21 - 31 Dementia

31 Dementia

and therefore, serial examinations and multimodal prognostication approaches are advised. For example, the absence of the cortical responses of the somatosensory evoked potentials has been shown to be a strong indicator of poor outcome following hypoxic injury, as has high elevations of serum neuron-specific enolase drawn at estab lished intervals after anoxia. The poor outcome of persistent vegetative and minimally conscious states has already been mentioned, but reports of a small number of patients displaying cortical activation on functional MRI in response to salient stimuli have begun to alter the perception of such individu als. In one series, about 10% of vegetative patients (mainly following traumatic brain injury) could activate their frontal or temporal lobes in response to requests by an examiner to imagine certain visuospatial tasks. Another series demonstrated that up to 15% of patients with various forms of acute brain injury and absence of behavioral responses to motor commands showed EEG activation in response to these com mands. It is prudent to avoid generalizations from these findings, but the need for future studies of novel techniques to help communication and possibly recovery is needed. ■ ■FURTHER READING Claasen J et al: Detection of brain activation in unresponsive patients with acute brain injury. N Engl J Med 380:2497, 2019. Edlow JA et al: Recovery from disorders of consciousness: Mechanisms, prognosis and emerging therapies. Nat Rev Neurol 17:135, 2021. Greer DM et al: Pediatric and adult brain death/death by neurologic criteria consensus guideline: Report of the AAN guidelines subcom mittee, AAP, CNS, and SCCM. Neurology 101:1112, 2023. Posner JB et al: Plum and Posner’s Diagnosis of Stupor and Coma, 5th ed. New York, Oxford University Press, 2019. Wijdicks EFM: Predicting the outcome of a comatose patient at the bedside. Pract Neurol 20:26, 2020. Gil D. Rabinovici, William W. Seeley,

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Dementia Dementia, a syndrome with many causes, affects over 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 activi ties 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. Neuropsy chiatric 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 fron totemporal dementia (FTD), memory loss is not typically a presenting feature. When dementia is caused by a progressive neurodegenerative disease, it is preceded by a prodromal clinical stage called mild cogni tive impairment (MCI), in which individuals experience cognitive decline but remain independent in most daily activities. Increasingly,

a preclinical stage is recognized for AD and other dementing illnesses, in which brain pathology is present but clinical symptoms are not yet manifest. Focal cerebral disorders are discussed in Chap. 32 and illustrated in a video library in Chap. V2; detailed discussions of AD can be found in Chap. 442; FTD and related disorders in Chap. 443; vascular dementia in Chap. 444; DLB in Chap. 445; Huntington's disease (HD) in Chap. 447; and prion diseases in Chap. 449.

FUNCTIONAL ANATOMY OF THE DEMENTIAS Dementia syndromes result from the disruption of specific large-scale neuronal networks by initially focal brain lesions, including neurode generative changes and vascular injury. Ultimately, the location and severity of synaptic and neuronal loss combine to produce the clinical features (Chap. 32). Behavior, mood, and attention are also modu lated by ascending noradrenergic, serotonergic, and dopaminergic pathways, whereas cholinergic signaling is critical for attention and memory functions. The dementias differ in the underlying molecular pathology and relative neurotransmitter deficit profiles; accordingly, accurate diagnosis guides effective therapy. Dementia CHAPTER 31 AD typically begins in the entorhinal region of the medial temporal lobe, spreads to the hippocampus and other limbic structures, moves through the basal temporal areas, and then into 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 prob lems and more likely to present with difficulties with judgment, mood, executive control, movement, and behavior. Lesions of frontal-striatal1 pathways produce specific and predict able effects on behavior. The dorsolateral prefrontal cortex has con nections 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 projec tions 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. Lesions in nodes of the dominant hemisphere speech and language networks can present as a primary progressive aphasia, with deficits in naming, word retrieval, motor speech, grammar, and comprehension of single words or more complex phrases (Chap. 443). Involvement of brainstem nuclei and cerebellar structures can further contribute to cognitive, behavioral, motor and autonomic 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 31-1. The frequency of each condition depends on the age group under study, access of the 1The striatum comprises the caudate/putamen.

TABLE 31-1 Differential Diagnosis of Dementia Most Common Causes of Dementia Alzheimer's disease Alcoholisma Vascular dementia PDD/LBD spectrum Multi-infarct Drug/medication intoxicationa' Diffuse white matter disease Limbic-predominant age-related TDP-43 encephalopathy (Binswanger's) Less Common Causes of Dementia Vitamin deficiencies Thiamine (B1): Wernicke's Toxic disorders Drug, medication, and narcotic PART 2 Cardinal Manifestations and Presentation of Diseases encephalopathya poisoninga B12 (subacute combined Heavy metal intoxicationa degeneration)a Organic toxins Psychiatric Depression (pseudodementia)a Nicotinic acid (pellagra)a Endocrine and other organ failure Hypothyroidisma Schizophreniaa Adrenal insufficiency and Cushing's Conversion disordera syndromea Degenerative disorders Huntington's disease Multisystem atrophy Hereditary ataxias (some forms) Frontotemporal lobar degeneration Hypo- and hyperparathyroidisma Renal failurea Liver failurea Pulmonary failurea Chronic infections HIV Neurosyphilisa spectrum Multiple sclerosis Adult Down's syndrome with Papovavirus (JC virus) (progressive Alzheimer's disease ALS-parkinsonism-dementia multifocal leukoencephalopathy) Tuberculosis, fungal, and protozoala complex of Guam Prion (Creutzfeldt-Jakob and Whipple's diseasea Gerstmann-Sträussler-Scheinker diseases) Miscellaneous Sarcoidosisa Head trauma and diffuse brain damage Chronic traumatic encephalopathy Chronic subdural hematomaa Postanoxia Postencephalitis Normal-pressure hydrocephalusa Vasculitisa CADASIL, etc. Acute intermittent porphyriaa Intracranial hypotension Neoplastic Primary brain tumora Recurrent nonconvulsive seizuresa Additional conditions in children or adolescents Pantothenate kinase–associated Metastatic brain tumora Paraneoplastic/autoimmune limbic neurodegeneration Subacute sclerosing panencephalitis Metabolic disorders (e.g., Wilson's and encephalitisa Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations) aPotentially 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. 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 dis ease is the second most frequent cause for dementia and is particularly common in elderly patients or populations with limited access to medi cal care, where vascular risk factors are undertreated. 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. 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 can occur con currently with or preceding the motor syndrome, as in DLB. A recently characterized dementia is limbic-predominant aging-related TDP-43

encephalopathy (LATE), which 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 high exposure to 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 treat able cause of dementia. Other disorders listed in Table 31-1 are uncom mon but important because many are reversible. The classification of dementing illnesses into reversible and irreversible disorders is a useful approach to differential diagnosis. 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 com mon potentially reversible diagnoses were depression, normal pres sure hydrocephalus (NPH), and alcohol dependence; medication side effects are also common and should be considered in every patient (Table 31-1). 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. 449) is the classic cause of a rapidly progressive demen tia, especially when associated with myoclonus, more often cases of RPD are due to AD or another neurodegenerative disorder, or to an autoimmune encephalitis (Chap. 99). 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 they could at age 18. The term sub jective cognitive decline is used to refer to individuals who experience a subjective decline from their cognitive baseline but perform within normal limits for their age and educational attainment on formal neu ropsychological testing. As noted earlier, 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, dysexecutive 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 on brain imaging, and positive AD biofluid or imaging biomarkers (see below). The term mild behavioral impairment (MBI) refers to the emergence of sustained and impactful neuropsychi atric symptoms in older adults (e.g., apathy, emotional dysregulation, impulse control, social inappropriateness, hallucinations, or delusions). Like its cognitive counterpart (MCI), MBI can reflect a neuropsychiat ric prodrome to a neurodegenerative dementia. The major degenerative dementias include AD, DLB, LATE, FTD and related disorders, HD, and prion diseases, including CJD. These disorders are all associated with the abnormal aggregation of a specific protein: Aβ and tau in AD; α-synuclein in DLB; TAR DNA-binding protein of 43 kDa (TDP-43) in LATE; tau, TDP-43, or the FET fam ily of proteins (fused in sarcoma [FUS], Ewing sarcoma [EWS], and TBP-associated factor 15 [TAF15]) in FTD; huntingtin in HD; and misfolded prion protein (PrPsc) in CJD (Table 31-2). The risk of developing dementia in late life is associated with numerous exposures that can happen across the lifespan. Modifi able risk factors based on large-scale epidemiologic studies include low education, hearing loss, social isolation, traumatic brain injury, hypertension, diabetes mellitus, obesity, heavy alcohol use, smoking, depression, physical inactivity, and air pollution exposure. Improved

TABLE 31-2 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) DLB α-Synuclein Very rare SNCA (4) Unknown α-Synuclein neuronal inclusions (Lewy bodies) LATE TDP-43 None identified TMEM106B, GRN TDP-43 neuronal “inclusion bodies” and neurites in neurons and glia, with or without hippocampal sclerosis FTD Tau MAPT exon and intron mutations (17) (~10% of familial cases) TDP-43 GRN (10% of familial cases), C9ORF72 (20–30% of familial cases), rare VCP, very rare TARDBP, TBK1, TIA1 FUS Very rare FUS FUS neuronal and glial inclusions varying in morphology and distribution CJD PrPSC PRNP (20) (up to 15% of patients carry these

dominant mutations) Abbreviations: AD, Alzheimer’s disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; LATE, limbic-predominant age-related TDP-43 encephalopathy. management of mid-life cardiovascular risk factors has been credited with a decreasing incidence of dementia noted in North America and western European countries. APPROACH TO THE PATIENT 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 demen tia is shown in Table 31-3. The major degenerative dementias can usually be distinguished by the initial symptoms; neuropsycho logical, neuropsychiatric, and neurologic findings; neuroimaging features; and other biomarkers (Table 31-4). 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. 29) and should trigger a search for intoxi cation, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD and/or LATE. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include anxiety or depression and difficulty with managing money, driv ing, 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 spar ing 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. 33]); 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 dis ease, smoking, and diabetes. In patients suffering from cerebrovas cular 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

Apo ε4 (19) Amyloid plaques, neurofibrillary tangles, and neuropil threads H1 MAPT haplotype Tau neuronal and glial inclusions varying in morphology and distribution Dementia CHAPTER 31 TDP-43 neuronal and glial inclusions varying in morphology and distribution Codon 129 homozygosity for methionine or valine PrPSC deposition, panlaminar spongiosis TABLE 31-3 Evaluation of the Patient with Dementia OPTIONAL FOCUSED TESTS OCCASIONALLY HELPFUL TESTS ROUTINE EVALUATION History Physical examination Laboratory tests Thyroid function (TSH) Vitamin B12 Complete blood

count Complete metabolic panel CT/MRI Psychometric testing HIV, RPR, or VDRL Lumbar puncture PET (FDG, amyloid, tau) Chest x-ray Urine toxin screen Apolipoprotein E Blood-based AD biomarkers EEG Parathyroid function Adrenal function Urine heavy

metals RBC sedimentation rate Lab screen for autoantibodies Angiogram Brain biopsy Diagnostic Categories IRREVERSIBLE/ DEGENERATIVE DEMENTIAS PSYCHIATRIC DISORDERS REVERSIBLE CAUSES Examples Hypothyroidism Thiamine deficiency Vitamin B12 deficiency Normal-pressure Examples Alzheimer's Frontotemporal Depression Schizophrenia Conversion reaction dementia Huntington's Dementia with Lewy hydrocephalus Subdural hematoma Chronic infection Brain tumor Drug intoxication Autoimmune bodies Vascular Leukoencephalopathies Parkinson's LATE encephalopathy Associated Treatable Conditions Depression Seizures Insomnia Agitation Caregiver "burnout" Drug side effects Abbreviations: CT, computed tomography; EEG, electroencephalogram; LATE, limbic-predominant age-related TDP-43 encephalopathy; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

TABLE 31-4 Clinical Differentiation of the Major Dementias DISEASE FIRST SYMPTOM MENTAL STATUS NEUROPSYCHIATRY NEUROLOGY IMAGING AD Memory loss Episodic memory loss Executive, language, and visuospatial functions variably affected Vascular Often but not always sudden; variable; apathy, falls, focal weakness Frontal/executive, cognitive slowing; can spare memory DLB Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism Drawing and frontal/ executive; spares memory; delirium-prone PART 2 Cardinal Manifestations and Presentation of Diseases LATE Memory loss Episodic memory loss Mild semantic deficits FTD Apathy; poor judgment/insight, speech/language; hyperorality Frontal/executive and/or language; spares drawing CJD Dementia, mood, anxiety, movement disorders Variable, frontal/executive, focal cortical, memory 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; LATE, limbic-predominant age-related TDP-43 encephalopathy; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement. risk factors for AD. Moreover, many patients with a major vascular contribution to their dementia lack a history of stepwise decline. The age at symptom onset can also aid in the differential diag nosis of dementia. AD and FTD are the most common neuro degenerative causes of "early-onset" (age at symptom onset <65) dementia. The most common causes of "late-onset" dementia (age at symptom onset >65) are AD, DLB, and vascular dementia. LATE neuropathological changes are increasingly common with older age and are found in ~20% of individuals with dementia who die at age <70 versus >50% of individuals with dementia who die at age

> 90. Most late-onset dementia is associated with multiple patho logical entities; it is common for individuals who suffered from dementia to show three or four different pathologies at autopsy. In one large community-based autopsy cohort of individuals who presented with an amnestic dementia during life (mean age at death 89.7 years), 39% of the attributable risk for dementia was explained by AD neuropathology,

> 25% by cerebrovascular disease, 17% by LATE, and 12% by Lewy body disease. Rapid progression with motor rigidity and myoclonus suggests CJD (Chap. 449). Seizures may indicate strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD. Gait distur bance is common in vascular dementia, PD/DLB, or NPH. A history of high-risk sexual behaviors or intravenous drug use should trig ger 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) hyperin tensities on magnetic resonance imaging (MRI) should raise con cern 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. 99). Alcohol abuse creates risk for malnutrition and thiamine deficiency. Pernicious anemia, veganism, bowel irradiation, a remote history

Irritability, anxiety, depression Initially normal Entorhinal cortex and hippocampal atrophy; posterior-predominant cortical atrophy Apathy, delusions, anxiety Usually motor slowing, spasticity; can be normal Cortical and/or subcortical infarctions, confluent white matter disease Visual hallucinations, depression, sleep disorder, delusions Parkinsonism Posterior parietal atrophy; hippocampi larger than in AD None described Normal Medial temporal and hippocampal atrophy, anterior predominant 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 Depression, anxiety, psychosis in some Myoclonus, rigidity, parkinsonism Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/ FLAIR MRI of gastric surgery, and chronic therapy with histamine H2-receptor antagonists for dyspepsia or gastroesophageal reflux are causes of B12 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, in the setting of dementia, to look for signs of nervous system involvement and to search for clues suggesting a systemic disease that might be responsible for the cognitive disorder. Typical AD spares motor sys tems until later 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 the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinat ing gait), but DLB often starts with visual hallucinations or cogni tive impairment, and symptoms referable to the lower brainstem (RBD, gastrointestinal or autonomic problems) may arise years or even decades before parkinsonism or dementia. Corticobasal syn drome (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 disor der. Progressive supranuclear palsy (PSP) is associated with unex plained 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 vascu lar dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B12 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 move ments 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 mitochon drial disorder. COGNITIVE AND NEUROPSYCHIATRIC EXAMINATION Brief screening tools such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) can be used to capture dementia and follow progression. None of these tests is highly sensitive to early-stage dementia or reliably discrimi nates 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 three objects); recall (e.g., remember the same three objects 5 min later); and language (e.g., name pencil and watch; repeat “no ifs, ands, or buts”; follow a three-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, lan guage, 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 abil ity. 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. Patients with LATE also present with prominent deficits in epi sodic memory and can be identified by sparing of other cognitive domains and relatively slow progression. Patients with PDD or DLB 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. In FTD, the earliest deficits on cognitive testing involve executive control or language (speech or naming) function, but some patients lack either finding

despite profound social-emotional deficits. 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, prog nosis, 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, agita tion, and sleep disturbance may emerge. In FTD, dramatic person ality changes 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 com plex 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 alterna tive is missing a treatable cause of dementia. Table 31-3 lists most screening tests for dementia. The American Academy of Neurol ogy recommends the routine measurement of a complete blood count; electrolytes; glucose; renal, liver, and thyroid functions; a vitamin B12 level; and a structural neuroimaging study (MRI or computed tomography [CT]). Dementia CHAPTER 31 Neuroimaging studies, especially MRI, help to rule out primary and metastatic neoplasms, locate areas of infarction or inflam mation, 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. 31-1). Marked hippocampal and medial temporal lobe atrophy is also the MRI signature of LATE. Focal frontal, insular, and/or anterior temporal atrophy suggests FTD (Chap. 443). DLB often features less prominent atrophy, with greater involvement of amygdala than hippocampus. In CJD, magnetic resonance 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. 31-2). Communicating hydrocephalus with vertex efface ment (crowding of dorsal convexity gyri/sulci), gaping Sylvian fissures despite minimal cortical atrophy, and additional features shown in Fig. 31-3 suggest NPH. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning shows temporal-pari etal or hypometabolism in AD, often with early and prominent involvement of the posterior cingulate cortex and precuneus. Conversely, patients with FTD show hypometabolism in frontal and anterior temporal cortices. The FDG signature of DLB fea tures hypometabolism in the occipital cortex and precuneus with sparing of the posterior cingulate ("cingulate island sign"), while LATE is characterized by severe medial temporal hypometabo lism with sparing of association cortices. Single-photon emission computed tomography (SPECT) demonstrates spatial patterns of hypoperfusion that mirror the FDG hypometabolic patterns described above. Amyloid and tau PET imaging can support the diagnosis of AD by directly detecting amyloid plaques and neurofibrillary tangles, the neuropathological lesions that define the disease. There are cur rently three amyloid PET ligands (18F-florbetapir, 18F-florbetaben, 18F-flutametamol) and one tau PET ligand (18F-

flortaucipir) approved by the U.S. Food and Drug Administration (FDA) for clinical use. Amyloid PET ligands bind to diffuse and neuritic amyloid plaques as well as to vascular amyloid deposits (cerebral amyloid angiopathy), while tau PET ligands bind to the paired helical filaments of tau characteristic of neurofibrillary tangles in AD. Current tau PET ligands do not reliably detect tau deposits in non-AD conditions. Because amyloid plaques are also commonly found in cognitively normal older persons (~25% of individuals at age 70), the main clinical value of amyloid imaging is to exclude AD as the likely cause of dementia in patients who have negative scans. In older patients presenting with a progressive amnestic disorder and hippocampal atrophy, a negative amyloid PET scan strongly suggests LATE as the underlying neuropathology. The spread of tau is more tightly linked to cognitive state (Chap. 442), and thus tau PET may be more useful for “ruling in” AD, as well as for disease staging. Amyloid PET is also useful to identify can didates for novel anti-Aβ monoclonal antibodies (e.g., lecanemab, donanemab) that reduce amyloid plaque load and slow cognitive decline in patients in early clinical stages of AD. Amyloid and tau PET can also assist with prognosis, as patients who are positive on both modalities show the most rapid decline in cognition and

62 y.o. HC 60 y.o. AD PART 2 Cardinal Manifestations and Presentation of Diseases A B C D FIGURE 31-1 Alzheimer’s disease (AD). Axial T1-weighted MRI and 18F-florbetapir amyloid PET images from a 62-year-old healthy control (left) and 60-year-old with dementia due to AD (right panels). Note the reduction in medial temporal volumes and prominent sulci on MRI in the patient with AD. Amyloid PET demonstrates a white matter only binding pattern in the healthy control (negative scan), whild the patient with AD demonstrates diffuse neocortical binding and blurring of gray/white matter contrast (positive scan). (Images courtesy of Gil Rabinovici, University of California, San Francisco.) function. Use of amyloid and tau PET in cognitively unimpaired older adults should for now be restricted to research studies and clinical trials testing interventions aimed at reducing the risk of MCI and dementia in asymptomatic individuals who are positive for AD biomarkers. Lumbar puncture is indicated when CNS infection or inflamma tion is a credible diagnostic possibility or to assess molecular bio markers for AD in lieu of PET imaging. A cerebrospinal fluid (CSF) pattern that shows low levels of Aβ42 (or a low Aβ42/Aβ40 ratio), mild to moderately elevated CSF total tau, and elevated CSF phosphory lated tau (p-Tau at residues 181 or 217) is highly suggestive of AD and sufficient for selecting patients for anti-Aβ antibody treatment. Novel fully automated CSF Aβ and tau assays perform comparably to amyloid PET, with the Aβ42/Aβ40 or p-Tau181/Aβ42 ratios show ing higher concordance with amyloid PET and neuropathology than any single CSF AD biomarker. Blood-based AD biomarkers, such as plasma Aβ42/Aβ40, p-Tau181 and p-Tau217 measured with FIGURE 31-2 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.

mass spectrometry or highly sensitive immunoassays, are evolving rapidly and are likely to be approved for clinical use in the near future, greatly enhancing the scalability and cost effectiveness of biomarker testing in patients with suspected AD (Chap. 442). Recently, there has been significant progress in developing bio markers of α-synuclein pathology, enabling a molecular diagnosis of PD or DLB. A CSF seed amplification assay for α-synuclein shows high sensitivity and specificity in clinically diagnosed PD patients and also detects pathology in a subset of individuals

at risk for PD based on the presence of anosmia or RBD. α-Synuclein can also be detected with high sensitivity and specificity in living patients with PD and DLB with skin biopsies immunostained for phosphorylated α-synuclein colocalizing with nerve fiber bundles. While still in early stages of validation, these biomarkers hold A B FIGURE 31-3 Normal-pressure hydrocephalus. A. Sagittal T1-weighted magnetic resonance image (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.

great promise for enhancing diagnostic accuracy and accelerating drug development for α-synuclein disorders. Active work is being done to develop PET tracers for α-synuclein and to discover both imaging and fluid-based biomarkers for other aggregated disease proteins underlying neurodegenerative dementias, such as non-AD tau and TDP-43. 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, potentially treatable 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. Magnetic resonance angiography should be considered when cerebral vasculitis or cerebral venous thrombosis is a possible cause of the dementia. ■ ■GLOBAL CONSIDERATIONS Vascular dementia (Chap. 444) is more common in Asian countries, 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 due to immunologically mediated white matter injury (acute disseminated encephalomyelitis [ADEM]) (Chap. 456). Some individuals infected with SARS-CoV-2 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 cannibalismassociated rapidly progressive dementia seen in tribal New Guinea, played a role in the discovery of human prion disease. ALS-parkin sonism-dementia complex of Guam (or lytico-bodig disease) is a poly proteinopathy, often with tau, TDP-43, and α-synuclein aggregation. The root cause of the disease remains uncertain, but its incidence has declined sharply over the past 60 years. TREATMENT Dementia The major goals of dementia management are to treat reversible causes and to provide comfort and support to the patient and their caregivers. Treatment of underlying causes includes thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B12 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 critical when appropriate. If the patient’s cognitive complaints stem from a psychiatric disorder, vigorous treatment of the condition should be sought to eliminate the cogni tive complaint or to confirm that it persists despite adequate resolu tion 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. 463), which feature anxiolytic properties but few cognitive side effects, provide the mainstay of treatment when necessary. Anticonvulsants are used to control seizures, with levetiracetam and lamotrigine being the preferred agents based on their efficacy in animal models of AD and favorable cognitive side

effect profiles. Furthermore, a small clinical trial found a potential cognitive benefit for levetiracetam over placebo in AD patients found to have epileptiform activity on electroencephalogram or magnetoencephalography.

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 aggres sively 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 benzodiaz epines may ameliorate the behavior problems but have untoward side effects such as sedation, rigidity, dyskinesia, and occasion ally paradoxical disinhibition (benzodiazepines). 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. Brexpiprazole, an atypical antipsychotic that acts on noradrenergic, serotonergic, and dopaminergic neurotransmitter systems, recently became the first FDA-approved drug for the treatment of agitation in patients with AD dementia based on evidence of short-term efficacy and safety in a 12-week, double-blind, placebo-controlled randomized clini cal trial. When patients do not respond to treatment, it is usually a mistake to advance to higher doses or to use anticholinergic drugs (e.g., diphenhydramine) or sedatives (e.g., barbiturates or ben zodiazepines). 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 monitor ing for efficacy and toxicity. Sometimes apathy, visual hallucina tions, depression, and other psychiatric symptoms respond to the cholinesterase inhibitors, especially in DLB, obviating the need for other more toxic therapies. Dementia CHAPTER 31 Cholinesterase inhibitors are being used to treat AD (donepezil, rivastigmine, galantamine) and PDD (rivastigmine). Memantine, which acts on N-methyl-D-aspartate (NMDA) glutamate receptors, proves useful when treating 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. In recent years, a novel class of drugs, monoclonal antibod ies that target Aβ, have been approved for the treatment of MCI and mild dementia due to AD. These drugs reduce amyloid plaque burden as measured by PET, and some have been found to modestly slow clinical decline. In 2021, aducanumab became the first anti-Aβ monoclonal antibody to receive accelerated FDA approval, based on strong biomarker evidence of amyloid plaque lowering on PET. However, clinical benefits were ques tionable based on discordant results in two

identically designed phase 3 randomized clinical trials (RCTs). In 2023, lecanemab received traditional FDA approval based on evidence of clinical efficacy in a phase 3 RCT, with treated patients showing 27% less decline over 18 months compared to placebo on the Clinical Dementia Rating–Sum of Boxes, a clinical scale that measures changes in cognition and function. A third antibody, donanemab, reported similar positive clinical results in a phase 3 RCT, and was approved by the FDA in 2024. All three drugs are infused intrave nously every 2 weeks (lecanemab) or monthly (aducanumab and donanemab). Significant side effects of this class of medications include infusion reactions and amyloid-related imaging abnor malities (ARIA), which manifest as edema or sulcal effusions

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