Chapter 29: Dementia

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INTRODUCTION

Dementia, a syndrome with many causes, affects nearly 6 million people in the United States and results in a total annual health care cost in excess of $300 billion. Dementia is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Episodic memory, the ability to recall events specific in time and place, is the cognitive function most commonly lost; 10% of persons age >70 years and 20–40% of individuals age >85 years have clinically identifiable memory loss. In addition to memory, dementia may erode other mental faculties, including language, visuospatial, praxis, calculation, judgment, and problem-solving abilities. Neuropsychiatric and social deficits also arise in many dementia syndromes, manifesting as depression, apathy, anxiety, hallucinations, delusions, agitation, insomnia, sleep disturbances, compulsions, or disinhibition. The clinical course may be slowly progressive, as in Alzheimer's disease (AD); static, as in anoxic encephalopathy; or may fluctuate from day to day or minute to minute, as in dementia with Lewy bodies (DLB). Most patients with AD, the most prevalent form of dementia, begin with episodic memory impairment, but in other dementias, such as frontotemporal dementia (FTD), memory loss is not typically a presenting feature. **Focal cerebral disorders are discussed in Chap. 30 and illustrated in a video library in Chap. V2; detailed discussions of AD can be found in Chap. 431; FTD and related disorders in Chap. 432; vascular dementia in Chap. 433; DLB in Chap. 434; Huntington's disease (HD) in Chap. 436; and prion diseases in Chap. 438.**

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementia syndromes result from the disruption of specific large-scale neuronal networks; the location and severity of synaptic and neuronal loss combine to produce the clinical features **(Chap. 30)**. Behavior, mood, and attention are modulated by ascending noradrenergic, serotonergic, and dopaminergic pathways, whereas cholinergic signaling is critical for attention and memory functions. The dementias differ in the relative neurotransmitter deficit profiles; accordingly, accurate diagnosis guides effective pharmacologic therapy.

AD typically begins in the entorhinal region of the medial temporal lobe, spreads to the hippocampus and other limbic structures, and moves through the basal temporal areas and then into the lateral and posterior temporal and parietal neocortex, eventually causing a more widespread degeneration. Vascular dementia is associated with focal damage in a variable patchwork of cortical and subcortical regions or white matter tracts that disconnects nodes within distributed networks. In keeping with its anatomy, AD typically presents with episodic memory loss accompanied later by aphasia, executive dysfunction, or navigational problems. In contrast, dementias that begin in frontal or subcortical regions, such as FTD or HD, are less likely to begin with memory problems and more likely to present with difficulties with judgment, mood, executive control, movement, and behavior.

Lesions of frontal-striatal[1] pathways produce specific and predictable effects on behavior. The dorsolateral prefrontal cortex has connections with a central band of the caudate nucleus. Lesions of either the caudate or dorsolateral prefrontal cortex, or their connecting white matter pathways, may result in executive dysfunction, manifesting as poor organization and planning, decreased cognitive flexibility, and impaired working memory. The lateral orbital frontal cortex connects with the ventromedial caudate, and lesions of this system cause impulsiveness, distractibility, and disinhibition. The anterior cingulate cortex and adjacent medial prefrontal cortex project to the nucleus accumbens, and interruption of this system produces apathy, poverty of speech, emotional blunting, or even akinetic mutism. All corticostriatal systems also include topographically organized projections through the globus pallidus and thalamus, and damage to these nodes can likewise reproduce the clinical syndrome associated with the corresponding cortical or striatal injuries. Involvement of brainstem nuclei and cerebellar structures can further contribute to cognitive, behavioral, and motor manifestations.

THE CAUSES OF DEMENTIA

The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade over age 50 and is usually associated with the microscopic changes of AD at autopsy. Yet some centenarians have intact memory function and no evidence of clinically significant dementia. Whether dementia is an inevitable consequence of normal human aging remains controversial although the prevalence increases with every decade of life.

The many causes of dementia are listed in **Table 29-1**. The frequency of each condition depends on the age group under study, access of the group to medical care, country of origin, and perhaps racial or ethnic background. AD is the most common cause of dementia in Western countries, accounting for more than half of all patients. Vascular disease is the second most frequent cause for dementia and is particularly common in elderly patients or populations with limited access to medical care, where vascular risk factors are undertreated. Measures of impaired left atrial function, as measured by echocardiography, have been associated with the development of incident dementia, likely on a vascular basis. Often, vascular brain injury is mixed with neurodegenerative disorders, particularly AD, making it difficult, even for the neuropathologist, to estimate the contribution of cerebrovascular disease to the cognitive disorder in an individual patient. The risk of dementia increases after ischemic stroke, independent of vascular risk factors, suggesting primary and secondary stroke prevention is an important intervention that may reduce the incidence of dementia. In a cohort study of older hospitalized survivors of COVID-19, an increased risk of longitudinal cognitive decline at 1 year was demonstrated, suggesting a potential link between severe infection and the development of dementia. Dementias associated with Parkinson's disease (PD) are common and may develop years after onset of a parkinsonian disorder, as seen with PD-related dementia (PDD), or they can occur concurrently with or preceding the motor syndrome, as in DLB. Limbic-predominant aging-related TDP-43 encephalopathy (LATE) is common after age 70 and has been linked to declining episodic memory function. Chronic traumatic encephalopathy (CTE), a unique disease found in individuals with a history of repetitive head impacts (e.g., professional athletes in collision or fighting sports, military veterans exposed to multiple blasts), presents with changes in cognition, mood, behavior, or motor function. Mixed pathology is common, especially in older individuals. In patients under the age of 65, FTD rivals AD as the most common cause of dementia. Chronic intoxications, including those resulting from alcohol and prescription drugs, are an important and often treatable cause of dementia. Other disorders listed in **Table 29-1** are uncommon but important because many are reversible. The classification of dementing illnesses into reversible and irreversible disorders is a useful approach to differential diagnosis. When effective treatments for the neurodegenerative conditions emerge, this dichotomy will become obsolete.

TABLE 29-1

Differential Diagnosis of Dementia

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism[a]
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication[a']
Diffuse white matter disease (Binswanger's)	Limbic-predominant age-related TDP-43 encephalopathy
Less Common Causes of Dementia	
Vitamin deficiencies Thiamine (B_1): Wernicke's encephalopathy[a] B_{12} (subacute combined degeneration)[a] Nicotinic acid (pellagra)[a] Endocrine and other organ failure Hypothyroidism[a] Adrenal insufficiency and Cushing's syndrome[a] Hypo- and hyperparathyroidism[a] Renal failure[a] Liver failure[a] Pulmonary failure[a] Chronic infections HIV Neurosyphilis[a] Papovavirus (JC virus) (progressive multifocal leukoencephalopathy) Tuberculosis, fungal, and protozoal[a] Whipple's disease[a] Head trauma and diffuse brain damage Chronic traumatic encephalopathy Chronic subdural hematoma[a] Postanoxia Postencephalitis Normal-pressure hydrocephalus[a] Intracranial hypotension Neoplastic Primary brain tumor[a] Metastatic brain tumor[a] Autoimmune (paraneoplastic) encephalitis[a]	Toxic disorders Drug, medication, and narcotic poisoning[a] Heavy metal intoxication[a] Organic toxins Psychiatric Depression (pseudodementia)[a] Schizophrenia[a] Conversion disorder[a] Degenerative disorders Huntington's disease Multisystem atrophy Hereditary ataxias (some forms) Frontotemporal lobar degeneration spectrum Multiple sclerosis Adult Down's syndrome with Alzheimer's disease ALS-parkinsonism-dementia complex of Guam Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases) Miscellaneous Sarcoidosis[a] Vasculitis[a] CADASIL, etc. Acute intermittent porphyria[a] Recurrent nonconvulsive seizures[a] Additional conditions in children or adolescents Pantothenate kinase–associated neurodegeneration Subacute sclerosing panencephalitis Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)

[a]Potentially reversible dementia.

Abbreviations: ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

In a study of 1000 persons attending a memory disorders clinic, 19% had a potentially reversible cause of the cognitive impairment and 23% had a potentially reversible concomitant condition that may have contributed to the patient's impairment. The three most common potentially reversible diagnoses were depression, normal pressure hydrocephalus (NPH), and alcohol dependence; medication side effects are also common and should be considered in every patient **(Table 29-1)**. Visual impairment is another important and common potentially modifiable risk factor for dementia.

The term *rapidly progressive dementia (RPD)* is applied to illnesses that progress from initial symptom onset to dementia within a year or less; confusional states related to toxic/metabolic conditions are excluded. Although the prion proteinopathy Creutzfeldt-Jakob disease (CJD) **(Chap. 438)** is the classic cause of a rapidly progressive dementia, especially when associated with myoclonus, more often cases of RPD are due to AD or another neurodegenerative disorder, or to an autoimmune encephalitis.

Subtle cumulative decline in episodic memory is a common part of aging. This frustrating experience, often the source of jokes and humor, has historically been referred to as *benign forgetfulness of the elderly. Benign* means that it is not so progressive or serious that it impairs successful and productive daily functioning, although the distinction between benign and significant memory loss can be subtle. At age 85, the average person is able to learn and recall approximately one-half of the items (e.g., words on a list) that he or she could at age 18. The term *subjective cognitive decline* describes individuals who experience a subjective decline from their cognitive baseline but perform within normal limits for their age and educational attainment on formal neuropsychological testing. *Mild cognitive impairment (MCI)* is defined as a decline in cognition that is confirmed on objective cognitive testing but does not disrupt normal daily activities. MCI can be further subcategorized based on the presenting complaints and deficits (e.g., amnestic MCI, executive MCI). Factors that predict progression from MCI to an AD dementia include a prominent memory deficit, family history of dementia, presence of an apolipoprotein ε4 (Apo ε4) allele, small hippocampal volumes, an AD-like signature of cortical atrophy, low cerebrospinal fluid Aβ and elevated tau, or evidence of brain amyloid and tau deposition on positron emission tomography (PET) imaging.

The major degenerative dementias include AD, DLB, FTD and related disorders, HD, and prion diseases, including CJD. All are associated with the abnormal aggregation of a specific protein: $A\beta_{42}$ and tau in AD; α-synuclein in DLB; tau, TAR DNA-binding protein of 43 kDa (TDP-43), or the FET family of proteins (*fu*sed in *s*arcoma [FUS], Ewing sarcoma [EWS], and TBP-associated factor 15 [TAF15]) in FTD; huntingtin in HD; and misfolded prion protein (PrP^{SC}) in CJD **(Table 29-2)**.

TABLE 29-2

The Molecular Basis for Degenerative Dementia

DEMENTIA	MOLECULAR BASIS	CAUSAL GENES (CHROMOSOME)	SUSCEPTIBILITY GENES	PATHOLOGIC FINDINGS
AD	Aβ/tau	*APP* (21), *PS-1* (14), *PS-2* (1) (<2% carry these mutations, most often in *PS-1*)	*Apo ε4* (19)	Amyloid plaques, neurofibrillary tangles, and neuropil threads
FTD	Tau	*MAPT* exon and intron mutations (17) (about 10% of familial cases)	H1 *MAPT* haplotype	Tau neuronal and glial inclusions varying in morphology and distribution
	TDP-43	*GRN* (10% of familial cases), *C9ORF72* (20%–30% of familial cases), rare *VCP*, very rare *TARDBP, TBK1, TIA1*		TDP-43 neuronal and glial inclusions varying in morphology and distribution
	FET	Very rare *FUS*		FET neuronal and glial inclusions varying in morphology and distribution
DLB	α-Synuclein	Very rare *SNCA* (4)	Unknown	α-Synuclein neuronal inclusions (Lewy bodies)
CJD	PrPSC	*PRNP* (20) (up to 15% of patients carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	PrPSC deposition, panlaminar spongiosis

Abbreviations: AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FET, FUS/EWS/TAF-15; FTD, frontotemporal dementia.

The risk of developing dementia in late-life is associated with exposures and lifestyle factors that can operate across the life span. Modifiable risk factors include low education, hearing loss, traumatic brain injury, hypertension, diabetes mellitus, obstructive sleep apnea, obesity, heavy alcohol use, smoking, depression, physical inactivity, and air pollution. Improved management of midlife vascular risk factors has been credited with a decreasing incidence of dementia observed in North America and Western Europe. A recent randomized trial of prevention of cognitive decline in cognitively normal patients with a family history of dementia using a combined low-salt and Mediterranean diet failed to show benefit after 3 years. A recent study demonstrated that diagnosis of early and middle-life depression increased the risk of dementia by 2-3 fold. Whether this represents another modifiable dementia risk factor remains to be seen.

APPROACH TO THE PATIENT WITH DEMENTIAS

Three major issues should be kept at the forefront: (1) What is the clinical diagnosis? (2) What component of the dementia syndrome is treatable or reversible? (3) Can the physician help to alleviate the burden on caregivers? A broad overview of the approach to dementia is shown in **Table 29-3**. The major degenerative dementias can usually be distinguished by the initial symptoms; neuropsychological, neuropsychiatric, and neurologic findings; and neuroimaging features **(Table 29-4)**.

TABLE 29-3

Evaluation of the Patient with Dementia

ROUTINE EVALUATION	OPTIONAL FOCUSED TESTS	OCCASIONALLY HELPFUL TESTS

History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B_{12}	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
		Autoantibodies
Diagnostic Categories		
REVERSIBLE CAUSES	**IRREVERSIBLE/DEGENERATIVE DEMENTIAS**	**PSYCHIATRIC DISORDERS**
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Autoimmune encephalopathy		
Associated Treatable Conditions		
	Depression	Agitation
	Seizures	Caregiver "burnout"
	Insomnia	Drug side effects

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, venereal disease research laboratory (test for syphilis).

TABLE 29-4

Clinical Differentiation of the Major Dementias

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy, poor judgment/insight, speech/language, hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive, spares memory, delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy, hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden, variable, apathy, falls, focal weakness	Frontal/executive, cognitive slowing, can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity, can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; REM, rapid eye movement.

History

The history should concentrate on the onset, duration, and tempo of progression. An acute or subacute onset of confusion may be due to delirium **(Chap. 27)** and should trigger a search for intoxication, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include anxiety or depression as well as difficulty managing money, driving, shopping, following instructions, finding words, or navigating. Personality change, disinhibition, and weight gain or compulsive eating suggest FTD, not AD. FTD is also suggested by prominent apathy, compulsivity, loss of empathy for others, or progressive loss of speech fluency or single-word comprehension with relative sparing of memory and visuospatial abilities. The diagnosis of DLB is suggested by early visual hallucinations; parkinsonism; proneness to delirium or sensitivity to psychoactive medications; rapid eye movement (REM) behavior disorder (RBD; dramatic, sometimes violent, limb movements during dreaming **[Chap. 31]**); or Capgras syndrome, the delusion that a familiar person has been replaced by an impostor.

A history of stroke with irregular stepwise progression suggests vascular dementia. Vascular dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, smoking, and diabetes. In patients suffering from cerebrovascular disease, it can be

difficult to determine whether the dementia is due to AD, vascular disease, or a mixture of the two because many of the risk factors for vascular dementia, including diabetes, high cholesterol, elevated homocysteine, and low exercise, are also risk factors for AD. Moreover, many patients with a major vascular contribution to their dementia lack a history of stepwise decline. Rapid progression with motor rigidity and myoclonus suggests CJD **(Chap. 438)**. Seizures may indicate strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD. Gait disturbance is common in vascular dementia, PD/DLB, or NPH. A history of high-risk sexual behaviors or intravenous drug use should trigger a search for central nervous system (CNS) infection, especially HIV or syphilis. A history of recurrent head trauma could indicate chronic subdural hematoma, CTE, intracranial hypotension, or NPH. Subacute onset of severe amnesia and psychosis with mesial temporal T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities on MRI should raise concern for autoimmune (paraneoplastic) encephalitis, sometimes in long-term smokers or other patients at risk for cancer. The spectrum of autoimmune etiologies producing RPD has rapidly expanded, and includes antibodies targeting leucine-rich glioma-inactivated 1 (LGI1; faciobrachial dystonic seizures); contactin-associated protein-like 2 (Caspr2; insomnia, ataxia, myotonia); *N-methyl-D-aspartate* (NMDA)-receptor (psychosis, insomnia, dyskinesias); and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-receptor (limbic encephalitis with relapses), among others **(Chap. 94)**. Alcohol abuse creates risk for malnutrition and thiamine deficiency. Veganism, bowel irradiation, an autoimmune diathesis, a remote history of gastric surgery, and chronic therapy with histamine H2-receptor antagonists for dyspepsia or gastroesophageal reflux predispose to B_{12} deficiency. Certain occupations, such as working in a battery or chemical factory, might indicate heavy metal intoxication. Careful review of medication intake, especially for sedatives and analgesics, may raise the issue of chronic drug intoxication. An autosomal dominant family history is found in HD and in familial forms of AD, FTD, DLB, or prion disorders. A history of mood disorder, the recent death of a loved one, or depressive signs such as insomnia or weight loss, raise the possibility of depression-related cognitive impairment.

Physical and Neurologic Examination

A thorough general and neurologic examination is essential to identify signs of nervous system involvement and search for clues suggesting a systemic disease that might be responsible for the cognitive disorder. Typical AD spares motor systems until late in the course. In contrast, patients with FTD often develop axial rigidity, supranuclear gaze palsy, or a motor neuron disease reminiscent of amyotrophic lateral sclerosis (ALS). In DLB, the initial symptoms may include a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinating gait), but DLB often starts with visual hallucinations or cognitive impairment, and symptoms referable to the lower brainstem (RBD, gastrointestinal, or autonomic problems) may arise years or even decades before parkinsonism or dementia. Corticobasal syndrome (CBS) features asymmetric akinesia and rigidity, dystonia, myoclonus, alien limb phenomena, pyramidal signs, and prefrontal deficits such as nonfluent aphasia with or without motor speech impairment, executive dysfunction, apraxia, or a behavioral disorder. Progressive supranuclear palsy (PSP) is associated with unexplained falls, axial rigidity, dysphagia, and vertical gaze deficits. CJD is suggested by the presence of diffuse rigidity, an akinetic mute state, and prominent, often startle-sensitive, myoclonus.

Hemiparesis or other focal neurologic deficits suggest vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B_{12} deficiency. Peripheral neuropathy could also indicate another vitamin deficiency, heavy metal intoxication, thyroid dysfunction, Lyme disease, or vasculitis. Dry cool skin, hair loss, and bradycardia suggest hypothyroidism. Fluctuating confusion associated with repetitive stereotyped movements may indicate ongoing limbic, temporal, or frontal seizures. In the elderly, hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Profound bilateral sensorineural hearing loss in a younger patient with short stature or myopathy, however, should raise concern for a mitochondrial disorder.

Cognitive and Neuropsychiatric Examination

Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), the Tablet Based Cognitive Assessment Tool, and Cognistat can be used to capture dementia and follow progression. None of these tests is highly sensitive to early-stage dementia or reliably discriminates between dementia syndromes. The MMSE is a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 minutes later); and language (e.g., name pencil and watch; repeat “no ifs ands or buts”; follow a 3-step command; obey a written command; and write a sentence and copy a design). In most patients with MCI and some with clinically apparent AD, bedside screening tests may be normal, and a more challenging and comprehensive set of neuropsychological tests will be required. When the etiology for the dementia syndrome remains in doubt, a specially tailored evaluation should be performed that includes tasks of working and episodic memory, executive function, language, and visuospatial and perceptual abilities. In AD, the early deficits involve episodic memory, category generation (“name as many animals as you can in 1 minute”), and visuoconstructive ability. Usually deficits in verbal or visual episodic

memory are the first neuropsychological abnormalities detected, and tasks that require the patient to recall a long list of words or a series of pictures after a predetermined delay will demonstrate deficits in most patients. In FTD, the earliest deficits on cognitive testing involve executive control or language (speech or naming) functions, but some patients lack either finding despite profound social-emotional deficits. PDD or DLB patients have more severe deficits in executive and visuospatial function but do better on episodic memory tasks than patients with AD. Patients with vascular dementia often demonstrate a mixture of executive and visuospatial deficits, with prominent psychomotor slowing. In delirium, the most prominent deficits involve attention, working memory, and executive function, making the assessment of other cognitive domains challenging and often uninformative.

A functional assessment should also be performed to help the physician determine the day-to-day impact of the disorder on the patient's memory, community affairs, hobbies, judgment, dressing, and eating. Knowledge of the patient's functional abilities will help the clinician and the family to organize a therapeutic approach.

Neuropsychiatric assessment is important for diagnosis, prognosis, and treatment. In the early stages of AD, mild depressive features, social withdrawal, and irritability or anxiety are the most prominent psychiatric changes, but patients often maintain core social graces into the middle or late stages, when delusions, agitation, and sleep disturbance may emerge. In FTD, dramatic personality change with apathy, overeating, compulsions, disinhibition, and loss of empathy are early and common. DLB is associated with visual hallucinations, delusions related to person or place identity, RBD, and excessive daytime sleepiness. Dramatic fluctuations occur not only in cognition but also in arousal. Vascular dementia can present with psychiatric symptoms such as depression, anxiety, delusions, disinhibition, or apathy.

Laboratory Tests

The choice of laboratory tests in the evaluation of dementia is complex and should be tailored to the individual patient. The physician must take measures to avoid missing a reversible or treatable cause, yet no single treatable etiology is common; thus a screen must use multiple tests, each of which has a low yield. Cost/benefit ratios are difficult to assess, and many laboratory screening algorithms for dementia discourage multiple tests. Nevertheless, even a test with only a 1–2% positive rate is worth undertaking if the alternative is missing a treatable cause of dementia. **Table 29-3** lists most screening tests for dementia. The American Academy of Neurology recommends the routine measurement of a complete blood count; electrolytes; glucose; renal, liver, and thyroid functions; a vitamin B_{12} level; and a structural neuroimaging study (MRI or CT).

Neuroimaging studies, especially MRI, help to rule out primary and metastatic neoplasms, locate areas of infarction or inflammation, detect subdural hematomas, and suggest NPH or diffuse white matter disease. They also help to establish a regional pattern of atrophy. Support for the diagnosis of AD includes hippocampal atrophy in addition to posterior-predominant cortical atrophy **(Fig. 29-1)**. Focal frontal, insular, and/or anterior temporal atrophy suggests FTD **(Chap. 432)**. DLB often features less prominent atrophy, with greater involvement of the amygdala than the hippocampus. In CJD, magnetic resonance (MR) diffusion-weighted imaging reveals restricted diffusion within the cortical ribbon and/or basal ganglia in most patients. Extensive multifocal white matter abnormalities suggest a vascular etiology **(Fig. 29-2)**. Communicating hydrocephalus with vertex effacement (crowding of dorsal convexity gyri/sulci), gaping Sylvian fissures despite minimal cortical atrophy, and additional features shown in **Fig. 29-3** suggest NPH. Single-photon emission computed tomography (SPECT) and fluoro-deoxyglucose PET scanning show temporal-parietal hypoperfusion or hypometabolism in AD and frontotemporal deficits in FTD, but abnormalities in these patterns can be detected with MRI alone in many patients. Recently, amyloid- and tau-PET imaging have shown promise for the diagnosis of AD. There are currently three amyloid PET ligands (F18-florbetapir, F18-florbetaben, F18-flutametamol) and one tau PET ligand (F18-flortaucipir) approved by the US Food and Drug Administration for clinical use. Amyloid PET ligands bind to diffuse and neuritic amyloid plaques, as well as to vascular amyloid deposits (prominent in cerebral amyloid angiopathy), while tau PET ligands bind to the paired helical filaments of tau characteristic of neurofibrillary tangles in AD **(Chap. 431)**. Because amyloid plaques are also commonly found in cognitively normal older persons (~25% of individuals at age 65), the main clinical value of amyloid imaging is to exclude AD as the likely cause of dementia in patients who have negative scans. The spread of tau is more tightly linked to cognitive state **(Chap. 431)**, and thus may be more useful than amyloid imaging for "ruling in" AD, as well as for disease staging. Once disease-modifying therapies become available, CSF or molecular PET biomarkers will likely be used to identify treatment candidates. In the meantime, the prognostic value of detecting brain amyloid in an asymptomatic elder to assess preclinical disease and risk of future cognitive decline remains a topic of vigorous investigation.

FIGURE 29-1

Alzheimer's disease (AD). Axial T1-weighted magnetic resonance images of a healthy 62-year-old (***A, B***) and a 60-year-old with AD (***C, D***). Note the

diffuse atrophy, plus temporal lobe volume loss, in the patient with AD. Aβ positron emission tomography (PET) with [^{11}C]PIB (***B*** and ***D***) reveals extensive radiotracer retention in neocortex bilaterally in AD, consistent with the known distribution of amyloid plaques. HC, healthy control. *(Source: Gil Rabinovici, University of California, San Francisco and William Jagust, University of California, Berkeley.)*

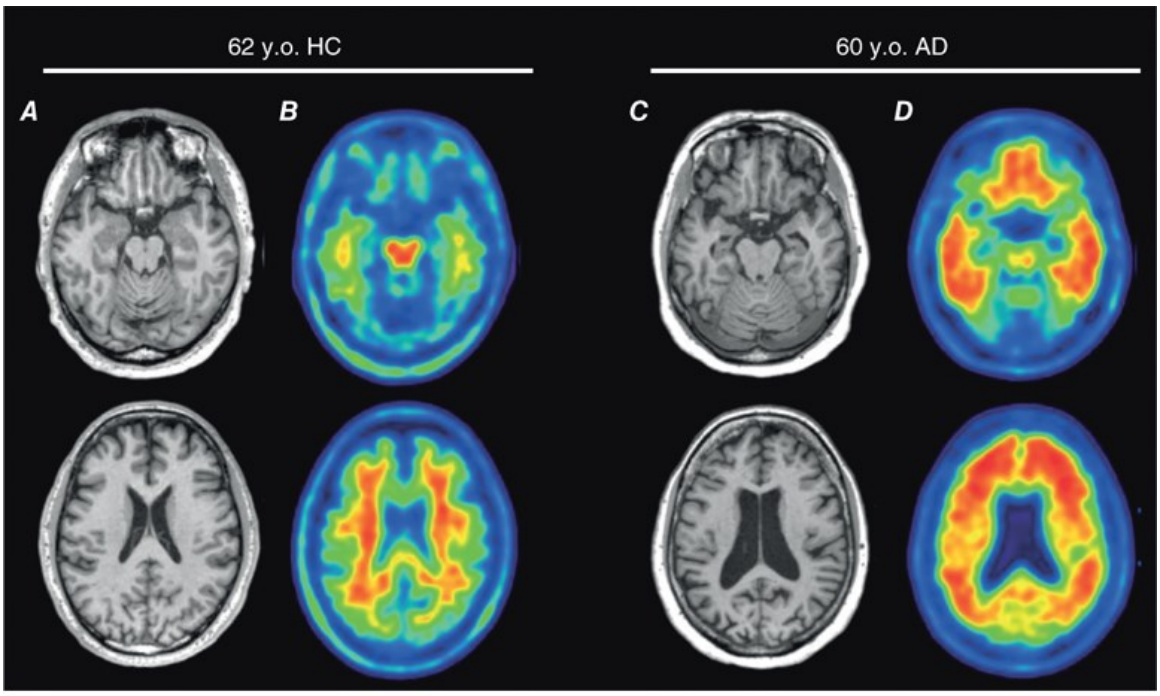


FIGURE 29-2

Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (*arrows*) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in patients with dementia of a vascular etiology. *(Source: JL Jameson, AS Fauci, DL Kasper, SL Hauser, DL Longo, J Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition Copyright © McGraw Hill Education. All rights reserved.)*

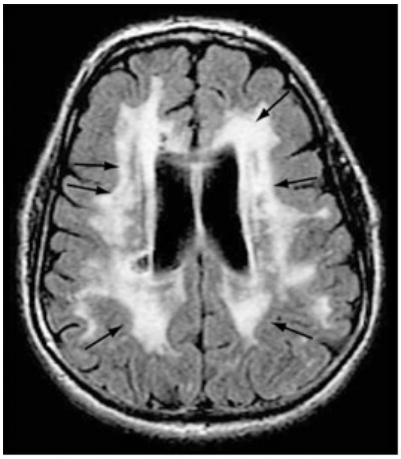
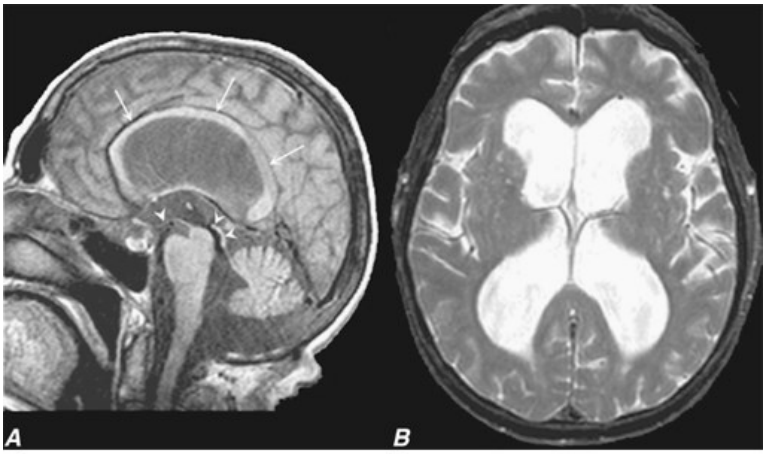


FIGURE 29-3

Normal pressure hydrocephalus. ***A.*** Sagittal T1-weighted MRI demonstrates dilation of the lateral ventricle and stretching of the corpus callosum (*arrows*), depression of the floor of the third ventricle (*single arrowhead*), and enlargement of the aqueduct (*double arrowheads*). Note the diffuse dilation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. ***B.*** Axial T2-weighted MRIs demonstrate dilation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting.



Lumbar puncture need not be done routinely in the evaluation of dementia, but it is indicated when CNS infection or inflammation are credible diagnostic possibilities. Cerebrospinal fluid (CSF) levels of $A\beta_{42}$ and tau proteins show differing patterns with the various dementias, and the presence of low $A\beta_{42}$ (or a low $A\beta_{42}/A\beta_{40}$ ratio), mild-moderately elevated CSF total tau, and elevated CSF phosphorylated tau (at residues 181 or 217) is highly suggestive of AD. Novel fully automated CSF Aβ and tau assays perform comparably to amyloid and tau PET respectively, though, as with PET, their routine use in the diagnosis of dementia is debated. Blood-based biomarkers for AD show promise as a less invasive screening tool but remain under development **(Chap. 431)**. Formal psychometric testing helps to document the severity of cognitive disturbance, suggests psychogenic causes, and provides a more formal method for following the disease course. Electroencephalogram (EEG) is not routinely used but can help to suggest CJD (repetitive bursts of diffuse high-amplitude sharp waves, or "periodic complexes") or an underlying nonconvulsive seizure disorder (epileptiform discharges). Brain biopsy (including meninges) is not advised except to diagnose vasculitis, neoplasms, or unusual infections when the diagnosis is uncertain. Systemic disorders with CNS manifestations, such as sarcoidosis, can often be confirmed through biopsy of lymph node or solid organ rather than brain. MR angiography should be considered when cerebral vasculitis or cerebral venous thrombosis is a possible cause of the dementia.

[1]The striatum comprises the caudate/putamen/nucleus accumbens.

GLOBAL CONSIDERATIONS

Vascular dementia **(Chap. 433)** is more common in Asia due to the higher prevalence of intracranial atherosclerosis. Rates of vascular dementia are also on the rise in developing countries as vascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus become more widespread. CNS infections, HIV (and associated opportunistic infections), syphilis, cysticercosis, and tuberculosis, likewise represent major contributors to dementia in the developing world. Systemic infection with SARS-CoV-2 may, in some individuals, have lasting effects on cognition due to involvement of brain microvasculature or to immunologically mediated white matter injury (acute disseminated encephalomyelitis [ADEM]) **(Chap. 444)**. Some individuals complain of lasting fatigue, changes in mood, and cognitive difficulties, but the long-term prognosis for SARS-CoV-2-related cognitive impairment remains unknown. Isolated populations have also contributed to our understanding of neurodegenerative dementia. Kuru, the cannibalism-associated rapidly progressive dementia seen in tribal New Guinea, played a role in the discovery of human prion disease. Amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam (or, Lytico-bodig disease) is a poly-proteinopathy, often with tau, TDP-43, and alpha-synuclein aggregation. The root cause of the disease remains uncertain, but its incidence has declined sharply over the past 60 years.

TREATMENT OF DEMENTIA

The major goals of dementia management are to treat reversible causes and provide comfort and support to the patient and caregivers. Treatment of

underlying causes includes thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B_{12} deficiency or for elevated serum homocysteine; antimicrobials for opportunistic infections or antiretrovirals for HIV; ventricular shunting for NPH; or surgical, radiation, and/or chemotherapeutic treatment for CNS neoplasms. Removal of cognition-impairing drugs or medications is essential when appropriate. If the patient's cognitive complaints stem from a psychiatric disorder, vigorous treatment of the condition should be tried to eliminate the cognitive complaint or to confirm that it persists despite adequate resolution of the mood or anxiety symptoms. Patients with degenerative diseases may also be depressed or anxious, and those aspects of their condition often respond to therapy while not necessarily improving cognition. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) **(Chap. 452)**, which feature anxiolytic properties but few cognitive side effects, provide the mainstay of treatment when necessary. Anticonvulsants are used to control AD-associated seizures.

Agitation, hallucinations, delusions, and confusion are difficult to treat. These behavioral problems represent major causes for nursing home placement and institutionalization. Before treating these behaviors with medications, the clinician should aggressively seek out modifiable environmental or metabolic factors. Hunger, lack of exercise, toothache, constipation, urinary tract or respiratory infection, electrolyte imbalance, and drug toxicity all represent easily correctable causes that can be remedied without psychoactive drugs. Drugs such as phenothiazines and benzodiazepines may ameliorate the behavior problems but have untoward side effects such as sedation, rigidity, or dyskinesia; benzodiazepines can occasionally produce paradoxical disinhibition. Despite their unfavorable side effect profile, second-generation antipsychotics such as quetiapine (starting dose, 12.5–25 mg daily) can be used for patients with agitation, aggression, and psychosis, although the risk profile for these compounds is significant, including increased mortality in patients with dementia. When patients do not respond to treatment, it is usually a mistake to advance to higher doses or to use anticholinergic drugs (like diphenhydramine) or sedatives (such as barbiturates or benzodiazepines). It is important to recognize and treat depression; treatment can begin with a low dose of an SSRI (e.g., escitalopram, starting dose 5 mg daily, target dose 5–10 mg daily) while monitoring for efficacy and toxicity. Sometimes apathy, visual hallucinations, depression, and other psychiatric symptoms respond to cholinesterase inhibitors, especially in DLB, obviating the need for other more toxic therapies.

Cholinesterase inhibitors are being used to treat AD (donepezil, rivastigmine, galantamine) and PDD (rivastigmine). Memantine is useful for some patients with moderate to severe AD; its major benefit relates to decreasing caregiver burden, most likely by decreasing resistance to dressing and grooming support. In moderate to severe AD, the combination of memantine and a cholinesterase inhibitor delayed nursing home placement in several studies, although other studies have not supported the efficacy of adding memantine to the regimen. Memantine should be used with great caution, or not at all, in patients with DLB, due to risk of worsening agitation and confusion. Therapies targeting the production, aggregation, and spread of misfolded proteins associated with dementia are under development. Recently the first drug in this class, the amyloid-beta targeting monoclonal antibody aducanumab, was approved by the United States Food & Drug Administration for treatment of Alzheimer's disease (Chap. 431). Other drugs under development target disease-associated neuroinflammation metabolic changes, synaptic loss, and neurotransmitter changes.

Proactive approaches reduce the occurrence of delirium in hospitalized patients. Frequent orientation, cognitive activities, sleep-enhancement measures, vision and hearing aids, and correction of dehydration are all valuable in decreasing the likelihood of delirium.

Nondrug behavior therapy has an important place in dementia management. The primary goals are to make the patient's life comfortable, uncomplicated, and safe. Preparing lists, schedules, calendars, and labels can be helpful in the early stages. It is also useful to stress familiar routines, walks, and simple physical exercises. For many demented patients, memory for events is worse than their ability to carry out routine activities, and they may still be able to take part in their favorite hobbies, sports, and social activities. Demented patients often object to losing control over familiar tasks such as driving, cooking, and handling finances. Attempts to help may be greeted with complaints, depression, or anger. Hostile responses on the part of the caregiver are counterproductive and sometimes even harmful. Reassurance, distraction, and calm positive statements are more productive when resistance is present. Eventually, tasks such as finances and driving must be assumed by others, and the patient will conform and adjust. Safety is an important issue that includes not only driving but controlling the kitchen, bathroom, and sleeping area environments, as well as stairways. These areas need to be monitored, supervised, and made as safe as possible. A move to a retirement complex, assisted-living center, or nursing home can initially increase confusion and agitation. Repeated reassurance, reorientation, and careful introduction to the new personnel will help to smooth the process. Providing activities that are known to be enjoyable to the patient can also help. In adults without dementia, but with reported subjective cognitive concerns, a trial of mindfulness training, exercise or both demonstrated no benefit at 6 months in improving episodic memory or executive function.

The clinician must pay special attention to frustration and depression among family members and caregivers. Caregiver guilt and burnout are common. Family members often feel overwhelmed and helpless and may vent their frustrations on the patient, each other, and health care providers. Caregivers should be encouraged to take advantage of day-care facilities and respite services. Education and counseling about dementia are

important. Local and national support groups, such as the Alzheimer's Association (*www.alz.org*), can provide considerable help.

FURTHER READING

Barton C et al: Non-pharmacological management of behavioral symptoms in frontotemporal and other dementias. Curr Neurol Neurosci Rep 16:14, 2016. [PubMed: 26750129]

Griem J et al: Psychologic/functional forms of memory disorder. Handb Clin Neurol 139:407, 2017.

Wesley SF, Ferguson D: Autoimmune encephalitides and rapidly progressive dementias. Semin Neurol 39:283, 2019. [PubMed: 30925620]

Additional Online Reference

Barnes LL et al: Trial of the MIND diet for prevention of cognitive decline in older persons. N Engl J Med 2023. [Epub ahead of print.]

Ehrlich JR et al: Addition of vision impairment to a life-course model of potentially modifiable dementia risk factors in the US. JAMA Neurol 2022. [Epub ahead of print.]

Elser H et al: Association of early-, middle-, and late-life depression with incident dementia in a Danish cohort. JAMA Neurol, 2023. [Epub ahead of print.]

Koton S et al: Association of ischemic stroke incidence, severity, and recurrence with dementia in the Atherosclerosis Risk in Communities cohort study. JAMA Neurol 2022. [Epub ahead of print.]

Lenze EJ et al: Effects of mindfulness training and exercise on cognitive function in older adults: A randomized clinical trial. JAMA 328:2218, 2022.

Liu Y-H et al: One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: A longitudinal cohort study. JAMA Neurol, 2022. [Epub ahead of print.]

Shieu MM et al: Positive airway pressure and cognitive disorders in adults with obstructive sleep apnea: A systematic review of the literature. Neurology 99:e334, 2022. [PubMed: 35523585]

Wang W et al: Association of echocardiographic measures of left atrial function and size with incident dementia. JAMA 327:1138, 2022.