As the population is aging, the burdens of Alzheimer disease (AD) and other dementias are substantial on the economy and society. Currently, there are approximately 5.8 million people age 65 or more in the US living with AD, the most common etiology of dementia. This number is expected to increase to 13.8 million by the midcentury.1

Diagnosis

There are many etiologies of dementia (Table 1), and diagnoses of the degenerative dementias are based on clinical criteria (Table 2).2–4 The goal of the diagnostic process is to make a specific diagnosis, stage the disease, and identify any systemic illnesses, psychiatric conditions, or delirium that might be contributing. Ruling out other disease processes supports the specific diagnosis. The earlier the diagnosis is made, the greater the benefit in managing the illness.5

A comprehensive history from the patient and a knowledgeable informant, a neurologic examination, an objective neurocognitive assessment, and a formal neuropsychologic evaluation are essential when the diagnosis cannot confidently be made by history and routine assessment alone. For AD, the National Institute on Aging-Alzheimer’s Association (NIA-AA) established clinical criteria that defines it as clinical syndrome with biomarkers for amyloid and neurodegeneration.2 The most recent version of the framework from 2018 defines AD as a biologic entity defined by positive biomarkers for amyloid and tau, and defines the clinical spectra independently.6

Demographics

Age at onset of dementia and estimated disease duration at the time of diagnosis are determined with information provided during the in-person assessment by patient and a knowledgeable informant. Most people with dementia are age 65 or more. Early-onset dementia is defined by age of onset at less than 65.7,8 Women have a higher incidence of dementia compared to men, which has been ascribed to the fact that women have tendency to live longer.9 There is also higher prevalence of dementia in minoritized racial and ethnic groups in the US.1 Individuals with low levels of education are at higher risk of developing dementia.10

Cognitive Symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a major neurocognitive disorder, previously known as dementia, is characterized by a significant decline in cognition compared with a previously known

<table>
<thead>
<tr>
<th>Degenerative disorders</th>
<th>Alzheimer disease,2,4 Lewy body dementia spectrum,2 frontotemporal dementia, Huntington disease, tauopathies, amyotrophic lateral sclerosis (ALS), and prion disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular dementias</td>
<td>Multi-infarct,4 diffuse white matter disease (Binswanger’s)4</td>
</tr>
<tr>
<td>Toxic conditions</td>
<td>Alcoholism,4 drug/medication intoxication,2 other toxic disorders</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Vitamin deficiencies (B12, B6, folate, niacin), endocrine disorders (thyroid, adrenal, parathyroid), uremia, hepatic encephalopathy, and cardiopulmonary failure</td>
</tr>
<tr>
<td>Infectious dementias</td>
<td>HIV, syphilis, progressive multifocal leukoencephalopathy (PML), and other chronic infections</td>
</tr>
<tr>
<td>Traumatic conditions</td>
<td>Chronic traumatic encephalopathy and others</td>
</tr>
<tr>
<td>Hydrocephalic syndromes</td>
<td>Normal pressure hydrocephalus</td>
</tr>
<tr>
<td>Psychiatric conditions</td>
<td>Depression, conversion disorder, and others</td>
</tr>
<tr>
<td>Autoimmune/inflammatory conditions</td>
<td>Multiple sclerosis, vasculitis, sarcoidosis, and more</td>
</tr>
<tr>
<td>Cancer or related mass effects</td>
<td></td>
</tr>
</tbody>
</table>

a among the most common causes of dementia
Behavioral and psychiatric symptoms of dementia (BPSD) are common in AD and other dementias (see Behavioral Approaches in Dementia Care in this issue). BPSD are distressing for persons with dementia and their caregivers and can lead to increased mortality, excessive cognitive and functional disability, early institutionalization, and caregiver burnout. The Neuropsychiatric Inventory is a checklist of BPSD that aids in evaluation of people with dementia for delusions, hallucinations, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviors, sleep disturbances, and eating disturbances.

### Medical History

Many medical conditions can contribute to cognitive impairments (Table 1). Some of these conditions may be reversible and or treatable. Individuals with stroke risk factors (eg, high blood pressure, diabetes, dyslipidemia, smoking, or other vascular disease) are at higher risk for vascular dementia. Cognitive impairments can be associated with Parkinson disease (PD), stroke, cancer, HIV infection, autoimmune disorders, depression and mental illness, and all current and past medications used, particularly chronic use of any anticholinergic medication.

### Family History and Genetics Risk Factors

Although having a first-degree family member with AD significantly increases risk of AD, most cases are sporadic and lack the dominant transmission of the disease. Many genes, however, increase the risk of AD. Apolipoprotein E (ApoE) determines age-dependent risk and age of onset of AD in some people and is a major risk factor for AD. ApoE ε4 genotype increases amyloid β (Aβ) aggregation and reduces amyloid clearance. Causative mutations of AD increase Aβ or the Aβ42/40 ratio, including mutations in amyloid precursor protein (APP), including the APP Arctic mutation (protopl

---

**TABLE 2. CLINICAL CHARACTERISTICS OF COMMON DEMENTIAS**

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer disease</th>
<th>Frontotemporal dementia</th>
<th>Lewy body dementia</th>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>&gt;65</td>
<td>&lt;65</td>
<td>&gt;65</td>
<td>&gt;65</td>
</tr>
<tr>
<td>First changes</td>
<td>Memory problems</td>
<td>Personality change</td>
<td>Fluctuating cognition, visual hallucinations, REM-sleep behavior disorder</td>
<td>Variable, focal neurologic symptoms</td>
</tr>
<tr>
<td>Progression</td>
<td>Insidious onset</td>
<td>Insidious onset</td>
<td>Insidious onset, gradual with fluctuations</td>
<td>Abrupt or gradual, stepwise</td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>Apraxia</td>
<td>Frontal release signs</td>
<td>Parkinsonism</td>
<td>Focal weakness</td>
</tr>
<tr>
<td>Imaging</td>
<td>Hippocampal and generalized atrophy, temporal and parietal hypometabolism</td>
<td>Frontal/temporal atrophy and hypometabolism</td>
<td>Generalized atrophy, occipital hypometabolism</td>
<td>Strokes, lacunar infarcts</td>
</tr>
<tr>
<td>Pathology</td>
<td>Neurofibrillary tangles and amyloid plaques</td>
<td>Tau, transactive response DNA binding protein (TDP-43), Pick cells and Pick bodies in cortex</td>
<td>α-synuclein+ Lewy bodies in cortex</td>
<td>Arterioles with thickened vessel wall</td>
</tr>
</tbody>
</table>
increase), presenilin 1, and presenilin 2. APP gene triplication reduces $\alpha$-secretase activity and drastically increases the risk of AD in people with Down syndrome. On the other hand, there are protective mutations that decrease A\textsubscript{\textbeta} amyloid pathology. They reduce $\alpha$-secretase which reduces A\textbeta aggregation and deposition and thus AD risk (see Genetics of Dementia in this issue).

Social History
A history of drug and alcohol use or smoking can be a risk factor for dementia, making it important to obtain detailed information about the amount and duration of smoking and alcohol use, and any other drugs used in the past and present.

Neurologic Examination
A thorough physical and neurologic exam is necessary and should include evaluation for signs of focal deficits, parkinsonian symptoms, abnormal movements, gait and balance disturbances, apraxia, frontal release signs, neglect, and other perceptual disturbances.

Cognitive, Behavioral, and Functional Assessments
Mental status examinations are not diagnostic by themselves but are an essential tool for diagnosis. They provide information on specific cognitive domains abilities. Baseline and longitudinal assessments are critical for monitoring the progression of the disease.

Many office-based multidomain mental status examinations that take 10 to 15 minutes to complete may be used including the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Self-Administered Gerocognitive Examination (SAGE). The self-administered feature of SAGE may promote cognitive testing by busy primary care and neurology clinicians for persons complaining of memory loss and lead to earlier diagnosis and treatment.

Longer instruments for use in clinical settings usually cover the same cognitive domains but in greater detail. A battery that takes approximately 45 to 50 minutes to administer is the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery. Standardized neuropsychologic testing typically takes 2 hours to complete. Standardized questionnaires assessing function, mood, and behaviors such as activities of daily living scales and the Neuropsychiatric Inventory also help with early diagnosis and treatment (see Neuropsychologic Approaches to Dementia in this issue).

Diagnostic Testing
Laboratory Studies
Laboratory tests can help rule out reversible causes of dementia, including vitamin B\textsubscript{12} and thyroid impairments. Routine evaluations including a complete blood count (CBC), electrolyte panel, and creatinine, blood urea nitrogen (BUN), calcium, and glucose levels check for metabolic abnormalities. HIV, syphilis, and other infections that can cause dementia should also be ruled out in appropriate settings.

Neuroimaging
Either noncontrast CT or MRI is recommended as part of the initial evaluation for dementia. Typically, brain MRI is preferred over CT to evaluate for strokes, tumors, and other structural lesions that can produce cognitive changes. In early stages of AD, hippocampal atrophy is often seen, whereas occipital and frontal atrophy is more likely in dementia with Lewy bodies, and frontal and anterotemporal atrophy is more likely in FTD. Persons with vascular dementia have significant microvascular changes. When available, volumetric MRI can quantify the volume loss by comparison to same age and sex referents and measure atrophy longitudinally.

Fluorodeoxyglucose (FDG)-positron emission tomography (PET) can be used to measure metabolism in the brain, help differentiate AD from other causes of dementia, and predict the progression from mild cognitive impairment (MCI) to AD. In FTD, there is decreased metabolism in the frontal lobes and at times in the anterior temporal lobes. With Lewy body dementia there is typically decreased metabolism in the occipital lobes. A dopamine transporter (DAT) scan can be useful to evaluate patients with parkinsonian syndromes. Brain amyloid PET imaging and brain tau PET imaging are still mostly research tools to identify amyloid and tau burden in AD and are very hard to incorporate in clinical practice so far because of insurance coverage and cost issues.

Other Tests
EEG can rule out seizure activity that can cause cognitive changes and reveal diffuse slowing in the case of metabolic disease or the periodic slow wave discharges of Creutzfeldt-Jakob disease (CJD). Cerebrospinal fluid (CSF) analysis may reveal a CNS infection or inflammation as a possible cause of rapidly progressing dementia. It may be useful to obtain cytology, autoimmune encephalitis panel, real-time quaking-induced conversion (RT-QuIC) test, prion panel, or 14-3-3 protein levels if CJD is suspected. If AD is suspected, A\textbeta and tau protein levels should be ordered. If pseudotumor cerebri is suspected, obtain opening and closing CSF pressures, and if normal pressure hydrocephalus is suspected, perform a high-volume lumbar puncture.

Management
Social and family support is crucial for persons with dementia, and it is important to know if they live by themselves and are able to continue doing so. If they live with others, it is important to ask if those individuals are able to provide care if needed. It is important to identify the psychosocial needs of
the person with dementia and their family and primary caregivers and to plan for the future including advance directives (see Dementia Caregiver Needs in this issue).

Pharmacologic Treatments

At this time, there is no treatment for neurodegenerative dementia that slows progression or is curative. Several medications, however, can alleviate cognitive and behavioral symptoms (Table 3).27,28 Cholinesterase inhibitors increase brain acetylcholine levels by interfering with its degradation and are indicated in AD.26 There is also some evidence that cholinesterase inhibitors are useful for other dementias (ie, Lewy body dementia and vascular dementia).30,31 Cholinesterase inhibitors and memantine, an N-methyl d aspartate (NMDA) receptor agonist/antagonist are approved by the Food and Drug Administration (FDA) for management of AD. Different medications are used to treat behavioral symptoms of dementia (eg, antidepressants and antipsychotics). Other medications are also used to treat behavior symptoms (see Behavioral Approaches in Dementia Care in this issue).

Lifestyle Modifications

Compelling evidence suggests regular exercise, particularly aerobic, reduces risk of dementia and may even improve cognitive networks as measured by functional MRI.32 The Mediterranean diet and a variant of it termed the Mediterranean-DASH Interventions for Neurodegenerative Delay (MIND) have been associated with better cognitive function. The MIND diet incorporates the Dietary Approaches to Stop Hypertension (DASH) diet, which includes consumption of fruits, vegetables, whole grains, legumes, fish, and unsaturated fats. Persons with dementia may also benefit from cognitive stimulation.33 Better control of hypertension and dyslipidemia may also delay the onset of AD and prevent worsening of vascular dementia.35

Conclusion

Early diagnosis is possible by screening individuals age 65 or more who have cognitive complaints and referring to the neurologist for evaluation and management when impairments are found. Earlier diagnosis may have clinical benefits, alleviate patient and caregiver burden, reduce hospitalization time, and delay admission to nursing homes.35 Goals of care include establishing an early and accurate diagnosis of dementia, evaluating for all treatable and reversible causes of memory loss, obtaining labs and structural or functional imaging of the brain to evaluate for causes of dementia, initiating appropriate cognitive and behavioral management, educating the caregiver in behavioral modification techniques, and providing appropriate counseling and education to the patients and families throughout the course of the disease. Referral to clinical trials for disease-modifying and symptomatic treatments is also encouraged.


(Continued on page 40)
(Continued from page 30)


