03 - 21.3 Dementia (Major Neurocognitive Disorder)

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Yang FM, Marcantonio ER, Inouye SK, Kiely DK, Rudolph JL, Fearing MA, Jones RN. Phenomenological subtypes of delirium in older persons: Patterns, prevalence, and prognosis. Psychosomatics. 2109;50:248. 21.3 Dementia (Major Neurocognitive Disorder) Dementia refers to a disease process marked by progressive cognitive impairment in clear consciousness. Dementia does not refer to low intellectual functioning or mental retardation because these are developmental and static conditions, and the cognitive deficits in dementia represent a decline from a previous level of functioning. Dementia involves multiple cognitive domains and cognitive deficits cause significant impairment in social and occupational functioning. There are four types of dementias based on etiology: Alzheimer’s disease, dementia of Lewy bodies, vascular dementia, frontotemporal dementia, traumatic brain injury (TBI), HIV, prion disease, Parkinson’s disease, and Huntington’s disease. Dementia can also be caused by other medical and neurological conditions or can be caused by various substances. (See Section 21.4: Amnestic Disorders.) The critical clinical points of dementia are the identification of the syndrome and the clinical workup of its cause. The disorder can be progressive or static; permanent or reversible. An underlying cause is always assumed, although, in rare cases, it is impossible to determine a specific cause. The potential reversibility of dementia is related to the underlying pathological condition and to the availability and application of effective treatment. Approximately 15 percent of people with dementia have reversible illnesses if treatment is initiated before irreversible damage takes place. EPIDEMIOLOGY With the aging population, the prevalence of dementia is rising. The prevalence of moderate to severe dementia in different population groups is approximately 5 percent in the general population older than 65 years of age, 20 to 40 percent in the general population older than 85 years of age, 15 to 20 percent in outpatient general medical practices, and 50 percent in chronic care facilities. Of all patients with dementia, 50 to 60 percent have the most common type of dementia, dementia of the Alzheimer’s type (Alzheimer’s disease). Dementia of the Alzheimer’s type increases in prevalence with increasing age. For persons age 65 years, men have a prevalence rate of 0.6 percent and women of 0.8 percent. At age 90, rates are 21 percent. For all of these figures, 40 to 60 percent of cases are moderate to severe. The rates of prevalence (men to women) are 11 and 14 percent at age 85, 21 and 25 percent at age 90 years and 36 and 41

percent at age 95 years. Patients with dementia of the Alzheimer's type occupy more than 50 percent of nursing home beds. More than 2 million persons with dementia are cared for in these homes. By 2050, current predictions suggest that there will be 14 million Americans with Alzheimer's disease and therefore more than 18 million people with dementia. The second most common type of dementia is vascular dementia, which is causally

related to cerebrovascular diseases. Hypertension predisposes a person to the disease. Vascular dementias account for 15 to 30 percent of all dementia cases. Vascular dementia is most common in persons between the ages of 60 and 70 and is more common in men than in women. Approximately 10 to 15 percent of patients have coexisting vascular dementia and dementia of the Alzheimer's type. Other common causes of dementia, each representing 1 to 5 percent of all cases, include head trauma; alcohol-related dementias; and various movement disorder-related dementias, such as Huntington's disease and Parkinson's disease. Because dementia is a fairly general syndrome, it has many causes, and clinicians must embark on a careful clinical workup of a patient with dementia to establish its cause. ETIOLOGY The most common causes of dementia in individuals older than 65 years of age are (1) Alzheimer's disease, (2) vascular dementia, and (3) mixed vascular and Alzheimer's dementia. Other illnesses that account for approximately 10 percent include Lewy body dementia; Pick's disease; frontotemporal dementias; normal-pressure hydrocephalus (NPH); alcoholic dementia; infectious dementia, such as HIV or syphilis; and Parkinson's disease. Many types of dementias evaluated in clinical settings can be attributable to reversible causes, such as metabolic abnormalities (e.g., hypothyroidism), nutritional deficiencies (e.g., vitamin B12 or folate deficiencies), or dementia syndrome caused by depression. See Table 21.3-1 for a review of possible etiologies of dementia. Table 21.3-1 Possible Etiologies of Dementia

Dementia of the Alzheimer's Type In 1907, Alois Alzheimer (Fig. 21.3-1) first described the condition that later assumed his name. He described a 51-year-old woman with a 4½-year course of progressive dementia. The final diagnosis of Alzheimer's disease requires a neuropathological examination of the brain; nevertheless, dementia of the Alzheimer's type is commonly diagnosed in the clinical setting after other causes of dementia have been excluded from diagnostic consideration.

FIGURE 21.3-1 Alois Alzheimer (1864–1915), a German psychiatrist, described a type of senile dementia that bears his name Genetic Factors. Although the cause of dementia of the Alzheimer's type remains unknown, progress has been made in understanding the molecular basis of the amyloid deposits that are a hallmark of the disorder's neuropathology. Some studies have indicated that as many as 40 percent of patients have a family history of dementia of the Alzheimer's type; thus, genetic factors are presumed to play a part in the development of the disorder, at least in some cases. Additional support for a genetic influence is the concordance rate for monozygotic twins, which is higher than the rate for dizygotic twins (43 percent vs. 8 percent, respectively). In several well-documented cases, the disorder has been transmitted in families through an autosomal dominant gene, although such transmission is rare. Alzheimer's type dementia has shown linkage to chromosomes 1, 14, and 21. AMYLOID PRECURSOR PROTEIN. The gene for amyloid precursor protein is on the long arm of chromosome 21. The process of differential splicing yields four forms of amyloid precursor protein. The β/A4 protein, the major constituent of senile plaques, is a 42amino acid peptide that is a breakdown product of amyloid precursor protein. In Down syndrome (trisomy 21) are found three copies of the amyloid precursor

protein gene, and in a disease in which a mutation is found at codon 717 in the amyloid precursor protein gene, a pathological process results in the excessive deposition of β/A4 protein. Whether the processing of abnormal amyloid precursor protein is of primary causative significance in Alzheimer's disease is unknown, but many research groups are studying both the normal metabolic processing of amyloid precursor protein and its processing in patients with dementia of the Alzheimer's type in an attempt to answer this question. MULTIPLE E4 GENES. One study implicated gene E4 in the origin of Alzheimer's disease.

People with one copy of the gene have Alzheimer's disease three times more frequently than do those with no E4 gene, and people with two E4 genes have the disease eight times more frequently than do those with no E4 gene. Diagnostic testing for this gene is not currently recommended because it is found in persons without dementia and not found in all cases of dementia. Neuropathology. The classic gross neuroanatomical observation of a brain from a patient with Alzheimer's disease is diffuse atrophy with flattened cortical sulci and enlarged cerebral ventricles. The classic and pathognomonic microscopic findings are senile plaques, neurofibrillary tangles, neuronal loss (particularly in the cortex and the hippocampus), synaptic loss (perhaps as much as 50 percent in the cortex), and granulovascular degeneration of the neurons. Neurofibrillary tangles (Fig. 21.3-2) are composed of cytoskeletal elements, primarily phosphorylated tau protein, although other cytoskeletal proteins are also present. Neurofibrillary tangles are not unique to Alzheimer's disease; they also occur in Down syndrome, dementia pugilistica (punchdrunk syndrome), Parkinson-dementia complex of Guam, Hallervorden-Spatz disease, and the brains of normal people as they age. Neurofibrillary tangles are commonly found in the cortex, the hippocampus, the substantia nigra, and the locus ceruleus.

FIGURE 21.3-2 Photomicrographs of Alzheimer's disease neuropathology. (A) Deposition of insoluble fibrillar Aβ into plaques begins in the neocortex, labeled here using an antibody against Aβ and appearing as reddish-brown deposits (arrows). (B) Bielchowsky stain of neocortex from an individual who died in advanced stages of Alzheimer's disease (Braak stage VI). The Aβ plaques appear as dark brown in this preparation (arrows) and can be seen to be associated with dystrophic neuronal processes (arrowheads) in which insoluble microtubule-associate protein τ (MAPT) aggregates appear as black deposits. This neurofibrillary pathology also appears extensively throughout the neuropil, and several neurofibrillary tangles can be seen (open arrowheads). (C) Bielchowsky stain of

neocortex from an individual who died in a less advanced disease stage (Braak stage IV). Although some neurofibrillary tangles are still evident (open arrowheads), the degree of neurofibrillary pathology in the neuropil is substantially diminished. (D) Isolated neurofibrillary tangles (open arrowheads) in entorhinal cortex that can be seen in normal aging (Bielchowsky stain). Notice the lack of Aβ plaques and limited neuropil involvement. (All images obtained at 200× magnification and provided courtesy of Dr. Ronald L. Hamilton, Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine.) Senile plaques, also referred to as amyloid plaques, more strongly indicate Alzheimer's disease, although they are also seen in Down syndrome and, to some extent, in normal aging. Senile plaques are composed of a particular protein, β/A4, and astrocytes, dystrophic neuronal processes, and microglia. The number and the density of senile plaques present in postmortem brains have been correlated with the severity of the disease that affected the persons. Neurotransmitters. The neurotransmitters that are most

often implicated in the pathophysiological condition of Alzheimer’s disease are acetylcholine and norepinephrine, both of which are hypothesized to be hypoactive in Alzheimer’s disease. Several studies have reported data consistent with the hypothesis that specific degeneration of cholinergic neurons is present in the nucleus basalis of Meynert in persons with Alzheimer’s disease. Other data supporting a cholinergic deficit in Alzheimer’s disease demonstrate decreased acetylcholine and choline acetyltransferase concentrations in the brain. Choline acetyltransferase is the key enzyme for the synthesis of acetylcholine, and a reduction in choline acetyltransferase concentration suggests a decrease in the number of cholinergic neurons present. Additional support for the cholinergic deficit hypothesis comes from the observation that cholinergic antagonists, such as scopolamine and atropine, impair cognitive abilities, whereas cholinergic agonists, such as physostigmine and arecoline, enhance cognitive abilities. Decreased norepinephrine activity in Alzheimer’s disease is suggested by the decrease in norepinephrine-containing neurons in the locus ceruleus found in some pathological examinations of brains from persons with Alzheimer’s disease. Two other neurotransmitters implicated in the pathophysiological condition of Alzheimer’s disease are the neuroactive peptides somatostatin and corticotropin; decreased concentrations of both have been reported in persons with Alzheimer’s disease. Other Causes. Another theory to explain the development of Alzheimer’s disease is that an abnormality in the regulation of membrane phospholipid metabolism results in membranes that are less fluid—that is, more rigid—than normal. Several investigators are using molecular resonance spectroscopic imaging to assess this hypothesis directly in patients with dementia of the Alzheimer’s type. Aluminum toxicity has also been hypothesized to be a causative factor because high levels of aluminum have been found in the brains of some patients with Alzheimer’s disease, but this is no longer considered

a significant etiological factor. Excessive stimulation by the transmitter glutamate that may damage neurons is another theory of causation. Familial Multiple System Taupathy with Presenile Dementia. A recently discovered type of dementia, familial multiple system taupathy, shares some brain abnormalities found in people with Alzheimer’s disease. The gene that causes the disorder is thought to be carried on chromosome 17. The symptoms of the disorder include short-term memory problems and difficulty maintaining balance and walking. The onset of disease occurs in the 40s and 50s, and persons with the disease live an average of 11 years after the onset of symptoms. As in patients with Alzheimer’s disease, tau protein builds up in neurons and glial cells of persons with familial multiple system taupathy. Eventually, the protein buildup kills brain cells. The disorder is not associated with the senile plaques seen with Alzheimer’s disease. Mr. J, a 70-year-old retired businessman, was brought to psychiatric services on referral by the family physician. His wife claimed that Mr. J had become so forgetful that she was afraid to leave him alone, even at home. Mr. J retired at age 62 years after experiencing a decline in work performance during the previous 5 years. He also slowly gave up hobbies he once enjoyed (photography, reading, golf) and became increasingly quiet. However, his growing forgetfulness went basically unnoticed at home. Then one day while walking in an area he knew well, he could not find his way home. From then on his memory failure began to increase. He would forget appointments, misplace things, and lose his way around the neighborhood he resided in for 40 years. He failed to recognize people, even those he knew for many years. His wife had to start bathing and dressing him because he forgot how to do so himself. On examination, Mr. J was disoriented in time and place. He was only able to recall his name and place of birth. Mr. J seemed lost during the interview, only responding to questions with an occasional shrug of his shoulders. When asked to

name objects or to recall words or numbers, Mr. J appeared tense and distressed. Mr. J had difficulty following instructions and was unable to dress or undress himself. His general medical condition was good. Laboratory examinations showed abnormalities on Mr. J's EEG and CT scans. Vascular Dementia The primary cause of vascular dementia, formerly referred to as multi-infarct dementia, is presumed to be multiple areas of cerebral vascular disease, resulting in a symptom pattern of dementia. Vascular dementia most commonly is seen in men, especially those with preexisting hypertension or other cardiovascular risk factors. The disorder affects primarily small- and medium-sized cerebral vessels, which undergo infarction and produce multiple parenchymal lesions spread over wide areas of the brain (Fig. 21.3-3).

The causes of the infarctions can include occlusion of the vessels by arteriosclerotic plaques or thromobemboli from distant origins (e.g., heart valves). An examination of a patient may reveal carotid bruits, funduscopic abnormalities, or enlarged cardiac chambers (Fig. 21.3-4). FIGURE 21.3-4 Patients with chronic dementia usually requires custodial care in their declining years. Regressive behavior, such as finger sucking, is typical in this state. (Courtesy of Bill Stanton for Magnum Photos, Inc.) FIGURE 21.3-3 Gross appearance of the cerebral cortex on coronal section from a patient with vascular dementia. The multiple bilateral lacunar infarcts involve the thalamus, the internal capsule, and the globus pallidus. (Courtesy of Daniel P. Perl, M.D.) Binswanger's Disease. Binswanger's disease (Fig. 21.3-5), also known as

subcortical arteriosclerotic encephalopathy, is characterized by the presence of many small infarctions of the white matter that spare the cortical regions (Fig. 21.3-6). Although Binswanger's disease was previously considered a rare condition, the advent of sophisticated and powerful imaging techniques, such as MRI, has revealed that the condition is more common than previously thought. FIGURE 21.3-5 Otto Binswanger (1852–1929), a Swiss psychiatrist who described a condition he call "encephalitis subcorticalis chronica progressive," now known as Binswanger's disease. FIGURE 21.3-6

Binswanger's disease. Cross-section demonstrating extensive subcortical white matter infarction, with sparing of the overlying gray matter. (Courtesy of Dushyant Purohit, M.D., Neuropathology Division, Mount Sinai School of Medicine, New York, NY.) Frontotemporal Dementia (Pick's Disease) In contrast to the parietal-temporal distribution of pathological findings in Alzheimer's disease, Pick's disease (Fig. 21.3-7) is characterized by a preponderance of atrophy in the frontotemporal regions. These regions also have neuronal loss; gliosis; and neuronal Pick's bodies, which are masses of cytoskeletal elements. Pick's bodies are seen in some postmortem specimens but are not necessary for the diagnosis. The cause of Pick's disease is unknown, but the disease constitutes approximately 5 percent of all irreversible dementias. It is most common in men, especially those who have a firstdegree relative with the condition. Pick's disease is difficult to distinguish from dementia of the Alzheimer's type, although the early stages of Pick's disease are more often characterized by personality and behavioral changes, with relative preservation of other cognitive functions, and it typically begins before 75 years of age. Familial cases may have an earlier onset, and some studies have shown that approximately half of the cases of Pick's disease are familial (Fig. 21.3-8). Features of Klüver-Bucy syndrome (e.g., hypersexuality, placidity, and hyperorality) are much more common in Pick's disease than in Alzheimer's disease. FIGURE 21.3-7 Arnold Pick (1851–1924), a Czech neurologist and psychiatrist who described frontotemporal dementia and the Pick bodies that are characteristic of the disorder.

FIGURE 21.3-8 Pick’s disease gross pathology. This demonstrates the marked frontal and temporal atrophy seen in frontotemporal dementias, such as Pick’s disease. (Courtesy of Dushyant Purohit, M.D., Neuropathology Division, Mount Sinai School of Medicine, New York, NY.) Lewy Body Disease Lewy body disease is a dementia clinically similar to Alzheimer’s disease and often characterized by hallucinations, parkinsonian features, and extrapyramidal signs (Table 21.3-2). Lewy inclusion bodies are found in the cerebral cortex (Fig. 21.3-9). The exact incidence is unknown. These patients often have Capgras syndrome (reduplicative paramnesia) as party of the clinical picture. FIGURE 21.3-9 Photomicrographs of Lewy body pathology. (A) Abnormal accumulation of α-synuclein aggregates demonstrated by immunocytochemistry in the amygdala of a subject with dementia. Lewy bodies appear as dense intracellular inclusions (arrows), but staining of neuronal processes can be seen throughout the neuropil (arrowheads). In individuals in whom Lewy body pathology occurs concurrently with Alzheimer’s disease, the amygdala is often the only region affected. (B) Classic appearance of a Lewy body (arrow) in a large pigmented neuron of the substantia nigra. (C) Lewy body pathology in the neocortex. Both Lewy bodies (arrows) and substantial labeling of neuronal processes in

the neuropil (arrowheads) are evident. (Magnification for [A] and [B] 200×, for [C] 400×. All images provided courtesy of Dr. Ronald L. Hamilton, Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine.) Table 21.3-2 Clinical Criteria for Dementia with Lewy Bodies (DLB) Huntington’s Disease Huntington’s disease (Fig. 21.3-10) is classically associated with the development of dementia. The dementia seen in this disease is the subcortical type of dementia, characterized by more motor abnormalities and fewer language abnormalities than in the cortical type of dementia (Table 21.3-3). The dementia of Huntington’s disease exhibits psychomotor slowing and difficulty with complex tasks, but memory, language, and insight remain relatively intact in the early and middle stages of the illness. As the disease progresses, however, the dementia becomes complete; the features distinguishing it from dementia of the Alzheimer’s type are the high incidence of depression and psychosis in addition to the classic choreoathetoid movement disorder.

FIGURE 21.3-10 George Huntington (1850–1916), an American physician who first described the disease that bears his name, Huntington’s disease. Table 21.3-3 Distinguishing Features of Subcortical and Cortical Dementias

Parkinson’s Disease As with Huntington’s disease, parkinsonism is a disease of the basal ganglia, commonly associated with dementia and depression. An estimated 20 to 30 percent of patients with Parkinson’s disease have dementia, and an additional 30 to 40 percent have measurable impairment in cognitive abilities. The slow movements of persons with Parkinson’s disease are paralleled in the slow thinking of some affected patients, a feature that clinicians may refer to as bradyphrenia. Mr. M, 77 years of age, came for a neurological examination because he noticed his memory was slipping and he was having difficulty concentrating, which interfered with his work. He complained of slowness and losing his train of thought. His wife stated that he was becoming withdrawn and was more reluctant to participate in activities he usually enjoyed. He denied symptoms of depression other than feeling mildly depressed about his disabilities. Two years prior, Mr. M developed an intermittent resting tremor in his right hand and a shuffling gait. Although a psychiatrist considered a diagnosis of Parkinson’s disease, it was not confirmed by a neurologist and therefore was never treated. During an initial neurological examination, Mr. M’s spontaneous

speech was hesitant and unclear (dysarthric). Cranial nerve examination was normal. Motor tone was increased slightly in the neck and all limbs. He performed alternating movements in his hands slowly. He had a slight intermittent tremor of his right arm at rest.

Reflexes were symmetrical. A neuropsychological examination was performed three weeks later. It was found that Mr. M showed impairment of memory, naming, and constructional abilities. HIV-Related Dementia Encephalopathy in HIV infection is associated with dementia and is termed acquired immune deficiency syndrome (AIDS) dementia complex, or HIV dementia. Patients infected with HIV experience dementia at an annual rate of approximately 14 percent. An estimated 75 percent of patients with AIDS have involvement of the CNS at the time of autopsy. The development of dementia in people infected with HIV is often paralleled by the appearance of parenchymal abnormalities in MRI scans. Other infectious dementias are caused by Cryptococcus or Treponema pallidum. The diagnosis of AIDS dementia complex is made by confirmation of HIV infection and exclusion of alternative pathology to explain cognitive impairment. The American Academy of Neurology AIDS Task Force developed research criteria for the clinical diagnosis of CNS disorders in adults and adolescents (Table 21.3-4). The AIDS Task Force criteria for AIDS dementia complex require laboratory evidence for systemic HIV, at least two cognitive deficits, and the presence of motor abnormalities or personality changes. Personality changes may be manifested by apathy, emotional lability, or behavioral disinhibition. The AIDS Task Force criteria also require the absence of clouding of consciousness or evidence of another etiology that could produce the cognitive impairment. Cognitive, motor, and behavioral changes are assessed using physical, neurological, and psychiatric examinations, in addition to neuropsychological testing. Table 21.3-4 Criteria for Clinical Diagnosis of HIV Type 1-Associated Dementia Complex

Head Trauma-Related Dementia Dementia can be a sequela of head trauma. The so-called punch-drunk syndrome (dementia pugilistica) occurs in boxers after repeated head trauma over many years. It is characterized by emotional lability, dysarthria, and impulsivity. It has also been observed in professional football players who developed dementia after repeated concussions over many years. Mrs. S, 75 years of age, was brought to the emergency department after being found wandering her neighborhood in a confused and disoriented state. She was in good health until a few months prior when her husband was hospitalized for 10 days for minor surgery. About a month after her husband returned home, he and their two adult children, who do not reside with them, reported a noticeable change in Mrs. S's mental status. Mrs. S became hyperactive and appeared to have excessive energy, was agitated and irritable, and had difficulty sleeping at night. At examination, Mrs. S was disoriented to time and place, agitated, and confused. Her husband revealed upon interview that Mrs. S has for many years suffered from dizziness and lightheadedness upon standing and occasionally suffered from falls, none of which caused any major damage. Not long before her confused symptoms began, Mrs. S had apparently suffered a fall one night, and her husband found her the next morning lying next to the bed in a confused state. Because of her history of falls,

neither Mr. S nor Mrs. S thought much of the incident. A CT scan revealed the presence of a subdural hematoma, which was then evacuated. Afterward, Mrs. S's confusion and disorientation cleared and she returned to her normal state of functioning. DIAGNOSIS AND CLINICAL FEATURES The DSM-5 diagnostic criteria are listed in Tables 21.3-5 and 21.3-6. DSM-5 makes a distinction between major and minor cognitive disorder based upon levels of functioning, but the underlying

etiology is similar. Table 21.3-5 DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder (Dementia) Table 21.3-6 DSM-5 Diagnostic Criteria for Major or Mild Neurocognitive Disorder Due to Alzheimer’s Disease

The diagnosis of dementia is based on the clinical examination, including a mental status examination, and on information from the patient’s family, friends, and employers. Complaints of a personality change in a patient older than age 40 years suggest that a diagnosis of dementia should be carefully considered. Clinicians should note patients’ complaints about intellectual impairment and forgetfulness as well as evidence of patients’ evasion, denial, or rationalization aimed at concealing cognitive deficits. Excessive orderliness, social withdrawal, or a tendency to relate events in minute detail can be characteristic, and sudden outbursts of anger or sarcasm can occur. Patients’ appearance and behavior should be observed. Lability of emotions; sloppy grooming; uninhibited remarks; silly jokes; or a dull, apathetic, or vacuous facial expression and manner suggest the presence of dementia, especially when coupled with memory impairment. Memory impairment is typically an early and prominent feature in dementia, especially in dementias involving the cortex, such as dementia of the Alzheimer’s type. Early in the course of dementia, memory impairment is mild and usually most marked for recent events; people forget telephone numbers, conversations, and events of the day. As the course of dementia progresses, memory impairment becomes severe, and only the earliest learned information (e.g., a person’s place of birth) is retained. Inasmuch as memory is important for orientation to person, place, and time, orientation can be progressively affected during the course of a dementing illness. For

example, patients with dementia may forget how to get back to their rooms after going to the bathroom. No matter how severe the disorientation seems, however, patients show no impairment in their level of consciousness. Dementing processes that affect the cortex, primarily dementia of the Alzheimer’s type and vascular dementia, can affect patients’ language abilities. Psychiatric and Neurological Changes Personality. Changes in the personality of a person with dementia are especially disturbing for their families. Preexisting personality traits may be accentuated during the development of a dementia. Patients with dementia may also become introverted and seem to be less concerned than they previously were about the effects of their behavior on others. Persons with dementia who have paranoid delusions are generally hostile to family members and caretakers. Patients with frontal and temporal involvement are likely to have marked personality changes and may be irritable and explosive. Hallucinations and Delusions. An estimated 20 to 30 percent of patients with dementia (primarily patients with dementia of the Alzheimer’s type) have hallucinations, and 30 to 40 percent have delusions, primarily of a paranoid or persecutory and unsystematized nature, although complex, sustained, and wellsystematized delusions are also reported by these patients. Physical aggression and other forms of violence are common in demented patients who also have psychotic symptoms. Mood. In addition to psychosis and personality changes, depression and anxiety are major symptoms in an estimated 40 to 50 percent of patients with dementia, although the full syndrome of depressive disorder may be present in only 10 to 20 percent. Patients with dementia also may exhibit pathological laughter or crying—that is, extremes of emotions—with no apparent provocation. Cognitive Change. In addition to the aphasias in patients with dementia, apraxias and agnosias are common. Other neurological signs that can be associated with dementia are seizures, seen in approximately 10 percent of patients with dementia of the Alzheimer’s type and in 20 percent of patients with vascular dementia, and atypical neurological presentations, such as nondominant parietal lobe syndromes.

Primitive reflexes, such as the grasp, snout, suck, tonic-foot, and palmomental reflexes, may be present on neurological examination, and myoclonic jerks are present in 5 to 10 percent of patients. Patients with vascular dementia may have additional neurological symptoms, such as headaches, dizziness, faintness, weakness, focal neurological signs, and sleep disturbances, possibly attributable to the location of the cerebrovascular disease. Pseudobulbar palsy, dysarthria, and dysphagia are also more common in vascular

dementia than in other dementing conditions. Catastrophic Reaction. Patients with dementia also exhibit a reduced ability to apply what Kurt Goldstein called the “abstract attitude.” Patients have difficulty generalizing from a single instance, forming concepts, and grasping similarities and differences among concepts. Furthermore, the ability to solve problems, to reason logically, and to make sound judgments is compromised. Goldstein also described a catastrophic reaction marked by agitation secondary to the subjective awareness of intellectual deficits under stressful circumstances. Persons usually attempt to compensate for defects by using strategies to avoid demonstrating failures in intellectual performance; they may change the subject, make jokes, or otherwise divert the interviewer. Lack of judgment and poor impulse control appear commonly, particularly in dementias that primarily affect the frontal lobes. Examples of these impairments include coarse language, inappropriate jokes, neglect of personal appearance and hygiene, and a general disregard for the conventional rules of social conduct. Sundowner Syndrome. Sundowner syndrome is characterized by drowsiness, confusion, ataxia, and accidental falls. It occurs in older people who are overly sedated and in patients with dementia who react adversely to even a small dose of a psychoactive drug. The syndrome also occurs in demented patients when external stimuli, such as light and interpersonal orienting cues, are diminished. Vascular Dementia The general symptoms of vascular dementia are the same as those for dementia of the Alzheimer’s type, but the diagnosis of vascular dementia requires either clinical or laboratory evidence in support of a vascular cause of the dementia. Vascular dementia is more likely to show a decremental, stepwise deterioration than is Alzheimer’s disease. Substance-Induced Persisting Dementia To facilitate the clinician’s thinking about differential diagnosis, substance-induced persisting dementia is listed in two places, with the dementias and with the substancerelated disorders. The specific substances that cross references are alcohol, inhalants, sedatives, hypnotics, or anxiolytics, and other or unknown substances. Alcohol-Induced Persisting Dementia. To make the diagnosis of alcoholinduced persisting dementia, the criteria for dementia must be met. Because amnesia can also occur in the context of Korsakoff’s psychosis, it is important to distinguish between memory impairment accompanied by other cognitive deficits (i.e., dementia) and amnesia caused by thiamine deficiency. To complicate matters, however, evidence also suggests that other cognitive functions, such as attention and concentration, may also be impaired in Wernicke-Korsakoff syndrome. In addition, alcohol abuse is frequently associated with mood changes, so poor concentration and other cognitive

symptoms often observed in the context of a major depression must also be ruled out. Prevalence rates differ considerably according to the population studied and the diagnostic criteria used, although alcohol-related dementia has been estimated to account for approximately 4 percent of dementias. PATHOLOGY, PHYSICAL FINDINGS, AND LABORATORY EXAMINATION A comprehensive laboratory workup must be performed when evaluating a patient with dementia. The purposes of the workup are to detect reversible causes of dementia and to provide the patient and family with a definitive diagnosis. The range of possible causes of dementia mandates selective use of

laboratory tests. The evaluation should follow informed clinical suspicion based on the history and physical and mental status examination results. The continued improvements in brain imaging techniques, particularly MRI, have made differentiation between dementia of the Alzheimer's type and vascular dementia, in some cases, somewhat more straightforward than in the past. An active area of research is the use of single-photon emission computed tomography (SPECT) to detect patterns of brain metabolism in various types of dementias; the use of SPECT images may soon help in the clinical differential diagnosis of dementing illnesses. A general physical examination is a routine component of the workup for dementia. It may reveal evidence of systemic disease causing brain dysfunction, such as an enlarged liver and hepatic encephalopathy, or it may demonstrate systemic disease related to particular CNS processes. The detection of Kaposi's sarcoma, for example, should alert the clinician to the probable presence of AIDS and the associated possibility of AIDS dementia complex. Focal neurological findings, such as asymmetrical hyperreflexia or weakness, are seen more often in vascular than in degenerative disease. Frontal lobe signs and primitive reflexes occur in many disorders and often point to greater progression. DIFFERENTIAL DIAGNOSIS Dementia of the Alzheimer's Type versus Vascular Dementia Classically, vascular dementia has been distinguished from dementia of the Alzheimer's type by the decremental deterioration that can accompany cerebrovascular disease over time. Although the discrete, stepwise deterioration may not be apparent in all cases, focal neurological symptoms are more common in vascular dementia than in dementia of the Alzheimer's type, as are the standard risk factors for cerebrovascular disease. Vascular Dementia versus Transient Ischemic Attacks Transient ischemic attacks (TIAs) are brief episodes of focal neurological dysfunction lasting less than 24 hours (usually 5 to 15 minutes). Although a variety of mechanisms may be responsible, the episodes are frequently the result of microembolization from a

proximal intracranial arterial lesion that produces transient brain ischemia, and the episodes usually resolve without significant pathological alteration of the parenchymal tissue. Approximately one-third of persons with untreated TIAs experience a brain infarction later; therefore, recognition of TIAs is an important clinical strategy to prevent brain infarction. Clinicians should distinguish episodes involving the vertebrobasilar system from those involving the carotid arterial system. In general, symptoms of vertebrobasilar disease reflect a transient functional disturbance in either the brainstem or the occipital lobe; carotid distribution symptoms reflect unilateral retinal or hemispheric abnormality. Anticoagulant therapy, antiplatelet agglutinating drugs such as aspirin, and extracranial and intracranial reconstructive vascular surgery are effective in reducing the risk of infarction in patients with TIAs. Delirium In general, delirium is distinguished by rapid onset, brief duration, cognitive impairment fluctuation during the course of the day; nocturnal exacerbation of symptoms; marked disturbance of the sleep–wake cycle; and prominent disturbances in attention and perception. Depression Some patients with depression have symptoms of cognitive impairment difficult to distinguish from symptoms of dementia. The clinical picture is sometimes referred to as pseudodementia, although the term depression-related cognitive dysfunction is preferable and more descriptive (Table 21.3-7). Patients with depression-related cognitive dysfunction generally have prominent depressive symptoms, more insight into their symptoms than do demented patients, and often a history of depressive episodes. Table 21.3-7 Major Clinical Features Differentiating Pseudodementia from Dementia

Factitious Disorder Persons who attempt to simulate memory loss, as in factitious disorder, do so in an erratic and inconsistent manner. In true dementia, memory for time and place is lost before

memory for person, and recent memory is lost before remote memory. Schizophrenia Although schizophrenia can be associated with some acquired intellectual impairment, its symptoms are much less severe than are the related symptoms of psychosis and thought disorder seen in dementia. Normal Aging Aging is not necessarily associated with any significant cognitive decline, but minor memory problems can occur as a normal part of aging. These normal occurrences are sometimes referred to as benign senescent forgetfulness, age-associated memory impairment, or normal benign age-related senescence. They are distinguished from dementia by their minor severity and because they do not interfere significantly with a person's social or occupational behavior. See Section 21.6 for a discussion of mild cognitive impairment. Other Disorders

Intellectual disability, which does not include memory impairment, occurs in childhood. Amnestic disorder is characterized by circumscribed loss of memory and no deterioration. Major depression in which memory is impaired responds to antidepressant medication. Malingering and pituitary disorder must be ruled out, but they are unlikely. COURSE AND PROGNOSIS The classic course of dementia is an onset in the patient's 50s or 60s, with gradual deterioration over 5 to 10 years, leading eventually to death. The age of onset and the rapidity of deterioration vary among different types of dementia and within individual diagnostic categories. The average survival expectation for patients with dementia of the Alzheimer's type is approximately 8 years, with a range of 1 to 20 years. Data suggest that in persons with an early onset of dementia or with a family history of dementia, the disease is likely to have a rapid course. In a recent study of 821 persons with Alzheimer's disease, the median survival time was 3.5 years. After dementia is diagnosed, patients must have a complete medical and neurological workup because 10 to 15 percent of all patients with dementia have a potentially reversible condition if treatment is initiated before permanent brain damage occurs. The most common course of dementia begins with a number of subtle signs that may, at first, be ignored by both the patient and the people closest to the patient. A gradual onset of symptoms is most commonly associated with dementia of the Alzheimer's type, vascular dementia, endocrinopathies, brain tumors, and metabolic disorders. Conversely, the onset of dementia resulting from head trauma, cardiac arrest with cerebral hypoxia, or encephalitis can be sudden. Although the symptoms of the early phase of dementia are subtle, they become conspicuous as the dementia progresses, and family members may then bring a patient to a physician's attention. People with dementia may be sensitive to the use of benzodiazepines or alcohol, which can precipitate agitated, aggressive, or psychotic behavior. In the terminal stages of dementia, patients become empty shells of their former selves—profoundly disoriented, incoherent, amnestic, and incontinent of urine and feces. With psychosocial and pharmacological treatment and possibly because of the selfhealing properties of the brain, the symptoms of dementia may progress slowly for a time or may even recede somewhat. Symptom regression is certainly a possibility in reversible dementias (dementias caused by hypothyroidism, NPH, and brain tumors) after treatment is initiated. The course of the dementia varies from a steady progression (commonly seen with dementia of the Alzheimer's type) to an incrementally worsening dementia (commonly seen with vascular dementia) to a stable dementia (as may be seen in dementia related to head trauma). Psychosocial Determinants The severity and course of dementia can be affected by psychosocial factors. The greater a person's premorbid intelligence and education, the better the ability to compensate for

intellectual deficits. People who have a rapid onset of dementia use fewer defenses than do those who experience an insidious onset. Anxiety and depression can intensify and aggravate the

symptoms. Pseudodementia occurs in depressed people who complain of impaired memory but, in fact, have a depressive disorder. When the depression is treated, the cognitive defects disappear. TREATMENT The first step in the treatment of dementia is verification of the diagnosis. Accurate diagnosis is imperative because the progression may be halted or even reversed if appropriate therapy is provided. Preventive measures are important, particularly in vascular dementia. Such measures might include changes in diet, exercise, and control of diabetes and hypertension. Pharmacological agents might include antihypertensive, anticoagulant, or antiplatelet agents. Blood pressure control should aim for the higher end of the normal range because that has been demonstrated to improve cognitive function in patients with vascular dementia. Blood pressure below the normal range has been demonstrated to further impair cognitive function in patients with dementia. The choice of antihypertensive agent can be significant in that β-adrenergic receptor antagonists have been associated with exaggeration of cognitive impairment. Angiotensin-converting enzyme (ACE) inhibitors and diuretics have not been linked to exaggeration of cognitive impairment and are thought to lower blood pressure without affecting cerebral blood flow, which is presumed to be correlated with cognitive function. Surgical removal of carotid plaques may prevent subsequent vascular events in carefully selected patients. The general treatment approach to patients with dementia is to provide supportive medical care; emotional support for the patients and their families; and pharmacological treatment for specific symptoms, including disruptive behavior. Psychosocial Therapies The deterioration of mental faculties has significant psychological meaning for patients with dementia. The experience of a sense of continuity over time depends on memory. Recent memory is lost before remote memory in most cases of dementia, and many patients are highly distressed by clearly recalling how they used to function while observing their obvious deterioration. At the most fundamental level, the self is a product of brain functioning. Patients' identities begin to fade as the illness progresses, and they can recall less and less of their past. Emotional reactions ranging from depression to severe anxiety to catastrophic terror can stem from the realization that the sense of self is disappearing. Patients often benefit from a supportive and educational psychotherapy in which the nature and course of their illness are clearly explained. They may also benefit from assistance in grieving and accepting the extent of their disability and from attention to self-esteem issues. Any areas of intact functioning should be maximized by helping patients identify activities in which successful functioning is possible. A psychodynamic

assessment of defective ego functions and cognitive limitations can also be useful. Clinicians can help patients find ways to deal with the defective ego functions, such as keeping calendars for orientation problems, making schedules to help structure activities, and taking notes for memory problems. Psychodynamic interventions with family members of patients with dementia may be of great assistance. Those who take care of a patient struggle with feelings of guilt, grief, anger, and exhaustion as they watch a family member gradually deteriorate. A common problem that develops among caregivers involves their self-sacrifice in caring for a patient. The gradually developing resentment from this self-sacrifice is often suppressed because of the guilt feelings it produces. Clinicians can help caregivers understand the complex mixture of feelings associated with seeing a loved one decline and can provide understanding as well as permission to express these feelings. Clinicians must also be aware of the caregivers' tendencies to blame themselves or others for patients' illnesses and must appreciate the role that patients with dementia play in the lives of family members. Pharmacotherapy Clinicians may prescribe benzodiazepines for insomnia and anxiety, antidepressants for depression, and antipsychotic drugs for delusions and

hallucinations, but they should be aware of possible idiosyncratic drug effects in older people (e.g., paradoxical excitement, confusion, and increased sedation). In general, drugs with high anticholinergic activity should be avoided. Donepezil (Aricept), rivastigmine (Exelon), galantamine (Remiryl), and tacrine (Cognex) are cholinesterase inhibitors used to treat mild to moderate cognitive impairment in Alzheimer's disease. They reduce the inactivation of the neurotransmitter acetylcholine and thus potentiate the cholinergic neurotransmitter, which in turn produces a modest improvement in memory and goal-directed thought. These drugs are most useful for persons with mild to moderate memory loss who have sufficient preservation of their basal forebrain cholinergic neurons to benefit from augmentation of cholinergic neurotransmission. Donepezil is well tolerated and widely used. Tacrine is rarely used because of its potential for hepatotoxicity. Fewer clinical data are available for rivastigmine and galantamine, which appear more likely to cause gastrointestinal (GI) and neuropsychiatric adverse effects than does donepezil. None of these medications prevents the progressive neuronal degeneration of the disorder. Prescribing information for anticholinesterase inhibitors can be found in Section 36.14. Memantine (Namenda) protects neurons from excessive amounts of glutamate, which may be neurotoxic. The drug is sometimes combined with donepezil. It has been known to improve dementia. Other Treatment Approaches. Other drugs being tested for cognitive-enhancing activity include general cerebral metabolic enhancers, calcium channel inhibitors, and

serotonergic agents. Some studies have shown that selegiline (Eldepryl), a selective type B monoamine oxidase (MAOB) inhibitor, may slow the advance of this disease. Ondansetron (Zofran), a 5-HT3 receptor antagonist, is under investigation. Estrogen replacement therapy may reduce the risk of cognitive decline in postmenopausal women; however, more studies are needed to confirm this effect. Complementary and alternative medicine studies of ginkgo biloba and other phytomedicinals are required to see if they have a positive effect on cognition. Reports have appeared of patients using nonsteroidal antiinflammatory agents having a lower risk of developing Alzheimer's disease. Vitamin E has not been shown to be of value in preventing the disease. REFERENCES Bondi MW, Salmon DP, Kaszniak AW. The neuropsychology of dementia. In: Grant I, Adams KM, eds. Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders. 3rd ed. New York: Oxford University Press; 2009:159. Brand BL, Stadnik R. What contributes to predicting change in the treatment of dissociation: Initial levels of dissociation, PTSD, or overall distress? J Trauma Dissociation. 2013;14:328. Clare L, Whitaker CJ, Nelis SM, et al. Self-concept in early stage dementia: Profile, course, correlates, predictors and implications for quality of life. Int J Geriatr Psychiatry. 2013;28(5):494–503. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia. Arch Neurol. 2009;66(3):300. Elvish R, Lever S-J, Johnstone J, Cawley R, Keady J. Psychological interventions for carers of people with dementia: A systematic review of quantitative and qualitative evidence. Counsel Psychother Res. 2013;13(2):106–125. Goldman J, Stebbins G, Merkitch D, Dinh V, Bernard B, DeToledo-Morrell L, Goetz C. Hallucinations and dementia in Parkinson's disease: clinically related but structurally distinct (P5. 257). Neurology. 2014;82(10 Supplement):P5-257. Graff-Radford NR, Woodruff BK. Frontotemporal dementia. Semin Neurol. 2007; 27:48. Hansen KF, Karenlina K, Sakamoto K, Wayman GA, Impey S, Obrietan K. miRNA-132: A dynamic regulator of cognitive capacity. Brain Structure Function. 2013;218:817. Insausti R, Annese J, Amaral DG, Squire LR. Human amnesia and the medial temporal lobe illuminated by neuropsychological and neurohistological findings for patient E.P. Proc Natl Acad Sci U S A. 2013;110:E1953. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: A review. Nucl Med Commun. 2007;28:511. McLaren AN, LaMantia MA, Callahan CM. Systematic review of non-pharmacologic interventions to delay functional decline in community-dwelling patients with

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