Alzheimer Disease

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ABSTRACT

Purpose of Review: This article discusses the recent advances in the diagnosis and treatment of Alzheimer disease (AD).

Recent Findings: In recent years, significant advances have been made in the fields of genetics, neuroimaging, clinical diagnosis, and staging of AD. One of the most important recent advances in AD is our ability to visualize amyloid pathology in the living human brain. The newly revised criteria for diagnosis of AD dementia embrace the use for biomarkers as supportive evidence for the underlying pathology. Guidelines for the responsible use of amyloid positron emission tomography (PET) have been developed, and the clinical and economic implications of amyloid PET imaging are actively being explored.

Summary: Our improved understanding of the clinical onset, progression, neuroimaging, pathologic features, genetics, and other risk factors for AD impacts the approaches to clinical diagnosis and future therapeutic interventions.

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Dr Apostolova discusses the unlabeled/investigational use of antidepressant and antipsychotic medications for behavioral management as well as antidementia therapy in mild cognitive impairment.

INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative disorder featuring gradually progressive cognitive and functional deficits as well as behavioral changes and is associated with accumulation of amyloid and tau depositions in the brain. Cognitive symptoms of AD most commonly include deficits in short-term memory, executive and visuospatial dysfunction, and praxis. Several rarer variants of AD with relative preservation of memory have been recognized. Clinical assessment, including cognitive testing, remains critical for the diagnosis and staging of AD, although recent advances in amyloid imaging and genetics show great promise for facilitating early and presymptomatic diagnosis of AD and its discrimination from other neurodegenerative disorders.

EPIDEMIOLOGY

AD is the most common neurodegenerative disorder and the sixth most common cause of death in the United States.[1] Although there is increasing evidence that AD pathology starts depositing in the brain in midlife, the first clinical symptoms usually occur after the age of 65.[2,3]

AD prevalence is rapidly increasing in large part because the proportion of people 65 years and older is growing faster than any other age sector of the population worldwide. Between 1997 and 2050, the elderly population, defined as subjects 65 years of age and older, will increase from 63 to 137 million in the Americas, from 18 to 38 million in Africa, from 113 to 170 million in Europe, and from 172 to 435 million in Asia.[4] One nationally representative US data set, the Aging, Demographics, and Memory Study (ADAMS), estimated that in the United States, 14% of people 71 years and older have dementia. AD dementia accounted for 70% of the dementia cases across the age spectrum in this cohort.[5] In a subsequent publication, the ADAMS investigators reported that an additional 22% (or 5.4 million

KEY POINTS

- Alzheimer disease prevalence is rapidly increasing.
- Although age is the greatest risk factor for the development of Alzheimer disease, old age is not sufficient, in and of itself, to cause Alzheimer disease.
- Memory impairment is the most pervasive feature of Alzheimer disease.

Americans) 71 years or older have cognitive impairment in the absence of overt dementia.[6]

Although age is the greatest risk factor for the development of AD, in and of itself, old age is not sufficient to cause AD. Other major risk factors include the presence of one or more apolipoprotein gene E4 alleles (*APOE4*), low educational and occupational attainment, family history of AD, moderate or severe traumatic brain injuries, and cardiovascular risk factors.

Gender modulates the prevalence of AD. Nearly two-thirds of all patients diagnosed with AD are women.[7] According to ADAMS, 16% of women, but only 11% of men, live with dementia after 71 years of age.[5] While it is true that women live longer than men, this alone does not explain the discrepancy. Genetic, hormonal, and societal factors (eg, lower education and occupational attainment among women currently in their 70s and 80s compared to men) likely play a significant role as well.

Racial disparities in AD prevalence have also been reported. Older African Americans and Hispanics have a higher prevalence of AD relative to older Caucasians in part because of lower education levels and higher prevalence of cardiovascular comorbidities,[8–10] although other genetic and societal factors likely play a role as well.

CLINICAL PRESENTATION

Recognition of the clinical features and presenting symptoms of AD remains essential for the diagnosis and management of patients, even as biomarker tests such as amyloid positron emission tomography (PET) imaging that detect the underlying neuropathology of AD are increasingly available for patient care. Ascertainment of symptoms of cognitive decline, behavioral symptoms, functional decline, and cognitive testing remain the cornerstones to the clinical diagnosis and staging of patients with AD.

Cognitive Decline

Memory impairment is the most pervasive feature of AD. Although nonmemory cognitive deficits (eg, aphasia, executive dysfunction, apathy, or personality change) can manifest early and even be the presenting feature, in general, memory decline is considered the leading symptom. Early in the disease course, recent episodic memories are most affected, while memories from the distant past are usually spared. As the disease progresses, all aspects of episodic memory become affected. In contrast to episodic memory, working memory and semantic memory are preserved until later in the disease course.

Language disturbance, especially word-finding difficulties, is a common early symptom in AD but is generally mild. Subtle decline in visuospatial skills likewise occurs in the mild dementia stages and progresses throughout the course of the disease. Executive dysfunction, on the other hand, begins even earlier—in the predementia stages—and, similar to all other cognitive domains, worsens over the disease course.

Neuropsychiatric Symptoms

Patients with AD exhibit a variety of neuropsychiatric symptoms. Behavioral symptoms, once manifest, tend to worsen over the course of the disease; however, these symptoms often fluctuate and are not consistently present at each visit. Attention to these treatable components of excess morbidity is important as they have a profound impact on caregiver burden and are the leading cause of institutionalization.[11]

The earliest AD-associated neuropsychiatric symptoms are apathy, anxiety, and irritability. The latter two

symptoms are often provoked in situations that the patient finds challenging. Mild to moderate depressive symptoms are also frequently present early on. Disturbances of appetite and sleep, disinhibition, and alterations in perception (hallucinations) or thought (delusions) commonly occur in the later stages of dementia. In addition to the classic neuropsychiatric behaviors, anosognosia (ie, lack of insight) often manifests early on and poses another difficult management problem.

Of all AD neuropsychiatric comorbidities, irritability, agitation, sundowning, psychosis, and diminished insight often present the most pressing therapeutic needs due to the psychological and physical strain they place on the family and caregivers.

Neurologic Examination

Outside of the mental status examination, findings on the neurologic examination are often normal in patients with AD. Parkinsonian symptoms can emerge in the later stages, but if these symptoms are present early in the course of the disease (eg, within 1 year of onset of cognitive problems) and especially when accompanied by cognitive fluctuations and early-onset psychosis, a diagnosis of dementia with Lewy bodies should be considered. Later in the disease course, pathologic reflexes such as grasp, root, and suck reflexes may be found. Patients become increasingly impaired in the moderate and severe stages and are ultimately mute, incontinent, and bedridden at the end stages of disease. At this stage, multiple complications arise such as risk of aspiration with unsafe swallowing, malnutrition, immobility with associated risks for bedsores, deep venous thrombosis, and infections. Often, these complications are the direct cause of death in patients with AD.

ATYPICAL ALZHEIMER DISEASE VARIANTS

In addition to the classic AD presentation, several less common AD variants should be recognized, which include frontal variant of AD, posterior cortical atrophy, and logopenic variant primary progressive aphasia due to AD.

Frontal variant of AD is characterized by substantial behavioral or personality changes that are out of proportion to the observed short-term memory loss. These patients are often profoundly impatient, irritable, impulsive, and disinhibited. On formal testing, they invariably show significant executive disturbances.[12]

Posterior cortical atrophy presents with visuospatial dysfunction often in the form of partial or full Balint syndrome (simultanagnosia, ocular apraxia, and ocular ataxia), partial or full Gerstmann syndrome (acalculia, agraphia, right/left disorientation, and finger agnosia), apperceptive visual agnosia, and environmental disorientation. Patients often develop constructional, dressing, and ideomotor apraxia early on in the presence of relatively preserved memory and insight.

Finally, the occasional patient with AD may also present with early progressive language involvement, most often in the form of logopenic aphasia with pronounced anomic deficits and impaired repetition but preserved grammar and syntax.

DIAGNOSTIC CRITERIA

Currently, the diagnostic standard for dementia is the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*).[13] *DSM-5* recognizes two cognitive syndromes: major neurocognitive impairment and mild neurocognitive impairment. The diagnosis of major neurocognitive impairment requires objective cognitive decline that is severe enough to

KEY POINTS

- Neuropsychiatric comorbidities often present the most pressing therapeutic needs due to the psychological and physical strain they place on the family and caregivers of patients with Alzheimer disease.
- Several less common Alzheimer disease variants should be recognized, which include frontal variant of Alzheimer disease, posterior cortical atrophy, and logopenic variant primary progressive aphasia due to Alzheimer disease.

KEY POINTS

- The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria no longer require the presence of memory impairment for the diagnosis of neurodegenerative dementia to be established.
- The National Institute on Aging and Alzheimer's Association criteria for probable Alzheimer dementia recognize the diagnostic utility of disease biomarkers.

interfere with activities of daily living and is not caused by delirium or another neurologic, medical, or psychiatric disorder. Patients with mild neurocognitive impairment have milder cognitive decline that does not yet deprive them of the ability to lead an independent lifestyle and perform complex daily activities such as managing finances or driving a car.

It should be noted that the *DSM-5* introduces a major change in terms of diagnostic criteria for cognitive disorders. The criteria no longer require the presence of memory impairment for the diagnosis of neurodegenerative dementia to be established, as was the case in all previous *DSM* editions. *DSM-5* thus recognizes that for some dementing disorders such as vascular and frontotemporal dementia, for instance, memory impairment is not an early symptom and may never manifest (**Table 3-1**).

Another set of diagnostic criteria spanning all three major stages of AD (ie, the preclinical, the prodromal, and the overt dementia stages) were recently developed by the National Institute on Aging (NIA) and the Alzheimer's Association (AA).[14–16] Similarly to the *DSM-5* criteria, the NIA-AA criteria for dementia of any cause no longer explicitly require memory impairment to be present, but rather, for the diagnosis of dementia to be established, call for documentation of impairment in two cognitive domains or one cognitive and one behavioral domain in addition to significant decline in day-to-day functioning (**Table 3-2**). For the first time, the NIA-AA criteria for probable Alzheimer dementia as a subtype of dementia recognized the diagnostic utility of disease biomarkers that have proven sensitivity, specificity, and pathologic validity (**Table 3-2**). At the present time, two types of biomarkers meet these criteria. Two neurodegenerative biomarkers—mesial temporal lobe atrophy on structural imaging (**Figure 3-1**) and posterior predominant hypometabolism with involvement of the posterior cingulate gyrus on fluorodeoxyglucose positron emission tomography (FDG-PET) (**Figure 3-2**)—have already received wide acceptance. However, neither of these are exclusively seen in AD dementia. Hippocampal atrophy

TABLE 3-1 Summary of Diagnostic Criteria for Mild and Major Neurocognitive Disorder[a]

▶ **Mild Neurocognitive Impairment**
Cognitive decline one to two standard deviations from normal on formal cognitive testing
Does not interfere with independence
Not due to delirium or other medical or psychiatric disorder
▶ **Major Neurocognitive Impairment**
Cognitive decline two standard deviations or more from normal on formal cognitive testing
Interferes with independence
Not due to delirium or other medical or psychiatric disorder

[a] Data from American Psychiatric Association.[13]

TABLE 3-2 Summary of Diagnostic Criteria for Dementia Syndrome and Probable Alzheimer Disease from the National Institute on Aging and the Alzheimer's Association[a]

▶ **Dementia Syndrome**
Objective cognitive or behavioral impairment in at least two of the following
Memory
Reasoning and handling complex tasks
Visuospatial abilities
Language functions
Personality, behavior, or comportment
Decline from previous level of functioning
Functional impairment
▶ **Probable Alzheimer Disease Dementia**
Criteria for dementia are met
Insidious onset
Gradual progression
Initial symptoms
Amnestic
Nonamnestic (language, executive)
No other neurologic, psychiatric, or general medical disorders of severity that can interfere with cognition
Positive biomarkers (eg, CSF amyloid-β [Aβ]/tau, amyloid positron emission tomography [PET], hippocampal atrophy on MRI) increase diagnostic certainty

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Data from McKhann GM, et al, Alzheimer Dement.[15] *www.alzheimersanddementia.com/article/S1552-5260(11)00101-4/fulltext*.

occurs in normal aging,[17,18] and both hippocampal atrophy and FDG-PET abnormalities occur in other dementing conditions.[19,20] On the other hand, amyloid protein–based biomarkers such as a low CSF level of β-amyloid or a positive amyloid PET scan have been shown to be highly sensitive and specific in their ability to detect amyloid pathology in the brain.[21,22]

Current Role of Biomarkers in Alzheimer Disease Diagnosis

In addition to supporting clinical diagnosis, biomarkers have historically played an important role in the workup of patients with dementia. The American Academy of Neurology (AAN) guidelines for the diagnostic evaluation of dementia require physicians to obtain a structural imaging scan in every patient with objective cognitive decline.[23] This recommendation follows the review of the evidence presented in a Class II study showing that 5% of all patients with cognitive complaints harbored a causative nondegenerative lesion, such as a slow-growing brain neoplasm (most commonly of the frontal lobes), subdural hematoma, or

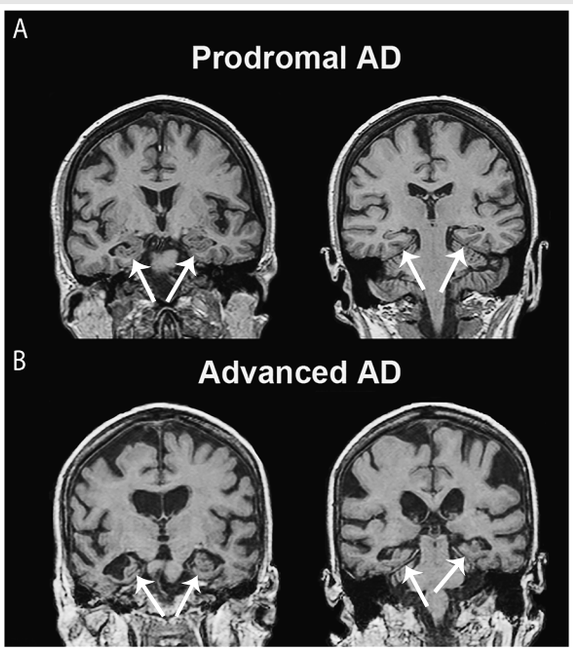

FIGURE 3-1 Coronal T1-weighted MRI slices with findings suggestive of Alzheimer disease (AD) pathology show mesial temporal atrophy (*A*, *B*, *arrows*) and, in the more advanced stages, global brain atrophy with pronounced ventricular enlargement.

normal pressure hydrocephalus.[24] In addition to identifying a potentially treatable lesion, a brain CT or MRI scan can uncover ischemic changes that would prompt further workup and potential initiation of therapy aiming to reduce vascular risk factors or introduce behavioral modifications. MRI, with its improved resolution, allows better quantification of cerebral structures and better discrimination of normal from mildly affected patients with AD than is possible with CT. Some of the findings suggestive of AD pathology include mesial temporal atrophy[25–27] and, in the more advanced stages, global brain atrophy with pronounced ventricular enlargement (**Figure 3-1**).[28,29] Cortico-subcortical microhemorrhages are often found on gradient echo MRI sequences and are suggestive of the presence of vascular amyloidosis (**Figure 3-3**).

Functional brain imaging using single-photon emission computed tomography (SPECT) and PET technologies can be used to identify AD-specific patterns such as temporoparietal hypoperfusion/hypometabolism in patients with AD (**Figure 3-2**). More recently, arterial spin-labeling MRI sequences have been shown to capture perfusion abnormalities.[30] Validation studies of SPECT and PET have generally shown high sensitivity yet relatively lower specificity, hence the increased risk for false-positive diagnoses.[31,32] Currently, FDG-PET and SPECT use is only covered by Medicare for differentiating AD from frontotemporal dementia.

The recent discovery and validation of amyloid PET imaging has the potential to change the approach to clinical

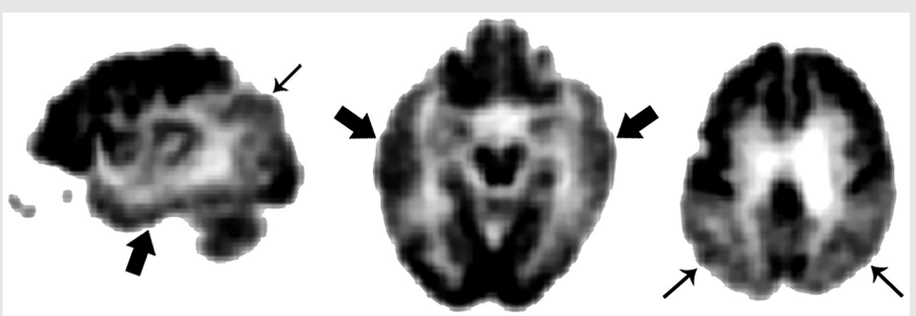

FIGURE 3-2 Temporal (*thick arrows*) and parietal (*thin arrows*) hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) is often seen in patients with Alzheimer disease dementia.

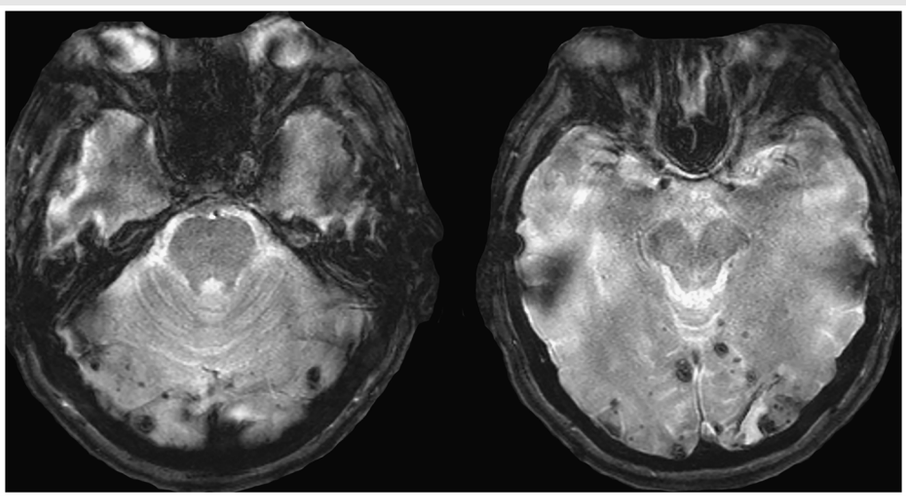

FIGURE 3-3 Cortico-subcortical microhemorrhages are often found on gradient echo MRI sequences and are suggestive of the presence of vascular amyloidosis.

KEY POINT

■ Amyloid positron emission tomography imaging allows the detection of moderate to severe amyloid deposition in the brain.

diagnosis of AD. This type of imaging allows the detection of moderate to severe amyloid deposition in the brain (**Figure 3-4**). Despite its well-documented sensitivity and specificity,[22] this technology has not yet entered routine clinical practice, in part because insurance companies do not provide coverage for it. The major drawbacks among insurance carriers are: (1) the unproven economic benefit of using this relatively expensive PET technology for diagnostic purposes while disease-modifying therapies are lacking and (2) the potential risk for it to be used in cognitively normal individuals. Clearly, the latter scenario (ie, detecting AD in the latent stages in the form of asymptomatic brain amyloidosis) could inflict an insurmountable psychological burden given the absence of effective therapeutic approaches to delay disease onset or modify its course. In response to these concerns, a group of imaging and dementia experts convened to establish a set of recommendations of which patients should be imaged. These suggestions are the Appropriate Use Criteria for amyloid PET imaging,[33,34] which recommend employing amyloid PET imaging in three specific clinical scenarios: (1) patients with amnestic mild cognitive impairment (ie, mild neurocognitive disorder), (2) patients in the dementia stages with suspected atypical AD or etiologically mixed presentation, and (3) those with early disease onset (younger than 65 years

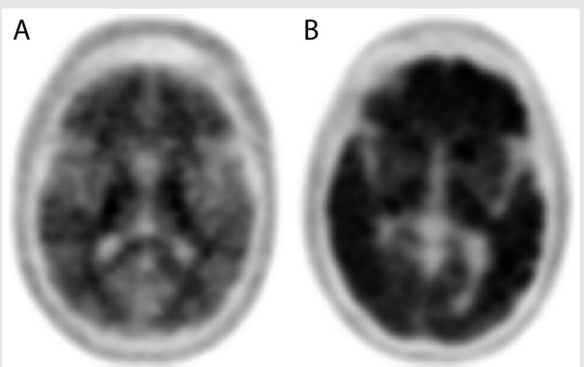

FIGURE 3-4 Amyloid positron emission tomography (PET) imaging allows the detection of amyloid pathology of the brain. A negative scan (*A*) shows only nonspecific white matter binding and indicates no to sparse amyloid plaque deposition, while a positive amyloid PET scan (*B*) shows significant uptake in multiple cortical areas and indicates the presence of moderate to severe amyloid pathology.

KEY POINTS

- Amyloid positron emission tomography scans are only appropriate if the scan results are expected to alter clinical management.
- The *APOE4* genotype should be considered a risk factor that is neither sufficient nor necessary for Alzheimer disease development.

of age). At present, the impact of amyloid PET imaging on clinical practice and health outcomes is not yet known. Given the lack of disease-modifying drugs for AD, the rationale for the use of amyloid PET imaging in clinical practice includes: (1) helping the practitioner to select appropriate treatments and avoid unnecessary interventions and to aid in accurate diagnosis, (2) improving diagnostic accuracy, (3) advising patients and families on the clinical course and prognosis, and (4) educating patients and families on community services and resources for medical, financial, and legal planing.[34] **Case 3-1** and **Case 3-2** describe exemplary scenarios.

The Appropriate Use Criteria also define the inappropriate uses of amyloid PET imaging. Patients who should not be scanned include those lacking objective cognitive decline. Scanning solely on the basis of family history or *APOE4* status was likewise determined to be inappropriate. Furthermore, amyloid PET scans cannot be used for determining dementia severity, as this is not feasible with this technology.

Another important suggestion of the Appropriate Use Criteria for amyloid PET imaging is the recommendation that the responsibility for determining patients' eligibility (ie, appropriateness for imaging) should lie with medical professionals with significant expertise in evaluating and treating patients with dementia (defined as 25% or greater proportion of clinical practice devoted to cognitive disorders of the elderly).[33] Last but not least, the committee recommended that amyloid PET scans are only appropriate if the scan results are expected to alter clinical management (see **Case 3-1** and **Case 3-2** for examples).

CSF amyloid-β (Aβ) and tau protein levels are the most established AD fluid biomarkers. Pathologic Aβ deposition in the brain tissue begins early in the disease course and is associated with decline in CSF Aβ.[35] CSF total and phosphorylated tau levels rise in AD secondary to neurodegeneration of tau-containing neurons.[36–39] CSF tau changes occur later in the disease course and are associated with cognitive decline.[40–43] CSF Aβ and tau measurements are covered by most insurance companies in the United States as part of the workup for AD. Despite this, they are not routinely used due to relative invasiveness of the lumbar puncture procedure and the risk for side effects such as back discomfort, headache, and, in rare cases, iatrogenic meningitis. However, CSF Aβ and tau testing can be quite useful in diagnostically challenging cases as well as in those with early disease onset or an unusual clinical course. CSF Aβ level is highly correlated with the presence of amyloid deposition in the cortex.[44] Thus, CSF Aβ levels can be used in lieu of an amyloid PET scan as a reliable proxy measure of the presence of brain amyloidosis.

GENETICS OF ALZHEIMER DISEASE

Although the *APOE4* gene variant is the most established genetic risk factor for sporadic AD, screening for *APOE4* is not recommended on a routine basis. While it has been estimated that one copy of this genetic variant increases the odds for developing AD threefold and two copies increase the odds 15-fold,[45] a large multicenter study demonstrated that the presence of the *APOE4* allele increased the positive predictive value of diagnosing AD by only 4% over diagnoses made on clinical grounds alone (from 90% to 94%).[46] The *APOE4* genotype should be considered a risk factor that is neither sufficient nor necessary for disease development.

Case 3-1

A 78-year-old man with 12 years of education presented to the memory disorder clinic reporting progressive memory difficulties for the past 1 to 2 years. His memory deficits were most noticeable when he recalled recent events as opposed to events from the distant past. He had on two occasions experienced mild spatial confusion when walking his dog but, in both instances, he was eventually able to find his way. He had no problems with attention, language skills, or judgment. He operated all appliances at home and safely drove a car. His family noticed mild anxiety in challenging situations and questioned whether he was a little depressed, as he had become quieter. The patient had no significant comorbidities and no family history of dementia. He had been prescribed memantine 10 mg once a day by an outside physician.

The patient's cognitive evaluation revealed a Mini-Mental State Examination (MMSE) score of 25 out of 30, poor recollection of recent events, lower than expected performance on category fluency (number of animals produced in 1 minute), poor encoding and retention of verbal and nonverbal information, mild anxiety, and minimal depression. His attention, visuospatial skills, and abstract thinking were preserved. Formal neuropsychological testing confirmed the above deficits and further clarified his memory profile as most consistent with retrieval memory loss, as he showed significant improvement on cued recall (ie, the recognition portion of the memory tests). Review of an outside MRI revealed age-appropriate atrophy.

The patient was given a diagnosis of mild neurocognitive disorder by *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*[13] criteria (ie, mild cognitive impairment), most likely due to a neurodegenerative etiology. Although the leading consideration was Alzheimer disease (AD), the observed significant improvement on cued recall, suggestive of retrieval rather than encoding deficits, was considered atypical. An amyloid positron emission tomography (PET) scan was ordered and revealed diffuse amyloid tracer uptake in the cerebral cortical gray matter with complete loss of the gray-white matter differentiation consistent with the presence of moderate to severe amyloid pathology.

A diagnosis of mild neurocognitive disorder due to AD was made. The patient was prescribed donepezil. He experienced significant gastrointestinal side effects as the dose was increased from 5 mg/d to 10 mg/d. A slower escalation regimen (introducing an additional titration step of 7.5 mg/d for 1 month before introducing 10 mg/d) was effective. Two years later, his MMSE score had declined to 19 out of 30. His family reported difficulties with managing finances, shopping, navigation, and cooking.

Comment. This patient presented with atypical amnestic mild cognitive impairment that met Appropriate Use Criteria[33,34] for amyloid PET imaging. The diagnostic uncertainty stemmed from the patient's pronounced memory retrieval deficit. The amyloid PET scan was beneficial in assisting the physician's therapeutic decisions and counseling the patient and family.

More recently, several large genome-wide association studies have uncovered and successfully replicated another 20 risk/protective genetic variants.[47] Relative to *APOE4*, these variants explain only a small fraction of the genetic

KEY POINT

■ The search for other gene variants that may affect risk of Alzheimer disease is ongoing.

Case 3-2

A 59-year-old woman with 12 years of education presented to the memory disorder clinic because of memory difficulties for the past 1 to 2 years. Her husband reported that for the past few months they had the same conversation multiple times a day. She misplaced items more often. Her recall of distant memories and visuospatial function were preserved. She was also becoming more distractible. She managed their household without a problem and safely operated a motor vehicle. On a few occurrences, she reportedly paid some bills twice while being on time with the rest. She was still able to manage her appointments and medications with occasional reminders. She had become quieter in social situations and more reluctant to go out. She was no longer interested in volunteering at their church.

On bedside cognitive testing the patient scored 22 out of 30 on the Mini-Mental State Examination (MMSE). She showed relatively preserved encoding, impaired delayed recall, and endorsed multiple false-positive items on recognition testing. Her language and visuospatial skills were preserved. She made a few errors on frontal executive tasks. On formal neuropsychological testing, additional deficits in category fluency and nonverbal memory were noted.

The patient's MRI revealed mild global atrophy with medial temporal lobe predominance and hippocampal atrophy. An amyloid PET scan was performed and showed diffusely increased tracer uptake throughout the cortical cerebral gray matter with loss of the normal gray-white matter contrast consistent with the presence of moderate to severe amyloid pathology. A diagnosis of mild neurocognitive disorder (ie, mild cognitive impairment) due to early-onset AD was made. The patient was started on donepezil.

Comment. This patient presented with early-onset prodromal AD. The patient met the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*[13] criteria for mild neurocognitive disorder (ie, mild cognitive impairment) and met the Appropriate Use Criteria for amyloid PET imaging by virtue of early disease onset. The amyloid PET scan was considered beneficial in assisting the physician's therapeutic decisions and counseling of the patient.

heritability of sporadic AD where each risk variant conveys a relative risk of 1.1 to 1.3.[47] The vast majority of these risk variants take part in processes implicated in the pathogenesis of AD such as amyloid metabolism, inflammation, oxidative stress, and energy metabolism. The search for other gene variants that may affect risk of AD is ongoing.

Family history of sporadic AD is a well-established risk factor. Individuals who have a first-degree relative diagnosed with AD are more likely to develop the disease than those who do not.[48] Genetic makeup is not the only risk; shared environmental and lifestyle factors likely also play a role.

Several rare autosomal dominant variants of AD have been described. The first symptoms usually affect individuals in their 30s and 40s. These families show multiple affected individuals across generations. These autosomal dominant AD variants have been traced to genetic mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes. Mutations in all three genes

increase the levels of β-amyloid. Early-onset autosomal dominant AD accounts for less than 2% of all AD cases.

ALZHEIMER DISEASE PATHOLOGY

AD is thought to result from overproduction and impaired clearance of β-amyloid. Downstream events are tau hyperphosphorylation and neuronal toxicity. The primary pathologic features of AD are brain atrophy from regional neuronal and synaptic loss, extracellular β-amyloid deposition in the form of neuritic plaques, and intraneuronal tau protein deposition in the form of intraneuronal neurofibrillary tangles. β-Amyloid also deposits in the cerebral blood vessels. Cerebral amyloid angiopathy ranges in severity from small amounts of amyloid to major deposits that distort the artery architecture and cause cortical microinfarcts, microaneurysms, and cerebral microhemorrhages or macrohemorrhages (multiple microhemorhages in the occipital lobes of a patient with AD are shown in **Figure 3-3**).

Amyloid deposition is thought to begin 20 years prior to development of clinical symptoms.[2] Longitudinal studies of cognitively normal individuals who are amyloid-positive are presently ongoing and are focusing on ascertainment of the risk for future development of dementia among these individuals. Neurofibrillary tangles are not exclusive to AD and can be found in other conditions, such as dementia pugilistica and chronic traumatic encephalopathy, prion disease, and in normal aging. Neurofibrillary tangle burden and neuronal loss show a robust association with global cognitive impairment.[49,50]

TREATMENT

The clinical management of patients with AD dementia should accomplish several important tasks. Patients need to receive diagnostic and prognostic counseling as well as appropriate medications in an optimized regimen. Patients' coexisting behavioral and non-neurologic conditions need to be optimally managed. Vital importance should be placed on coordinating care among physicians, nurse practitioners, and social workers, and instituting appropriate oversight and safety precautions when patients have functional impairment and poor judgment. It is important to encourage patients to participate in social activities, adult day care centers and exercise programs, as well as to encourage both patients and caregivers to take part in support groups.

Acetylcholinesterase Inhibitors

Two classes of medications have been approved for AD: the acetylcholinesterase inhibitors (AChEIs) and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine. Treatment with AChEIs should be considered in patients with mild to moderate AD per the AAN practice guidelines for dementia.[51] Three agents are currently approved and marketed in the United States: donepezil, rivastigmine, and galantamine. All three have been shown to be effective in double-blind placebo-controlled trials, showing some benefit on cognitive measures including memory and concentration as well as global and functional outcome measures; however, their therapeutic cognitive and functional effects seem to be modest in size and purely symptomatic. Gastrointestinal side effects, more commonly seen during the dose escalation phase of treatment, occur with all three agents. Bradycardia and heart block may occur, especially in patients with underlying cardiac conduction deficits or in those individuals taking medications that cause PR interval prolongation such as beta-blockers. If

KEY POINTS

- Amyloid deposition is thought to begin 20 years prior to development of clinical symptoms.
- Vital importance should be placed on coordinating care among physicians, nurse practitioners, and social workers, and instituting appropriate oversight and safety precautions when patients have functional impairment and poor judgment.
- Treatment with acetylcholinesterase inhibitors should be considered in patients with mild to moderate Alzheimer disease per the American Academy of Neurology practice guidelines for dementia.

KEY POINTS

- Memantine is US Food and Drug Administration approved for the moderate to severe stages of Alzheimer disease.
- The first line of treatment for behavioral and neuropsychiatric symptoms of Alzheimer disease are nonpharmacologic modalities.

one agent causes intolerable side effects, another AChEI should be tried.

Glutamate Receptor Modulators

Memantine is a low to moderate affinity NMDA receptor antagonist that is used as an add-on to ongoing AChEI therapy. A recent meta-analysis of nine trials with a combined sample size of 2433 revealed that memantine had a beneficial effect on cognition, behavior, activities of daily living, and global function.[52] Memantine is approved by the US Food and Drug Administration (FDA) for the moderate to severe AD stages (Mini-Mental State Examination [MMSE] score of 5 to 15) in the United States. The main side effects of confusion and dizziness occur only rarely.

The timing of initiation of cholinesterase inhibitors and memantine therapy is an area of some controversy.[53] Cholinesterase inhibitors and memantine are frequently prescribed off-label for mild cognitive impairment in the United States.[54] Recent meta-analyses have not demonstrated a benefit of cholinesterase inhibitors in mild cognitive impairment, although a benefit for subgroups of patients remain undetermined.[55,56] A separate meta-analysis suggests there is not a benefit of memantine in patients with mild AD.[57] While the 2001 AAN practice parameter for treatment of dementia is currently under revision, 2011 guidelines from the National Institute for Health and Clinical Excellence now recommend memantine as an option for managing moderate AD for people who cannot take AChEIs and as an option for managing severe AD.[58] In contrast, Canadian Consensus guidelines on dementia from 2013 state that, while combination therapy of a cholinesterase inhibitor and memantine is rational and appears to be safe, there is insufficient evidence to support or refute use of memantine in moderate to severe AD.[59]

Medications for Behavioral Symptoms

The first line of treatment for behavioral symptoms of AD are nonpharmacologic techniques. A quiet, familiar environment with labels on doors and sufficient lighting in all rooms is important to reduce disorientation. Aggressive behavior should always be addressed with positive and clear language to reassure and distract the patient.

Depressive symptoms are treated with selective serotonin reuptake inhibitors (SSRIs) due to their low propensity to cause anticholinergic effects. SSRIs may also ease anxiety, irritability, or other nonspecific symptoms that may accompany depression. The SSRI citalopram may be useful for agitation.

Agitation or disruptive behavior may require a neuroleptic for optimal therapeutic response. The newer ''atypical'' antipsychotic medications (quetiapine, risperidone, olanzapine) are often used in low doses with careful titration. Typical and atypical antipsychotic agents, however, carry a black box warning label due to an association with increased cardiovascular morbidity and mortality (higher for the typical compared to atypical antipsychotics) and cerebrovascular adverse events in the elderly with dementia-related psychosis.[60–62] In addition, these medications have additional adverse effects: anticholinergic adverse events and orthostatic and metabolic disturbances. Traditional neuroleptics are more likely to produce extrapyramidal symptoms, which may worsen cognitive function. All antipsychotics, typical as well as atypical, when used in older adults with

dementia, are associated with risk for death. This risk is quite comparable among atypical and typical antipsychotics. It is a black box warning for all antipsychotics as a class when used in older adults with dementia.[62] Thus, judicious use of antipsychotics with frequent reassessment of the therapeutic need is appropriate.

Future Therapies

The majority of currently ongoing clinical trials are focused on interventions that directly influence the pathologic cascade in AD. One active immunization trial in humans was interrupted due to the development of neuroinflammation in a subset of the subjects. There was remarkable clearance of amyloid in the cortex in multiple subjects from that trial who died,[63,64] suggesting that amyloid deposits can indeed be removed. Current major efforts are focused on passive immunization (ie, antibody infusion) as well as interference with β-amyloid and tau production and polymerization.

CONCLUSION

AD is an irreversible neurodegenerative disorder that affects over 5 million Americans. Although we are now able to diagnose AD in the early and even in the presymptomatic stages, we are still lacking preventative or disease-modifying medications that can alter its course. The effect of AD on individual patients and their families and caregivers is devastating. As the number of patients with AD climbs, families, caretakers, the medical system, and society as a whole will have to bear the burden of this disease unless we find a cure.

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