

Alzheimer's Disease: A Clinical and Basic Science Review

Igor O. Korolev*

College of Osteopathic Medicine and Neuroscience Program, Michigan State University, East Lansing, MI, USA

*Corresponding author: Igor Korolev, PhD, MSIII; korolevi@msu.edu

Alzheimer's disease (AD) is the most common cause of dementia in older adults and an important public health problem. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI that medical students should be familiar with. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

Keywords: Alzheimer's disease; mild cognitive impairment; dementia; neurodegeneration; neuroimaging; biomarkers.

INTRODUCTION

The world's population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer's disease (AD), the most common cause of dementia. For comparison, according to the Centers for Disease Control and Prevention (2009–2012 estimates), about 3 million older adults in the United States have asthma, 10 million have diabetes, 20 million have arthritis, and 25 million have hypertension. Primary care physicians and specialists alike will encounter older adults with dementia at an increasing frequency during their careers. As dementia carries significant implications for patients, their families, and our society, it is imperative for well-rounded physicians to have a solid understanding of this topic. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI with which medical students should be familiar. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

ALZHEIMER'S DISEASE

Alois Alzheimer and Auguste D

The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease

of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.^{1–3} Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD today.

Dementia

Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive deterioration of intellectual function.⁴ Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. In individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation, and social behaviors. Importantly, the cognitive and behavioral changes that occur with dementia interfere with work, social activities, and relationships and impair a person's ability to perform routine daily activities (e.g., driving, shopping, housekeeping, cooking, managing finances, and personal care). Table 1 summarizes the clinical criteria for all causes of dementia.^{4,5}

There are several reversible and irreversible causes of dementia.^{4,6} Reversible dementias (also referred to as 'pseudo-dementias') are relatively rare but potentially treatable and occur secondary to another medical condition, including depression, nutritional deficiencies (e.g., vitamin B12), metabolic and endocrine disorders (e.g., hypothyroidism), space occupying lesions (e.g., brain tumor), normal pressure hydrocephalus, or substance

Table 1. Clinical criteria for dementia

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1. Progressive impairment in two or more areas of cognition:
 - a) Memory (ability to learn and remember new information)
 - b) Language (speaking, reading, writing)
 - c) Executive function (reasoning, decision making, planning)
 - d) Visuospatial function (ability to recognize faces and objects)
 - e) Praxis (ability to perform purposeful movements)
 - f) Changes in personality, mood, or behavior
 2. Cognitive deficits:
 - a) Interfere with functioning (ability to perform activities of daily living)
 - b) Represent a decline from previous levels of functioning
 - c) Are not due to delirium or psychiatric disorder (e.g., depression)
 - d) Are established using history from patient, corroborated by informant (e.g., family member), and objective cognitive assessment
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Adapted from Ref. [5].

abuse. Certain classes of medications also have the potential to cause cognitive impairment in older adults (e.g., anti-cholinergics, psychotropics, analgesics, sedative-hypnotics). Irreversible (primary) dementias involve neurodegenerative and/or vascular processes in the brain. AD is the most common cause of irreversible dementia, accounting for up to 70% of all dementia cases in the United States.⁷ Other types of primary dementia include vascular dementia (10–20%), dementia associated with Parkinson's disease, dementia with Lewy bodies, and frontotemporal dementia.

Epidemiology of AD

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.⁸ In the United States, AD is the fifth leading cause of death among older adults, and about \$200 billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).⁹

AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling

every 5 years after age 65.^{10,11} The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (>95% of all cases). Rare genetic mutations are associated with the development of AD before age 65, which is known as 'early-onset' or 'familial' AD (<5% of all cases).¹² People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD.¹³ The prevalence of AD is higher among females, reflecting the longer life expectancy of women.¹⁴ Lower educational attainment has been associated with increased risk of AD dementia,¹⁰ consistent with the idea that education serves to increase a person's cognitive reserve and resilience to AD pathology.¹⁵ A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the development and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.¹⁶ Family history of AD in first-degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of AD.⁴

Neuropathology of AD

AD is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level, AD is characterized by a progressive loss of cortical neurons, especially pyramidal cells, that mediate higher cognitive functions.^{17,18} Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions.¹⁹ AD-related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus.²⁰ Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of AD. The degeneration then spreads throughout the temporal association cortex and to parietal areas. As the disease progresses, degeneration can be seen in the frontal cortex and eventually throughout most of the remaining neocortex. Of note is the fact that AD causes pronounced

damage to multiple components of the limbic system,^{12,21} including the hippocampal formation and the major fiber tracts that connect it to the cerebral cortex (fornix and cingulum), amygdala, cingulate gyrus, and thalamus. This widespread pattern of neurodegeneration, affecting both limbic and neocortical regions, correlates closely with the array of cognitive deficits and behavioral changes that AD patients exhibit.¹² In addition to cognitive impairment across multiple domains (memory, language, reasoning, executive, and visuospatial function), patients with AD show an impaired ability to perform activities of daily living and often experience psychiatric, emotional, and personality disturbances.

It has been theorized that the neuronal damage seen in AD is related to the deposition of abnormal proteins both within and outside of neurons. These are the hallmark pathological lesions of AD known as 'plaques and tangles.' The abnormal proteins are deposited in the cerebral cortex following a stereotypical pattern of spread along neural pathways that mediate memory and other cognitive functions.¹⁸ 'Senile plaques' are extracellular accumulations of amyloid protein and consist of insoluble amyloid-beta protein (A β). Normally, cells throughout life release soluble A β after cleavage of the APP – a cell surface receptor. AD involves abnormal cleavage of APP that results in the precipitation of A β into dense beta sheets and formation of senile plaques. It is believed that microglia and astrocytes then mount an inflammatory response to clear the amyloid aggregates, and this inflammation likely causes destruction of adjacent neurons and their neurites (axons and dendrites).^{11,18} 'Neurofibrillary tangles' (NFT) are intracellular aggregates of abnormally hyper-phosphorylated protein tau, which in normal form serves as a microtubule stabilizing protein and plays a role in intracellular (axonal and vesicular) transport. It is possible that NFT interfere with normal axonal transport of components necessary for proper neuronal function and survival (e.g., synaptic vesicles with neurotransmitters, neurotrophic factors, and mitochondria), eventually causing neurons to die.^{11,18} Substantial evidence supports the idea that amyloid formation and deposition in the cerebral cortex is one of the earliest pathological processes in AD, preceding the clinical onset of the disease by 10–20 years.¹² Despite this, the temporal sequence of events in the deposition of amyloid plaques and formation of NFT during development of AD remains open to debate. In fact, a recent study suggests that the initial formation of NFT may occur in the brainstem rather than the medial

temporal lobe and may precede the appearance of the first amyloid plaques in the neocortex.²²

Diagnosis of AD

The gold standard for the diagnosis of AD is an autopsy-based (post-mortem) pathological evaluation. The presence and distribution of amyloid plaques and NFT in the brain is used to establish the diagnosis of 'definitive' AD and stage the disease.²² In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70–90% relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics.²³ The cornerstone of the clinical diagnosis is a set of consensus criteria first established in 1984²⁴ and last updated in 2011 by the National Institute on Aging – Alzheimer's Association (NIA-AA) workgroup.⁵ The NIA-AA clinical criteria for the diagnosis of 'probable' AD dementia are summarized in Table 2. When the patient's cognitive impairment has an atypical clinical course or is suspected to be due to other etiologies in addition to AD, the diagnosis of 'possible' AD dementia is recommended. Patients with AD generally have normal findings on physical and neurological examinations.^{6,25} To help with the differential diagnosis, Table 3 summarizes some of the clinical features that distinguish

AD dementia from other causes of irreversible dementia.

Laboratory and neuroimaging studies are used only for investigational purposes or as an adjunct to the clinical criteria for AD, particularly to rule out structural brain lesions and identify 'reversible' causes of dementia. The only laboratory studies that the American Academy of Neurology recommends to be performed on a routine basis as part of dementia work-up are serum B12, thyroid stimulating hormone (TSH), and free thyroxine

Table 2. Clinical criteria for probable AD dementia

1. Presence of dementia (as per criteria in Table 1)
2. Gradual onset of symptoms over months to years
3. History of progressive cognitive decline
4. Initial presentation may be amnesic (typical) or non-amnesic (atypical)
5. No evidence for another cause of cognitive impairment: cerebrovascular disease, other dementia syndromes, or neurological/medical disease

Adapted from Ref. [5].

Table 3. Clinical features that distinguish AD from other dementias

Clinical feature	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementia with Lewy bodies	Frontotemporal dementia
Patient profile	> 65 years old	> 40 years old Vascular risk factors	> 65 years old	75 years old (mean)	50–70 years old 50% autosomal dominant
History	Gradual onset and deterioration	Acute onset, step-wise deterioration	Gradual onset and deterioration	Gradual onset and deterioration	Gradual onset and deterioration
Initial symptoms	Memory loss	Executive dysfunction	Visual hallucinations	Visual hallucinations Fluctuating attention	Memory intact Disinhibition, apathy or aphasia
Physical findings	No motor impairment (until late stage)	Pyramidal (upper motor neuron) signs	Parkinsonism (precedes dementia by > 1 year)	Parkinsonism (presents within 1 year of dementia)	Usually none (rarely associated with motor neuron disease)

Notes: Pyramidal (upper motor neuron) signs include hyperreflexia, spasticity, weakness, and extensor plantar responses (Babinski sign). Parkinsonism refers to the following features: bradykinesia, cogwheel rigidity, resting tremor, and postural instability. Information compiled from Refs. [4, 25].

(T4) levels.²⁶ Structural magnetic resonance imaging (MRI) or non-contrast computed tomography (CT) may be useful to rule out normal pressure hydrocephalus, cerebral hematomas, brain tumors, and cerebrovascular lesions.

Treatment of AD

There is no cure for AD, and drug therapy for the disease is still in its infancy. Approved medications for the treatment of probable AD help control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself.¹² At present, the mainstay of AD therapy are drugs that target neurotransmitter systems in the brain. AD primarily damages glutamate- and acetylcholine-producing neurons and their associated synapses, and this damage correlates well with early cognitive symptoms of AD.¹⁹ Acetylcholinesterase inhibitors help improve memory function and attention in AD patients by interfering with the breakdown of acetylcholine, thereby increasing the levels of the neurotransmitter at the synapse. There are currently three FDA-approved cholinesterase inhibitors:²⁷ *rivastigmine* and *galantamine* (for mild to moderate AD), and *donepezil* (for all stages of AD). *Memantine* is another FDA-approved medication for use in moderate to severe AD but belongs to a different class of drugs known as NMDA (glutamate) receptor antagonists.²⁷ Both classes of medications are generally well-tolerated, with gastrointestinal upset, dizziness, and headache being the most common adverse effects observed.

In recent years, a number of potential disease-modifying AD drugs have been evaluated in clinical trials, and several others are being evaluated in ongoing trials.

Drugs that act to decrease the amount of A β protein in the brain have received the most attention due to the prominent pathogenic role ascribed to A β in the AD literature. One class of such drugs are secretase inhibitors, which inhibit the secretase (protease) enzymes that cleave APP to produce A β .^{28,29} Another strategy that has been attempted is by using drugs that promote the clearance of A β through active or passive immunization.³⁰ Unfortunately, as of the writing of this article, several completed phase three trials with different amyloid-lowering drugs have failed to demonstrate clinical efficacy.³¹ Various explanations have been proposed to account for the repeated clinical trial failures observed with these disease-modifying agents. One possibility is that A β may play a less prominent or different role in AD pathogenesis than previously hypothesized,^{32,33} an issue certain to remain controversial in the near future. Regardless, other therapeutic strategies for AD are being investigated alongside the amyloid-based therapies, although with no major clinical successes yet to report. A promising avenue is the development of drugs that target the abnormal tau protein comprising the NFT.³¹ Another important source for potential AD drugs is the pool of medications on the market that are already approved for non-AD indications, such as diabetes, hypertension, and infectious disease. This strategy of drug 'repurposing' or 'repositioning' can greatly expedite the discovery of novel AD treatments and has been used in the past for other neurodegenerative disorders (e.g., anti-viral drug amantadine for use in Parkinson's disease).³⁴ An alternative explanation for the clinical trial failures is that the trials were conducted in patients with mild to moderate AD

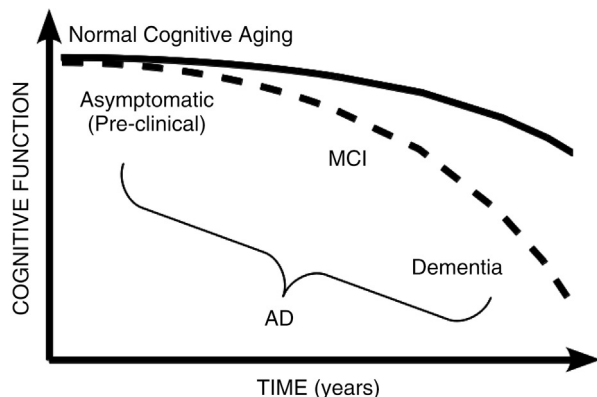


Figure 1. Progressive development of Alzheimer's disease (AD). The relationship among pre-clinical, mild cognitive impairment (MCI), and dementia stages of AD (dashed line) is shown relative to normal cognitive aging (solid line). Adapted with permission from Elsevier.³⁷

dementia, at a stage when the disease process is likely irreversible and brain damage is too great for the anti-AD therapy to have a clinically significant effect. Early diagnosis of AD and timely therapeutic intervention is critical given that the disease may begin years or even decades prior to the onset of dementia.^{12,35} As such, greater emphasis is being placed on conducting clinical trials in populations of persons with no dementia who are at risk for developing AD, such as individuals with MCI.³⁶

MILD COGNITIVE IMPAIRMENT

The MCI Concept

MCI is a syndrome characterized by memory and/or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia (Fig. 1).³⁷ The most widely used clinical criteria for the diagnosis of MCI are those proposed by Petersen and colleagues at the Mayo Clinic (Table 4).³⁸ Researchers have also proposed several subtypes of MCI based on distinct neuropsychological profiles.³⁹ Amnesic MCI involves memory-only impairments, while non-amnesic MCI involves only impairments in cognitive domains other than memory (e.g., executive function/attention, language, and visuospatial function). Multi-domain MCI is characterized by impairments in both memory and non-memory functions.

Epidemiology of MCI

Large population-based epidemiological studies³⁹⁻⁴¹ in both the US and Europe have estimated that the

Table 4. Clinical criteria for MCI

1. Subjective cognitive complaint, preferably corroborated by an informant
2. Objective memory and/or other cognitive impairments that:
 - a) Are abnormal for the individual's age and education, as documented using neuropsychological testing
 - b) Represent a decline from previous levels of functioning
3. Normal ability to perform activities of daily living
4. Absence of dementia

Adapted from Ref. [38].

prevalence of MCI among adults aged 65 and older is 3–24%, with higher prevalence in older individuals. Prospective longitudinal studies indicate that patients with MCI exhibit annual rates of progression to dementia of 3–15%, with highest rates for people in specialty clinic-based cohorts as compared to those in community-based cohorts.^{42,43} Overall, rates of progression from MCI to dementia are elevated well above the annual 1–2% incidence rate of dementia in the general older adult population.³⁹ Among MCI patients who convert to dementia, AD is the most prevalent etiology.⁴⁰ However, progression risks vary according to MCI subtype; amnesic MCI and multi-domain MCI subtypes progress more frequently to AD whereas non-amnesic MCI progresses more frequently to non-AD forms of dementia, including vascular dementia.^{39,41} Furthermore, patients with multi-domain MCI have a greater risk of developing AD than those with single-domain amnesic MCI.⁴⁴ While many individuals with MCI develop dementia, a substantial proportion remain cognitively stable or even improve, reverting to normal cognitive status (Fig. 2).⁴¹ Taken as a whole, epidemiological research suggests that MCI is a useful concept that describes the pre-dementia stage of AD but that it is a heterogeneous clinical syndrome in terms of both etiology and outcomes.^{39,45,46}

BIOMARKERS OF AD AND MCI

Several neuroimaging and other biomarker approaches are being used to study AD and MCI. In the short term, biomarkers of AD are needed to improve the selection of patients in clinical trials, while in the long term biomarkers are needed to identify high-risk patients for early treatment as well as for monitoring disease progression and response to treatment. This section describes some of the widely used biomarker approaches and the related findings in AD and MCI.

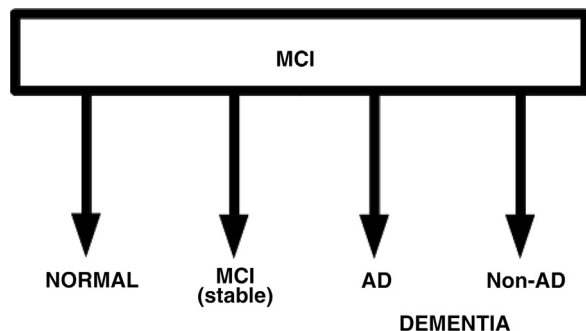


Figure 2. Clinical outcomes in patients with mild cognitive impairment (MCI). Many patients with MCI eventually develop dementia, either due to Alzheimer's disease (AD) or other causes (e.g., cerebrovascular). However, a substantial proportion of MCI patients stay cognitively stable and some even revert to normal cognitive status.

Magnetic Resonance Imaging

MRI uses a strong magnetic field and radio frequency waves to non-invasively characterize the structure of the brain by measuring the energy released by protons within various tissue components, such as gray matter, white matter, and cerebrospinal fluid (CSF). Volumetric MRI has been used to study regional patterns of brain atrophy in patients with MCI and AD.^{20,47,48} Medial temporal lobe atrophy, involving the hippocampus and entorhinal cortex in particular, is the earliest and most prominent MRI feature evident in AD and predicts progression from MCI to AD dementia.⁴⁹ On volumetric MRI, AD patients also show marked enlargement of the lateral ventricles, portions of which are adjacent to the medial temporal lobe.⁵⁰ Diffusion tensor imaging (DTI) is another MRI-based technique that, by measuring the diffusion of water molecules, is able to delineate the organization of white matter in the brain and allows researchers to quantitatively assess the integrity of white matter fiber tracts.⁵¹ DTI studies have shown that AD and MCI disrupt major white matter pathways in the brain, especially those within the limbic system (e.g., fornix and cingulum).^{21,52} Finally, functional MRI (fMRI) is a neuroimaging technique that indirectly assesses brain function by measuring blood-oxygen-level-dependent (hemodynamic) activity. One promising application of fMRI (known as 'resting-state' fMRI) is the measurement of intrinsic brain activity, which occurs irrespective of any external stimulation.⁵³ Resting-state fMRI studies have shown that AD and MCI are associated with decreased communication (functional connectivity) within the default mode network (DMN), a network of brain

regions involved in memory and internal information processing.⁵²

Positron Emission Tomography

Positron emission tomography utilizing 18F-fluorodeoxyglucose (FDG-PET) as a radioactive tracer is a nuclear imaging technique which measures regional brain metabolism. The earliest sign of AD detectable on an FDG-PET scan is the hypometabolism of the posterior cingulate cortex and precuneus.⁵⁴ This hypometabolism is also detectable at the MCI stage of the disease.⁵⁵ FDG-PET has also proven to be of value in distinguishing different forms of dementia, especially AD versus frontotemporal dementia.^{55,56} A recent advance is the development of *in vivo* PET-based amyloid imaging, which uses a special radioactive ligand that binds to amyloid plaques in the brain. Pittsburgh compound B (PiB) is a carbon-11-based amyloid-labeling ligand that is widely used in the research setting. Patients with AD show increased binding of PiB in temporal, parietal, and frontal brain regions, indicating widespread cortical distribution of amyloid deposition.⁵⁷ The FDA approved a different amyloid-labeling ligand, the fluorine-18-based florbetapir, for clinical use in 2012.⁵⁸ PET-based amyloid imaging is a novel and exciting diagnostic tool that non-invasively detects one of the hallmark molecular lesions of AD, but there remain several practical concerns about its use in the clinical setting. In addition to its high cost, there is a concern about the clinical utility of a positive amyloid scan. While a negative amyloid scan appears to rule out that a patient's cognitive impairment is due to AD (high negative predictive value), a positive amyloid scan is much less informative because it can be positive in many cognitively normal older adults and people with other non-AD neurological conditions (low positive predictive value).⁵⁹ For now, PET-based amyloid imaging is not covered by Medicaid or Medicare for routine clinical use in AD patients but only approved for limited use (e.g., to rule out AD or for selection of patients in clinical trials).⁶⁰

Fluid Biomarkers

CSF-based and blood plasma-based protein biomarkers are also being investigated for diagnosis of AD. Several studies have used immunoassays to measure the levels of various proteins in the CSF, finding that patients with AD show decreased levels of the 42 amino acid isoform of the A β (A β -42) peptide and elevated levels of the phosphorylated tau (P-tau) peptide.^{61,62} A recent longitudinal study showed that baseline A β -42/P-tau ratio could accurately predict the progression

from MCI to AD.⁶³ In 2007, plasma biomarkers were proposed as a promising alternative to CSF biomarkers for early detection of AD.⁶⁴ In recent years, other studies have examined the clinical utility of cell-signaling, immune, metabolic, and disease-related plasma proteins, but findings have been inconsistent.^{65–67} Overall, furtherwork must be done to standardize the measurement of CSF and plasma proteins and to determine the clinical utility of protein biomarkers for diagnosis of AD.

CONCLUSION

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available for managing AD. Our ability to find the 'cure' for AD ultimately depends not only on having an accurate view of the cellular and molecular processes that go awry but also on having optimal biomarkers to enable early diagnosis and timely therapeutic intervention in at-risk individuals. Recognizing the urgent need to develop clinically useful neuroimaging and other biomarkers for the early detection of AD, the NIA sponsored the ongoing Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in 2004.⁶² The ADNI, which is akin to the Framingham Heart Study in its ambitions, is a public-private partnership and the largest project of its kind that seeks to collect longitudinal neuroimaging data along with clinical data, neuropsychological assessments, and biological specimens (e.g., blood and CSF) from MCI, AD, and healthy older subjects. The ADNI and similar large-scale initiatives are likely to rapidly advance our knowledge on dementia and AD and will catalyze the development of significantly more effective therapies for AD than exist today. To conclude, the reader is left with some important issues that must be resolved in the future as we move toward a 'cure' for AD in the 21st century:

- (1) What is the optimal combination of biomarkers for (a) early detection of AD; and (b) monitoring disease progression and response to treatment?
- (2) What is the optimal therapeutic strategy for (a) prevention of AD; (b) treatment of AD; and (c) sporadic versus familial AD? (i.e., therapeutic targets, role of medications versus lifestyle modification, optimal time to intervene)
- (3) What are the potential benefits and harms associated with shifting the therapeutic strategy from (a) one that involves treating people with overt AD dementia to (b) one where we treat people with MCI, and ultimately to (c) one where we treat people who are asymptomatic but show an AD-like biochemical and/or imaging biomarker pattern? Are we moving closer to treating abnormal lab results as opposed to the patient? For example, would we be abiding by the oath to 'first, do no harm' by treating an asymptomatic person who shows an AD-like biomarker pattern but is not destined to develop cognitive impairment (e.g., due to his/her high cognitive reserve or resilience in the face of AD pathology).

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