Alzheimer Disease: Standard of Diagnosis, Treatment, Care, and Prevention

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Alzheimer disease (AD) is the most frequent cause of dementia in people 60 y old or older. This white paper summarizes the current standards of AD diagnosis, treatment, care, and prevention. Cerebrospinal fluid and PET measures of cerebral amyloidosis and tauopathy allow the diagnosis of AD even before dementia (prodromal stage) and provide endpoints for treatments aimed at slowing the AD course. Licensed pharmacologic symptomatic drugs enhance cholinergic pathways and moderate excess of glutamatergic transmission to stabilize cognition. Disease-modifying experimental drugs moderate or remove brain amyloidosis, but so far with modest clinical effects. Nonpharmacologic interventions and a healthy lifestyle (diet, socioaffective inclusion, cognitive stimulation, physical exercise, and others) provide some beneficial effects. Prevention targets mainly modifiable dementia risk factors such as unhealthy lifestyle, cardiovascular–metabolic and sleep–wake cycle abnormalities, and mental disorders. A major challenge for the future is telemonitoring in the real world of these modifiable risk factors.

Key Words: PET; dementia; amyloid; biomarkers; prevention; treatment

Seven of the top 10 causes of death include Alzheimer disease (AD) and related dementias, as well as associated risk factors: ischemic heart disease, stroke, chronic obstructive pulmonary disease, and type 2 diabetes (1). There are about 55 million people with dementia. Dementia is expected to increase 42% (to 78 million people) by 2030 and more than 250% (to 139 million people) by 2050, mostly among women (2). Longitudinal associations exist between AD and overweight and obesity, hypertension, high cholesterol, low respiratory function, high blood levels of homocysteine, and cooccurring vascular comorbidities. Concomitant associations exist for vascular risk factors and AD-related brain pathologies as well as white matter hyperintensities, neurodegeneration, blood–brain barrier disruption, cerebral infarcts, and various forms of cerebrovascular disease. The evidence base for AD prevention appears strongest for control of vascular risk factors.

Other AD risk factors include environmental risk factors such as high stress, air pollution, and lack of social support; depression; and sociodemographic factors, including low education, low income, and social isolation (3). Susceptibility genes for AD support systems-biology approaches for dyslipidemias, blood pressure dysregulation, body weight dysregulation, type 2 diabetes, systemic inflammation, neuroinflammation, and immune alterations.

These data provide a solid foundation for understanding the pathogenesis of AD as a multifactorial process and for AD prevention strategies.

AD PATHOGENESIS

The most widely accepted view on AD pathogenesis is based on the amyloid cascade hypothesis, published in 1992 (4) and repeatedly revised. This hypothesis is based on the disease-defining presence of amyloid plaques in the brain at autopsy and the observation that rare cases of autosomal-dominant AD are associated with mutations in amyloid-related genes encoding the amyloid precursor protein or one of the two secretases involved in amyloid precursor protein processing, presenilin-1 and presenilin-2. The *APOE* ε4 allele is the most strongly and consistently associated risk gene for sporadic AD. It is associated with many pathogenic pathways, including increased amyloid production.

The widespread failure of amyloid-centered treatments triggered the search for a broader perspective on AD pathogenesis (5). In addition to amyloid, pathologic phosphorylation and subsequent loss of function of the microtubule-associated protein tau, oxidative stress, impaired glucose metabolism, and upregulation of neuroinflammation play key roles in AD pathogenesis and interact with amyloid pathology. Supplemental Table 1 reports AD pathogenic events that are amenable to molecular brain imaging (supplemental materials are available at http://jnm.snmjournals.org).

CLINICAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF AD

Cognitive symptoms such as forgetfulness—or concern by family members—prompts patients to make initial contact with a primary care physician. This physician has a decisive role in the diagnostic journey of the patient. The first diagnostic step, already accessible in primary care, is the medical history of the patient (self or per proxy), complemented by a cognitive screening test and physical examination. These clinical examinations can determine, in most cases, whether cognitive impairment or dementia is present.

One important clinical distinction is a full syndrome of dementia (i.e., cognitive impairment severe enough to impair daily activities) versus mild cognitive impairment (MCI) (i.e., impairment in one or more cognitive domains with maintained global cognitive function and daily activities) versus subjective cognitive decline (i.e., cognitive complaints without impairment on cognitive tests). Both MCI and subjective cognitive decline are recognized as risk states for development of dementia, but most countries do not endorse specific pharmacologic treatments outside clinical trials.

The etiologic diagnosis of MCI or a dementia syndrome will typically be conducted by a specialist. Diagnosis requires in-depth neuropsychologic and neurologic examinations, basic laboratory testing, and structural brain imaging using MRI or CT. Further diagnostic work-up may include biomarkers from PET brain imaging, cerebrospinal fluid (CSF), and (in the future) peripheral blood. Etiologic diagnosis is challenging, since autopsy studies show that comorbidities of two or more neurodegenerative proteinopathies are common.

Clinical and pathologic features of AD and its differential diagnoses are reported in Supplemental Table 2. A thorough account of the AD diagnostic process is provided in the World Alzheimer Report 2021 (6).

Research criteria ushered in the diagnoses of prodromal and preclinical stages of AD. Based on earliest presence of MCI and positive AD biomarkers, the International Working Group 2 criteria allow diagnosis of prodromal AD (7). The criteria of the U.S. National Institute on Aging and Alzheimer Association endorse a diagnosis of preclinical AD with the presence of positive AD biomarkers (CSF or amyloid imaging) and the absence of cognitive impairment (8). These criteria have further been systematized as the A/T/N classification scheme (Table 1) (9).

NEUROPSYCHOLOGY

The diagnostic work-up of patients with suspected AD includes cognitive screening using, for example, the Mini–Mental State Examination or Montreal Cognitive Assessment. Short clinical instruments are well suited to the detection of impairment consistent with dementia and to the quantification of dementia progression over time. However, neuropsychologic tests of specific cognitive domains are more sensitive to early changes and provide useful information for differential dementia diagnoses. Popular short test batteries suited for the detection and characterization of MCI are the Consortium to Establish a Registry for AD Neuropsychological Battery (10), the Uniform Dataset Test Battery of the American AD Research Centers (11), and the Repeatable Battery of Neuropsychological Status (12).

More recent approaches to sensitively detect cognitive decline and account for day-to-day variations in performance include continuous monitoring of cognitive performance using digital devices, such as serious games applications. Descriptions of these approaches are beyond the scope of this standard-of-care article but have been published (13).

BIOMARKER-BASED DIAGNOSIS

Fluid Biomarkers

Several CSF biomarkers are well established and standard for AD diagnosis. A lower CSF $A\beta_{1-42}$ and higher CSF total tau or phosphorylated tau provide in vivo evidence of AD pathology, as integrated into the A/T/N scheme (Table 1). A lower CSF $A\beta_{1-42}$ concentration is associated with greater amyloid plaque formation (9). Total tau and phosphorylated tau reflect neuronal degeneration and tangle pathology, respectively (9). The combination of CSF markers—CSF $A\beta_{1-42}$ and total tau or phosphorylated tau—performs better than each individually for diagnosing AD (14).

Since CSF collection involves lumbar puncture, this led to the search for minimally invasive blood-based biomarkers. One candidate is plasma neurofilament light chain, which is increased in patients with AD and may be useful to monitor neurodegeneration, disease progression, and treatment response. In addition, plasma $A\beta_{42}$ and $A\beta_{40}$ predict brain amyloid burden status at any stage of AD (15). Plasma $A\beta_{42}$ and $A\beta_{40}$ could be used to screen for individuals likely to develop brain amyloidosis and who are at risk for AD (16). Furthermore, plasma phosphorylated tau 181 levels are increased in AD patients, compared with controls, and are strongly associated with both $A\beta$ and tau PET (17). Moreover, plasma phosphorylated tau 217 has also accurately discriminated AD from other neurodegenerative diseases and was more accurate than other established plasma- and MRI-based biomarkers (18). The sensitivity and specificity of fluid biomarkers for AD are provided in Table 2.

Neuroimaging/PET Biomarkers

Neuroimaging techniques provide the best opportunity to visualize and quantify neurodegenerative and molecular changes in the living human brain over the course of AD (Fig. 1). MRI has been included in dementia-screening protocols for decades. The most widely used MRI techniques to support a diagnosis of clinical AD are measures of regional brain volumes using T1-weighted images. These images are visually assessed by a trained radiologist who uses standardized rating scales to determine the level of atrophy in the medial temporal lobe, posterior brain, or global brain. In addition,

TABLE 1
A/T/N Classification

Classification	Description
A (amyloid)	Decreased CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio or positive amyloid PET
T (tau)	Increased CSF phosphorylated tau or positive tau PET
N (neurodegeneration)	Atrophy on structural MRI or decreased uptake on ^{18}F-FDG PET or increased CSF total tau

Amyloid and tau are considered defining biomarkers of AD. Neurodegeneration is used to stage severity of disease (independently from AD pathology).

TABLE 2
Sensitivity and Specificity of CSF- and Blood-Based Biomarkers for AD

Parameter	Biomarker	Sensitivity	Specificity	Reference
CSF	$A\beta_{1-42}$	96.4%	89%	(37)
	Phosphorylated tau	81%	91%	(37)
	Mean value of phosphorylated tau			
	Phosphorylated tau 181	79%	96%	(38)
	Phosphorylated tau 217	91%	91%	(38)
	Total tau	81%	91%	(37)
	Combination of $A\beta_{1-42}$ and total tau or phosphorylated tau	90%–95%	90%	(14)
Plasma	Neurofilament light chain*			(39)
	$A\beta_{42}/A\beta_{40}$	70%	70%	(16)
	Phosphorylated tau 181	92%	87%	(17)
	Phosphorylated tau 217	93%	83%	(18)

*Unspecific marker of neurodegeneration, useful for monitoring progression of disease.

various forms of vascular pathology can be assessed, including white matter hyperintensities (using T2-weighted or fluid-attenuated inversion recovery MRI sequences), infarcts, and microhemorrhages (using susceptibility-weighted T2* MRI sequences). MRI is also used to exclude other causes of cognitive impairment such as stroke, brain tumors, or multiple sclerosis.

Another established neuroimaging marker of neurodegeneration is glucose hypometabolism measured with ^{18}F-FDG PET. In persons with AD, ^{18}F-FDG PET shows a hypometabolic pattern that affects primarily the posterior cingulate, precuneus, and lateral temporal and parietal regions.

The neurodegenerative patterns observed on structural MRI and ^{18}F-FDG PET images show modest differential diagnostic accuracy between AD and non-AD neurodegenerative disorders (~70%–80%). Neurodegenerative disorders are characterized by substantial functional and anatomic heterogeneity; hence, there is substantial overlap between neurodegenerative disorders on MRI and ^{18}F-FDG PET. The advent of PET tracers that detect the neuropathologic hallmarks of AD in vivo represents a genuine breakthrough in the field. The first PET tracer that could detect the presence of fibrillar amyloid-β pathology was ^{11}C-Pittsburgh compound B. There is a strong association between antemortem ^{11}C-Pittsburgh compound B PET signal and postmortem amyloid-β load (sensitivity, 92%; specificity, 97%) (19). Findings on ^{11}C-Pittsburgh compound B PET are abnormal early in the disease process, and investigational use of this tracer in the clinic shows positive changes in diagnostic confidence and patient management. Subsequently, several ^{18}F amyloid-β tracers became available, that is, ^{18}F-flutemetamol, ^{18}F-florbetaben, and ^{18}F-florbetapir, which showed characteristics similar to those of ^{11}C-Pittsburgh compound B and are now approved for clinical use with a visual read metric as the method to determine amyloid-β status by, for example, the U.S. Food and Drug Administration (FDA) and European Medicines Association. The primary strength of amyloid-β tracers for diagnostic purposes is their negative predictive value. A diagnosis of AD can be ruled out with high certainty if the amyloid-β PET scan yields a negative result. A downside of this sensitivity of the amyloid-β tracers is their limited specificity. Amyloid-β–positive PET scans are observed in 10%–40% of the cognitively normal population, and this percentage increases with age (20).
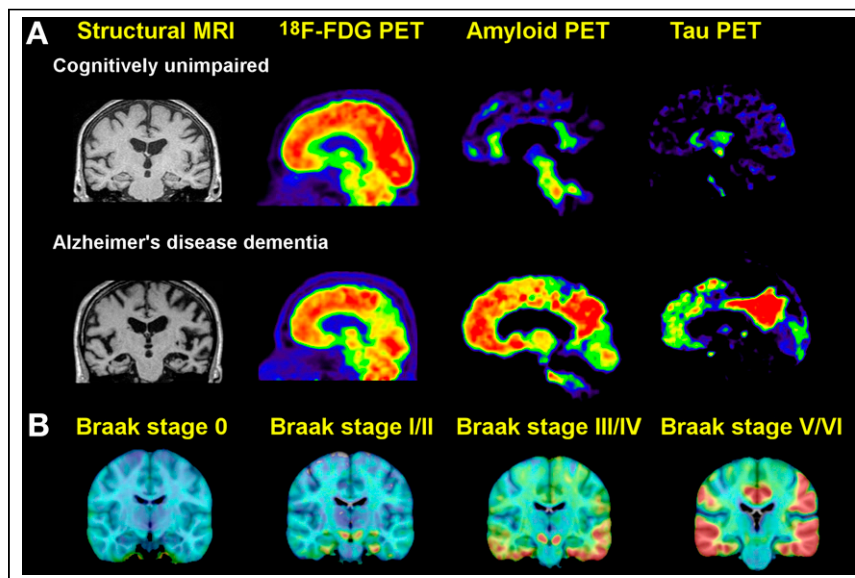

FIGURE 1. Imaging features of AD. (A) Different neuroimaging profiles of cognitively normal individual and patient with AD dementia in terms of brain atrophy on T1-weighted MRI, glucose hypometabolism on ^{18}F-FDG PET, amyloid burden on ^{11}C-Pittsburgh compound B PET, and tau load on ^{18}F-flortaucipir PET. (B) Neuropathologic staging system of neurofibrillary tangles proposed by Braak and Braak can be recapitulated using tau PET with ligand ^{18}F-RO948 and shows increasing tau PET retention from stage 0 to stage V/VI.

Recently, several novel tau PET tracers (e.g., ^{18}F-flortaucipir, ^{18}F-MK6240, and ^{18}F-RO948) were introduced that detect the presence of AD-like tau aggregates (i.e., a combination of 3R and 4R tau in paired helical filaments) with high affinity and selectivity. In May 2020, the first tau PET tracer was approved by the FDA to support the diagnosis of suspected AD dementia. Future work regarding tau PET tracers will define optimal methodologies (i.e., visual read metrics or quantitative thresholds) and the most appropriate use.

Section 1 of the supplemental materials expands the perspective on imaging markers to resting-state electroencephalography as a potential screening instrument for AD (*21*).

MEDICAL TREATMENT OF AD

Pharmacologic treatment of clinically symptomatic AD has 2 major elements. The first element is critical review of the patient's current medications, particularly for potential anticholinergic side effects that impair memory and increase the risk of delirium. Other contraindicated drugs are sedatives, such as benzodiazepines, and (low-potency) antipsychotics. Several indices are available for clinicians and pharmacists to identify potentially inappropriate medication combinations and possible alternatives (*22*).

The second element is the prescription of an antidementia drug. Supplemental Table 3 lists approved antidementia drugs with their clinical indications, major side effects, and typical dosages. None of these drugs has convincingly shown disease-modifying effects, but all have shown symptomatic benefits, with reduced rates of cognitive decline, reduction of caregiver burden, and, in some studies, delayed institutionalization when compared with placebo (*23*). Of note, AD is severely underdiagnosed in primary care. Studies show that fewer than 50% of people with AD receive specific dementia drug treatment (*24,25*). There is much room for improvement.

DISEASE-MODIFYING TREATMENTS

Repeated antiamyloid failures were a setback for patients and scientists, but they also led to sharpening of inclusion criteria and an early diagnosis of AD. However, until January 2022, and including aducanumab, recently approved by the FDA, no antiamyloid antibody therapy has successfully reached the clinical endpoint in a completed phase 3 study. Phase 3 trials are ongoing with antiamyloid antibodies, such as gantenerumab, lecanemab, and donanemab, which, in preclinical studies, selectively bound to aggregated Aβ,. These newer-generation antiamyloid antibodies have consistently shown removal of brain Aβ through amyloid PET imaging studies (*26*) and, in phase 2 studies, have shown improvements in primary cognitive outcomes (*26,27*).

Aducanumab (Aduhelm; Biogen) was approved by the FDA on June 7, 2021, using the FDA's accelerated-approval pathway. On December 16, 2021, the European Medicines Agency recommended refusing the marketing authorization for aducanumab. Of note, treatment with aducanumab was restricted by the FDA in July 2021 to prodromal and mild stages of AD with proven amyloid positivity via CSF or amyloid PET.

Nonpharmacologic treatment options are described in section 2 of the supplemental materials (*28,29*).

AD PREVENTION AND MULTIMODAL INTERVENTIONS

It is estimated that 40% of all dementias in high-income countries could be prevented or delayed with elimination of low early-life education, midlife obesity, hypertension, alcohol consumption above 21 units a week, diabetes mellitus, depression, physical inactivity, smoking, traumatic brain injury, late-life hearing loss, social isolation, and exposure to air pollution (*3*).

In 2019, the World Health Organization issued widely recognized guidelines on risk reduction for cognitive decline and dementia (*30*). The guidelines provide the knowledge base for health-care providers, governments, policy makers, and other stakeholders to reduce the risks of cognitive decline and dementia.

Knowledge about risk factors is also translated into preventive interventions for individuals at risk (selective prevention) to preserve or improve cognitive function and delay or prevent dementia (*31*). Although early intervention studies focused on one factor at a time (single-domain intervention studies), multidomain interventions focus on several modifiable risk factors simultaneously among those at risk for cognitive decline and dementia. The prototype Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGERS) reported a benefit from a multidomain lifestyle intervention on cognitive function over 2 y (*32*). Similar European trials, such as the French Multidomain Alzheimer Preventive Trial and the Dutch Prevention of Dementia by Intensive Vascular Care Trial have been less conclusive. However, benefits for cognitive function in specific subgroups of adults with higher risk for dementia were suggested (*33,34*). These promising but still inconsistent results have led to World-Wide FINGERS, a global, interdisciplinary network with a mission to share knowledge and experiences on trials for dementia prevention and risk reduction, harmonize data, and plan joint international initiatives for the prevention of cognitive impairment and dementia (https://wwfingers.com/#about). World-Wide FINGERS brings together, from over 40 countries, culturally specific lifestyle trials comprising dietary guidance, physical exercise, cognitive training, social activities, and management of vascular and metabolic risk factors. These trials differ by individuals targeted (asymptomatic states to early symptomatic stages of dementia); risk factors addressed; and cultural, geographic, and economic settings (*31*). Another ongoing multidomain lifestyle trial is the German AgeWell.de, a pragmatic, clustered, randomized controlled trial addressing cognitive decline in a primary-care population at increased risk for dementia (*35*).

Although multidomain interventions seem promising for selected prevention in high-risk individuals, the data are inconclusive. Questions remain with regard to the intervention "dose" needed to change behavior, the optimal intervention window during the life course, target groups, best modes of intervention delivery (face-to-face vs. virtual), and suitable implementation settings (e.g., primary care) (*36*). AD prevention is a dynamic research field. The potential for dementia prevention is huge and not even close to being fully understood.

DISCLOSURE

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