Neurodegenerative Disorders: Dementia

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INTRODUCTION

The word *dementia* is an ancient term used by the Roman poet and philosopher Lucretius to describe the state of “being out of one’s mind.” Today, the term *dementia* describes a clinical syndrome characterized by acquired impairment in multiple neuropsychological and behavioral domains, including memory, cognition, visuospatial skills, and language. Most definitions of *dementia* refer to intellectual or cognitive deficits of severity sufficient to interfere with social or occupational functioning; however, the term *dementia* does not imply a specific cause or pathologic process.

Dementia is one of the most disabling and costly diseases associated with aging. More than 70 illnesses, some of which are nonprogressive, can cause dementia. All types of dementia are treatable—at least with psychosocial interventions—therefore, accurate diagnosis is essential to initiate appropriate treatment and provide information about prognosis and factors affecting the cause of illness. Although Alzheimer’s disease is the most common form of dementia, less common causes of dementia must also be considered when evaluating a patient with cognitive decline. For example, focal neurologic findings or progressive deterioration raise the suspicion of vascular dementia, whereas early onset of language dysfunction or personality changes suggests frontotemporal dementia; rapid progression of neurologic impairment should initiate evaluation for treatable/partially reversible conditions and prion disease.

Although dementia has often been considered a global disorder, no dementing illness involves all areas of the brain equally. The specific topography of involvement is manifested by two basic patterns of neuropsychological impairment: (1) cortical dementias such as Alzheimer’s disease and frontotemporal dementia, and (2) subcortical dementias such as vascular dementia, extrapyramidal syndromes, and normal pressure hydrocephalus. The clinical features of cortical and subcortical dementias differ as noted in Table 1.

This manual reviews the common and uncommon dementias. Three brief cases vignettes are discussed at the end of this review.

MILD COGNITIVE IMPAIRMENT

DIAGNOSIS

In general terms, mild cognitive impairment (MCI) is an intermediate stage between normality and dementia. Although the general concept is easy to grasp, the development of precise diagnostic criteria for MCI has been slow. Use of cut-off scores on neuropsychological tests ignores the possibility that individual patients may have always performed poorly and thus may not have a true decline in intellectual capacity. In contrast, patients who have deteriorated significantly might still score above the cut-off if their pre-morbid level of performance was high. These considerations have led to development of both research and practical guidelines for diagnosis of MCI. Practical guidelines for a diagnosis of amnestic MCI (adapted from the Petersen criteria) include: (1) memory complaint by patient, confirmed by family or physician, (2) normal activities of daily living, (3) normal general cognitive function, (4) objective memory impairment for age and education, and (5) no dementia present.

The research definition of MCI uses global staging scales such as the Global Deterioration Scale (score of 2 or 3) and the Clinical Dementia Rating Scale (score of 0.5) to define MCI. The Mini-Mental State Examination (MMSE) score for MCI is greater than 24 and usually in the range of 26 to 28. Because different cut-offs are used depending on the demographic group to maintain the sensitivity and specificity of the MMSE, this test is more useful to track the degree of impairment in a given individual than to make the diagnosis. Rather than the MMSE, neuropsychological testing using one or several memory tests with published norms is more appropriate for determining objective memory impairment. Memory function is usually assessed by learning over trials or delayed recall on a multiple-trial free-recall task, such as the Auditory Verbal Learning Test or the Wechsler Memory Scale-Revised or Wechsler Memory Scale-III, Logical Memory II, or Visual Reproduction II tests. Generally, scores of patients with MCI tend to fall 1.5 standard deviations below age- and education-matched controls.
Three clinical subtypes of MCI have been described: amnestic, multiple domains, and single, non-memory domain impaired. Amnestic MCI is most extensively described in current literature. In the multiple domains subtype, the patient may have slight impairment of multiple cognitive domains but of insufficient severity for a diagnosis of dementia. Outcome for these patients is unknown; some may progress to Alzheimer’s disease (AD) or other types of dementia. Patients with MCI are at risk to convert to AD at an annual rate of 10% to 15% compared with 1% to 2% in the general population.1,2

NEUROPATHOLOGY

Very few neuropathologic studies exist for MCI. Typically, patients do not die in the mild stage of impairment, so autopsies are uncommon. Neuropathologic evaluation of MCI patients has demonstrated hippocampal pathology, supporting the assertion that MCI is a transitional state between normal aging and AD. Autopsy studies have shown neuropathologic changes (ie, neuritic plaques and neurofibrillary tangles) of AD in most cases of MCI.3-5

NEUROIMAGING

Structural as well as functional brain imaging techniques reveal abnormalities in patients with MCI that are intermediate between healthy patients and those with AD. Magnetic resonance imaging (MRI) studies show volume reductions involving medial temporal lobe structures, including the hippocampus and entorhinal cortex. Hippocampal atrophy has been shown to predict subsequent dementia in MCI patients.6,7 Unfortunately, age-related atrophy in individuals without dementia also occurs, limiting the diagnostic utility of such measurements. However, serial MRI assessments show a substantially greater rate of progression of hippocampal, entorhinal, and whole brain atrophy in patients who progress from having no cognitive impairment to MCI and in those who progress from MCI to AD compared with patients who have no progression.8 Metabolic reductions in the posterior cingulate gyrus have been demonstrated on positron emission tomography in MCI patients.9

TREATMENT

Pharmacotherapy for MCI is controversial. Currently available medications for AD, such as acetylcholinesterase inhibitors (AChEIs), are being tested in MCI. Use of donepezil may have some benefits.10,11

ALZHEIMER’S DISEASE

AD is a progressive, neurodegenerative disorder associated with neuronal cell death and synaptic loss as well as gradual deterioration in cognition, activities of
daily function, and behavior. AD is the most common cause of dementia, responsible for 60% to 65% of all progressive dementias. AD affects approximately 4 million individuals in the United States and 30 million worldwide. AD is the third most costly disease in the United States and the fourth leading cause of death.

RISK FACTORS AND ETIOLOGY

Although the initiating events are still unknown, the sporadic form of AD clearly results from the combination of genetic risk factors with epigenetic events. Several factors may increase the risk of AD.

Demographic Risk Factors

Age seems to be the most powerful risk factor for AD. Prevalence studies indicate that the risk of AD doubles every 5 years after age 65 years. AD affects approximately 6% to 8% of individuals older than age 65 years and 30% to 50% of those older than 85 years.12 A positive family history is also an important risk factor. One affected first-degree family member increases the risk of AD four times. The risk to children is increased if both parents are affected. Despite the strong association between a positive family history and the risk of AD, more than 75% of cases are sporadic. Some evidence suggests that severe head trauma increases the likelihood of manifesting symptoms of AD earlier.13 Studies have shown an increased prevalence of AD in women.14 The risk of AD was found to be greater in people who had both high blood pressure and high cholesterol.15 Also, moderately increased levels of homocysteine have been shown in patients with AD or other dementias.16

Genetic Risk Factors

Mutations of chromosomes 1, 14, and 21. AD-type pathology develops in all persons with Down’s syndrome who survive beyond age 40 years. Certain mutations of chromosome 1, 14, and 21 cause rare, early-onset familial forms of AD. Presence of amyloid precursor protein (APP) and presenilin-1 and presenilin-2 (PSEN1, PSEN2) mutations can predict AD with 95% to 100% certainty. More than 20 different mutations have been found in the PSEN1 gene. The PSEN1 gene is on chromosome 14 and encodes a membrane protein, S182. Mutations in this gene cause early-onset AD (often < age 50 years) that is transmitted in an autosomal dominant, highly penetrant fashion. The PSEN2 gene is on chromosome 1 and encodes the protein STM2. Both S182 and STM2 are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. Although the function of the presenilin gene products is not yet known, recent studies show that the presenilins are probably γ-secretase (as discussed later in text).17,18

The utility of APP, PSEN1, and PSEN2 testing is limited because mutations are found almost exclusively in early-onset familial AD, which comprises less than 5% of all AD cases. Some forms of late-onset AD have also been linked to chromosome 12.

Apolipoprotein E ε4. The apolipoprotein E (ApoE) gene (APOE) on chromosome 19 is implicated in the pathogenesis of late-onset-familial and sporadic forms of AD. ApoE is involved in cholesterol transport. The exact mechanism of its influence in the pathophysiology of AD is still unknown. ApoE is present in neuritic amyloid plaques of AD; it may also be involved in neurofibrillary tangle formation because it binds to tau protein. APOE is a susceptibility gene: susceptibility genes modify genetic predisposition to dementia but are not sufficient or essential to cause disease. The 3 forms of the gene are APOE ε2, ε3, and ε4. Of these, ε3 is by far the most common variant, occurring in 60% to 80% of humans. In the United States, the frequency of APOE ε4 in AD patients is 40% compared to 15% to 20% among unaffected persons of the same age. Having one allele of APOE ε4 increases the risk of AD by 2-fold; having two alleles is associated with a 5-fold increase.

Insulin-Degrading Enzyme

Insulin-degrading enzyme is one of the proteins that have been shown to play a key role in degrading monomeric precursors of β-amyloid in neurons in vivo. Insulin competes for degradation by this enzyme; high insulin levels thus are expected to increase the risk for AD, as supported by several studies.19 In the short term, higher insulin levels appear to enhance cognition, possibly through a direct effect on central nervous system insulin receptors.20

CLINICAL FEATURES

Memory and Language

Memory deficit is the hallmark of AD. More precisely, the deficit is in new learning and in the encoding of information. Early in the course of disease, families note the patient’s repetition of conversations and questions. Patients may have difficulty remembering to attend appointments or to take medications. Symptoms may be so insidious in onset that they are not readily recognized by family members, and patients with AD frequently deny or minimize their deficits. Early in disease, the patient may have word-finding difficulty (anomia) manifesting as poor word-list generation, circumlocution, or paraphasic errors. Later in disease, “empty speech” and impaired comprehension develop.
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Visuospatial Skills

Early in disease, patients exhibit difficulty with complex visuoconstructive tasks such as clock drawing. Patients may become lost in unfamiliar places and, later in disease, become disoriented in familiar places. A variant of AD called posterior cortical atrophy (PCA) manifests as a progressive visual-cognitive syndrome associated with atrophy of occipital and occipitoparietal regions. PCA causes a range of complex visual disturbances, including Balint’s syndrome, prosopagnosia, ocular apraxia, constructional disturbances, alexia, and hemiachromatopsia. PCA may result from several diseases; however, in more than 50% of cases, PCA is a variant of AD in which the usual temporoparietal pathology has shifted posteriorly to first involve the occipitoparietal regions.

Executive Function, Praxis, and Behavioral Symptoms

Subtle impairments in executive function occur early in disease. Deficits in problem solving, judgment, reasoning, and abstraction are examples of executive impairment, which may manifest as a lack of insight into deficits, difficulty with planning more complex tasks, and difficulty with managing finances. Apraxia is the inability to perform motor tasks in absence of impairment in primary motor or sensory function. Apraxia is usually a late finding in AD.

Patients with mild AD manifest apathy, social withdrawal, or signs of depression. As disease progresses, patients may exhibit disruptive behaviors, including verbal aggression, agitation, and wandering. Many patients also experience delusions and hallucinations as well as disturbances of sleep, appetite, and sexual behavior.

DIAGNOSIS

Differential Diagnosis

AD is characterized by an insidious onset and slowly progressive cognitive decline. Clinical criteria commonly used for a provisional diagnosis have been developed by the National Institute of Neurological and Communicative Disorders and Stroke in conjunction with the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) and by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Currently, AD is a diagnosis of inclusion rather than exclusion. Clinical diagnosis is based on history, physical and neurologic examination, and neuropsychological criteria; however, many causes of cognitive, behavioral, and functional changes other than AD are possible. Primary differential diagnoses are vascular dementia and frontotemporal lobar degeneration.

Initial presentation in frontotemporal lobar degeneration often includes behavior or language problems in contrast to the memory deficit in AD; however, presenting symptoms and symptom progression varies widely in both diseases, and all cognitive domains are eventually affected in both. Many AD patients also have cerebrovascular disease (CVD). Focal findings on neurologic examination, gait problems, and parkinsonian features can occur early in the course of vascular dementia but are unusual in early AD. In contrast to AD, visuospatial skills in frontotemporal degeneration and vascular dementia tend to be well-preserved early in disease (unless focal parietal infarcts are responsible).

Neuropathology

Definitive diagnosis of AD requires pathologic confirmation at autopsy. On gross pathologic examination, the brains of AD patients are atrophic; brain weight is reduced by an average of 100 to 200 g. Atrophy involves predominantly the temporal and parietal lobes. On microscopic pathology, hallmarks of AD are neurofibrillary tangles and senile/neuritic plaques. Also seen are granulovacular degeneration, amyloid angiopathy, and neuronal and synaptic loss. Neurofibrillary tangles are intraneuronal cytoplasmic structures composed of a hyperphosphorylated form of the microtubule-associated tau protein. In healthy nerve cells, tau protein stabilizes the microtubular components of the neuronal cytoskeleton that are involved in transporting substances between cellular compartments. Neurofibrillary pathology is not unique to AD but also occurs in other diseases, called tauopathies, including frontotemporal dementia and progressive supranuclear palsy.

Neuritic plaques occur in all AD patients. These plaques are extracellular aggregations of amyloid protein. The major component is the β-amyloid protein, which is a polypeptide derived from the much larger APP. APP is a glycoprotein found in high concentrations in virtually all mammalian cell membranes and in especially high concentrations in neuronal cell membranes. APP may have a role in nerve growth during development. APP can be cleaved by a group of proteases called secretases, α-secretase cuts within the β-amyloid sequence, preventing the release of soluble protein. Two other secretases also cleave APP; β-secretase cleaves near the N terminus and γ-secretase cleaves near the C terminus. Peptides of 39 to 43 amino acids in length are generated via these cleavage events. Longer peptides, especially abeta 42, are more prone to aggregation into neuriti plaques. Alterations in PSEN1 and PSEN2 alter γ-secretase activity such that a higher proportion of β-amyloid produced is of the amyloidogenic 42 amino
Acid form (Abeta 42). Inflammatory changes and degenerating neuronal processes surround the plaque.

Neuroimaging

Consensus guidelines from the American Academy of Neurology recommend neuroimaging by conventional computed tomography (CT) or MRI in the evaluation of patients with dementia. Although no specific abnormalities on conventional neuroimaging techniques are diagnostic of AD, these studies are necessary to assist in excluding other, primarily structural, causes of dementia. In advanced AD, MRI scans usually demonstrate bitemporal atrophy (Figure 1).

Neuroimaging research in AD has shown consistent findings of temporoparietal hypometabolism on functional imaging studies and hippocampal and entorhinal atrophy on volumetric studies. Functional MRI has shown abnormal activation patterns in frontal and medial temporal lobe regions. MR spectroscopy has shown reduced N-acetylaspartate levels (which correlate with neuronal density and function) and elevated myo-inositol levels (a measure of glial cell density and phosphatidylinositol-mediated signaling), especially in medial temporal and limbic structures.

Treatment

Abnormalities of all neurotransmitter systems have been documented in AD; however, deficits in cholinergic and glutamergic function have been the most widely investigated and are the basis for current medications approved for treatment. Cholinergic activity has been shown to be reduced 80% to 90% in affected cortical regions. Glutamergic hyperactivity via N-methyl-D-aspartate (NMDA) overstimulation resulting in calcium-mediated excitotoxicity has also been posited to play a role in the pathophysiology of AD. Cholinergic neurons in the septal and basalis nuclei, which project widely throughout the neocortex, entorhinal, and hippocampal cortices, are lost, thereby causing deficient cholinergic transmission and deficits in memory, learning, and cognition. Thus, prolonging activity of acetylcholine at the synapse should improve memory, and other cognitive processes, including behavioral and functional abilities, in AD patients.

Four AChEIs are approved for treatment of mild to moderate AD: tacrine (now rarely used because of potential hepatic side effects and frequent dosing), donepezil, rivastigmine, and galantamine. Cholinergic side effects of these agents include nausea, vomiting, and diarrhea. Although response to treatment varies widely, AChEIs generally produce mild to moderate benefits in ameliorating cognitive, functional, and behavioral abnormalities.

As noted previously, the neurotransmitter glutamate may also play a role in AD pathophysiology. Glutamergic dysfunction can cause prolonged neural excitation and calcium-induced neurotoxicity, thus triggering apoptosis. Memantine is an uncompetitive NMDA-receptor antagonist recently approved for the treatment of moderate to severe AD. Memantine has been shown to produce mild to moderate benefits in cognitive, functional, and behavioral domains in AD patients.

High doses of vitamin E and C, based on modest clinical support and a relatively benign risk-to-benefit ratio, are also widely used in AD treatment. Other compounds currently under investigation include lipid- and glucose-lowering agents, neuroprotective and neurotrophic factors, neuro-immunotherapeutic agents (vaccines and antibodies to β-amyloid), and compounds that interfere with amyloid processing and aggregation.

Addressing behavioral problems common in middle and later stages of disease is also important. Use of nonpharmacologic and behavioral techniques should be stressed as primary interventions, but pharmacologic therapy should be considered if these continue to fail. Guidelines for the management of AD patients in the primary-care setting are now available.28
**FRONTOTEMPORAL LOBAR DEGENERATION**

Frontotemporal lobar degeneration (FTLD) syndromes are characterized by different symptomatology depending on the degree of anterior and temporal lobe degeneration and neuropathology; these include frontotemporal dementia (FTD), primary progressive aphasia, and semantic dementia. Pick’s disease is a pathologic type of FTLD. The diagnosis of Pick’s disease is now restricted to cases of frontal and temporal lobar atrophy plus Pick’s cells (chromatolytic ballooned neurons) and Pick’s bodies (argyrophilic inclusion bodies within the neuronal cytoplasm).

**FRONTOTEMPORAL DEMENTIA**

FTD is commonly misdiagnosed as AD. The actual prevalence of FTD is unknown, but FTD may cause up to 10% of all dementias and potentially a much larger proportion of presenile dementias.

**Genetic Defects**

Approximately 20% to 40% of FTD cases are familial with an autosomal dominant inheritance pattern. Three genes responsible for familial forms of FTD have been mapped. FTD with parkinsonism inherited as an autosomal dominant trait linked to chromosome 17 is referred to as FTDP-17. The candidate gene is the gene for the protein tau. Another locus has been found on chromosome 9. These cases, termed familial FTD with motor neuron disease, are characterized by tau-negative, ubiquitin-positive inclusions. Chromosome 3 has also been linked to FTD (termed FTD-3) and lacks distinctive histopathology. The disease affects both sexes equally.

**Clinical Features**

The most common and early symptom of FTD is a decline in social conduct that precedes cognitive changes. Cognitive changes include changes in language, memory, executive function, and personality. In terms of language, spontaneity may be lost; echolalia, automatic speech, or (more rarely) pressured speech can occur. As the disease progresses, verbal output diminishes and eventually patients become mute. In contrast to AD, memory and visuospatial skills are typically preserved early in the course of disease. Executive deficits in planning, insight, mental flexibility, problem solving or abstract thinking, and environmental dependency may develop.

Personality changes that may be presenting symptoms include decline in manners, loss of concern for personal appearance, disinhibited behavior (inappropriate verbal or physical acts), and loss of interest and apathy. Patients may show obsessive/compulsive traits or lack empathy and emotional warmth. Disinhibition phenomena, such as hyperorality, hypersexuality and utilization behavior, are grouped under the term Kluver-Bucy syndrome.

On neurologic examination, motor impersistence, environmental dependency, and utilization behavior may be noted. Primitive reflexes may occur early in disease. Urinary incontinence, parkinsonian features, dysphagia, and signs of anterior horn cell degeneration occur in some patients.

**PRIMARY PROGRESSIVE APHASIA**

Patients with primary progressive aphasia present with a slowly progressive difficulty with expressive language that is often of presenile onset. Core features of primary progressive aphasia include nonfluent spontaneous speech with at least one of the following impairments: phonemic paraphasia, agrammatism, and anomia. Speech is hesitant, effortful, and broken. Patients are aware of their deficits. Primary progressive aphasia may be initially mistaken for stroke; however, the aphasia is gradual in onset and slowly progressive in contrast to its sudden maximal onset in stroke. After many years, patients ultimately become mute. Even in patients who are mute, memory and visuospatial skills may be relatively well preserved.

**SEMANTIC DEMENTIA**

Patients with semantic dementia often present with difficulty in naming and in comprehension. These patients progressively lose the meaning of words but retain fluency. Core features include fluent aphasia with effortless speech but empty content. There is relative preservation of phonology, repetition, syntax, and the ability to write common words and read aloud. Semantic dementia patients develop nonfluent speech later in disease and also frequently develop behavioral disturbances. Face and object agnosia may be present. Repetition of common single words is preserved, whereas repetition of longer phrases is impaired.

**NEUROPATHOLOGY**

In FTD, gross pathologic examination reveals prominent bilateral and symmetrical atrophy involving the frontal and temporal lobes. The superior temporal gyrus is usually spared. In primary progressive aphasia, the atrophy is often asymmetric and involves the left frontal lobe (Figure 2). In semantic dementia, the atrophy is often bilateral and mostly involves the anterior temporal lobes.
Two characteristic histopathologic findings, intracytoplasmic Pick’s bodies and Pick’s cells, are found in approximately 25% of patients with FTD; the diagnosis of Pick’s disease should be reserved for these pathologically confirmed cases. Pick’s cells are enlarged, ballooned neurons with displaced nuclei and silver-staining cytoplasm. Pick’s bodies are dense silver-staining intraneuronal inclusions. Antibodies against phosphorylated tau protein and ubiquitin antibodies bind to Pick’s bodies.

In the remaining 75% of cases of FTD, nonspecific changes (eg, gliosis, neuronal loss, superficial linear spongiosis) are found. Cases lacking these features have also been found and are termed dementia lacking distinctive pathology. Some of the cases previously labeled as dementia lacking distinctive pathology have tau-negative, ubiquitin-positive inclusions.

**VASCULAR DEMENTIA**

The prevalence of vascular dementia varies among populations but accounts for 10% to 20% of all cases of dementia. In Western countries, vascular dementia is the second most common form of dementia after AD. In contrast, the frequency of vascular dementia in Asia may exceed that of AD. The prevalence of vascular dementia has also been demonstrated to increase with age and is more common in men. African-Americans have higher rates of vascular dementia than Caucasians.

Risk factors for vascular dementia are assumed to be the same as those for stroke and include hypertension, smoking, atrial fibrillation, diabetes, peripheral vascular disease, CVD, dyslipidemia, cardiovascular disease, hyper-homocystinemia and age.

**DIAGNOSTIC CRITERIA**

The most widely used criteria for vascular dementia are the DSMIV and the criteria created by the National Institute of Neurological Disorders and Stroke (NINDS) (Bethesda, MD) with the support of the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN). The NINDS-AIREN criteria require dementia and evidence of CVD on the basis of both imaging and clinical examination in addition to a temporal relationship between stroke and dementia or a stepwise progression of cognitive deficits. The DSMIV criteria, which require imaging or clinical evidence of prior stroke, are more sensitive but less specific than the NINDS-AIREN criteria. The modified Hachinski ischemic score, derived from clinical history and evidence of previous stroke on physical examination, was used prior to the availability of detailed neuroimaging to distinguish clinically between vascular dementia and AD.

**CLINICAL FEATURES**

The presentation of vascular dementia is related to the underlying pathology. Dementia may follow a single vascular insult or occur in a progressive pattern associated with cumulative cortical or subcortical events. After each event (ie, stroke, transient ischemic attack), the patient’s deficits initially worsen; the deficits may subsequently improve but never completely resolve.
Neurodegenerative Disorders: Dementias

Patients frequently present with a mixture of cortical and subcortical deficits, depression, or emotional lability (pseudobulbar signs). In contrast to AD, insight may be relatively preserved early in disease. The memory deficit in vascular dementia is often less severe than that in AD and includes impaired retrieval with relatively intact recognition. Gait disturbances and urinary frequency and incontinence are not caused by urologic disease and are often early features of vascular dementia.

The causes of vascular dementia are divided into 2 categories also used for stroke management: large-vessel and small-vessel disease. Large-vessel disease can produce cortical infarcts in strategic locations, such as the hippocampus, angular gyrus, thalamus, or frontal lobe, producing cognitive deficits that meet criteria for dementia. Multiple smaller infarcts can also cause dementia via the cumulative volume of brain tissue involved, termed multi-infarct dementia. For patients with small-vessel disease, it may be difficult to establish a relationship between stroke and dementia. Two pathologic features are typical in small-vessel disease: (1) lacunar infarcts in strategic locations such as the deep nuclei, and (2) periventricular white matter lesions, termed leukoaraiosis orBinswanger’s disease. Both features indicate disruption of the cortico-subcortical circuits that are important for executive function.

An unusual hereditary form of CVD—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy—can also produce vascular dementia. The disease is marked by multiple, confluent, lacunar infarcts involving subcortical white matter but sparing the U-fibers. The underlying lesion is a widespread vasculopathy. Genetic analysis demonstrated linkage to chromosome 19q12 and later identified a mutation in the Notch3 gene.

DEMENTIA OF LEWY BODY TYPE

Dementia of Lewy body type (DLB) is probably the second most common cause of primary neurodegenerative dementia after AD, accounting for up to 10% to 20% of cases.41,42 The nosology has varied over time; terms such as diffuse Lewy body disease, Lewy body variant, and Lewy body dementia were used until consensus guidelines were developed, with evolution to the term dementia of Lewy body type. Diagnostic criteria include progressive cognitive deterioration plus 1 (for possible DLB) or 2 (for probable DLB) of the major criteria.43 Major criteria include fluctuating cognition, recurrent well-formed visual hallucinations, and spontaneous parkinsonism. Other features supportive of the diagnosis include falls, syncope, loss of consciousness, neuroleptic sensitivity, systematized hallucinations, and delusions. The specificity of the diagnostic criteria is high, whereas the sensitivity is relatively low. Typically, DLB follows a sporadic inheritance pattern.

CLINICAL FEATURES

DLB patients present clinically with extrapyramidal signs, such as axial rigidity (most often) and bradykinesia; patients do not usually have rest tremor. Extrapyramidal symptoms are present early in the course of dementia. Conversely, onset of dementia within 1 year of onset of parkinsonism has also been suggested as indicative of the diagnosis of DLB. Patients present cognitively with episodic worsening and improvement in context of progressive deterioration. Prominent deficits in sustained attention and visuospatial skills are present. Prominent psychiatric symptoms such as hallucinations, delusions, apathy, and anxiety are common early in disease.44 Marked fluctuations in levels of arousal and attention, which can vary from periods of complete lucidity to periods of apparent delirium, are characteristic of disease. DLB patients are exquisitely sensitive to neuroleptic medications and experience marked worsening of extrapyramidal symptoms when these agents are used to treat psychiatric symptoms.45 Autonomic abnormalities are common in patients with DLB and include orthostatic hypotension, falls, and syncope.46 Rapid eye movement sleep behavior disorder is frequently seen in patients with DLB as in other synucleinopathies.47

DIFFERENTIAL DIAGNOSES

The main differential diagnoses are AD, idiopathic Parkinson’s disease, vascular dementia, other parkinsonian syndromes, and prion diseases. Many clinical
features of DLB overlap with AD, and the premorbid distinction between the two can be difficult. The presence of extrapyramidal features, visual hallucinations, and fluctuations early in disease may distinguish DLB from AD. However, one study showed diagnostic accuracy of only approximately 28% in diagnosing DLB prior to autopsy, thus stressing the importance of familiarity with diagnostic criteria as well as a high index of suspicion. Although patients with Parkinson’s disease may develop dementia, this typically occurs later in the course of disease. Unilateral symptoms at onset are also suggestive of Parkinson’s disease rather than DLB. Absence of tremor is seen in 25% to 30% of patients with idiopathic Parkinson’s disease and is unhelpful in distinguishing it from DLB.

**DIAGNOSIS**

Definitive diagnosis of DLB is at autopsy. To date, no specific cerebrospinal fluid biomarkers have been identified for DLB. Neuroimaging may be helpful; compared with AD, a relative preservation of temporal lobe volume has been reported in DLB, often in the context of generalized cerebral atrophy. Occipital hypoperfusion on single photon emission CT (SPECT) imaging with technetium-99m hexamethylpropylene amine oxime (HMPAO) as well as abnormalities in caudate and putamen on dopaminergic SPECT and positron emission tomography have been reported. In contrast to Parkinson’s disease, dopaminergic tracer uptake abnormalities in the striatum of DLB patients tends to be symmetric and without an anterior-posterior spatial gradient.

**PATHOLOGY**

Lewy bodies are the essential feature in the pathologic diagnosis of DLB. The classic Lewy bodies of Parkinson’s disease are spherical, intracytoplasmic, eosinophilic neuronal inclusions seen primarily in the substantia nigra and locus ceruleus identified by ubiquitin and α-synuclein immunocytochemistry. In DLB, cortical Lewy bodies are found in limbic (hippocampus, entorhinal and cingulate cortex) as well as in neocortical regions (frontal, parietal, and temporal cortex). Additionally, other features such as Lewy-related neuritis (a neurofilament abnormality associated with Lewy bodies when using ubiquitin staining in hippocampus, nucleus basalis, and brain stem), neurofibrillary tangles, plaques, regional neuronal loss in the brain stem and nucleus basalis, and spongiform changes also occur in DLB, although the extent of these changes is variable. Pathological differentiation between DLB and AD is based on the presence in DLB of extensive cortical Lewy bodies and Lewy-related neuritis in addition to a negligible amount of tangles and neuronal loss. The most significant correlates of cognitive failure in DLB appear to be cortical Lewy bodies and Lewy neurites rather than AD-type pathology.

**TREATMENT**

Patients may receive a modest benefit from dopaminergic agents, especially carbidopa/levodopa, to treat motor symptoms. However, treatment with low doses is recommended because of increased incidence of hallucinations with higher doses of levodopa and particularly with dopamine agonists. Neuropsychiatric symptoms are often treated with atypical antipsychotics with a lower extrapyramidal side-effect profile such as quetiapine. Clozapine may also be used, but serum leukocyte monitoring is required. Use of antipsychotic agents frequently leads to worsening of parkinsonism. AChEIs are the mainstay of treatment for both cognitive and behavioral problems associated with DLB and provide modest improvements in cognition. Neuropsychiatric symptoms of DLB, such as visual hallucinations, also have been shown to improve with AChEIs. Depression can be treated with selective serotonin reuptake inhibitors, which are usually well tolerated. Severe rapid eye movement sleep behavior disorder can be treated with long-acting benzodiazepines such as clonazepam.

**CREUTZFELDT-JACOB DISEASE**

Creutzfeldt-Jacob disease (CJD) occurs in several forms, including sporadic, familial, iatrogenic, and new variant. Sporadic CJD (sCJD) is the most common form—approximately 80% of CJD cases—with an incidence between 0.5 and 1 per million worldwide. The familial form accounts for 10% to 15% of the cases. Iatrogenic forms have been described in patients who have received cadaveric growth hormone, dura matter grafts, and corneal grafts. The new variant form (nvCJD) (also termed mad cow disease) has mainly been described in Britain and other European countries and is postulated to be caused by ingestion of beef from cows infected with bovine spongiform encephalitis. The disease affects men and women equally. In sCJD, the median age of onset is 65 years, although the disease may occur as early as in the 20- to 30-year-old age range. Age of onset tends to be earlier in nvCJD and the familial and iatrogenic forms.
The primary presenting clinical feature, especially of sCJD, is a rapidly progressive dementia with startle myoclonus. The first clinical symptoms can be nonspecific, such as insomnia; however, memory complaints and focal neurologic symptoms can also be present. Focal neurologic symptoms can be visual loss, aphasia, ataxia, and either hyperkinetic or hypokinetic extrapyramidal symptoms. These symptoms are inevitably followed by rapidly progressive dementia. Startle myoclonus develops in approximately 80% of patients. Akinetic mutism is seen in terminal stages of the disease, with death occurring invariably within 1 year, except in some familial cases in which disease course may be longer.60

Eponyms have been attached to several variants of sCJD. Patients with the Heidenhain variant of CJD present with visual complaints including field defects, difficulties with depth or color perception, and visual hallucinations. Eye movement abnormalities may also be seen. A high index of suspicion is necessary for diagnosis, which can be delayed until evolution of dementia or myoclonus.

Patients with nvCJD also frequently present in atypical fashion. At the outset, psychiatric symptoms such as dysphoria, anergia, loss of interest, insomnia, anxiety, and withdrawal may lead to diagnosis of depression. Failing delusions and hallucinations have also been reported.61 Initial neurologic symptoms of nvCJD may include paresthesias and gait ataxia. Confusion, myoclonus and other features seen in sCJD occur late in the disease course.62

Pathophysiologically, all forms of CJD are thought to be caused by misfolding of a naturally occurring cellular protein, the prion protein PrPc (α-helical, cellular form), to PrPSc (β-pleated sheet, protease-resistant form).65 This disease model provides an explanation for how the disease may occur by infectious, inherited, and sporadic mechanisms. In the infectious forms (nvCJD and iatrogenic CJD), the infectious agent PrPSc interacts with endogenous PrPc to cause misfolding of the protein that is then propagated. In the inherited form, the prion protein genetic sequence produces a protein that is susceptible to misfolding; in sCJD, accidental misfolding of the cellular protein leads to disease. Certain genotypes (methionine or valine at codon 129) are found in 95% of cases of sCJD, and the clinical phenotypes vary according to the mutations. For example, in the classic form of sCJD, homozygosity to methionine at codon 129 is most commonly seen. In familial forms, many mutations have been described, the most common of which is at codon 200 (described in Libyan Jews, who have a high incidence of disease).64 The PrP is encoded by the PRNP gene, which is mapped to chromosome 20p12.65 The normal function of PrPc is unknown. In CJD, the insoluble protein PrPSc accumulates in neuronal nuclei. This process is accompanied by neuronal death, gliosis, and vacuolization, termed spongiform change.

In patients with clinically evident dementia, assay for protein 14-3-3 in cerebrospinal fluid (CSF) can be used in the diagnosis of CJD. Protein 14-3-3 is widely present in the nervous system; therefore, any condition that causes neuronal destruction, including viral encephalitis, stroke, and multiple sclerosis may cause an elevation of protein 14-3-3 in CSF. However, in a patient with rapidly progressive dementia and without CSF pleocytosis, sensitivity and specificity of elevated protein 14-3-3 in CSF can reach 96% and 99%, respectively.66

Castellani et al67 recently evaluated the specificity and sensitivity of protein 14-3-3 assay in various subtypes of sCJD, which were classified based on the mutations in the PrPSc. In the classic form of sCJD, sensitivity of protein 14-3-3 assay reached 94% when other neurologic disease is excluded, versus sensitivity of approximately 77% for the nonclassic forms of sCJD. Sensitivity of protein 14-3-3 analysis is lower in nvCJD and familial CJD. Electroencephalography may be helpful in diagnosis, especially during the later stages if complexes of periodic sharp waves and slow waves (often triphasic sharp waves superimposed on a depressed background) are seen and which may lateralize to one hemisphere.

MRI has been recently shown to aid in diagnosis of CJD. MRI demonstrates signal alteration in the basal nuclei, occipital lobes (Heidenhain variant), and the cortical ribbon. Restricted diffusion is seen very early in disease, whereas signal alterations are later seen on T2-weighted images and fluid-attenuated inversion-recovery (FLAIR) sequences.68-70 In nvCJD, increased signal is seen in the pulvinar nuclei of the thalamus.71 A recent study showed that the sensitivity and specificity of MRI for the diagnosis of sCJD is 63% and 88%, respectively.72 In this study, Meissner et al72 also found that typical MRI findings occur only with certain PrPSc genotypes (those with methionine or valine homozygosity).
Spongiform changes are seen across all the layers of the cerebral cortex. Spongiform changes can be diffuse or localized in basal nuclei, cerebellum, and cerebral cortex. In Heidenhain variant, spongiform changes predominate in the visual cortex; in nvCJD, the occipital and frontal lobes are primarily involved. nvCJD is distinct in that these changes are also present in the thalamus, possibly accounting for sensory symptoms. Neuronal loss and astrocytosis is seen in areas of spongiform change. The hippocampus is relatively spared in the process. Florid plaques are characteristically seen in nvCJD, whereas amyloid plaques may be seen in all forms of CJD. Immunohistochemistry for PrPSC is positive in all forms of CJD. In nvCJD, PrPSC immunostaining is seen in peripheral tissues, such as the tonsils, thymus, retina, and adrenal glands.

TREATMENT

There is no effective treatment for CJD available to date. However, various agents are under currently investigation, including quinacrine, chlorpromazine, and pentosan polysulfate.

CASE DISCUSSIONS

A PATIENT WITH DECLINE FROM PREVIOUS FUNCTIONING

Initial Presentation

The patient, a 66-year-old woman who works as a part-time substitute teacher, presents to her primary care physician with the complaint of “forgetting things.” She reports difficulty remembering names, even of her colleagues. She continues to drive a car, perform daily household activities, and manage finances without apparent difficulty. Her husband confirms some decline in short-term memory evident in the patient’s increased reliance on notes and repetition of conversations. The patient also spends more time preparing for school and has become apprehensive about teaching. No changes in instrumental activities of daily living (IADL) or activities of daily living (ADL) are reported. She has hypertension and mild diet-controlled diabetes. Family history is significant for dementia in both maternal grandparents.

Physical examination is normal. The patient’s MMSE score is 27/30; she misses 2 points on delayed recall and 1 point on orientation. Language fluency and comprehension are normal with no difficulty naming low-frequency words; no apraxia is noted. No difficulty interpreting proverbs or drawing a clock face is noted. Remaining neurologic examination is normal.

Case Discussion

This patient presents with a subjective memory complaint confirmed by her husband. Her MMSE score of 27 is within the low-normal range for her age and education level and suggests memory deficit, especially in context of missing 2 points for delayed recall.

The median MMSE score for college-educated patients age 65 to 69 years is 29/30. Decline from previous functioning noted by the patient and particularly by family members should never be disregarded as normal aging without further investigation. This patient’s condition may be characterized as amnesic MCI; however, further formal neuropsychological testing is needed to more sensitively assess overall cognitive function, particularly in the context of her relatively high education level and pre-morbid level of intellectual functioning.

Subsequent Presentation

The patient returns for follow-up 6 months later. She has retired from teaching. Her husband reports that she has been lost a few times since her last visit and has had difficulty with finances. She seems more socially withdrawn and is not interested in visiting friends. Her MMSE score is now 23 versus her previous score of 27. She has difficulty drawing a clock face and is able to name only 10 animals in 1 minute (normal 1-minute category fluency for this age group is 16 unique items). She also has anomia for low-frequency words and had difficulty with praxis maneuvers.

Discussion

The patient is now having problems with other cognitive domains in addition to memory. She has difficulty with executive function, language, visuospatial skills, and praxis. Based on her history of an insidious onset, slowly progressive course, and decline in memory and other cognitive functions, the diagnosis of probable AD is made.

A PATIENT WITH PROGRESSIVE COGNITIVE DECLINE, GAIT DISTURBANCE, AND HALLUCINATIONS

Initial Presentation

A 59-year-old man presents to a neurologist with a 2-year history of progressive cognitive deterioration and progressive gait disturbance leading to occasional falls. The patient’s levels of alertness and attention to his surroundings vary from complete lucidity to disorientation. He has visual hallucinations initially described as illusory phenomena at periphery of his visual field; he now reports seeing small elves as well as animals that are clearly not present. He denies tremor but reports slow movement and generalized weakness. His medical
history is unremarkable and family history is negative for neurodegenerative disorders. He has no prior history of depression, orthostasis, or urinary incontinence. Neurologic examination reveals that the patient has significant difficulty following instructions. Mild limb rigidity without tremor, decreased arm swing, slow narrow based gait, stooped posture, and hypophonic dysarthria are noted.

Case Discussion

This patient presents with a 2-year history of fluctuating attention, cognitive impairment in several domains, hallucinations, falls, and hypokinetic extrapyramidal signs. Although delirium should be considered in patients with fluctuating attention, the course of this patient’s disease and presence for extrapyramidal signs are more suggestive of DLB.

A PATIENT WITH RAPIDLY PROGRESSIVE COGNITIVE DECLINE

Initial Presentation

A 56-year-old man with a 5- to 6-month history of progressive memory problems and language disturbance is referred to a neurologist for evaluation. He has a 15 pack-year history of smoking and consumes 4 to 5 alcoholic beverages each week. Initial symptoms included a tendency to repeat himself, word substitutions (paraphasic errors), and difficulty with driving directions. Two months after symptom onset, he lost his job as a car salesman because of poor job performance. Approximately 1 month later, he became increasingly agitated, tremulous, withdrawn, and confused.

Physical examination shows normal vital signs. Turning on the overhead light or subjecting the patient to a loud sound produces a synchronous jerk in all limbs. The patient has mild expressive aphasias with difficulty in naming and fluency. He is able to follow simple commands. Cranial nerve examination is unremarkable. Motor examination shows mild diffuse paratonia, but normal muscle strength and bulk. Sensory examination is difficult to assess. Coordination testing reveals a low-amplitude, symmetrical action tremor. The patient is unable to ambulate independently because of poor postural stability.

Case Discussion

For a patient presenting with rapidly progressive dementia with extrapyramidal signs, both treatable/partially reversible causes of dementia (Table 2) and prion disease should be considered. The American Academy of Neurology practice parameter recommends the following minimum work-up for patients with dementia: complete blood counts; electrolyte levels; liver function and renal function tests; thyroid-stimulating hormone, vitamin B12, and folic acid levels; and cerebral imaging studies (preferably MRI). VDRL and rapid plasma reagin assays for syphilis are no longer recommended routinely.

Diagnostic Evaluation

Results of laboratory studies as just noted are normal in this patient; however, brain MRI shows restricted diffusion in the caudate, basal nuclei, and cortical ribbon of the left hemisphere. Similar changes are seen on

| Table 2. Potentially Treatable and Preventable Causes of Dementia |
|------------------|------------------|
| Infections       |                  |
| HIV              |                  |
| Chronic viral, bacterial, fungal or mycobacterial meningitis |
| Spirochetes: neurosyphilis, Lyme disease |
| Whipple’s disease |
| Neurosarcoaidosis|
| Depression       |                  |
| Normal-pressure hydrocephalus |
| Space-occupying lesions |
| Drugs and toxins |                  |
| Alcoholic dementia syndrome |
| Heavy metal poisoning |
| Traumatic brain injury |
| Cerebrovascular disease |
| Organ failure (hepatic, renal) |
| Nutritional deficiencies |          |
| Vitamin B12 deficiency |
| Thiamine deficiency |
| Niacin deficiency (pellagra) |
| Vitamin E deficiency |
| Metabolic disorders |          |
| Hypothyroidism |
| Hypo- or hypercalcemia |
| Addison’s disease |
| Inborn errors of metabolism (metachromatic leukodystrophy, Wilson’s disease) |
| Mitochondrial diseases |
| Hashimoto’s encephalopathy |
| Paraneoplastic syndromes (limbic encephalitis) |
| Multiple sclerosis |
Although neurodegenerative dementias are current-

In all cases of dementia, investigations for less com-

In AD, formation of new memories is almost always

dysfunction and language disorders are more fre-

Patients with MCI are at significantly increased risk

Early symptoms of a dementia syndrome reflect the
cortical or subcortical location of pathology.

In AD, formation of new memories is almost always


