ABSTRACT

Alzheimer’s disease (AD) accounts for an estimated 50% to 75% of dementia cases. However, AD very often coexists with several forms of dementia: vascular dementia, Lewy body disease, or frontotemporal dementia. Increasing age is the greatest risk factor for AD; 1 in 10 individuals older than age 65 years and nearly 50% of those older than age 85 years are affected. AD is an important and growing concern in the United States, primarily because of the aging Baby Boomers—the group of people who are at the highest risk of AD is also the fastest growing segment of the population. AD has traditionally been defined by the presence of neuritic plaques of beta amyloid protein and neurofibrillary tangles in the brain. However, its pathophysiology is much more complex at the cellular level than these macroscopic changes suggest. This article reviews our current understanding of AD pathophysiology (including the role of both cholinergic and glutamatergic neurotransmission, in addition to oxidative stress and inflammation) and the many questions that remain, 100 years after it was first described by Alois Alzheimer. Also reviewed are the different forms of AD: familial and sporadic, and their patterns of inheritance, in addition to the clinical presentation of AD at its different stages, its diagnosis, and its potential precursor, mild cognitive impairment.


EPISTEMOLOGY

The year 2006 marked the centennial anniversary of Alois Alzheimer first describing what is now the eponymous form of dementia. Alzheimer’s disease (AD; also known as dementia of the Alzheimer’s type) is the most common form of dementia, accounting for an estimated 50% to 75% of dementia cases. However, exact measure of incidence and prevalence are difficult to obtain because AD is one of several forms of dementia—vascular dementia (VaD), Lewy body disease (LBD), frontotemporal dementia—that both share clinical and pathophysiologic characteristics and may coexist with AD. For example, as shown in Figure 1, in an autopsy series from the Florida Brain Bank, AD was the most common type of dementia for both “pure” and “mixed” cases, but a mixed pathology with VaD or LBD was found in more than 40% of the AD cases. Also, mixed AD plus VaD is increasingly recognized as a common presentation, in part because of the common “latency period” before clinical presentation with AD and atherosclerosis and the common environmental and genetic risk factors (Table 1).

Alzheimer’s disease is also now the most well known of the dementias, in part because of several widely known individuals who have been open about their diagnoses (eg, the late President Ronald Reagan and actor Charlton Heston). Also, AD now commands the attention of the clinical and scientific research communities. According to the Alzheimer’s Association, more than $185 million in research grants have been awarded by the Association since 1982, and Congress appropriated $652 million for Alzheimer’s disease research in fiscal year 2006. However, the Alzheimer’s Association has called on Congress to appropriate $1 billion for Alzheimer research at the National Institutes of Health.

EPIDEMIOLOGY

An estimated 4.5 million Americans have AD. Increasing age is the greatest risk factor for AD; in fact,
1 in 10 individuals older than age 65 years and nearly 50% of those older than age 85 years are affected. A person with AD will live an average of 8 years and as many as 20 years or more from the onset of symptoms, as estimated by relatives. Survival time varies based on age at diagnosis and severity of comorbid conditions, which are common in this age group.

Alzheimer's disease is an important and growing concern in the United States, primarily because of the aging Baby Boomers (ie, those born from 1946–1964). In 2011, just 4 years from now, the first Boomers will be 65 years old. By 2031, all Baby Boomers will be older than 65 years of age and the first Boomers will be 85 years old. Thus, the group of people who are at the highest risk of AD, those aged 85 years and older, is also the fastest growing segment of the population.

ETIOLOGY AND PATHOPHYSIOLOGY

Alzheimer's disease has traditionally been defined by the presence of neuritic plaques of beta amyloid protein and neurofibrillary tangles in the brain. However, its pathophysiology is much more complex at the cellular level than these macroscopic changes suggest. In addition to the “amyloid cascade hypothesis” is evidence illustrating the role of both cholinergic and glutamatergic neurotransmission, in addition to oxidative stress and inflammation.

Amyloid Cascade Hypothesis

Plaques are formed by aggregates of Aβ42, a naturally occurring peptide resulting from enzymatic cleavage of amyloid precursor protein (APP) by secretases (α, β, or γ). In healthy individuals, cleavage by β-secretase, followed by γ-secretase, yields either a 40- or 42-amino acid peptide, the latter being much less soluble than the former and therefore more prone to plaque formation. In AD, a variant form of the γ-secretase leads to increased production of the 42-amino acid peptide, Aβ42. α-secretase also acts on APP, cleaving at a different site than β-secretase and thus precluding production of the 40- or 42-amino acid peptide. Therefore, α-secretase is considered to serve a protective function against AD. Under normal conditions, both Aβ40 and Aβ42 are cleared from the brain. However, in AD, there is a gradual accumulation of Aβ42 into oligomers, which aggregate to extracellular plaques on neurons and ultimately disrupt neuronal function. The intracellular neurofibrillary tangles result from hyperphosphorylation of the tau protein, which binds to microtubules to promote assembly and stability and is thus critical to neuronal structure and neurotransmission. Hyperphosphorylated tau leads to disassembled microtubules and impaired axonal transport, and also aggregates to form insoluble fibrils in tangles. Technically, AD can be diagnosed only with post-mortem evidence of these pathophysiologic dis-

![Figure 1. Frequency of Postmortem Dementia Diagnoses from the Florida Brain Bank](image)

Brains from 382 patients were included in the study. The duration from time of clinical diagnosis to time of death was 5.5 ± 3.6 years, and the average age at death was 79 ± 13 years (range 47–102 years). Half of the study participants were females; 98% were white non-Hispanic. Patients were referred to the Brain Bank primarily from memory disorder clinics (38%), in addition to medical centers, AD resource centers (eg, the Alzheimer’s Association), and community physicians. Of those diagnosed postmortem with AD (pure or mixed), 82% had been diagnosed clinically with AD.

AD = Alzheimer’s disease; FTD = frontotemporal dementia; LBD = Lewy body dementia; VaD = vascular dementia.

Data from Barker et al.

<table>
<thead>
<tr>
<th>Table 1. Common Genetic and Environmental Risk Factors for Alzheimer’s Disease and Atherosclerosis</th>
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<tbody>
<tr>
<td>APOE4 polymorphism</td>
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<tr>
<td>Hypercholesterolemia</td>
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<td>Hypertension</td>
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<td>Hyperhomocysteinemia</td>
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<td>Diabetes mellitus</td>
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<td>Metabolic syndrome</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Systemic inflammation</td>
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<td>Increased fat intake and obesity</td>
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</table>

ease hallmarks. It is unclear whether the presence of plaques and tangles is a cause or consequence of the clinical presentation of dementia. Even the relationship between plaque count and dementia severity remains in question. However, it is interesting to note that protein aggregates on neurons are found in most neurodegenerative diseases, although the protein of interest varies with the disease (ie, Lewy body dementia, Huntington’s disease, amyotrophic lateral sclerosis, and Parkinson’s disease).

We are also developing a better understanding of the complex relationship between vascular disease and AD, in line with the emerging recognition of mixed VaD and AD. As mentioned earlier in this article, many of the risk factors for AD are also risk factors for vascular disease, and these risk factors for AD are additive. For example, Luchsinger et al followed 1138 individuals for a mean of 5.5 years and measured the risk of developing AD with vascular risk factors. They found that 4 risk factors were individually associated with a higher risk of AD (diabetes, hypertension, heart disease, and current smoking), although the relationship was not statistically significant ($P < .10$). However, when considered in aggregate, the presence of 3 or more of these risk factors increased the adjusted hazards ratio for AD to 3.4 (95% confidence interval, 1.8–6.3; $P < .0001$ for the trend). Diabetes and current smoking were the strongest risk factors, but clusters including hypertension and heart disease also increased the risk of AD.

The brain contains the highest amount of cholesterol of any human organ. Although the central nervous system (CNS) accounts for only 2% of body mass, it contains almost 25% of the body’s unesterified cholesterol. Casserly and Topol have recently reviewed the converging evidence regarding atherosclerosis and AD. For example, in vitro and animal studies have shown that increased concentrations of free cholesterol stimulate increased Aβ production. Inflammation is now known to play a key role in atherosclerosis pathology, and inflammatory elements in the brain (cytokines, chemokines, growth factors, enzymes, complement, coagulation factors, and reactive oxygen species produced by macrophages; pro-inflammatory products secreted by astrocytes; and inflammatory mediators and complement factors produced by neurons) are consistently colocalized with neuritic plaques. Furthermore, as will be discussed later in this article, the strongest genetic risk factor for sporadic AD is involved in cholesterol transport.

**CHOLINERGIC HYPOTHESIS**

Another striking feature of AD pathology is the targeted degeneration of cholinergic neurons in the brain, and in specific regions of the brain. Acetylcholine is an important neurotransmitter in brain regions involving memory, and memory loss is one of the first signs of AD (described later in this article). In fact, loss of cholinergic activity correlates with cognitive impairment, and cholinergic abnormalities are the most prominent neurotransmitter changes in AD, primarily due to the reduced activity of choline acetyltransferase (an enzyme involved in acetylcholine synthesis). By late-stage AD, the number of cholinergic neurons is markedly reduced (>75%), particularly in the basal forebrain.

**GLUTAMATERGIC AND EXCITOTOXIC HYPOTHESIS**

Glutamate is the primary excitatory neurotransmitter, and glutamatergic neurotransmission is involved in learning, memory, and the shaping of neuronal architecture (plasticity). Virtually ubiquitous in the CNS, glutamate is estimated to be involved in roughly 66% of all brain synapses, and essentially all CNS functions. There are 3 types of glutamate receptors (AMPA, kainate, and N-methyl-D-aspartate [NMDA]), and brains of patients with AD have fewer NMDA receptors than normal. As well, there appears to be excessive or unregulated glutamate signaling (ie, sustained low-level activation) in AD, which eventually leads to neurotoxicity through excessive excitation of the neurons (excitotoxicity). Based on animal studies, continuous activation of the glutamate NMDA receptor leads to chronic calcium influx that interferes with normal signal transduction and, over time, increases production of Aβ.

**PROGRESSION OF NEURODEGENERATION**

The brain areas responsible for memory include the cortex, entorhinal cortex, and hippocampus (Figure 2). Preclinical AD begins as neuronal loss in the entorhinal cortex and proceeds to the hippocampus. As the brain atrophies, cerebrospinal fluid fills in the space previously occupied by brain tissue. Magnetic resonance imaging (MRI) studies showing atrophy in these regions suggest that neuronal loss may start years before signs of memory loss emerge.

As AD progresses to mild or moderate severity, memory loss becomes more prominent and is accompanied by a decline in the ability to process complex thoughts.
In the brain, atrophy continues within the cerebral cortex (Figure 3). By the severe stage of AD, the lateral and third ventricles increase in size dramatically (Figure 4), and the cortical areas affected control speech, reasoning, sensory processing, and conscious thought.23,26

**GENETICS**

There appear to be at least 2 forms of AD—familial and sporadic—but genetic studies now show 3 types of inheritance—autosomal dominant (or familial AD), familial AD without clear Mendelian inheritance (ie, familial aggregation, perhaps due to shared genetic and/or environmental risk factors), and sporadic AD without familial aggregation.27 To date, 3 genes have been implicated in familial AD; they control the expression of γ-secretase subunits (presenilin 1 [PSEN1] and presenilin 2 [PSEN2]) and APP.28-30 For patients with the familial form of AD, onset is usually before age 65 years, but this form of AD is rare, with a prevalence of 0.1%.10,31

The vast majority of AD cases are referred to as “sporadic AD” (ie, other factors besides genetics appear to play a role in determining onset, although there is a genetic component). Twin studies show heritability is almost 80% for those who develop AD after 65 years of age.25 The gene implicated in sporadic AD is ε4 allele of the APOE gene on chromosome 19, which encodes apolipoprotein E (ApoE).32,33 A single APOE-ε4 allele (ie, heterozygosity) increases the risk of AD by a factor of 3; in homozygotes, the risk of AD is increased 15 fold.32 The degree of increased risk with homozygosity varies widely by ethnicity and education level, again suggesting an interaction between environment and genetics.27,32 The additive effect of each ε4 allele acts mainly by decreasing the age of disease onset by almost 10 years per allele.33,37 However, we are far from understanding the genetics of familial or sporadic AD. According to the American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and AD, genetic testing (for diagnostic or prognostic purposes) of APOE or any other susceptibility gene under investigation is not recommended. However, those whose family history suggests autosomal dominant inheritance may find genetic testing for APP, PSEN1, or PSEN2 mutations useful.27,38

Numerous risk factors for AD have also been identified, including sociodemographic variables (such as education level and intelligence), lifestyle (nutrition,
aerobic fitness, and mental exercise), environment (head trauma), vascular disease, previous or current use of nonsteroidal anti-inflammatory agents or statins, and, of course, age.\textsuperscript{10,39,40}

**Clinical Manifestations**

Alzheimer’s disease is characterized by progressive impairment in memory and cognition. Short-term memory is the first type of memory to be affected. Other early signs include confusion about the location of familiar places (getting lost begins to occur), taking longer to accomplish normal daily tasks, trouble handling money and paying bills, poor judgment leading to bad decisions, loss of spontaneity and sense of initiative, mood and personality changes, and increased anxiety. With disease progression, more severe cognitive impairment becomes apparent, which affects the patient’s ability to perform activities of daily living (ADLs) and, ultimately, instrumental ADLs. Noncognitive symptoms, such as delusions, agitation, depression, and personality changes, emerge. Table 2 lists some of the most frequent signs of AD at the mild, moderate, and severe stages.\textsuperscript{23,41} As you can see from the lists, the delineations between each stage are somewhat arbitrary; AD progression is a continuum.

**Mild Cognitive Impairment**

Mild cognitive impairment (MCI) is a condition characterized by cognitive decline greater than what would be expected for an individual’s age and educational level, but which does not interfere with ADLs.\textsuperscript{42} First described in 1999 by Petersen, MCI is a broad concept that has since been subtyped into amnestic and nonamnestic MCI.\textsuperscript{43} Amnestic MCI focuses on complaints of memory loss, preferably corroborated by an informant, with no signs of dementia. Nonamnestic MCI, also referred to as cognitive impairment no dementia, includes global cognitive impairment.\textsuperscript{44} The overall prevalence of MCI in the elderly is estimated to range from 3% to 19%, but most studies indicated a prevalence closer to 3%.\textsuperscript{44,45} Of those with MCI, approximately 18% progress to dementia, especially AD, although one study showed that 27% progressed to dementia over 10 years.\textsuperscript{45,46}

### Table 2. Signs of Alzheimer’s Disease at Different Disease Stages

<table>
<thead>
<tr>
<th>Normal Behavior</th>
<th>Mild AD</th>
<th>Moderate AD</th>
<th>Severe AD</th>
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<tbody>
<tr>
<td>• Forgetting names or appointments occasionally</td>
<td>• Memory loss</td>
<td>• Weight loss</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Occasionally forgetting why you came into a room or what you planned to say</td>
<td>• Confusion about the location of familiar places (getting lost begins to occur)</td>
<td>• Seizures, skin infections, and difficulty swallowing</td>
<td>• Seizures</td>
</tr>
<tr>
<td>• Sometimes having trouble finding the right word</td>
<td>• Taking longer to accomplish normal daily tasks</td>
<td>• Groaning, moaning, or grunting</td>
<td>• Skin infections</td>
</tr>
<tr>
<td>• Forgetting the day of the week or where you were going</td>
<td>• Trouble handling money and paying bills</td>
<td>• Increased sleeping</td>
<td>• Difficulty swallowing</td>
</tr>
<tr>
<td>• Making a questionable or debatable decision from time to time</td>
<td>• Poor judgment leading to bad decisions</td>
<td>• Lack of bladder and bowel control</td>
<td>• Groaning, moaning, or grunting</td>
</tr>
<tr>
<td>• Finding it challenging to balance a checkbook</td>
<td>• Loss of spontaneity and sense of initiative</td>
<td>• Hallucinations, delusions, suspiciousness or paranoia, and irritability</td>
<td>• Inability to sit up</td>
</tr>
<tr>
<td>• Misplacing keys or a wallet temporarily</td>
<td>• Rapid or dramatic mood swings or personality changes (eg, confusion, suspicion, fear, and dependency); increased anxiety</td>
<td>• Loss of impulse control (shown through sloppy table manners, undressing at inappropriate times or places, or vulgar language)</td>
<td>• Increased sleeping</td>
</tr>
<tr>
<td>• Occasionally feeling sad or moody</td>
<td></td>
<td>• Perceptual-motor problems (such as trouble getting out of a chair or setting the table)</td>
<td>• Lack of bladder and bowel control</td>
</tr>
<tr>
<td>• Personality changes with age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Occasional fatigue or weariness of work or social obligations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease.

Data from Alzheimer’s Disease Education and Referral Center\textsuperscript{23}; Alzheimer’s Association Web site.\textsuperscript{41}
those with amnestic MCI, the rate of progression in one study was 64% after 2 years. Other studies have shown progression rates to AD of 16% per year. Thus, amnestic MCI is considered by some to be a prodrome of AD. The roles of neuritic plaques and neurofibrillary tangles in MCI is not yet clear; individuals with MCI appear to have intermediate amounts of these pathophysiologic features compared to healthy individuals and those with dementia.

**DIAGNOSIS OF ALZHEIMER’S DISEASE**

Despite the remaining questions in AD pathophysiology and spectrum of disease, AD can be diagnosed clinically with surprising accuracy. Diagnosis includes a short cognitive screening test (eg, the Mini-Mental State Examination, the Clock Draw Test, or the Mini-Cog), in addition to laboratory studies to rule out secondary causes of dementia (eg, hypothyroidism, vitamin B12 deficiency, and HIV). A comprehensive medication review, psychiatric testing for depression, and neuroimaging (noncontrast MRI or computed tomography to rule out cerebrovascular disease or tumor) are all components of diagnosis. Also important is an interview with a reliable informant. Diagnostic criteria from the American Psychiatric Association include gradual and continual impairments in memory and learning along with aphasia, apraxia, agnosia, and/or deficits in executive functioning, with “substantial impairments in social or occupational functioning.” Because the latter criterion (in quotes) is loosely defined and mental status examination scores depend on the patient’s age, education level, and native language, a diagnosis of AD must be made with a complete picture of the patient and in the context of corroborating evidence from a reliable informant.

**CONCLUSIONS**

Alzheimer’s disease is a complex neurodegenerative disease, and its etiology, pathophysiology, and risk factors are not yet completely understood, despite having been recognized more than 100 years ago. With the aging of the Baby Boomers and the expected rise in healthcare costs associated with elderly persons, understanding AD becomes even more imperative. The more we understand this disease and its relationship to other forms of dementia and common comorbidities with aging, the better we as a society will be able to deal with the imminent explosion in its prevalence, especially as we seek both treatments and preventive strategies.

**REFERENCES**


