There is some evidence that AD is more common among women, although study results are conflicting. In population-based studies, more than half reported a greater risk of AD in women, while the others found no difference. Some data support that estrogen deficiency following menopause may contribute to the development of AD; however, the effect of hormone replacement therapy on cognition remains controversial. The discrepant findings between studies assessing sex-based variations in dementia risk are likely due to methodologic differences in accounting for potential gender-related variability in life-expectancy, education, occupation, and lifestyle factors that can directly affect AD risk.

PATHOPHYSIOLOGY

Genetics of Alzheimer Disease

Based on the onset of symptoms, AD is normally divided into two groups: younger-onset (< 65 years) and late-onset (> 65 years) disease. Younger-onset patients include individuals with familial AD which accounts for between 1% and 5% of all AD cases and to date has been linked to mutations in the genes for the APP (gene name *APP*) on chromosome 21, presenilin 1 (PS1; gene name *PSEN1*) on chromosome 14, and presenilin 2 (PS2; gene name *PSEN2*) on chromosome 1. Among these genes, more than 250 different mutations have so far been identified, accounting for approximately 40% of all cases of familial AD, yet only 0.5% of AD cases overall. Most of the mutations (~ 200) are found in the *PSEN1* gene and account for 78% of the familial AD mutations. *APP* mutations (~ 33) account for about 18% of younger-onset autosomal dominant cases and *PSEN2* (~ 22 mutations) for about 4%. Familial AD is characterized by younger onset of cognitive symptoms (typically in the late 40s or early 50s), but is clinically indistinguishable from late-onset AD.

Late-onset AD, also called sporadic AD, accounts for greater than 95% of all cases of the disease. *APOE* is the only established susceptibility gene consistently found associated with late-onset AD in both case-control and genetic studies. *APOE* maps to chromosome 19 in a cluster with the genes encoding translocase of outer mitochondrial membrane 40 (*TOMM40*), apolipoprotein C1, and apolipoprotein C2. The *APOE* gene exists as three major alleles (ε2, ε3, and ε4) that encode three different ApoE isoforms: ApoE2, ApoE3, and ApoE4. Interestingly, these isoforms only differ in

amino acid sequences at either position 112 or 158 of the protein. The inheritance of the ε4 allele confers an increased risk for developing AD, while the ε2 allele confers protection. For example, presence of one copy of the ε4 allele increases risk of AD fourfold, whereas inheritance of two copies enhances the risk by 12-fold. However, unlike genetic mutations associated with familial AD, the presence of *APOE* ε4 alone is insufficient to cause AD without additional factors. Even though the first report of an association between *APOE* ε4 and AD was published decades ago, the precise molecular mechanisms underlying this association still remain elusive. It is currently unknown if the *APOE4* allele influences the rate of production, clearance, or aggregation of Aβ peptide or whether it influences cholesterol metabolism and inflammation that reportedly play a major role in the pathobiology of AD.

With the advent of genome-wide association studies (GWASs), a number of new genetic loci with genome-wide significance have been identified. In addition to *APOE4*, more than 40 other polymorphisms have been associated with increased risk for late-onset AD. However, none of these associations has been uniformly confirmed in every population group studied to date. Over 20 genetic loci have been associated with late-onset AD, leading to four main mechanisms: Aβ metabolism, lipid metabolism, immune response, and cell signaling. Further research is needed to clarify the impact of other genetic changes on AD risk, genetic-environmental interactions, and the impact of such genetic factors on mechanisms of neurodegeneration and neuroprotection.

Neuropathology of Alzheimer Disease

The neuropathologic hallmarks of AD include amyloid plaques, neurofibrillary tangles, and neuritic plaques (**Figure 59-1**). The latter are a subset of amyloid plaques that are closely associated with neuronal injury and occur with dystrophic neurites. Cerebral amyloid angiopathy (CAA) frequently co-occurs with amyloid plaques, resulting from deposition of Aβ into cerebral vessels. Sporadic CAA is observed in 80% to 90% of AD patients and may cause lobar intracerebral hemorrhages and microbleeds. Together these processes contribute to loss of neurons and synapses in the neocortex, hippocampus, and other subcortical regions of the brain. The predominance of amyloid plaques versus neurofibrillary tangles or amyloid angiopathy can differ from one patient to another. However,

neuronal/synaptic loss is a constant feature and eventually the direct cause of dementia. The distribution of the disease pathology seems to follow a region-specific pattern with amyloid plaques being more prevalent in the neocortex and neuronal/synaptic loss being more prevalent in the hippocampus, posterior cingulate, and corpus callosum—areas of the brain closely involved with memory formation and higher cortical activities. Finally, brains of persons with AD are also characterized by a diffuse and widespread invasion of reactive astrocytes, mostly concentrated in the hippocampus and around areas of neuronal loss. These astrocytic changes are not specific to AD and can be observed in other neurodegenerative disorders associated with inflammation and neurotoxic insults.

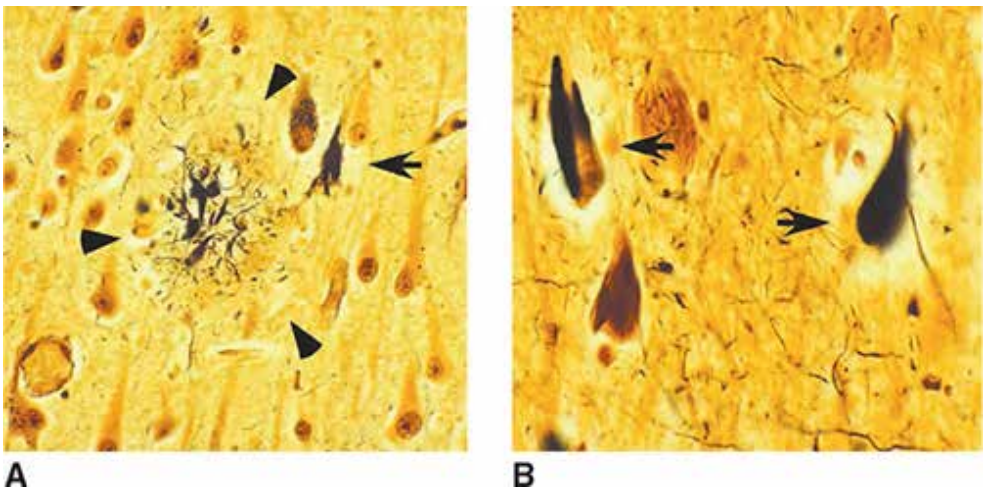

FIGURE 59-1. Small section of the neocortex from a patient with Alzheimer disease showing two classical neuropathologic lesions of the disease. **A.** The modified silver staining shows one dense senile (amyloid) plaque indicated by three arrowheads. The plaque consists of aggregated extracellular deposits of amyloid β-peptide (Aβ) fragments surrounded by silver-positive dystrophic neurites. The arrow indicates a neuron containing neurofibrillary tangles, which appear as dark masses of abnormal filaments occupying most of the cytoplasm. **B.** The image shows higher magnification of two neurons containing neurofibrillary tangles (*indicated by arrows*). (Reproduced with permission from Shahriar Salamat, MD, PhD, University of Wisconsin School of Medicine and Public Health, Department of Pathology and Laboratory Medicine.)

The dominant component of the amyloid plaque core is Aβ organized in fibrils of approximately 7 to 10 nm intermixed with nonfibrillar forms of the peptide. Neuritic plaques are characterized by a dense core of aggregated fibrillar Aβ, surrounded by dystrophic dendrites and axons, activated

microglia, and reactive astrocytes. In addition, diffuse deposits of Aβ, likely representing a prefibrillary form of the aggregated peptide, are found without any surrounding dystrophic neurites, astrocytes, or microglia. These diffuse plaques can be found in limbic and association cortices, as well as in the cerebellum.

The other neuropathologic hallmark of AD is the presence of neurofibrillary tangles found exclusively in the cytoplasm of neurons (see **Figure 59-1**). The tangles appear as paired, helically twisted protein filaments composed of highly stable polymers of cytoplasmic proteins called tau. Tau comprises a group of alternatively spliced proteins found in the cytoplasm that possess either three or four microtubule-binding domains and can assemble with tubulin, thus helping the formation of cross bridges between adjacent microtubules. Tau proteins can be phosphorylated in multiple sites, and the degree of phosphorylation is inversely correlated with binding to microtubules. As a result, highly phosphorylated tau proteins dissociate from microtubules and polymerize into filaments forming neurofibrillary tangles. In addition to AD, the abnormal accumulation of filamentous tau is observed in frontotemporal forms of dementia, progressive supranuclear palsy, corticobasal degeneration, and Pick disease. Contrary to prior belief, tau proteins themselves can cause dementia, and multiple mutations in the *tau* gene have been found in frontotemporal dementia (FTD) with parkinsonism. The precise role of tau proteins in the pathogenesis of AD and their potential interaction with Aβ are still unclear.

In 2012, NIA and the Alzheimer's Association published revised criteria for AD neuropathologic change. These criteria recommended reporting on the presence and extent of hallmark lesions for AD observed at autopsy independent of the individual's cognitive state. These new guidelines took into account several well-established neuropathologic scoring criteria and integrated them into an "ABC score" based on three parameters (*A*myloid, *B*raak, *C*ERAD): criterion "A" ranks the Aβ plaque score (based on criteria from Thal et al.), criterion "B" measures the neurofibrillary tangle stage (modified from Braak criteria), and criterion "C" assesses the neuritic plaque score (modified from the Consortium to Establish a Registry for Alzheimer Disease [CERAD]). For reporting, these ABC scores are then transformed into one of four levels of neuropathic change: none, low, intermediate, or high. While CAA is not considered in the "ABC" score, the guidelines recognize that these changes frequently co-occur with

parenchymal Aβ plaques and recommend neuropathologists comment on such changes separately within the neuropathology report.

Amyloid Precursor Protein Processing and Generation of Aβ

Aβ is a 39 to 43 amino acid hydrophobic peptide proteolytically released from a much larger precursor, APP. Although APP is the major source of toxic Aβ, it also exerts several important functions in the nervous system, including serving as a cell-surface receptor, growth factor, protease inhibitor, cell–cell interaction molecule, coreceptor/partner in the endocytic/lysosomal network, coagulation inhibitor factor, cell-surface scaffold protein, kinesin-interacting molecule for axonal transport, and transcription factor. The generation of Aβ from APP (**Figure 59-2**) requires the sequential recruitment of two enzymatic activities: β-secretase, also called BACE1, and γ-secretase, a multimeric protein complex containing presenilin, nicastrin, Aph-1, Pen-2, and CD147. The β-cleavage is the rate-limiting step and occurs before the γ-cleavage. It liberates a large N-terminal fragment of the protein (sβAPP) that is released in the extracellular milieu and a small (~12 kDa) membrane-anchored fragment called β-APP-CTF (or C99). The release of the large N-terminal domain allows subsequent γ-cleavage, and liberation of Aβ and the signaling of active intracellular domain (AICD) of APP (see **Figure 59-2**). Generation of Aβ40 and Aβ42 results from γ-cleavage of Aβ at positions 40 and 42, respectively. The release of Aβ in the extracellular milieu is followed by oligomerization and aggregation in the form of fibrils and amyloid plaques. Additionally, small Aβ aggregates are also found in the soma of the neurons suggesting that the Aβ fragments can escape secretion and aggregate in the intracellular environment. The molecular mechanisms underlying the toxicity of Aβ are still being investigated and currently incompletely understood. However, research seems to indicate that small Aβ aggregates (oligomers), which represent the “preplaque” neurotoxic species of Aβ, act as the proximate cause of neuronal injury and synaptic loss associated with AD. Additionally, the C-terminal tail of APP can undergo further processing at amino acid 664 of APP695 liberating two small cytosolic fragments, Jcasp and C31. Both of these fragments are generated only after γ-cleavage, require caspase-mediated processing of APP, and can activate proapoptotic pathways in a variety of cellular systems.

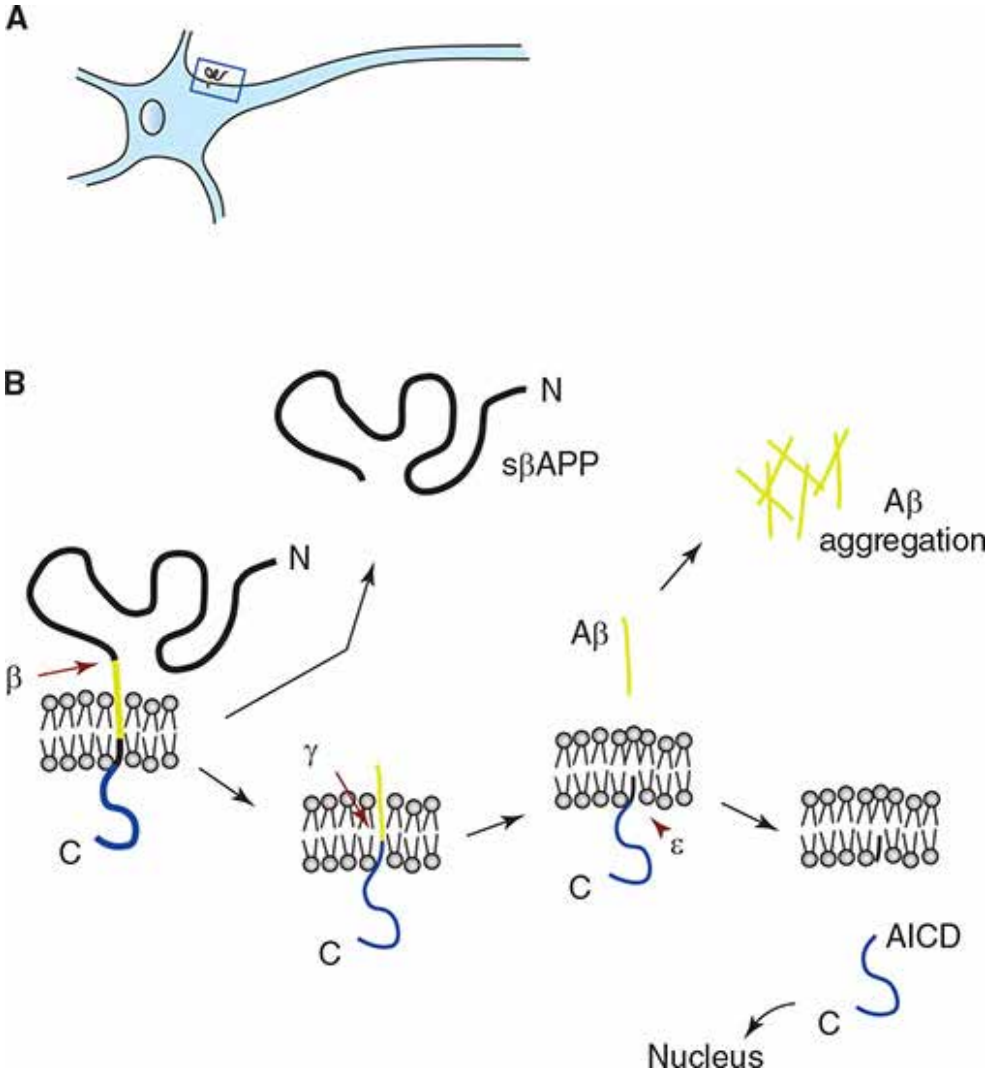

FIGURE 59-2. Generation of amyloid β-peptide (Aβ) from amyloid precursor protein (APP). APP is a type 1 membrane protein with a large extracellular domain, a single membrane-spanning domain, and a short cytoplasmic tail. The Aβ region of APP (*in yellow*) includes the first 12 to 14 amino acids of the membrane domain. (**A**) Shows a schematic image of APP on the cell surface of a neuron, whereas (**B**) provides a closer view of APP processing. The initial enzymatic step for the generation of Aβ requires proteolysis of APP at β-site (amino acid 1 of the Aβ region). This event liberates a large N-terminal fragment (sβAPP) that is rapidly secreted into the extracellular milieu and a small C-terminal fragment (β-APP-CTF) of 99 amino acids (also called C99). The removal of sβAPP most likely induces a conformational change that allows subsequent cleavage by γ-secretase. Once generated, the Aβ peptides aggregate in the brain in the form of plaques. Further cleavage of β-APP-CTF at the site liberates the signaling active APP intracellular domain (AICD). In addition to the above β/γ pathway, APP can also be cleaved at the α-site (between amino acids 16 and 17 of the Aβ region) precluding the generation of Aβ.

The most critical clinical link between Aβ and AD came from the observation that patients with Down syndrome (trisomy 21) had a higher propensity for developing a clinical and pathologic phenotype resembling AD, thereby suggesting a potential association between AD and chromosome 21. This observation was further strengthened by the fact that Aβ was the major component in plaques from both patients with Down syndrome and AD, and that its genesis was related to a gene (*APP*) located on chromosome 21, close to the obligate Down syndrome region. Following the identification of APP, several groups found mutations in the *APP* gene that were linked to familial forms of AD. Given that the duplication of the *APP* locus could result in early AD and that Down syndrome patients with partial trisomy 21 developed AD only when the trisomy was proximal to the *APP* locus, the potential direct relationship between APP metabolism and AD seems strong. Furthermore, causative mutations in the genes that encode for PS1 and PS2, which are also implicated in the metabolism of APP, have been found and are associated with familial forms of AD, thereby conferring additional strength to the linkage between APP/Aβ metabolism and AD.

Although the generation of Aβ from APP seems to be a pivotal step in the pathobiology of AD, it does not explain all the neuropathologic changes observed in patients with AD. For example, examination of the brain of transgenic mice expressing human APP harboring one or more familial AD-associated mutations reveals the presence of amyloid plaques and some synaptic loss and cognitive deficits, but absence of tau pathology and astrocytosis. This suggests that additional biochemical/molecular events are required to develop the full pathologic spectrum of AD. To circumvent this issue, several new animal models have been generated where human APP is accompanied by additional genes. These genes include the *presenilins* (harboring familial AD-associated mutations), *tau*, and *APOE*. Recently, several transgenic mice models harboring three or five familial AD-associated mutations (respectively called 3X and 5X mice) in two or more genes have been generated. All of these models demonstrate that Aβ is an essential element for the development of AD-like neuropathology and revealed a close relationship between Aβ and the phosphorylation/aggregation state of tau. However, none of the mouse models fully reproduce the classical AD phenotype, thereby again suggesting that Aβ seems to be necessary but not sufficient to produce the entire spectrum of AD neuropathology. Transgenic mice expressing the human microtubule-

associated protein tau develop the typical tau-related pathology found in individuals suffering from FTD with parkinsonism; however, they do not develop amyloid plaques, suggesting that tau is not required for the formation of plaques. Crossing these mice with APP transgenic mice potentiates tau-related pathology and neuronal loss but does not aggravate plaque pathology, suggesting that Aβ acts upstream of tau in the classical AD phenotype. However, studies from patients with AD, mouse models, and ex vivo cellular systems indicate that Aβ and tau can interact synergistically, thereby fostering their respective aggregation and neuronal loss. Thus, the true relationship between Aβ and tau is more complex than previously thought and likely involves additional molecular and biochemical pathways acting upstream of both Aβ and tau production in the AD brain.

CLINICAL PRESENTATION

The most common clinical onset of AD is an amnestic presentation, characterized by slowly progressive memory loss for recent events. Patients with AD frequently have problems remembering recent conversations, dates, appointments, and may misplace items. Many patients are not aware of these deficits and are brought to medical attention by their family members or friends. For some patients, memory loss symptoms are first noted by others during a stressful life event, such as the patient's hospitalization or the death of a spouse; however, a thorough interview frequently reveals that the cognitive deficits preceded such an event by months to years. The memory deficits of AD are generally differentiated from those caused by normal aging by the fact that AD-related deficits are progressive and interfere with the individual's usual daily activities. Memory loss leading to a change in functional status is not a part of normal aging and warrants further evaluation.

Nonamnestic presentations of AD are also common and may include prominent initial impairments in language abilities, visuospatial skills, and executive function. As these presentations are less commonly recognized by patients, families, and clinicians alike as being early symptoms related to AD, individuals with nonamnestic presentations are frequently misdiagnosed or experience a delay in diagnosis. In addition to the more common amnestic presentation, nonamnestic presentations are specifically identified in the NIA-AA diagnostic criteria for AD (see **Table 59-1**). Patients who initially present with language impairment frequently will complain of marked word-

finding problems with subsequent progression to paraphasic errors and circumlocution. AD patients with a visuospatial presentation may have prominent deficits in spatial cognition, including poor object and face recognition, an inability to perceive multiple visual elements simultaneously, and difficulty understanding written language. Executive dysfunction is another common initial presenting symptom of AD, leading to impairments in reasoning, judgment, problem solving, and an inability to complete complex demanding tasks. Deficits in concentration and attention frequently occur in patients with AD, but these changes may also be notable in persons with depression, attention deficit disorder, sleep disorders, or adverse medication effects.

As the disease progresses, changes in personality are commonly seen in patients with AD and may include increased passivity, lack of interest, agitation, restlessness, and/or overactivity. AD patients may exhibit increased irritability when confronted with memory loss symptoms, such as when struggling to find a word, being reminded of a prior conversation or event, or searching for a misplaced item. More than 30% of persons with AD develop symptoms of depression, which may be the first clinical presentation of the disease. Early signs of depression in patients with AD include increased irritability, alterations in appetite or sleep, trouble concentrating or making decisions, low energy, social withdrawal, and a decline in physical function. Worsening of behavior and cognitive symptoms in the evening is also common in patients with AD and may be related to changes in circadian rhythm from loss of sunlight.

In the later stages of the disease, individuals may have increased confusion, dysphagia, impaired gait, and repeated falls. In some patients with AD, disruptive behaviors may increase with aggression, agitation, and physical or verbal hostility; in others, these behavioral symptoms lessen with disease progression. The majority of patients become increasingly frail and dependent for self-care and activities of daily living with many patients developing bowel and bladder incontinence. Persons in the late stages of AD may become immobile and bed-bound, which increases their risk of developing pressure sores, malnutrition, and dehydration. The most common causes of death in patients with AD include pneumonia, urinary sepsis, dehydration, pressure sores, fractures, and malnutrition. The median survival period from the time of diagnosis to death generally ranges from 7 to 10 years, although some patients, especially those with familial AD, die earlier.

EVALUATION

For many older patients with cognitive complaints, their evaluation, diagnosis, and management may be effectively completed within a primary care setting. If available, utilization of multidisciplinary team members from nursing, social work, psychology, and/or pharmacy can greatly aid a primary care physician in the diagnosis and management of patients with cognitive concerns. A smaller subset of patients will need more in-depth neuropsychological assessment and clinical evaluation from a dementia specialist. The NIA-AA clinical diagnostic criteria for dementia, AD, and MCI (see **Tables 59-1** and **59-2**) were designed to be used across all clinical settings, including primary care, specialty clinics, and long-term care. The clinical diagnoses of MCI and dementia are primarily ascertained through completion of a focused interview with the patient and an informant who knows the patient well, a thorough review of the patient's medical history and medication use, a comprehensive physical examination, a formal assessment of cognitive function, basic laboratory tests, and neuroimaging (**Table 59-3**). While the differential diagnosis for AD is extensive (**Table 59-4**), a systematic approach to dementia diagnosis can help primary care clinicians identify common confounding medical and psychiatric conditions and medications that can adversely affect cognition. In addition, a structured evaluation may facilitate accurate diagnosis of the most common causes of dementia—AD and AD mixed with vascular dementia as well as predementia syndromes such as MCI. Integrating various established diagnostic criteria, **Figure 59-3** shows a primary care diagnostic algorithm developed to guide clinicians in their assessment of patients with cognitive complaints.

TABLE 59-2 ■ NIA-AA CORE CLINICAL DIAGNOSTIC CRITERIA FOR MILD COGNITIVE IMPAIRMENT

MILD COGNITIVE IMPAIRMENT[a]
The patient, an informant who knows the patient well, or a clinician observing the patient notes a concern regarding a change in cognition in comparison to the patient's previous level.
There is evidence of lower performance in one or more cognitive domains (memory, executive function, attention, language, and/or visuospatial skills) that is greater than would be expected for the patient's age and educational background.
The patient maintains preserved independence in functional abilities, although they may take more time, be less efficient, and make more errors at performing such activities than in the past.
The patient does ***not*** meet criteria for dementia.

[a]DSM-5 "mild neurocognitive disorder" criteria also state that these deficits do not occur exclusively in the context of a delirium or other mental disorder (eg, major depressive disorder, schizophrenia). Identification and exclusion of other neurologic, psychiatric, and medical disorders is implied in the text of the NIA-AA MCI diagnostic criteria.

Modified with permission from Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 2011;7(3):270–279.

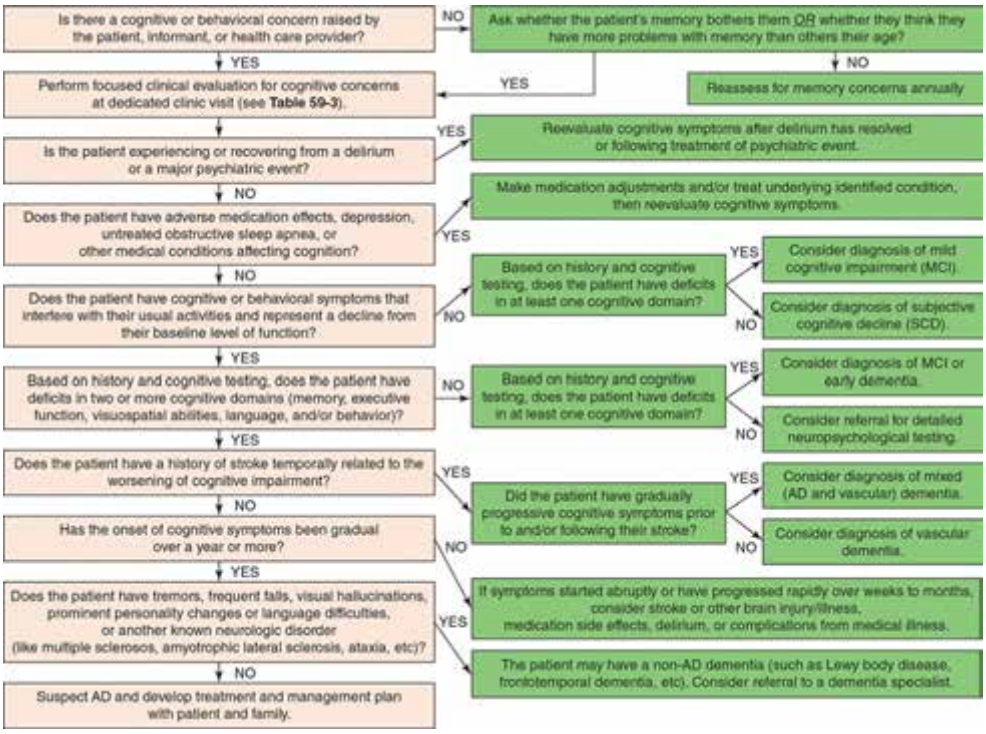

FIGURE 59-3. Algorithm for the clinical diagnosis of Alzheimer disease.

Identification of a cognitive concern is the first step in the evaluation. While early cognitive changes in some patients may be readily identified by the individuals themselves, their families, and/or their clinicians, such symptoms may not be as apparent in other patients due to a variety of factors, including poor insight, attribution of such changes to normal aging, cultural views of dementia, or lack of corroborative history from others. Whether all older adults should undergo routine screening for dementia remains controversial. The US Preventive Services Task Force recommends against routine screening for dementia in asymptomatic older adults based on insufficient evidence that such widespread screening impacts individual or societal outcomes. However, the US Medicare Annual Wellness Visit requires that clinicians assess cognitive function by "direct observation," although no cognitive screening tool is endorsed. In an effort to operationalize the Medicare Annual Wellness Visit requirements, the Alzheimer's Association recommends using self-reported memory concerns, clinician observations, or concerns from a person who knows the patient well to trigger a formal memory assessment. Screening questions such as "Does your memory bother you?" or "Do you think your memory is worse than others of your age?" also may be used to determine which older patients

need a formal evaluation of cognitive performance. Identifying memory concerns through self-report or screening questions may reduce the number of unnecessary formal cognitive screening tests administered to asymptomatic adults at low risk for dementia. However, individuals without a close informant may need structured cognitive tests to identify memory concerns. When a cognitive concern is identified, a separate clinic visit should be arranged to investigate the underlying cause (see **Figure 59-3** and **Table 59-3**).

TABLE 59-3 ■ EVALUATION OF THE PATIENT WITH COGNITIVE CONCERNS

History of cognitive changes
Primary symptom(s) at onset (memory loss, language/spelling errors, impaired reasoning, difficulties in multitasking, personality changes, etc)
Date of onset and time course of cognitive decline (gradually progressive, stepwise, fluctuating, abrupt, rapidly progressive, etc) and whether or not it was associated with delirium
Past and present function at higher level tasks (including tasks at work, hobbies, daily household chores including instrumental activities of daily living [IADLs])
Safety concerns (medication management, driving, kitchen safety, use of firearms or heavy equipment, wandering, financial scams, etc)
Other associated symptoms (depression, tremor, frequent falls, visual hallucinations, stroke and/or transient ischemic attack symptoms, ataxia, urinary incontinence, agitation, personality changes, etc)
Past medical and psychiatric history
Vascular risk factors (including how well they have been controlled over time)
Strokes and/or transient ischemic attacks (assess whether cerebrovascular event was associated with onset of cognitive symptoms)
Atrial fibrillation, carotid artery disease, patent foramen ovale, and/or other risk factors for stroke
Coronary artery bypass surgery (assess whether surgery was associated with onset of cognitive symptoms)
Other major central nervous system (CNS) event (traumatic brain injury with loss of consciousness, anoxic brain injury, postoperative cognitive dysfunction, etc)
Hearing and/or vision loss
Obstructive sleep apnea (including how well it is treated with continuous positive airway pressure [CPAP] or other modalities)
Alcohol or other substance abuse
Depression, anxiety, posttraumatic stress disorder, or other psychiatric illness
Parkinson disease, parkinsonism, amyotrophic lateral sclerosis, or multiple sclerosis
Seizure disorder
History of malignancy with or without prior treatment with chemotherapy
Medication review
Prescription and nonprescription medications and supplements (especially those with anticholinergic or sedating side effects)
Timing of onset of cognitive symptoms with medication/supplement initiation or dose change
Social history
Family, friends, and other social support
Use of community resources (including home aides, senior centers, meal services, etc)
Educational history (including formal years of education and/or technical training, any interruption in schooling or repeated grades, any suspected or diagnosed learning disabilities or attention deficit disorder, etc)
Work history (including types of responsibilities associated with occupation)
Military history (including exposure to combat or blast injuries)
Hobbies and other daily activities
Substance use history (including any prior history of heavy alcohol use)
Family history
History of AD or other dementias (including age of onset of symptoms in affected family members)
History of other neurodegenerative disorders, strokes, psychiatric illnesses, etc
Physical examination
General appearance (attention, comprehension, cooperation, personal hygiene and grooming, social appropriateness, psychomotor slowing, word-finding difficulties)
Mental status (behavior, attitude, mood, affect, insight, judgment, thought content, thought process, speech, language)
Cranial nerves (facial symmetry, visual acuity, pupillary responses, eye movements, visual fields, hearing impairment)
Motor function and integration (strength, tone, cogwheeling, simulation of motor actions to test for apraxia)
Sensory function and integration (sensation to light touch, identification by touch of an object placed in the hand or a number written on the hand, ability to perceive simultaneous bilateral tactile stimuli)
Coordination (rapid alternating movements, finger-to-nose testing, heel-shin testing)
Deep tendon reflexes
Gait

Screening cognitive tests (time to administer)
Mini Mental State Examination (MMSE) (5–10 min)
Montreal Cognitive Assessment (MoCA) (10 min)
Saint Louis University Mental Status (SLUMS) Examination (5–10 min)
Mini-Cog (3 min)
Memory Impairment Screen (MIS) (3–4 min)
General Practitioner Assessment of Cognition (GPCOG) (4 min)
Depression screen
Geriatric Depression Scale—Short Form (GDS-SF) (5–7 min—may be self-administered)
Informant assessment
Eight-Item Interview to Differentiate Aging and Dementia (AD8) (3 min)
GPCOG Informant Questionnaire (2 min)
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (10–15 min)
Laboratory evaluation
Vitamin B_{12}, thyroid-stimulating hormone (TSH), 25-OH vitamin D, complete blood count, glucose, blood urea nitrogen and creatinine, basic metabolic profile, liver enzymes
Neuroimaging
Noncontrast head CT
MRI

Within a dedicated primary care clinic visit, an optimal cognitive assessment includes gathering information not only from the patient's perspective, but also independently in a separate interview from an informant who knows the patient well. Depending on available time and resources, an independent informant interview may be accomplished through utilizing a variety of health care team members, such as social workers, medical assistants, nurses, or psychologists to conduct a brief structured informant interview or a full detailed assessment. Important historical elements include establishing when the cognitive symptoms began and the very first symptoms noted (such as problems with memory, language, executive function, apraxia, or personality changes). A careful delineation of the time course of progression will narrow the differential diagnosis and will help identify whether there are multiple contributing factors or one underlying process. Frequently, an inciting event that disrupts coping skills, such as a hospitalization or the death of a spouse, will draw the attention of family members to a patient's memory problems. The family may give a history of an acute onset of memory impairment following the inciting event, but careful questioning may identify cognitive problems preceding that time period and point to a gradually progressive course.

A key component to the interview is establishing the patient's baseline cognitive and functional performance, taking into account past educational opportunities, estimated baseline intellectual function, occupational history, and prior established skills and abilities. Understanding the patient's

baseline function will put neuropsychological test results into context in order to prevent over- or underdiagnosing dementia in patients who present with cognitive concerns. Changes in the person's ability to carry out tasks related to their occupation, hobbies, household management, and other volunteer activities should then be ascertained.

There are common reversible causes of cognitive dysfunction that next should be addressed. One of the first steps should be a careful review of prescription and nonprescription medications. Drugs with known anticholinergic properties (such as antihistamines, tricyclic antidepressants, bladder antispasmodic agents, etc) or sedating side effects (such as high-dose gabapentin, other antiepileptic medications, narcotic analgesics, benzodiazepines, sleeping aids, etc) should be carefully reviewed to see if the benefit of the offending medication outweighs the adverse cognitive effects. Patients should be included in shared decision-making with any medication adjustments as the value placed on various symptoms is likely to differ between individuals.

Clinicians should carefully evaluate their older patients for depression, anxiety, or other mood disorders that can affect cognitive performance. Depression may be a prodromal syndrome prior to dementia onset, but also commonly co-occurs with this syndrome. Pointed questions assessing for changes in sleep duration and/or quality, interest in activities, feelings of guilt, loss of energy, impaired concentration, changes in appetite, psychomotor slowing, and suicidal thoughts should be assessed. A brief screening tool such as the Geriatric Depression Scale (GDS) can be administered by a health care team member or self-administered while the patient is waiting for the clinician. Older patients with depression frequently complain of problems with poor concentration and forgetfulness and may perform poorly on tests of attention, speed of processing, and memory. In such patients, it is important to differentiate a loss of interest related to depression from a lack of initiative due to a neurodegenerative disorder. Treating depression and anxiety may lead to improvements in cognitive performance as well as mood.

Hearing loss may mimic cognitive dysfunction as patients who cannot hear well may not be able to properly encode new information from conversations or other auditory-received information. Questions on hearing loss symptoms and use and fit of any prescribed hearing aids can alert the provider as to whether hearing loss is contributing to cognitive symptoms or

if further hearing evaluation is needed (see Chapter 34 for approach to screening for hearing loss).

A careful assessment of alcohol use should be completed in all patients, especially if cognitive performance varies widely from visit to visit or if the patient lives alone. Risk for obstructive sleep apnea should be assessed with several screening questions assessing the patient's snoring, witnessed apneic episodes, excessive daytime sleepiness, or nonrestorative sleep. In patients with diagnosed sleep apnea, their ability to effectively and regularly use their continuous positive airway pressure (CPAP) device should be assessed and any difficulties should be reported to the sleep medicine and/or respiratory therapy team to seek out other mask options for better fit and tolerance. Obstructive sleep apnea with its related hypoxia can cause profound effects on cognition.

Vascular disease may contribute to cognitive impairment through a variety of mechanisms. In addition to stroke causing acute cognitive decline, chronic low cerebral blood flow leading to subclinical hypoperfusion may also contribute to cognitive impairment and AD. Thus, a careful assessment of vascular risk factors should be completed to make sure they are well treated. Carotid bruits or a history of sudden cognitive changes should prompt work-up for cerebrovascular disease with neuroimaging (computed tomography [CT] or preferably magnetic resonance imaging [MRI]) and either carotid ultrasound or magnetic resonance angiogram (MRA).

Delirium is associated with an acute or subacute onset of fluctuating cognitive dysfunction and may be caused by a wide variety of medical conditions and medications. In patients with delirium, a careful history frequently can tease out the temporal relationship between the onset of potentially reversible cognitive symptoms and contributing underlying medical problems or medications. Patients who have had a significant medial illness may exhibit signs of delirium for weeks to months following the inciting illness. Care should be made to avoid making a diagnosis of dementia in the presence of a resolving delirium. Since dementia is a risk factor for delirium, however, the presence of a delirium may suggest an underlying neurodegenerative disorder.

Additional information on safety should be obtained, including inquiries on medication management, driving, kitchen safety, use of firearms or heavy equipment or power tools, wandering, and susceptibility to financial scams. A review of systems should include questions on depression, tremors, falls,

visual hallucinations, symptoms of stroke or transient ischemic attack, ataxia, dysphagia, urinary incontinence, waxing and waning level of consciousness, agitation, and personality changes.

The patient's past medical history should be reviewed for medical and psychiatric conditions affecting cognition, including cardiovascular and cerebrovascular disease and associated risk factors, surgical procedures including coronary artery bypass surgery, significant hearing loss, depression, Parkinson disease, TBI, seizures, and/or heavy alcohol use. A thorough medication review should be conducted to assess all prescription and nonprescription medications and the association of any medication initiation and/or dose adjustment with changes in cognitive symptoms. Patients should be encouraged to bring in all pill bottles to the clinic visit. The social history should assess the patient's education and occupational baseline, their social support network, and their use of community resources. An accurate assessment of prior or current alcohol or illicit drug use and a sexual history with special attention to sexually transmitted disease (notably syphilis and HIV) risk factors are critical to a correct diagnosis. An assessment of family history of dementia should include age of onset and time course of any symptoms of family members with memory loss.

The physical examination should include assessment of general appearance and a mental status examination (see **Table 59-3**). Careful observation upon interviewing a patient can provide rich information as to their ability to care for themselves, their organizational ability, their ability to provide detail within their conversation, and their comprehension of posed questions and the appropriateness of their response. Ears should be checked for any cerumen accumulation and/or hearing loss. A neurologic examination should screen for focal deficits, gaze palsies, increased muscle tone, cogwheeling, tremors, and ataxia. A detailed review of a comprehensive mental status and neurologic examination in older adults is described in Chapter 9. Cardiac arrhythmias, carotid bruits, or abdominal or femoral bruits may suggest a vascular contribution. The remainder of the physical examination should focus on ascertaining any major medical conditions that could have significant cognitive effects, such as hypoxia or significant active infection.

While there is no consensus as to which is the best cognitive screening tool, there are a variety of cognitive screening tests that have been validated in a primary care setting. Clinicians should identify several with which they

are comfortable so that they can be used consistently over time with their patient population. The Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Saint Louis University Mental Status Examination (SLUMS) have been widely used in primary care settings. The Alzheimer's Association recommends use of the General Practitioner Assessment of Cognition (GPCOG), the Mini-Cog, or the Memory Impairment Screen (MIS) for cognitive screening related to the Medicare Annual Wellness Visit, as these tests take less than 5 minutes to administer, have good psychometric properties, and can be administered by a variety of health care team members. Informant assessment of changes in patient performance may include the GPCOG informant questionnaire, the Eight-Item Interview to Differentiate Aging and Dementia (AD8), or the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (see **Table 59-3**). If time and resources allow, additional interview time with an informant may identify specific areas of safety concerns and help tailor the management plan.

In adults with high baseline cognitive functions, these screening tests may be normal in the presence of obvious functional impairment necessitating referral to a neuropsychologist for more detailed cognitive testing. In individuals with lower educational levels or learning disabilities, cognitive screening tests may suggest impairment, but the history may not suggest any changes in functional status. Thus, it is critical to use age- and education-adjusted norms, and integrate historical information on baseline function to decide if further neuropsychological testing is warranted or if abnormal testing actually reflects the patient's baseline cognitive performance.

Laboratory data can assist in identifying factors that may be contributing to cognitive decline. Rarely do these factors alone account for the overall cognitive changes that lead to the presentation of a patient with significant memory loss. Nevertheless, treating such factors may improve cognitive symptoms in patients with pronounced laboratory abnormalities, numerous comorbid illnesses, or an underlying neurodegenerative process. Recommended laboratory tests include vitamin B_{12}, folate, thyroid-stimulating hormone (TSH), electrolytes, complete blood count, liver enzymes, and 25-OH vitamin D. If symptoms are atypical or if there are specific risk factors, then an HIV test or serologic test for syphilis may be performed. In patients with assumed heavy alcohol use, thiamine (vitamin B_1) levels should be checked. In some European countries, routine

assessment of cerebrospinal fluid (CSF) for β-amyloid and tau levels is done as part of the clinical evaluation. While CSF β-amyloid and tau levels may increase diagnostic accuracy of MCI and dementia due to AD, in general they are not recommended for widespread clinical practice as in most cases they do not change a patient's management plan. CSF collection may be used in memory specialty clinics, though, to differentiate between different dementias, including Creutzfeldt–Jakob disease, normal pressure hydrocephalus (NPH), or other less-common causes of neurodegeneration (see **Table 59-4**). Genetic testing for *APOE ε4* genotype is not recommended in routine clinical practice. Testing for *PSEN1, PSEN2*, or *APP* genes should be reserved for specialists evaluating cases in which there is a suspicion for familial AD.

TABLE 59-4 ■ DIFFERENTIAL DIAGNOSIS FOR ALZHEIMER DISEASE

DEPRESSION	LEWY BODY DEMENTIA
Adverse medication effects	Vascular dementia/vascular cognitive impairment
Delirium	Frontotemporal dementia
Acute alcohol intoxication	Parkinson disease dementia
Substance use disorders	Progressive supranuclear palsy
Obstructive sleep apnea	Corticobasal degeneration
Other sleep disorders	Prion-related diseases (Creutzfeldt–Jakob, bovine spongiform encephalopathy)
Chronic hypoxia and/or hypercapnia	Normal pressure hydrocephalus (NPH)
Recurrent hypoglycemia	Huntington disease
Thyroid diseases	Alcohol-related dementia
Other metabolic-endocrine disorders	Wernicke–Korsakoff syndrome
Vitamins B_1 (thiamine), B_{12}, and/or D deficiencies	Traumatic brain injury
Uremia	Chronic traumatic encephalopathy (CTE)
Hepatic encephalopathy	Mass lesions (neoplasms, benign tumors, hematomas)
Environmental toxicity (lead, mercury, polychlorinated biphenyls [PCBs], dioxins, etc)	Central nervous system rheumatologic/autoimmune disorders (systemic lupus erythematosus, sarcoidosis, vasculitis, multiple sclerosis, etc)
Lyme disease	Paraneoplastic syndromes
HIV-associated neurocognitive disorders (HAND)	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Progressive multifocal leukoencephalopathy (PML)	Carotid artery disease
Chronic meningitis/encephalitis	Postoperative cognitive dysfunction
Neurosyphilis	Seizure disorder

In patients with documented cognitive impairment, it is recommended that either a CT or MRI scan of the brain be obtained. If neuroimaging was

obtained for another indication prior to the onset of cognitive symptoms, in most cases the patient should be reimaged. Typical findings for AD on neuroimaging can range from a fairly normal scan to focal or diffuse cerebral atrophy. A CT of the head without contrast is usually sufficient to screen for significant cerebrovascular disease, brain tumors, subdural hematoma, or NPH. MRI can provide more information if lacunar infarcts are suspected. MRA may be helpful in identifying significant stenosis that could cause hypoperfusion. In persons with suspected seizure disorder or Creutzfeldt–Jakob disease, an electroencephalogram (EEG) may be considered. Use of fluorodeoxyglucose (FDG) positron emission tomography (PET) and amyloid PET imaging to differentiate FTD from AD should be reserved for specialty clinic use. Tau PET imaging is a novel research tool that is not yet approved for clinical practice.

Formulating a Diagnosis

Once a cognitive concern is recognized and delirium is ruled out, the clinician should identify and document any impaired cognitive domains (such as memory, executive function, language, or visuospatial skills) on cognitive testing and any functional loss in the individual's daily activities. Each potentially reversible cause of cognitive impairment should be outlined (ie, medication side effects, alcohol, sleep apnea, depression, or other medical comorbidities) and a plan to address these conditions should be developed. Objective cognitive impairment in the context of a supportive clinical history plus a decline in the individual's daily functional abilities are key elements necessary to differentiate normal cognitive aging and subjective cognitive decline (SCD) from MCI and dementia. With normal aging, individuals may experience a decline in mental processing speed and may have more difficulty learning new material, but these cognitive changes should not affect their usual function within their daily activities. For example, a healthy older adult may have more difficulty recalling an acquaintance's name or learning a new computer program, but their cognitive testing should be normal and daily functional activities should remain intact. SCD is a term used primarily in research settings to broadly describe symptoms within a pre-MCI stage of neurodegeneration. SCD is currently defined as a self-identified persistent decline in cognitive capacity compared with the individual's previous normal status in a person who still performs in the normal range on standardized cognitive tests. An example would be a business manager with

normal performance on cognitive testing, who has noticed a subjective decline in her efficiency in managing numerous projects simultaneously despite maintaining a similar work load for many years. It is not yet known what percentage of patients presenting with SCD progress on to MCI and eventually AD; however, there is converging evidence that risk for progression to MCI and dementia increases in persons with SCD. Identification of patients with SCD allows clinicians to complete a thorough evaluation for other medical, psychological, and medication factors that could contribute to cognitive decline. Patients with SCD should be screened for cognitive dysfunction annually to evaluate for objective evidence of a decline in cognitive performance.

Once a person with SCD develops deficits in at least one cognitive domain, they may meet criteria for MCI (see **Table 59-2**), a symptomatic predementia syndrome noted in up to 15% to 20% of older adults. Individuals with MCI may present with cognitive complaints and describe a variety of methods they use to compensate for these cognitive changes, such as increasing use of lists, calendars, alarms, and other reminders. They maintain their level of function, but are less efficient in doing so. For example, a cabinetmaker who demonstrates impairment in executive function on testing may complain that in order to complete a cabinet work order with his same level of quality workmanship, it now takes him 2 to 3 weeks, whereas a few years ago he could complete such an order in 1 week. Once an individual's cognitive impairment progresses to the point that they can no longer maintain their baseline level of function, they may meet criteria for dementia. In the previous example, as the cabinetmaker's cognition declines he may no longer be able complete a cabinet order at all or may finish it with poorer-quality workmanship. At that point he may have progressed to a dementia.

Approximately 12% to 15% of persons with MCI will progress each year to AD or other forms of dementia. MCI patients who have impairment in memory performance (single-domain amnestic MCI) or in memory plus another cognitive area (multidomain amnestic MCI) are more likely to progress to AD. Older individuals with nonamnestic MCI may be more likely to progress to other forms of dementia, such as FTD, dementia with Lewy bodies, or vascular dementia. Once a diagnosis of dementia is suspected, the clinician must differentiate between various causes of dementia. AD is the most common form of dementia in the United States, accounting for 50% to

90% of all dementia cases. Dementia with Lewy bodies, vascular dementia, and FTD are other common forms of dementia (**Table 59-5**). Details of the clinical and pathologic features of these dementias are covered in Chapter 63. Differentiating AD from other causes of memory loss can help clinicians choose effective therapies, anticipate behavior changes and other potential complications, and provide patients and caregivers information on prognosis.

TABLE 59-5 ■ CLINICAL FEATURES OF COMMON DEMENTIAS

TYPE OF DEMENTIA	ALZHEIMER DISEASE	VASCULAR DEMENTIA	DEMENTIA WITH LEWY BODIES	FRONTOTEMPORAL DEMENTIA
MUST FIRST MEET DIAGNOSTIC CRITERIA FOR DEMENTIA (SEE TABLE 59-1)				
Typical Course	Insidious onset and gradually progressive	Acute onset of cognitive impairment with some stabilization (if only one vascular event) and/or stepwise deterioration (if multiple infarcts)	Progressive cognitive decline with fluctuating cognition, attention, and alertness	Insidious onset and gradually progressive
Cognitive Symptoms	Memory is the most commonly affected cognitive domain May also have impairments in executive function, language, and/or visuospatial skills	Various cognitive domains may be affected depending on the location of the clinical stroke(s) and/or severe subcortical cerebrovascular disease	Cognitive symptoms may fluctuate May have prominent impairment in visuospatial ability, attention, and/or executive function	Will have early behavioral disinhibition and apathy (frontal lobe predominance) or early prominent language abnormalities (temporal lobe predominance) Deficits are chiefly noted in executive tasks with relative sparing of memory and visuospatial skills
Other Associated Symptoms/ Signs	Some patients may have agitation and/or behavioral changes	May or may not have focal neurologic signs on examination Should have evidence of relevant cerebrovascular disease by brain imaging	May have recurrent well-formed visual hallucinations (usually people or animals), parkinsonism (including tremor, rigidity, and postural instability), recurrent falls and syncope, rapid eye movement (REM) sleep behavior disorder, neuroleptic sensitivity, and/or delusions	In behavioral variant frontotemporal dementia, may have early behavioral disinhibition, apathy, loss of empathy, perseverative behaviors, and hyperorality

If a patient does not meet the criteria for AD yet clinical suspicion remains, the clinician may consider obtaining more detailed neuropsychological testing or repeating screening cognitive testing in 6 to 12 months to clarify the diagnosis as the symptoms become more apparent. Persons with suspected MCI should be reassessed on an annual basis to evaluate for progression to dementia. If the symptoms or course of the disease are atypical for AD, the level of functional decline is out of proportion to neuropsychological testing results, or if there are significant

behavioral issues that need to be addressed, then referral to a geriatrician, neurologist, or psychiatrist with expertise in dementia is recommended.

Future Diagnostic Tools

Novel biomarkers are continually being investigated for use in the diagnosis of AD and other types of dementia, as well as in identifying predementia syndromes. Many of these tools are still used chiefly in research settings, but are being studied to evaluate their potential role in clinical practice. Current investigations are focusing on specific neuroimaging modalities and biomarkers (including blood and CSF) with strong relationships to clinically relevant outcomes that could be used not only for diagnosis of dementia, but also for identifying asymptomatic persons at risk for cognitive decline. Neuroimaging modalities have shown great promise in documenting not only the late effects of neuronal damage in AD (regional and global cerebral atrophy), but also in identifying preclinical pathology (such as in vivo amyloid and tau imaging on PET) and the functional consequences of such pathology (such as changes in activation patterns on functional MRI or glucose uptake on FDG-PET). CSF levels of Aβ and tau have been shown to predict risk for progression to AD in older adults and persons with MCI. With the recent advances in the safety and acceptability of lumbar punctures, CSF markers may eventually find their way into the widespread clinical diagnostic work-up of preclinical AD. Identification of reliable blood biomarkers is a rapidly expanding field with significant clinical applications. Future research is focusing on how novel biomarkers may be used in combination with cognitive tests to identify which individuals are at greatest risk for AD, who would benefit most from preventive therapies, and how effective these therapies are in modifying the underlying disease process in asymptomatic and symptomatic individuals.

Updated NIA-AA Research Framework

As noted earlier, the NIA-AA criteria for AD diagnosis were created in 2011. In April 2018, the NIA-AA released a report proposing a new research framework for studying AD that served to update the 2011 guidelines with subsequent scientific progress. The most important, paradigm-shifting change in the 2018 report was redefining AD by its biological changes in the brain rather than the clinical phenotype. By moving away from the prior definition based on clinical-pathological presentation to

biological characterization, the NIA-AA framework aimed to create a common language in research studies, allow for more aligned comparison of research findings, and facilitate future clinical trials.

The current clinical framework for diagnosing AD is based on symptoms reported by the patient and corroborated by a collateral historian, together with an objective assessment of cognitive decline. The level of confidence in this diagnosis ranges from possible to probable, depending on the presence of typical symptoms, as well as the absence of alternative causes of cognitive decline. A biological diagnosis of AD, which is considered the only definitive diagnosis, presently relies on autopsy findings of amyloid plaques and tau neurofibrillary tangles. Numerous studies have found discordant findings between clinical diagnoses and neuropathological outcomes. It is reported that 10% to 30% of clinically diagnosed persons with AD dementia do not display the neuropathological hallmarks of amyloid plaques and tau neurofibrillary tangles on autopsy. Differentiating the clinical syndrome, composed of symptoms not necessarily specific to AD, from the biological changes seen on neuropathology would allow discovery of novel mechanisms underlying AD neurobiology. Furthermore, enrollment of participants with biologically confirmed AD diagnosis will be critical in evaluating efficacy of disease-modifying therapies as they become available in the future.

The 2018 updated research framework proposed a biomarker classification system called AT(N). The framework categorizes individuals based on the presence or absence of the following core AD pathological features: aggregated amyloid beta protein (A), aggregated tau protein (T), and neurodegeneration or neuronal injury (N). The biomarkers for amyloid and tau were selected for their high specificity to AD-related changes found in autopsy studies. In the AT(N) framework, AD is defined by the presence of both amyloid (A) and tau (T). Since neurodegeneration is not a feature used in the neuropathological diagnosis of AD and is seen in other neurodegenerative disorders as well, it is in parentheses in the proposed research framework. However, its inclusion in the framework was necessary to reflect disease severity. **Table 59-6** provides a list of validated biomarkers used to identify each component of the AT(N) framework.

TABLE 59-6 ■ CSF BIOMARKERS OF ALZHEIMER DISEASE

AD PATHOLOGY-RELATED MECHANISM	CSF MEASURE
Amyloid deposition	Aβ40, Aβ42, sAPPα, sAPPβ, Aβ oligomers, BACE1 levels/ activity, ratios, eg, Aβ42/p-tau, Aβ40/Aβ42, N-terminal truncated Aβ42 APLP-1
Neurodegeneration	Total tau, p-tau, oligomeric forms of tau
Neuronal/axonal damage and white matter integrity	Neurofilament L (NFL)
Synaptic function/damage	Neurogranin, SNAP25, visinin-like-protein 1 (VLP1)
Neuroinflammation	YKL-40, MCP1, soluble form of TERM2, cytokines, chemokines, com3, S-100

The AT(N) framework has accelerated discovery of novel CSF and more recently blood-based biomarkers of amyloid, tau, neurodegeneration, neuroinflammation, and other pathological changes seen in AD. Many of these biomarkers, especially the core AD biomarkers including Aβ-42, total tau (t-tau), and phosphorylated tau-181 (p-tau-181), can now be reliably measured in CSF and correlate well with PET brain imaging and neuropathological findings. Although validation of various AD biomarkers in CSF, blood, and autopsy brain studies is ongoing, they are being actively used to enroll participants in treatment trials and clinical and translational studies. Based on data emerging from longitudinal cohort studies and randomized clinical trials, the reported accumulation of AD biomarkers over time points to a continuum of disease progression, as opposed to the older clinical conceptualization of distinct levels of disease staging.

There is converging evidence that amyloid deposition in the brain is the first neuropathological change seen in persons with AD. This conclusion is based on studies of people with early-onset AD due to an autosomal dominant mutation, those living with Down syndrome, and findings from transgenic animal models of AD. However, the presence of amyloid alone is

viewed as only an early stage within the Alzheimer continuum and is necessary, but not sufficient, for the biological diagnosis of AD. While the amyloid cascade hypothesis suggests amyloid accumulation causes changes leading to tau accumulation and eventually neurodegeneration, it is also accepted that, unlike tau, amyloid is not strongly linked to cognitive function. Amyloid may have downstream effects on tau and neurodegeneration, but the AT(N) framework does not assume an order of causality.

One of the most notable contributions of the AT(N) framework is to effectively screen and identify participants for enrollment in clinical trials based on their biomarker profile rather than nonspecific clinical presentations. The framework also provides validated and uniform biological outcome measures to assess the efficacy of disease modifying therapies, and determine dose-response relationships. Given AD is a chronic and slowly progressive condition, trials to find effective treatments are challenged with finding reliable surrogate outcomes that could change quickly, rather than wait for alterations in clinical or behavioral phenotype that would require longer and costly trials. The AT(N) framework would enrich treatment trials with biologically confirmed AD participants at higher risk of decline, as well as serve as a surrogate end-point in disease modifying therapy trials. Additionally, it could serve as a marker of treatment response.

The AT(N) framework is not meant to be comprehensive and exclusive, but rather adaptive to newer scientific discoveries. A new evolution in the framework is ATX(N), with "X" representing novel candidate biomarkers to help expand and explain underlying mechanisms in AD. Examples of potential mechanisms include neuroinflammation, synaptic dysfunction, microvascular changes, mitochondrial oxidative damage, glial activation, neurochemical deficits, and BBB dysfunction. The ATX(N) framework would help expand the scientific understanding of AD as well as investigate the heterogeneity of the disease.

AD Biomarkers

Cerebrospinal fluid AD biomarkers Amyloid and tau biomarkers are central in identifying AD pathology and will help explore disease heterogeneity. They will likely play critical roles in AD, including early diagnosis, disease progression, screening, risk prediction, target engagement, treatment monitoring, and validation of novel biomarkers. The core AD biomarkers,

namely amyloid Aβ-42, t-tau, and p-tau181, have been validated through multiple CSF, PET brain imaging, and neuropathological studies. Given their proven reliability, amyloid and tau biomarkers will serve as a framework for identification of novel biomarkers to address contributions from potential coexisting pathologies, such as vascular insults, Lewy body dementia, Parkinson disease, and TDP (TAR DNA-binding protein)-43 that likely contribute to clinical symptoms and cognitive decline.

In the past decade, new CSF biomarkers have been identified representing multiple mechanisms active in AD. These mechanisms include glial activation, neuroinflammation, synaptic degeneration, and neuronal/axonal death. Importantly, many AD biomarkers can now be measured in CSF and several in blood as well. Although the validation of CSF biomarkers is currently ongoing, once approved, they will have major clinical applications in the diagnosis, progression, and treatment of AD and related disorders. **Table 59-6** summarizes CSF biomarkers representing various molecular pathways active in AD. While some of the CSF biomarkers, such as t-tau, NfL, YKL-40, and interleukins, may not be specific to AD, they elucidate disease progression and are related to symptoms. Measures of neurodegeneration may be particularly important, given clinical features of AD tend to track closely with synaptic dysfunction, and eventually neuronal death. Synaptic loss is an early pathological change in AD and closely associated with cognitive impairment.

Neuroimaging AD biomarkers The multimodal neuroimaging AD biomarkers, including CAT, MRI, amyloid PET, and tau PET brain scans, have been examined over years and validated as effective measures to help in the diagnosis and progression of AD, and exclusion of other treatable causes of dementia, such as stroke, tumor, or NPH. Recent advances in neuroimaging include novel PET radiotracers to image neuroinflammation and translocator protein (TSPO) PET and synaptic vesicle protein 2A (SV2A) PET, respectively, to study synaptic dysfunction and loss. Clinically, [18F] FDG PET is available to visualize synaptic dysfunction, neuronal cell loss, and metabolic dysfunction to help differentiate AD from non-AD dementias such as FTD and Lewy body disease. Additionally, amyloid PET and tau PET are available in research settings, but not yet approved for clinical use or reimbursement. Once approved, amyloid and tau PET scans will become important for biological diagnosis of AD.

Blood-based AD biomarkers Although highly informative, the utility of CSF and PET biomarkers is limited by their cost, logistical matters and practical barriers related to the lumbar puncture procedure. These limitations make CSF measures unlikely to become widely used in the clinical setting. Consequently, the pursuit of blood-based AD biomarkers has intensified. Several AD biomarkers can now be measured in blood through emerging analytical techniques. However, a major limitation in broad utility of these biomarkers is significant heterogeneity in results due to multiple factors, including variance in sample collection, storage, preanalytical processing, assays, and data analysis. Among the AD biomarkers that can be measured in plasma include Aβ42, Aβ40, total tau, p-tau181, p-tau217, p-tau231, neurofilament light (NfL), interleukins, and YKL-40. Highly sensitive mass spectrometry assays are used to measure plasma levels of Aβ42, Aβ40, and their ratios, while single molecule array (SIMOA) technology is used to assay NfL, interleukins, and p-tau and its analogues in plasma. Phosphorylation of tau occurs at multiple sites and certain isoforms, such as threonine 231 (p-tau231) and threonine 217 (p-tau217) change early in AD pathobiology and have been shown to accurately identify amyloid positivity along the AD biomarker continuum and clinical spectrum.

Plasma neurofilament light (NfL), a promising biomarker of neurodegeneration, albeit not specific to AD, has been shown to increase in persons with cognitive impairment due to many neurodegenerative disorders, including AD, Parkinson disease, FTD, and cerebral vascular disease. Elevated plasma NfL is a sign of early neuronal death and can increase during preclinical stages of AD. The field of plasma AD biomarkers is advancing rapidly and new biomarkers that change during early stages of AD will become invaluable for early diagnosis, progression from preclinical to symptomatic stages of AD, and treatment monitoring and response. However, these biomarkers are not yet ready for clinical applications, given that larger studies are necessary to validate, examine the relationship with clinical phenotype, and harmonize their measurement in plasma.

MANAGEMENT

Managing patients with AD involves presentation of the diagnosis, initiation of medical therapy, assessment and treatment of concomitant depression and/or behavioral concerns, identification of a social support network,

education of patients and caregivers, provision of caregiver support, and initiation of appropriate safety measures.

Presenting the Diagnosis

Presenting the diagnosis of AD to a patient is difficult, as it may generate significant emotional responses from the patient and their family and trigger fear of future demise. Frequently, patients and family members suspect the diagnosis before it is presented, but how they respond to the news depends on personal coping mechanisms, cultural influences, family dynamics, and their preconceived understanding of AD. Clinicians may help patients and families adjust to this diagnosis by using an empathetic, yet honest approach and by providing them with educational and support resources, including those provided by agencies such as the Alzheimer's Association and the National Institute on Aging Alzheimer's Disease Education and Referral (ADEAR) Center. In addition, the clinician should emphasize the goals of diagnosing AD in order to take steps to protect the patient's memory, delay the progression of the disease, and maintain the person's safety. It is widely recommended to tell both the patient and family the diagnosis using the term "Alzheimer disease," thus, providing patients and families with a starting point for education. Encouraging both persons with the disorder and caregivers to utilize resources such as local support groups, community resources, and national Alzheimer organizations is an important part of the patient management plan.

Drug Therapy and Nonpharmacologic Therapy

Acetylcholinesterase inhibitors (AChEIs) are the mainstay of therapy for AD. AChEIs increase the levels of the neurotransmitter acetylcholine in neuronal synapses, thereby enhancing cholinergic activity in the affected brain regions. Although 18% to 48% of persons may experience improvements in cognition after taking these medications, the majority of patients do not have any noticeable improvement, but instead experience a plateau or slowing of their rate of cognitive decline. While prior studies raised questions as to the cost-effectiveness of treating AD patients with AChEIs, newer studies integrating generic drug cost estimates have demonstrated that these drugs are cost-effective. Delaying the progression of cognitive decline may lead to improvements in quality of life, reduced caregiver burden, and decreased economic cost associated with long-term care. AChEIs have not been shown