with Alzheimer disease (AD) generally have no motor or sensory deficits at presentation. (See 'Dementia syndromes' above.)

This examination, along with the medical and neurologic history, will allow tailoring of further testing.

Laboratory testing — We suggest limited laboratory testing in most patients being evaluated for cognitive impairment and dementia.

- The AAN recommends screening for B12 deficiency (serum vitamin B12 level, complete blood count) and hypothyroidism (serum thyroid-stimulating hormone [TSH]) in patients with dementia [3]. Limited data suggest that treating deficiencies may improve cognition. (See "Neurologic manifestations of hypothyroidism", section on 'Cognitive impairment and dementia' and "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Laboratory testing' and "Treatment of vitamin B12 and folate deficiencies", section on 'Treatment of vitamin B12 deficiency'.)

- Screening for neurosyphilis is not recommended unless there is a high clinical suspicion based on sexual history or travel to areas where exposure may be more common; screening for HIV may also be appropriate in this subgroup of patients. (See "Neurosyphilis", section on 'Unknown syphilis history' and "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)

- We do not order other laboratory tests unless there is a specific suspicion for abnormality. As an example, some specialized tests can be tailored to patients with a compatible history (eg, red blood cell folate in a patient with alcoholism, or ionized serum calcium in a patient with multiple myeloma, prostate cancer, or breast cancer). There are no clear data to support or refute ordering "routine" laboratory studies such as electrolytes, glucose, and renal and liver function tests.

  An exception is a patient with a presentation that is possibly acute or subacute in whom delirium may be the cause of or a contributor to the clinical picture (see 'Dementia mimics' above). The evaluation of a patient with delirium is discussed separately. (See "Diagnosis of delirium and confusional states", section on 'Diagnostic tests'.)

The cost effectiveness of obtaining multiple laboratory studies routinely in all patients is questioned because the yield is low [24]. The prevalence of reversible dementia has fallen since 1972. In a 1994 study, this was less than 1 percent, and in a 2006 community-based series, none of the 560 patients with dementia screened had a treatable metabolic cause [24,25].

Neuroimaging

Indications — Neuroimaging with a head computed tomography (CT) or MRI scan is unequivocally indicated in patients with acute onset of cognitive impairment and/or rapid neurologic deterioration. Neuroimaging is also indicated when there are historical features or findings on physical examination suggestive of a subdural hematoma, thrombotic stroke, cerebral hemorrhage, or another structural lesion [26].

The more routine use of neuroimaging in patients with dementia is controversial. Some patients with clinical features consistent with a neurodegenerative condition are found to have a reversible cause of dementia on an imaging study (eg, subdural hematoma, normal pressure hydrocephalus [NPH], treatable cancer). Because these are uncommon, many published guidelines on the clinical evaluation of dementia do not recommend routine imaging studies but include clinical prediction rules to identify patients who might have one of these reversible causes [3,25,27-33]. The prediction rules vary but often include factors such as younger age (<60 years), focal signs, and short duration of symptoms (less than two years), among others. However, the sensitivity and specificity of these prediction rules are low [34].

By contrast, the AAN recommends structural neuroimaging with either a noncontrast head CT or MRI in the routine initial evaluation of all patients with dementia [3].

Our practice is to order imaging when patients present with unusual or atypical findings or when imaging findings may be reassuring for patients and their families or caregivers. Such differences in practice may be attributable to the context in which the patient is seen. Neurologists, who may only see a person once or for a very limited time period, will usually obtain imaging on a patient referred from primary care, whereas a primary care clinician who has the advantage of serial observations over time in patients known to them may order imaging studies more selectively. Some families will request imaging studies; we generally honor such requests after explanation of the limited yield of such studies.

Serial imaging is not informative unless there is an unexpected clinical change, such as abrupt mental status changes without a readily identified cause, new focal neurologic findings, or seizure.

Preferred modality — In most cases, MRI is preferred over CT because it is more sensitive for a broad range of potential pathologies while avoiding exposure to potentially harmful ionizing radiation. (See "Radiation-related risks of imaging".)

A CT scan is the best option when the patient is too claustrophobic for an MRI, has a pacemaker or ferromagnetic implants, or is unable to remain still enough to undergo the more time-consuming MRI. CT scans are generally less costly than MRI and may be preferable in the acute/emergency care situation when extra-axial or intraparenchymal hemorrhage must be ruled out quickly and/or when agitation mandates very short scanning times.

Patients who are anxious or restless can be sedated for structural imaging studies, if need be, since there is little potential for sedatives to interfere with these imaging results.

While intravenous contrast agents highlight acute stroke, expanding neoplasms, certain brain infections, and localized inflammation, noncontrast brain imaging is sufficient for the routine evaluation of patients with suspected neurodegenerative dementia. Intravenous contrast poses risks of allergic reactions and impaired renal function and is generally reserved for patients with unexplained focal central neurologic findings or in whom there is a suspicion of neoplasm or central nervous system (CNS) infection.

Findings — Structural imaging findings can assist in the primary diagnosis of dementia or suggest the presence of comorbidities that may exacerbate dementia symptoms.

Structural imaging findings in specific types of dementia are discussed in more detail elsewhere. (See "Clinical features and diagnosis of dementia with Lewy bodies", section on 'Indicative biomarkers' and "Clinical features and diagnosis of Alzheimer disease", section on 'Neuroimaging' and "Frontotemporal dementia: Clinical features and diagnosis".)

Some of the more common findings of structural brain imaging that have relevance to dementia are:

- **Cerebral atrophy** – Cerebral atrophy is common in patients with neurodegenerative dementia but also in normal aging. Atrophy may be generalized or regionally localized.

  Cortical atrophy is manifested by widening of sulci, narrowing of gyri, decreased grey matter thickness, diminished white matter volume, and/or enlargement of the cerebral ventricles and subarachnoid spaces. Atrophy must be interpreted relative to the patient's age and other factors. Normal brain aging is associated with some of the same changes, although typically age-related atrophy is less rapid, and usually less severe, than that of neurodegenerative disease. It is estimated that the brain loses approximately 0.5 percent of its volume each year in normal aging, compared with 1 to 2 percent in MCI and 2 to 4 percent in dementia due to AD [35].

  Certain regions of the brain show selective vulnerability to different neurodegenerative disorders. This results in distinctive clinical presentations and characteristic atrophy patterns visible on brain imaging (table 6). Asymmetric cortical atrophy is often observed in neurodegenerative dementias and sometimes manifests as disproportionate impairments in the functions mediated by the more atrophic regions. A number of other rare disorders with circumscribed cortical atrophy syndromes have also been described [36].

  Hippocampal atrophy can be one of the earliest and most salient manifestations of AD. It can be appreciated by visual inspection of volumetric T1 images sliced in coronal planes perpendicular to the long axis of the hippocampus. Hippocampal atrophy supports the diagnosis of AD but also occurs in mesial temporal sclerosis, temporal lobe epilepsy, and certain vascular insults and should not be considered pathognomonic of AD. (See "Clinical features and diagnosis of Alzheimer disease", section on 'Neuroimaging'.)

- **Ventriculomegaly** – Ventricular enlargement may occur in association with cortical atrophy and without evidence of obstruction; this is often referred to as hydrocephalus ex vacuo. Alternatively, ventricular enlargement may occur in association with NPH. NPH is a potentially treatable cause of dementia that typically presents as the symptomatic triad of dementia, gait disturbance, and incontinence. NPH may be due to a variety of causes,

including disturbances of cerebrospinal fluid (CSF) production and circulation [37]. (See "Normal pressure hydrocephalus", section on 'Pathophysiology'.)

Either CT or MRI can readily document ventricular enlargement, but it is somewhat more challenging to determine whether the enlargement is explained by or disproportionate to the degree of cerebral atrophy (image 1). This assessment is discussed in more detail separately. (See "Normal pressure hydrocephalus", section on 'Magnetic resonance imaging'.)

- **Ischemic cerebrovascular disease** – Imaging manifestations of cerebrovascular disease include focal areas of infarction and diffuse white matter ischemic changes, sometimes called leukoaraiosis.

  Cerebrovascular disease can cause cognitive impairment and dementia. The increasing prevalence of white matter ischemic changes with advancing age has been implicated as one of the factors responsible for age-related cognitive decline. Most forms of vascular cognitive impairment (VCI) manifest visible alterations on structural brain imaging studies. Neuroimaging findings are a required element of some of the commonly used diagnostic criteria for vascular dementia, including the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement Neurosciences (NINDS-AIREN) criteria (table 7) [38].

  Although CT can readily identify frank infarction and moderate to severe subcortical ischemic changes, MRI is more sensitive to chronic cerebrovascular changes. Common MRI findings associated with vascular dementia include cortical and subcortical infarctions and periventricular white matter lesions. Since the incidence of ischemic changes is increased with aging in the absence of dementia as well as in diseases such as AD, these findings do not necessarily indicate a vascular etiology for the patient's dementia. (See "Etiology, clinical manifestations, and diagnosis of vascular dementia", section on 'Neuroimaging' and "Etiology, clinical manifestations, and diagnosis of vascular dementia", section on 'Diagnosis'.)

- **Microhemorrhages** – Cerebral microhemorrhages can be observed with vascular anomalies, cerebral amyloid angiopathy (CAA; occurs in the vast majority of AD patients), or hypertensive microangiopathy.

  Microhemorrhages are best detected by gradient echo MRI pulse sequences and with higher-sensitivity susceptibility-weighted imaging (SWI) (image 2). In population-based studies, cerebral microhemorrhages are detected in approximately 15 to 25 percent of older individuals and become more common with advancing age [39,40].

Microhemorrhages associated with CAA are primarily in the cerebral cortex, whereas those associated with hypertension typically occur in the basal ganglia, thalamus, or pons [41]. CAA can occur in subjects without dementia but has an increased prevalence in patients with AD [42]. (See "Cerebral amyloid angiopathy", section on 'Pathogenesis'.)

MAKING A PRESUMPTIVE DIAGNOSIS

Criteria for dementia — Although a number of definitions exist for dementia, the Diagnostic and Statistical Manual of Mental Disorders (DSM) definition provides a reasonable framework for the concept of dementia in clinical practice. According to DSM-5, the criteria for dementia (called major neurocognitive disorder) include the following [1]:

- Evidence from the history and clinical assessment that indicates significant cognitive impairment in at least one of the following cognitive domains:
  - Learning and memory
  - Language
  - Executive function
  - Complex attention
  - Perceptual-motor function
  - Social cognition
- The impairment must be acquired and represent a significant decline from a previous level of functioning
- The cognitive deficits must interfere with independence in everyday activities
- The disturbances are not occurring exclusively during the course of delirium
- The disturbances are not better accounted for by another mental disorder (eg, major depressive disorder, schizophrenia)

The DSM-5 definition differs substantively from prior versions in that the cognitive domains were renamed and expanded to include social cognition and complex attention. While previous DSM definitions of dementia listed memory as an essential feature for the diagnosis, the centrality of memory dysfunction has been deemphasized in DSM-5, with all six cognitive domains given equal weight in the criteria (table 3). The change from DSM-IV to DSM-5 presumably reflects the problem that some individuals with dementia due to causes other than Alzheimer disease (AD; as well as many early-onset AD phenotypes) did not meet definitional criteria because memory function was intact or at least relatively intact compared with norms.

That being said, for the most common forms of dementia, memory and language dysfunction are generally always present.

Prior versions of the DSM definition have had good to very good reliability for the diagnosis of dementia [3]. The performance of the DSM-5 criteria in relation to prior versions is not yet known, but it is likely that the changes will have some impact on research and possibly clinical practice in the future.

The pretest probability of dementia and of various causes of dementia depends upon patient characteristics such as age and race. Given that 5 percent of individuals over age 65 years and 35 to 50 percent of persons over age 85 years have dementia, the pretest probability of dementia in an older person with verified memory loss is estimated to be at least 60 percent. By contrast, subjective memory complaints are common and not predictive of dementia in isolation.

Mild cognitive impairment — The diagnosis of mild cognitive impairment (MCI) is similar. MCI is generally defined by the presence of memory difficulty greater than expected for age, and objective memory impairment, but preserved ability to function in daily life. The same exclusions (delirium, psychiatric disease) apply. A formal neuropsychiatric assessment might be needed in order to make this diagnosis, given that the cognitive deficits are mild. After ruling out medications or over-the-counter drugs that interfere with memory and ascertaining that comorbid conditions (depression, congestive heart failure, etc) are not causing the amnestic syndrome, there is often no imperative to make a formal diagnosis in most cases, as there are no specific treatments. The diagnosis and management of MCI are discussed separately. (See "Mild cognitive impairment: Epidemiology, pathology, and clinical assessment" and "Mild cognitive impairment: Prognosis and treatment".)

Identifying the underlying disease — The bedside evaluation combined with historical information from a reliable informant and, in selected patients, neuroimaging provides the information needed to ascertain the likely cause of dementia in most patients [15]. As a practical (albeit simplistic approach), a presumptive diagnosis of AD is made in most cases on the basis of a typical clinical syndrome, with vascular dementia considered as an alternative or contributor in the setting of known cerebrovascular or cardiovascular disease and/or risk factors and/or suggestive neuroimaging findings (see 'Dementia syndromes' above). Clinical pathologic studies suggest that this presumptive diagnosis will be incorrect in a significant minority of patients; however, the absence of specific treatments for neurodegenerative disorders means that such errors do not affect patient care.

When features atypical for AD predominate, particularly early in the disease course, other diagnoses are often considered. As examples:

- Parkinsonism suggests dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA). These conditions are reviewed briefly above and in more detail in individual topic reviews. (See 'Dementia syndromes' above.)

- Visual hallucinations and rapid eye movement (REM) sleep behavior disorder can be a prominent early feature of DLB. (See "Clinical features and diagnosis of dementia with Lewy bodies".)

- Behavioral abnormalities (including inappropriate behaviors and personality change) suggest behavioral variant frontotemporal dementia (FTD). (See "Frontotemporal dementia: Clinical features and diagnosis", section on 'Behavioral variant FTD'.)

- Aphasia out of proportion to memory impairment suggests primary progressive aphasia. (See "Frontotemporal dementia: Clinical features and diagnosis", section on 'Primary progressive aphasia'.)

- Gait impairment and urinary incontinence with dementia is the classic triad of normal pressure hydrocephalus (NPH). In NPH, gait disturbance and urinary incontinence occur early in the course of disease in patients who have less severe cognitive impairment; this contrasts with other forms of dementia in which gait disturbance and incontinence are common only in later stages. (See "Normal pressure hydrocephalus".)

- Rapidly progressive dementia and dementia in younger-age patients typically require additional evaluation and are discussed in detail separately. (See "Early-onset dementia in adults" and "Creutzfeldt-Jakob disease", section on 'Evaluation'.)

SPECIALIZED TESTING IN SELECTED PATIENTS

Patients with an atypical syndrome (eg, younger patients [<60 years] or those with rapidly progressive dementia) may benefit from a more extensive evaluation that may include lumbar puncture (LP), electroencephalography (EEG), and/or serologic tests (table 8) [26,43]. These evaluations are discussed separately. (See "Early-onset dementia in adults".)

Neuropsychological testing — Neuropsychological testing usually involves extensive evaluation of multiple cognitive domains (eg, attention, orientation, executive function, verbal memory, spatial memory, language, calculations, mental flexibility, and conceptualization). Most

patients do not require a full neuropsychological examination as part of an evaluation for dementia; however, testing is useful when bedside cognitive testing is equivocal, in evaluating for milder impairments, and in distinguishing depression or other psychiatric condition. (See 'Cognitive testing' above.)

Most observational studies have demonstrated a relatively high sensitivity (80 to 98 percent) and specificity (44 to 98 percent) for detection of dementia [4,44-50]. In a 2001 practice parameter, the American Academy of Neurology (AAN) concluded that neuropsychological batteries are useful in identifying patients with dementia, particularly when administered to those at higher risk by virtue of memory impairment [4]. Aggregate total score accurately differentiated normal individuals from those with mild cognitive impairment (MCI) and Alzheimer disease (AD) [51]. However, it is important to recognize that scores can also be influenced by education, age, and fluency with the language of testing [52].

In addition to its role in helping to discriminate between normal aging and dementia, neuropsychological testing can identify patterns of deficits that suggest a particular cause of dementia (eg, AD versus dementia with Lewy bodies [DLB]) [53]. However, no single item on the panel has high discriminatory ability, and the pattern of performance on various domains must be interpreted in conjunction with the history, neuroimaging studies, and other testing to arrive at a presumptive etiologic diagnosis [54].

Follow-up testing or just serial observations generally provide more helpful information than a single study, particularly when results are equivocal, in that evidence of decline can predict future decline [55]. Perhaps the most important thing to remember is that AD is a progressive disorder, as are other neurodegenerative causes of dementia, so unless a diagnosis is needed urgently (not likely), observations over time have high diagnostic utility. (See "Mild cognitive impairment: Epidemiology, pathology, and clinical assessment", section on 'Neuropsychological testing'.)

Genetic testing — Genetic testing for the apolipoprotein E epsilon 4 allele (which increases the risk of developing AD) is not currently recommended [56], nor is genetic testing for other potential causes of dementia (eg, specific mutations) unless there is a specific characteristic family history suggesting a familial dementia [3]. (See "Clinical features and diagnosis of Alzheimer disease", section on 'Genetic testing' and "Frontotemporal dementia: Clinical features and diagnosis", section on 'Genetic testing'.)

In the absence of a family history, genetic testing for AD in patients with dementia is controversial because of the potential for misinterpretation. As an example, not all patients who

are homozygotes for the apolipoprotein E epsilon 4 allele will develop AD [57]. In addition, the lack of specific treatments for these disorders makes this type of testing less imperative.

Advanced neuroimaging — The use of positron emission tomography (PET) imaging using beta amyloid and other tracers, single-photon emission computed tomography (SPECT), and other functional neuroimaging techniques to assist in the differential diagnosis of neurodegenerative dementia is an area of ongoing evolution. They are utilized most frequently by specialists assessing complex or unclear cases, and in research. (See "Frontotemporal dementia: Clinical features and diagnosis" and "Clinical features and diagnosis of Alzheimer disease", section on 'Neuroimaging' and "Clinical features and diagnosis of dementia with Lewy bodies", section on 'Neuroimaging'.)

Lumbar puncture — The role of LP and cerebrospinal fluid (CSF) analysis in the evaluation of dementia is primarily to identify infectious, inflammatory, or neoplastic processes. These are unusual causes of dementia and also have unusual presentations. Thus, LP is typically performed only in the setting of a rapidly progressive dementia, or in a younger patient, or as a follow-up to another abnormality identified on clinical history (eg, HIV), examination, laboratory testing (eg, abnormal syphilis serology), or neuroimaging (eg, meningeal enhancement). (See "Early-onset dementia in adults", section on 'Lumbar puncture and other laboratories' and "Neurosyphilis", section on 'Spinal fluid examination' and "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis", section on 'CSF findings' and "Creutzfeldt-Jakob disease", section on 'Differential diagnosis'.)

CSF biomarkers currently have a limited role in the diagnosis of neurodegenerative conditions such as AD and DLB and are discussed separately. (See "Clinical features and diagnosis of Alzheimer disease", section on 'Role of biomarkers' and "Clinical features and diagnosis of dementia with Lewy bodies", section on 'Investigational biomarkers'.)

Brain biopsy — Brain biopsy has a very limited role in the diagnosis of dementia; the diagnostic yield is low, and the test is invasive with a significant risk of serious complications. Typically, it is reserved for younger patients and those with atypical clinical presentations in which a treatable cause of dementia (eg, inflammatory disorders such as vasculitis or multiple sclerosis) is considered plausible. In one series of 90 consecutive biopsies undertaken for the investigation of dementia, 57 percent were diagnostic, although biopsy-obtained information led to specific treatment interventions in only 11 percent [58].

Increasingly, LP for specific biomarkers and PET scans for specific proteins have made consideration of cortical biopsy even less necessary and narrowed biopsy indications even further.

SPECIAL POPULATIONS

Younger patients — The evaluation of younger patients with dementia is presented separately. (See "Early-onset dementia in adults".)

Rapidly progressive dementia — The differential diagnosis and evaluation of rapidly progressive dementia syndromes is discussed separately. (See "Creutzfeldt-Jakob disease", section on 'Differential diagnosis'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cognitive impairment and dementia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Dementia (including Alzheimer disease) (The Basics)" and "Patient education: Mild cognitive impairment (The Basics)" and "Patient education: Evaluating memory and thinking problems (The Basics)")
- Beyond the Basics topics (see "Patient education: Dementia (including Alzheimer disease) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Role of dementia screening** – We do not routinely screen asymptomatic older adults for cognitive impairment. However, cognitive difficulty observed in a patient encounter, and family or patient concerns for memory and cognition, require thorough evaluation. (See 'Screening for dementia' above.)

- **History** – Family members or other informants who know the patient well are invaluable resources for providing an adequate history of cognitive and behavioral changes. A drug history is particularly important, as many medications may impact cognition in older patients. (See 'History' above.)

- **Cognitive and neurologic examination** – Adequate time should be arranged for a full assessment of cognitive function, followed by a complete physical examination, including neurologic examination.

  A brief screening assessment such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) is useful and may be sufficient cognitive assessment in some patients. (See 'Cognitive testing' above and 'Physical examination' above.)

- **Depression screening** – Depression is a common treatable comorbidity that may also masquerade as dementia. (See 'Screening for depression' above and 'Dementia mimics' above.)

- **Laboratory testing** – Screening for B12 deficiency and hypothyroidism is recommended for patients being evaluated for dementia. Other laboratory testing is performed selectively. (See 'Laboratory testing' above.)

  Genetic testing for the apolipoprotein E epsilon 4 allele is not currently recommended, nor is genetic testing for other potential causes of dementia. (See 'Genetic testing' above.)

- **Neuroimaging** – A noncontrast MRI or head CT should be considered in the initial evaluation of all patients with dementia.

  The purposes of structural imaging are to detect treatable causes of dementia and to differentiate among various dementia subtypes. (See 'Neuroimaging' above.)

- **Diagnosis and ongoing assessment** – History and examination along with limited laboratory testing and a neuroimaging study are usually sufficient to make a diagnosis of

dementia and in most cases to identify a presumptive cause.

As most causes of dementia are progressive, a follow-up visit after several months can often confirm the original diagnosis, can offer ongoing treatment and monitoring, and, in some cases, may cause a clinician to reconsider the original diagnosis if the progression does not occur or is atypical. (See 'Criteria for dementia' above and 'Dementia syndromes' above.)

- **Role of specialized testing** – Other tests (neuropsychological assessment, advanced neuroimaging techniques, lumbar puncture [LP], and, rarely, brain biopsy) are performed in selected patients (such as those who are younger or have a rapidly progressive course) and when the presentation is otherwise atypical. (See "Early-onset dementia in adults" and 'Specialized testing in selected patients' above and "Creutzfeldt-Jakob disease", section on 'Differential diagnosis'.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Marie-Florence Shadlen, MD, who contributed to an earlier version of this topic review.

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Topic 5083 Version 38.0

GRAPHICS

Differential diagnosis of memory loss

Symptom	Usual cause	Examples
Gradual onset of short-term memory loss (ie, loss of memory for recent events) and functional impairment in more than one domain: I. Executive function (finances, shopping, cooking, laundry, transportation) II. Basic activities of daily living (feeding, dressing, bathing, toileting, transfers)	Dementia	Alzheimer disease, Parkinson dementia, Lewy body dementia, frontotemporal dementia, alcohol-related dementia, Creutzfeldt-Jakob disease
Stepwise, sudden deterioration in cognition; episodes of confusion, aphasia, slurred speech, focal weakness	Cerebrovascular disease	Vascular dementia, multi-infarct dementia, Binswanger dementia (subcortical dementia)
Acute cognitive impairment with clouded sensorium; difficulty with attention; may have hypersomnolence	Delirium	Hypo- or hyperglycemia, hypo- or hypernatremia, hypoxemia, anemia, intermittent cerebral ischemia, thyrotoxicosis, myxedema, alcohol withdrawal, sepsis, drugs (especially cholinergics, benzodiazepines, etc)
Complains of memory loss, decreased concentration, impaired judgment, feels worse in morning and hopeless	Depression	Minor depression, dysthymic disorder, major depression, pathologic grief reaction

Graphic 51421 Version 5.0

Clinical features of delirium versus dementia

	Delirium	Dementia
Onset	More abrupt decline in cognitive function over hours to days, with waxing and waning course	Typically insidious, progressive decline in cognition over months to years
Attention and orientation	Impaired	Generally preserved; can be altered in later stages
Level of consciousness	Fluctuating, sometimes reduced	Normal
Speech and language	Incoherent, disorganized speech	Variable impairments in word retrieval, naming, fluency, and comprehension
Memory for recent and past events	Variable, fluctuating impairments	Often impaired for recent events; memory for remote events becomes impaired in later stages

Graphic 103327 Version 1.0

DSM-IV and DSM-5 criteria for dementia

DSM-IV criteria for dementia	DSM-5 criteria for major neurocognitive disorder (previously dementia)
A1. Memory impairment	**A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
A2. At least one of the following: - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning	
B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.	**B.** The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively during the course of delirium.	**C.** The cognitive deficits do not occur exclusively in the context of a delirium.
	D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).

For diagnostic criteria of dementia subtypes such as Alzheimer disease or frontotemporal dementia, please refer to UpToDate topics on the clinical manifestations and diagnosis of individual dementia subtypes.

DSM: Diagnostic and Statistical Manual of Mental Disorders.

* Evidence of decline is based on concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

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Graphic 91276 Version 6.0

Drugs believed to cause or prolong delirium or confusional states*

Analgesics
NSAIDs
Opioids (especially meperidine)
Antibiotics and antivirals
Acyclovir
Aminoglycosides
Amphotericin B
Antimalarials
Cephalosporins
Cycloserine
Fluoroquinolones
Isoniazid
Interferon
Linezolid
Macrolides
Metronidazole
Nalidixic acid
Penicillins
Rifampin
Sulfonamides
Anticholinergics
Atropine
Benztropine
Diphenhydramine
Scopolamine
Trihexyphenidyl
Antiseizure medications
Carbamazepine
Levetiracetam

Corticosteroids
Dopamine agonists
Amantadine
Bromocriptine
Levodopa
Pergolide
Pramipexole
Ropinirole
Gastrointestinal agents
Antiemetics
Antispasmodics
Histamine 2 receptor blockers
Loperamide
Herbal preparations
Atropa belladonna extract
Henbane
Mandrake
Jimson weed
St. John's wort
Valerian
Hypoglycemics
Hypnotics and sedatives
Barbiturates
Benzodiazepines
Muscle relaxants
Baclofen
Cyclobenzaprine
Other CNS-active agents
Disulfiram

Phenytoin	Cholinesterase inhibitors (eg, donepezil)
Valproate	Interleukin 2
Vigabatrin	Lithium
Antidepressants	Phenothiazines
Mirtazapine	
Selective serotonin reuptake inhibitors	
Tricyclic antidepressants	
Cardiovascular and hypertension drugs	
Antiarrhythmics	
Beta blockers	
Clonidine	
Digoxin	
Diuretics	
Methyldopa	

NSAIDs: nonsteroidal antiinflammatory drugs; CNS: central nervous system.

* Not exhaustive, all medications should be considered.

Graphic 70449 Version 9.0

Short Patient Health Questionnaire (PHQ-2)

Name:			**Date:**		
Over the past 2 weeks, how often have you been bothered by any of the following problems?		**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
Little interest or pleasure in doing things?		0	1	2	3
Feeling down, depressed, or hopeless?		0	1	2	3
Total point score:	___	___	+ ___	+ ___	+ ___

Score interpretation[1]:

PHQ-2 score	**Probability of major depressive disorder (%)**	**Probability of any depressive disorder (%)**
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

Reference:

1. *Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003; 41:1284.*

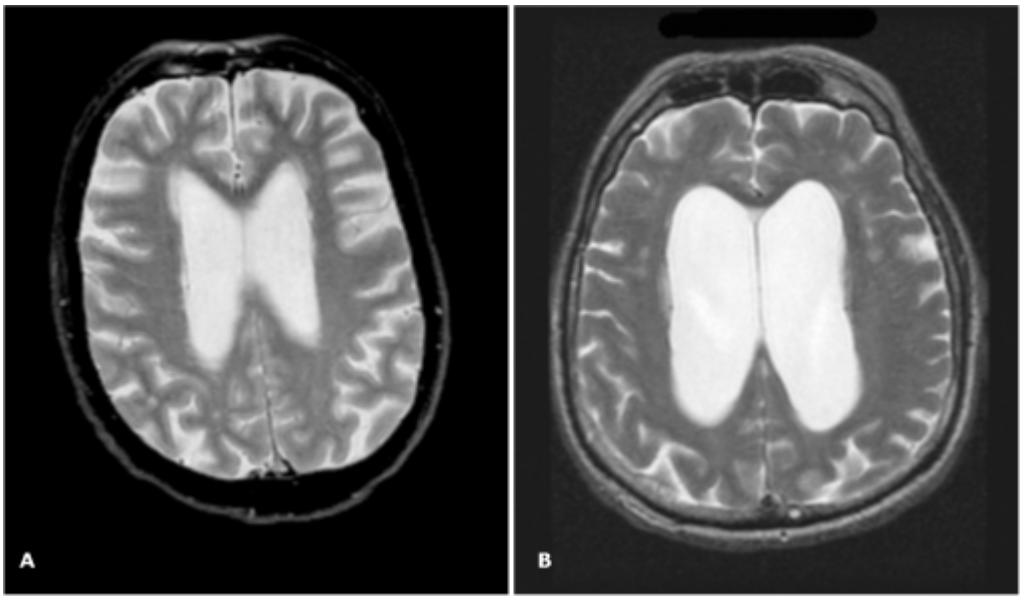
Graphic 89663 Version 3.0

Regional atrophy patterns in neurodegenerative dementias

Dementia syndrome	Atrophy pattern
Alzheimer dementia	Temporal (including hippocampal), parietal atrophy sparing sensorimotor strip and occiput
Behavioral variant frontotemporal dementia	Prefrontal, anterior temporal
Huntington disease	Head of the caudate
Nonfluent variant primary progressive aphasia	Dominant perisylvian
Posterior cortical atrophy	Bilateral superior parietal-occipital junction
Progressive supranuclear palsy	Diminished midbrain anteroposterior diameter
Semantic variant primary progressive aphasia	Anterior inferior temporal lobes

Graphic 94377 Version 5.0

MRI ventriculomegaly atrophy versus NPH



(A) Axial T2-weighted image at level of lateral ventricles in a patient with Alzheimer disease demonstrates increased size of the ventricular system in proportion to sulcal dilatation, consistent with brain parenchymal volume loss.

(B) Axial T2-weighted image at level of lateral ventricles in a patient with NPH shows ventricular dilatation out of proportion to the sulci.

MRI: magnetic resonance imaging; NPH: normal pressure hydrocephalus.

Graphic 76428 Version 5.0

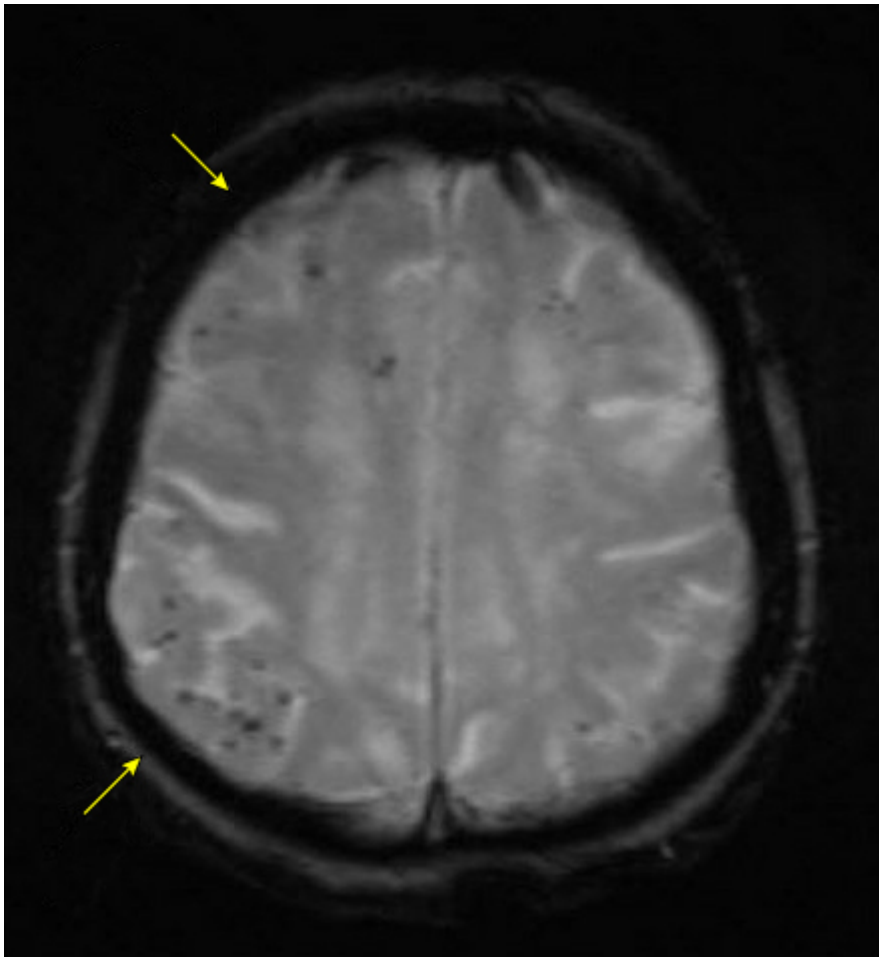
NINDS-AIREN criteria for probable vascular dementia

The criteria for the clinical diagnosis of probable vascular dementia include all of the following:
Dementia
Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
Exclusion criteria: Cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
Cerebrovascular disease
Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.
A relationship between the above two disorders
Manifested or inferred by the presence of one or more of the following:
(a) Onset of dementia within three months following a recognized stroke;
(b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits

NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement Neurosciences; AD: Alzheimer disease; CVD: cerebrovascular disease; CT: computed tomography; MRI: magnetic resonance imaging; PCA: posterior cerebral artery; ACA: anterior cerebral artery.

Graphic 67333 Version 4.0

Multiple cerebral microhemorrhages in a patient with amyloid angiopathy and Alzheimer disease



Gradient echo magnetic resonance imaging (MRI) showing multiple areas of punctate susceptibility artifact consistent with cerebral microhemorrhages (arrows) due to amyloid angiopathy in a patient with Alzheimer's disease.

Graphic 97714 Version 3.0

Rapidly progressive dementia: Potential diagnostic testing

In all patients:
Brain MRI, including FLAIR and DWI, with and without gadolinium enhancement
Serum electrolytes, liver, renal, and thyroid function tests
Vitamin B12, homocysteine
Urinalysis, culture
In most patients:
Lumbar puncture, cell count and differential, protein, glucose, syphilis serology
EEG
In selected patients (based on abnormalities in above tests or suggestive clinical features):
CSF
Cryptococcal antigen
Bacterial fungal AFB stains and cultures
Cytology
Viral PCRs and cultures
Lyme serology
14-3-3 protein
Paraneoplastic antibodies
Blood
Rheumatologic screen (ESR, ANA, CRP)
Antithyroglobulin, anti-thyroperoxidase antibodies
HIV
Lyme
Paraneoplastic and nonparaneoplastic autoimmune antibodies
Copper, ceruloplasmin
Whipple PCR
Urine copper, heavy metal screen
Further imaging (angiography, PET, SPECT)
Brain biopsy

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; DWI: diffusion-weighted imaging; EEG: electroencephalography; CSF: cerebrospinal fluid; AFB: acid-fast bacilli; PCR: polymerase chain reaction; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibodies; CRP: C-reactive protein; HIV: human immunodeficiency virus; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Graphic 55420 Version 8.0