Preclinical, Prodromal, and Dementia Stages of Alzheimer’s Disease

Identifying the correct stage of Alzheimer’s disease helps in managing risk, diagnosis, and management decisions.

By Douglas W. Scharre, MD

Definitions

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by the neuropathologic findings of amyloid plaques and neurofibrillary, tau-based, tangles.\(^1\) The neuropathologic features begin 15 to 20 years before obvious cognitive symptoms. Individuals with AD will progress from their normal baseline cognitive abilities through subtle changes of the preclinical stages to obvious symptoms of brain dysfunction, termed prodromal AD, and finally, to AD dementia, which eventually impairs ability to perform activities of daily living (ADL) that they were previously independently performing, owing to cognitive deficits.

The preclinical stage of AD is often considered the stage occurring before a clinical diagnosis of a cognitive disorder is considered. As we are discovering new AD biomarkers and performing careful evaluations of individuals, however, we find it more and more possible to identify those individuals who are in a preclinical stage of AD. Early identification could be critical because recent clinical trials of disease-modifying agents suggest that therapeutics work best if started at early stages. The International Working Group (IWG) and the American Alzheimer’s Association have begun to define the boundaries of this preclinical stage of AD.\(^2\) Individuals with autosomal dominant mutations, should they live long enough, who will develop AD have been termed as having presymptomatic AD. Those with familial and other risk factors are at higher risk to develop AD later in life. Because these individuals may not have the start of the neuropathologic changes of AD, they are not included in this preclinical stage. The National Institute on Aging/Alzheimer’s Association (NIA/AA) definitions are based on positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis findings (Box). In this article, however, we will discuss only those early clinical features and symptoms that could represent the subtle changes that a neurologist or practitioner could identify by a clinical evaluation. The challenge is in distinguishing these subtle changes from normal aging and taking into consideration education level, cultural background, and primary language.

The prodromal stage of AD is also referred to as mild cognitive impairment (MCI) due to AD, and this is the stage where there are obvious symptoms of brain dysfunction. Not only does the individual have to meet criteria for MCI but also the primary underlying pathophysiology is judged by a clinician to be due to AD.\(^5\) This can be verified most accurately if there is biomarker evidence of accumulating AD neuropathology. Even without biomarker evidence, however, an experienced clinician can make the diagnosis of prodromal AD if based on their assessments and evaluations, the likely underlying pathophysiology is thought to be AD. Greater precision is necessary for clinical trials where verification of the underlying pathology is required; clinical diagnosis is confirmed in most participants with MCI and a greater number of those diagnosed with mild AD dementia when the clinical symptoms are more definitive. The standard criteria for MCI are: a concern about changes in cognit-

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Box. National Institute on Aging/Alzheimer’s Association (NIA/AA) Definitions\(^3,4\)

Preclinical Stage 1: evidence of amyloidosis on PET imaging or CSF analysis

Preclinical Stage 2: evidence of amyloidosis and neurodegeneration on PET imaging and CSF analysis

Preclinical Stage 3: evidence of amyloidosis, neurodegeneration, and subtle cognitive changes
tive abilities, impairment in 1 or more cognitive domains more than expected for the patient’s age and education, preservation of independence in functional abilities, and no significant impairment in social or occupational functioning (not demented). Determining preservation of independence in ADL and social/occupational functioning can be challenging. If an individual decided to stop paying the bills owing to lack of confidence related to his or her cognitive impairment, it might mean that she or he could still be independent at the task (MCI) but prefers not to do it or that they actually would require assistance from others to complete the task (dementia). Practically speaking, for practicing clinicians, individuals who are classified as being in the prodromal stage of AD will be a combination of those with MCI due to AD and those with very mild AD dementia.

The dementia stage of AD occurs when there is significant impairment in an individual’s social and occupational functioning, manifested by loss of independence to perform ADL because of cognitive impairments. In these cases, the individual can no longer perform a task without the help of another person. Typically, AD dementia involves impairment of memory plus other cognitive domains (eg, executive, language, and visuospatial functions). Serial evaluations improve the ability to correctly classify an individual’s stage of disease (Table 1).

**Preclinical Stages**

For individuals at increased risk for AD from genetic factors (eg, family history or APOE genotype), it may be wise to watch for preclinical signs of AD. Alternatively if there are very mild progressive changes noted in cognition or behaviors in an individual over age 55, considering the possibility of preclinical AD may be worthwhile. Identification of subtle cognitive and behavioral changes is enhanced by having a knowledgeable informant who knows the person’s premorbid abilities and behaviors very well. Identifying cognitive changes is also enhanced by having a prior baseline evaluation of an individual’s cognitive skills. At times, these subtle changes in thinking abilities are first noticed by the individual, termed subjective cognitive impairment (SCI) when cognitive testing reveals no significant evidence of objective impairments.

Although there are no specific criteria to define what constitutes the subtle thinking and behavior changes in preclinical AD, there are some common signs and symptoms that are noticed in many individuals who later develop

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<th>TABLE 1. KEY CHARACTERISTICS OF ALZHEIMER’S DISEASE STAGES</th>
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<td><strong>Preclinical</strong></td>
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<tr>
<td><strong>Cognition</strong></td>
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<td><strong>Function</strong></td>
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<td><strong>Behaviors</strong></td>
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<td><strong>Biomarkers</strong></td>
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<td><strong>Clinical considerations</strong></td>
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Abbreviations: AD, Alzheimer’s disease; ADL, Activities of Daily Living; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; PET, positron emission tomography.
prodromal AD. Emerging research using sensitive neuro-psychologic testing, neuroimaging, and CSF biomarkers will reveal abnormalities that can be detected to diagnose preclinical AD.

The earliest cognitive impairments appear to involve episodic memory loss, related to hippocampal damage, and executive deficits. Anomia, visuospatial impairments, and disorientation typically occur later. The earliest memory impairments include reduced word list learning curves, lower-than-expected free delayed recall, possible false positive intrusions on word recall, but perfect or near perfect recognition recall. Normal aging would result in a normal learning curve and less false positive intrusions. A cognitive composite test of episodic memory, executive abilities, and orientation is thought to represent some of the earliest cognitive changes noted in cohort studies from normal individuals who later progressed to prodromal AD and AD dementia. This composite, consisting of the Free and Cued Selective Reminding Test (FCSRT), delayed paragraph recall, Digit-Symbol Substitution Test, and Mini-Mental Status Examination (MMSE), is used in the antiamyloid treatment in asymptomatic AD (A4) trial. Cognitive deficits remain the best biomarker sensitive to change over time.

The earliest changes in behaviors include apathy, mild irritability, dysphoria, and impaired insight. Individuals may reduce their normal activities for no apparent reason, socialize less, and exercise less. Often slowing down in activities is attributed to normal aging. Recent studies have focused on defining mild behavioral impairment changes as a potential early marker for neurodegenerative disease. Neuroimaging and CSF biomarkers are being used to detect preclinical AD (see Imaging in Differential Diagnosis of Dementia and Biomarkers in Alzheimer’s Disease in this issue). The neuropathology of AD begins many years before symptoms appear and as much as 30 years before dementia occurs. In the preclinical AD stage, β amyloid can be detected in the CSF and on amyloid positron emission tomography (PET); tau can be detected in CSF and on tau PET imaging; and brain glucose hypometabolism in a pattern of mesial temporal and parietal regional loss can be detected by fluorodeoxyglucose (FDG) PET neuroimaging.

When there is suspicion for preclinical AD, despite a lack of specific treatments, an individual can seek out and participate in clinical trials to investigate new biomarkers or treatments. The individual and their family can begin planning financial and resource needs, set up durable powers of attorney and advance care directives, and consider informed decision making for research participation in the future.

**Prodromal Stages**

Although it can be very difficult for a health care provider to identify the preclinical AD stage, it is imperative that neurologists, psychiatrists, and primary care providers easily recognize the prodromal AD stage (MCI due to AD plus very mild AD dementia) when obvious symptoms of brain dysfunction are evident (Table 1). Unfortunately, although individuals may be cognizant of declines in thinking, they may be embarrassed to bring it up to their health care team, somehow worried that it reflects poorly on them. They may often conclude that they are experiencing just normal forgetfulness of aging and that their symptoms are minimal (impaired insight). Consequently, these persons present to a physician an average of 3 to 4 years after cognitive symptoms began. It is critical to obtain history from someone other than the affected individual. Family members typically will report that they noticed a person’s cognitive deficits earlier than the person himself or herself, but they usually do not notify the person’s health care team.

Early identification of prodromal AD is enhanced greatly using an office-based multidomain cognitive assessment to detect the degree and type of deficits. Objective assessment of cognitive abilities is essential to obtain a baseline score, identify cognitive impairments, and follow changes over time in at-risk patients. This may practically be performed in the US during the Medicare Annual Wellness Visit. Individuals who perform very well on an office-based multidomain test but are suspected by informants of definite decline in cognitive function may require formal neuropsychologic testing. Multidomain brief cognitive tests listed in Table 2 are an easy way to obtain a standardized score across a range of cognitive domains in approximately 10 to 15 minutes. Simple wordlist learning tests, verbal fluency tests, and clock draw tests take less time to perform but do not provide as robust an assessment of other cognitive domains. Office-based cognitive tests for MCI need to be sensitive enough to detect early deficits.

Individuals in the prodromal AD stage will exhibit obvious short-term memory deficits (Table 1). The family will often report that they ask the same question over again as if they had not asked it before. They may misplace items more frequently and have more difficulty learning something new. Formal memory testing will typically reveal a reduced wordlist learning curve, lower-than-expected free delayed recall, false positive intrusions on word recall, and not clueing as well on recognition word testing. Often the individual will not recall the date correctly. Language skills, working memory, and sense of direction are generally intact, but there is usually some decline in problem solving and decision-making skills.

In late MCI and early stages of AD dementia there are difficulties with completely independent performance of instrumental ADL (eg, driving, paying bills, working, participating in community affairs, shopping, and cooking) that noticeably affect people’s ability to function. They may still...
### TABLE 2. FEATURES OF COMMONLY USED OFFICE-BASED MULTIDOMAIN COGNITIVE TESTS FOR DEMENTIA

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<tr>
<td><strong>Scoring range</strong></td>
<td>0-30; higher score better</td>
<td>0-30; higher score better</td>
<td>0-30; higher score better</td>
<td>0-22; higher score better</td>
</tr>
<tr>
<td><strong>Domains tested</strong></td>
<td>Orientation, memory, constructions, language, calculations, attention</td>
<td>Orientation, memory, clock drawing, constructions, fluency, language, abstraction, calculations, executive, attention</td>
<td>Orientation, memory, clock drawing, animal fluency, attention</td>
<td>Orientation, memory, clock drawing, constructions, fluency, language, abstractions, calculations, executive function</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Clinician with patient</td>
<td>Clinician with patient</td>
<td>Clinician with patient</td>
<td>Self-administered paper (SAGE) or electronic (BrainTest)</td>
</tr>
<tr>
<td><strong>Time to administer</strong></td>
<td>7-10 minutes</td>
<td>10-13 minutes</td>
<td>10 minutes</td>
<td>10-15 minutes</td>
</tr>
<tr>
<td><strong>Formats available</strong></td>
<td>Paper with serial 7s and WORLD backwards versions</td>
<td>Paper with 3 alternate versions; electronic via app store using a tablet</td>
<td>Paper; 1 version</td>
<td>Paper (SAGE) with 4 equivalent forms; electronic (BrainTest) via mobile apps (iOS/Android/Amazon) using a tablet or at <a href="http://www.braintest.com">www.braintest.com</a></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Well-known scale; often used as proxy to stage dementia severity</td>
<td>Less ceiling effect than MMSE due to greater difficulty and more executive function tests; more sensitive to mild impairments than MMSE</td>
<td>Less ceiling effect than MMSE due to greater difficulty; Emphasizes memory tasks; different cutoffs for Mild NCD and dementia</td>
<td>Less ceiling effect than MMSE due to greater difficulty and more executive function tests; able to distinguish between MCI and dementia</td>
</tr>
<tr>
<td><strong>Pitfalls</strong></td>
<td>Ceiling effect especially in more educated patients; executive testing limited; does not distinguish between MCI and dementia</td>
<td>Some difficulty distinguishing between MCI and dementia</td>
<td>Less evaluation of language, constructions, and executive abilities than MoCA or SAGE</td>
<td>Memory testing limited</td>
</tr>
<tr>
<td><strong>Specificity/ sensitivity to detect dementia</strong></td>
<td>84%/78% with cutoff 26 or less[^18]</td>
<td>87%/100% with cutoff of 25 or less[^15]</td>
<td>Comparable to MMSE but better at detecting mild NCD[^16]</td>
<td>SAGE: 95%/95% with cutoff 16 or less for dementia and 95%/79% with a cutoff of 16 or less for cognitive impairment[^17]; BrainTest: 100%/95% with a cutoff of 14 or less for dementia and 90%/71% with a cutoff of 15 or less for cognitive impairment[^19]</td>
</tr>
<tr>
<td><strong>Correlations to neuropsychologic tests</strong></td>
<td>0.587 Spearman rank correlation[^19]</td>
<td>0.727 Spearman rank correlation[^19]</td>
<td>Significantly correlated with every neuropsychologic measure (r = .25 to .46), except for Trails B (r = .14)^[^20]</td>
<td>0.678 for paper SAGE and 0.729 for electronic BrainTest Spearman rank correlation[^19]</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>50 tests for $89 through PAR</td>
<td>Free for paper; $10/month for electronic app subscription</td>
<td>Free</td>
<td>Free for paper SAGE; $25 semi-annually for electronic BrainTest subscription</td>
</tr>
<tr>
<td><strong>Obtaining test</strong></td>
<td>PAR</td>
<td>Mocatest.org for paper MoCA and via app store for electronic</td>
<td><a href="http://aging.slu.edu/pdf-surveys/mentalstatus.pdf">http://aging.slu.edu/pdf-surveys/mentalstatus.pdf</a></td>
<td>Sagetest.osu.edu for paper SAGE and <a href="http://www.braintest.com">www.braintest.com</a> or via app store for electronic BrainTest</td>
</tr>
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Abbreviations: MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; NCD=Neurocognitive disorder; PAR, Psychological Assessment Resources; SAGE, Self-Administered Gerocognitive Examination; SLUMS, Saint Louis University Mental Status.
be able to write out checks correctly to pay a bill but are no longer involved in financial decisions. Perhaps they are able to cook simple meals but would no longer be able to prepare a complete dinner for a family of 4. Reduced engagement in previously pleasurable activities is observed.

Neuropsychiatric disturbances in the prodromal AD stage are common and typically involve impaired insight, apathy, irritability, dysphoric mood, and anxiety.

If the diagnosis is uncertain for an individual, prodromal AD can be verified most accurately by evaluating for biomarker evidence of AD neuropathology or temporal/parietal hypometabolism with CSF analysis (amyloid β-42, tau, and phosphorylated tau [p-tau]), FDG PET, or amyloid PET evaluations. Tau PET is currently only a research tool. Brain atrophy in a pattern of mesial temporal and cortical parietal regions can be detected by structural neuroimaging.

When someone has been diagnosed with prodromal AD, a Food and Drug Administration (FDA)-approved cholinesterase inhibitor indicated for AD dementia can be prescribed and/or participation in a clinical trial encouraged. The sooner individuals start treatment, the better the outcomes. It is suggested that families increase their supervision of the individual to reduce potential poor judgment with finances, driving, medication use, and symptom reporting. This enhanced supervision may improve rate of adherence to treatment for any other chronic medical conditions, reduce medication errors, decrease hospital admissions or emergency room visits, improve quality of life for the patient, and reduce financial and caregiver burden. Financial planning and advanced directives need to be completed.

**Dementia Stages**

Unfortunately, too often, individuals present to a neurologist or primary care provider already demented and not treated. At this stage cognitive impairment is present to such a degree that a person unfamiliar with them would usually be able to identify thinking problems after a short visit with them (Table 1). The person would be unable to perform independently many ADL they used to perform well.

The use of an office-based multidomain cognitive assessment tool (Table 2) will typically be sufficient to detect the degree and type of deficits. Assessments every 6 months are commonly obtained and will identify persons who are progressing from the prodromal AD stage to the AD dementia stage. Serial assessments can also help determine the utility of treatments over time. Because AD dementia often progresses at a steady decline, any rapid drops in assessment scores warrant investigation for other factors that can influence cognition (eg, infection or new medications).

People with AD dementia have easily discernible progressive short-term and eventually long-term memory loss. Misplacing items and repeating questions often occur on a daily basis. Formal memory testing will reveal a reduced wordlist learning curve, very poor free delayed recall, false positive intrusions on word recall, and poor ability for clues to help them recall a newly told story or a word list. Typically, they will not be able to recall the correct date, day of week, and eventually month or year. Word finding difficulty for everyday objects is now obvious when they speak. Impaired comprehension skills require use of simpler words, no compound sentences, and single-topic conversations. Verbal fluency is reduced and commonly they are unable to name more than 12 animals in 1 minute. Individuals reduce their reading to headlines and short stories and writing skills are degraded. Executive impairments are now obvious with reduced ability to plan ahead, think more concretely and less abstractly, multitask, make insights, use good judgment, and make complex and then simple decisions. Individuals with dementia stage AD will not be able to handle a household emergency well on their own. The individual now typically will get turned around in familiar places and struggle copying 3-dimensional and then 2-dimensional figures. Later they become unable to even recognize family members or familiar places.

In AD dementia stages, loss or significant decline in performance of instrumental ADL (eg, working, driving, finances, medication management, shopping, cooking, using appliances, housekeeping, yard work, computer/tablet use, cell phone use, and TV remote use) and then even basic ADLs (eg, dressing, grooming, bathing, feeding, toileting, and continence) occur gradually over time.

Neuropsychiatric disturbances in the AD dementia stage are increasingly common as the individual moves from the mild to moderate AD stage. Behaviors then often improve when severe dementia occurs. Common neuropsychiatric behavioral disturbances in the mild-to-moderate stages that often lead to institutionalization are irritability, resistance to care, anger, delusions, and wandering/restless behaviors. Environmental adjustments, behavioral modification, and pharmacotherapy can help. Other common behaviors seen are depression, anxiety, and sleep disturbances, which often can be treated successfully.

Biomarker evidence of AD neuropathology or temporal/parietal hypometabolism is not often obtained for those in AD dementia stage unless the clinical course and features are questionable or atypical. Despite normal basic labs and structural neuroimaging if the individual has parkinsonism, other significant motor abnormalities, prominent executive disturbances, or early behavioral and personality changes, then it may be prudent to consider dopamine transporter (DaT) single-photon emission computed tomography (SPECT) or FDG PET scans.

After a person is diagnosed with AD dementia, cholinesterase inhibitors, memantine, and clinical trials should (Continued on page 47)
be considered. Driving evaluations, increased supervision, socialization, physical exercise, and sufficient balanced nutrition should be provided. Caregiver support and education, considering change of living arrangements, advanced directives, and financial planning are all required.