The Alzheimer's Disease Continuum – A New Diagnostic Approach

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ABSTRACT

The management of Alzheimer's disease (AD) is in the process of transitioning into a new era, enabled by 50 years of scientific progress elucidating biological and clinical aspects of the AD continuum. Newly FDA-approved disease modifying therapies have driven greater access to amyloid positron emission tomography imaging, and fluid biomarker technology has produced the first blood-based biomarkers for AD that are currently entering the marketplace. Community practitioners are increasingly finding themselves on the front lines of advanced AD biomarker decision-making that was in the very recent past the domain of subspecialty memory center providers. The goal of this brief review is to orient community practitioners to fundamental principles necessary for informed AD diagnostic decision-making as biomarker technologies evolve and point out some emerging diagnostic challenges that have arisen as a consequence of more readily available advanced diagnostic options.

KEYWORDS: Alzheimer's disease; biomarkers; diagnostic criteria

INTRODUCTION

In the past several years, we have witnessed a series of monumental shifts in the diagnosis and treatment of AD. Major developments resulting from advances in understanding of the AD continuum have included FDA approval of the first disease-modifying therapies (DMTs) for the treatment of symptomatic AD.[1,2] Additionally, secondary prevention trials underway (the Ahead A3-45 and Trailblazer-ALZ-3 studies) assessing utility of the same DMTs in participants with biomarker evidence of AD who have yet to develop symptoms of cognitive or functional decline, the so-called "preclinical" stage of AD. In parallel, more detailed knowledge of biological underpinnings of the AD continuum has led to increasingly accurate and accessible diagnostic technologies that have played a pivotal role in DMT development. These changes have prompted a recent shift in the field from purely clinically based to more biologically oriented diagnostic approaches and enabled advanced diagnostic technologies to cross over from research and subspecialty clinics to community practice settings at an unprecedented pace. Due to greater access to amyloid positron emission tomography (PET) imaging[3] and very recent introduction of the first blood-based biomarkers (BBM) of brain-based AD-specific amyloid-beta (Aβ) and tau pathologies,[4,5] community practitioners now find themselves on the front lines of making complicated management and treatment decisions that were previously relegated to subspecialty providers.

The objective of this brief review is to provide community practitioners with a basic understanding of key concepts that are necessary for informed decision-making in accordance with intended use criteria for AD-specific biomarkers described in recently updated diagnostic criteria for AD.[6,7] It should be noted that historic and recently updated AD diagnostic criteria and recommendations for biomarker use therein have been geared to driving research toward more effective disease-specific treatments for AD,[8] and not intended as outpatient diagnostic guidelines, per se. However, diagnostic criteria over time have reflected evolving evidence-based principles that inform the diagnostic approach utilized by research-oriented subspecialty practitioners, and the most recently updated criteria outline biomarker use parameters that, for the first time, can specifically be applied to an outpatient work-up.[7]

DIAGNOSTIC CRITERIA FOR AD AND EVOLVING CONCEPTS OF THE ALZHEIMER'S DISEASE CONTINUUM

The first diagnostic criteria for AD were published in 1984 by a work group of collaborators from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, later to be known as the Alzheimer's Association).[9] At that time, comparatively little was known about the biology of Alzheimer's disease beyond the initial neuropathological description of plaques and neurofibrillary tangles (NFT) by Alois Alzheimer in 1907. AD was primarily "defined" by clinical features, with dementia and evidence of impairment in at least two areas of cognition as core criteria. Supporting evidence was based upon additional clinical features, and together with absence of clinical or laboratory evidence of alternative etiologies, a patient would qualify for a "probable AD" diagnosis. A diagnosis of "possible AD" was assigned if AD was suspected but alternative

etiologies could not be definitively ruled out, and the only available biomarker-based diagnosis of "definite AD" was assessed by postmortem confirmation of AD pathology.

Significant progress thereafter elucidating the biological underpinnings of AD driven by the first in-vivo biomarkers for AD-specific Aβ and tau pathology in cerebrospinal fluid in the early 1990s eventually paved the way for validation of the first Aβ PET imaging tracer in 2004.[10] More widely available disease-specific biomarkers enabling longitudinal research in living patients led to the realization that initial stages of detectable pathology began with Aβ deposition possibly 15 years or more[11] prior to initial symptomatic onset in a "preclinical" (or, asymptomatic) stage of illness, followed by a transitional stage of mild cognitive and functional impairment (MCI) preceding the dementia stage. It was also recognized that various aspects of AD pathology develop along different temporal trajectories: Initial Aβ in the preclinical stage leads to downstream progressive tau pathology, which then leads further downstream to synaptic loss and neurodegeneration (**Figure 1a-b**). This conceptualization of successive stages of AD pathological change has been driven by the "amyloid cascade hypothesis,"[12] which has remained the prevailing force behind biomarker and clinical trial development since. It is important to note here that the pathological cascade has typically progressed to the stage of synaptic loss and neurodegeneration by the time of onset of symptomatic stages of AD[7] (**Figure 1a-c**).

Milestones noted above prompted researchers to consider reformulating diagnostic criteria by adding biomarkers as supporting evidence for a "probable AD" diagnosis in the early 2000s.[13] Subsequently updated diagnostic criteria published for dementia in 2011 allowed for increased certainty for "probable AD" by biomarker evidence of AD pathophysiologic processes.[14] Additionally, a new category of symptomatic pre-dementia AD (mild cognitive impairment) with

Figure 1. Schematic of current conceptualization of the Alzheimer's disease continuum from a biomarker perspective

Biomarkers herein are named in terms of their designation in the "AT_1T_2 NISV" staging schematic proposed in the 2024 AD diagnostic criteria.[7]

a. The biological Alzheimer's disease (AD) continuum begins with amyloid-beta (Aβ) deposition (A) in the asymptomatic, preclinical stage, leading to downstream progressive tau pathology (T1 and T2). T1 biomarkers are of early-stage tau pathology that coincides with early Aβ biomarker positivity, while T2 tau biomarkers indicate more advanced stages of tau–mediated pathological change.

b. Sequential Aβ and tau pathologic change leads to downstream neuronal injury or neurodegeneration (N); neurodegeneration can occur irrespective of the inciting cause and is thereby considered "nonspecific" from a biomarker standpoint. Inflammation (I) is known to play an important role in AD-mediated neurodegenerative processes, although biomarkers have not been formally validated for clinical use. The timing of onset of inflammation with respect to sequential progression of AD biological staging is unclear (indicated by "?" in the arrow pentagon).

c. The biological AD spectrum begins and progresses during a lengthy cognitively unimpaired ("preclinical") phase, prior to the onset of the earliest signs of the symptomatic stage (i.e., mild cognitive impairment or dementia). Note that the duration of the entire AD continuum is estimated to be 15–25 years[11] **(d.)** and that biomarkers of Aβ (A), tau (T1 and T2), and neurodegeneration (N) pathology typically become positive prior to symptomatic onset.

The asterisk (*) in the "cognitively unimpaired" category refers to an ongoing debate among expert consensus groups as to whether or not the presence of early, isolated Aβ pathology is significant by itself to cause inevitable progression along the biological and clinical AD continuum.

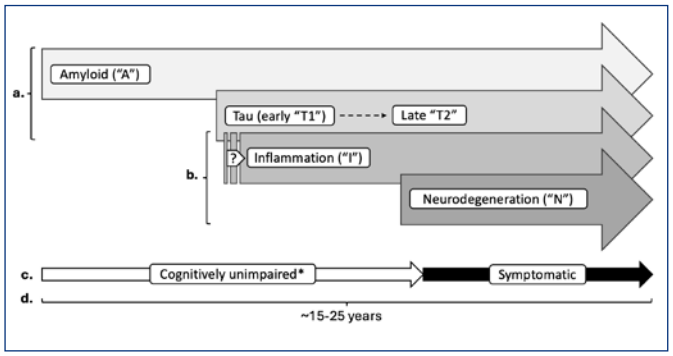

Figure key: A, amyloid; AD, Alzheimer's disease; Aβ, amyloid-beta; I, Inflammation; N, neurodegeneration; T, tau; T1, early-stage tau pathology; T2, later-stage tau pathology

Figure 2. The effects of co-pathologies on timing of onset of neurodegeneration and symptomatic decline

Biomarkers herein are named in terms of their designation in the "AT_1T_2NISV" staging schematic proposed in the 2024 AD diagnostic criteria.[7]

a. The presence of co-pathologies such as alpha-synuclein (S) pathology (i.e., Lewy body pathology) and/or vascular brain injury (V) in patients with Alzheimer's disease (AD) can hasten onset of **b.** neurodegeneration (N) (compared with Figure 1b) and/or **c.** earlier transition from cognitively unimpaired to symptomatic stages (compared with Figure 1c).[27] The timing of onset of alpha-synuclein (S) pathology and/or vascular brain injury (V) with respect to sequential progression of AD biological staging is unclear (indicated by "?" in the arrow pentagon).

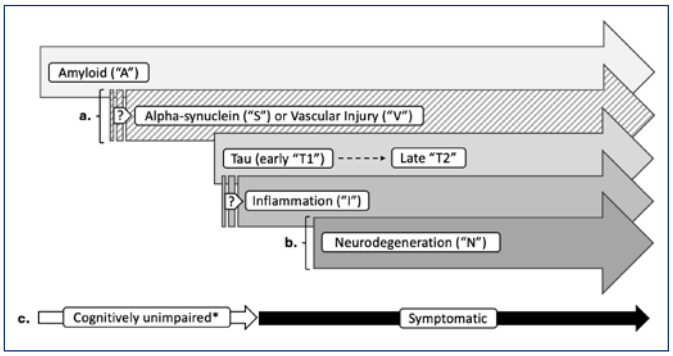

Figure key: AD, Alzheimer's disease; N, neurodegeneration; S, alpha-synuclein; V, vascular brain injury

a similar probabilistic staging scheme bolstered by biomarkers was published,[15] as well as criteria for a proposed asymptomatic, biomarker-determined preclinical stage of AD.[16,17] Importantly, authors of the preclinical AD criteria introduced the concept of a formalized in-vivo biomarker staging scheme for the first time, describing a new biologically based "definition" for AD to facilitate research efforts aimed at targeting specific early biological changes. The so-called "AT(N) framework" (Aβ ("A"), tau ("T"), and neurodegeneration ("N")) assigned diagnostic staging categories reflective of successive positivity ("+") of Aβ (A+T–(N)–), tau (A+T+(N)–), and neurodegeneration (A+T+(N)+) biomarkers as a patient progresses along the biological AD continuum.[16] It is important to understand that although biomarkers can be sensitive for underlying pathology, biomarker use has its limitations, as the full extent of the underlying pathological AD continuum can only be determined by neuropathological staging.[18]

The most recently updated 2024 Alzheimer's Association diagnostic criteria[7] provided an expanded and more elaborate biological-staging scheme, based upon further elucidation of the biological AD continuum and advances in biomarker technologies. The previous "AT(N)" framework was replaced by the current "AT_1T_2NISV" schematic (**Figures 1,2**) to reflect a) separation of tau biomarker categories into early ("T1") and more advanced ("T2") stages of disease (note that biomarkers of the T2 stage are currently of limited availability), and b) to set the stage for formal incorporation of inflammatory ("I"), alpha-synuclein ("S"), and/or vascular ("V") co-pathology biomarkers in development as they become available for research and clinical use. Authors also provided guidance on currently available biomarkers that are now deemed to have sufficient validation for research as well as outpatient clinical use.[7] Additionally, as clinical diagnosis is still integral to the diagnostic process despite biomarker advances, a formalized, integrated biological and clinical staging scheme that puts equivalent weight on clinical and biological aspects of diagnosis was introduced for the first time.[7]

THE APPLICATION OF FOUNDATIONAL DIAGNOSTIC PRINCIPLES TO DIAGNOSTIC DECISIONS IN THE CURRENT ERA

With this brief background of key historical milestones in the evolving concepts of AD diagnosis as a foundation, we'll outline important principles used by subspecialists to inform advanced biomarker diagnostic decision-making, and common circumstances that might require troubleshooting in the era of increasingly available biomarker tests.

Principle 1: Recognizing the distinction between Alzheimer's "disease" and its resulting clinical "illness"

In the early era of AD diagnostic criteria, the preclinical and mild cognitive impairment (MCI) stages preceding dementia were not recognized, and it took many years to elucidate the relationship between underlying pathology (Alzheimer's "disease") and symptoms that manifest from underlying disease (i.e., the clinical "illness" of AD). Understanding the relationship between disease-causing processes and clinical manifestations of that disease is, of course, a fundamental concept throughout medicine that informs development of effective diagnostic and treatment modalities. Many areas of medicine outside of memory care centers have long benefited from well-founded scientific knowledge demonstrating those relationships, and management of AD is finally poised to develop approaches in a similar manner to treatment of oncologic and infectious diseases.

In contrast to other fields, however, where reliable biomarker detection can guide approved, disease-specific treatments in a secondary prevention manner, the clinical application of scientific knowledge related to the full biological AD continuum is still in its infancy. Although current biomarker technologies allow for accurate diagnosis of underlying AD pathology many years in advance of clinical symptomatic onset, there are no currently FDA-approved treatments for AD in the preclinical stage in the outpatient setting. Indications for the diagnosis and treatment of preclinical AD could arise by the end of the decade pending results of the Ahead A3-45 and Trailblazer-ALZ-3 studies; however, in the meantime, practitioners should be aware of the implications of potentially diagnosing Alzheimer's "disease" in an objectively asymptomatic stage lacking approved treatment options.

In the discussion below, we will extend the topic of this new diagnostic conundrum and point out useful longstanding fundamentals of the clinical diagnosis of AD that still apply in the current era.

Principle 2: The importance of clinical staging

Knowledge that AD pathogenesis is one-to-two decades in the making prior to onset of clinical symptoms has motivated the field to develop advanced diagnostic approaches that can identify the earliest stages of clinical decline to more effectively triage symptomatic patients for interventions of the earliest stage of illness. The emerging concept of "subjective cognitive decline" (SCD)[19] as a subtle transitional "stage" to MCI along the AD continuum is under intensive investigation; however, there are neither currently established clinical diagnostic criteria nor indicated treatments for SCD due to AD. As it stands now, a clinical stage of MCI or greater is required by expert consensus-guided intended use criteria for AD-specific biomarkers,[7] and existing DMTs are only indicated in the MCI to mild dementia stages of AD.[20] The challenge providers often face in the clinic is accurately staging patients who are questionably impaired, and distinguishing between SCD arising from worry about normal cognitive aging and signs that might be suggestive of symptomatic decline proximal to conversion to MCI along the AD continuum. The approach to clinical

staging requires integrating data from cognitive testing with surveys of behavioral and functional status, and for the MCI stage some degree of objectively measurable decline from cognitive or functional baseline is required. Highly functioning patients with subtle symptoms of possible decline are often the most challenging to clinically stage, even for subspecialists, and frequently require referral for formal neuropsychological testing to increase accuracy of staging.

Principle 3: The importance of clinical phenotyping and integration of biomarker with clinical data

Clinical phenotyping has remained at the core of the approach to AD diagnosis throughout the evolution of published diagnostic criteria. This remains true in the current era despite greater emphasis on integrating biological data, and is still highly relevant from both clinical management and research perspectives. Phenotyping in this context is the process of characterizing a patient's clinical syndrome with respect to normal versus abnormal functioning in various cognitive domains (i.e., memory, language, visual perception, executive functioning, etc.), which, in conjunction with knowledge of functional neuroanatomy, is used to localize symptoms to infer potential underlying pathology and inform the differential diagnosis. The typical syndrome of late-onset AD is characterized by a triad of impairment in memory, language, and visual-spatial domains but considered a predominantly amnestic syndrome.[9,14,15] Patients presenting in the prodromal MCI stage can be difficult to clinically characterize, as early symptoms are often vague and difficult to localize, often with a subtle but predominant dysexecutive phenotype in very early MCI. This stems from the fact that AD "disease" does not reliably produce a stereotyped clinical "illness" in a predictable, stepwise manner, which, in part, led to inclusion of biomarker data to bolster confidence in AD diagnosis.[15] Clinical phenotyping is further complicated by the fact that language-, visual-spatial-, and executive/behavioral-predominant "variants" of AD exist,[21] and the fact that AD and other neurodegenerative pathologies are often coexistent in the same patient.[22] For example, the typical syndrome of Lewy body disease (which is highly co-morbid with AD) is of executive and visual perceptual dysfunction in addition to neuropsychiatric symptoms such as visual hallucinations,[23] which can confound efforts at phenotyping or staging when mixed pathologies are present (**Figure 2a**, "S" denoting alpha-synucleinopathy). Moreover, patients within the typical age demographic for AD and other neurodegenerative disorders frequently harbor numerous comorbidities such as cerebrovascular disease (**Figure 2a**, "V" denoting vascular brain injury), sleep apnea, thyroid dysfunction, etc. These disorders often present with a dysexecutive phenotype and can independently cause cognitive impairment in parallel with neurodegenerative changes.

The presence of neurodegenerative co-pathologies and/or highly frequent comorbidities can have the effect of hastening timing of onset of symptomatic decline or even nonspecific neurodegenerative processes (**Figure 2a-c**). Differentiating potential effects of multiple comorbidities on clinical presentation is a pervasively challenging diagnostic problem that has necessitated inclusion of a "possible" AD category beginning with the original 1984 diagnostic criteria, for cases where it is not possible to determine the likely primary driver of a patient's presenting symptoms.[9]

Greater access to currently-available advanced biomarkers for early AD-related biologic change[7] promises to significantly improve diagnostic clarity in diagnostically challenging patients. However, until biomarkers of more advanced AD pathology become validated and readily available, it will be difficult in some symptomatic patients with multiple comorbidities contributing to cognitive impairment to determine if AD is the primary driver of presenting symptoms. In other words, in a patient with a positive amyloid PET scan, can it be reliably determined that AD has been detected in the symptomatic stage, or could it be that biological AD has been incidentally diagnosed in the preclinical stage with cognitive impairment being primarily driven by a non-AD comorbidity? Readers engaged in clinical management decisions related to advanced AD biomarkers and DMT are encouraged to become familiar with the distinction between early- and later-stage AD biomarkers and the "integrated biological and clinical staging" scheme recommended in the most recently published AD diagnostic criteria.[7] We would also recommend becoming familiar with a highly relevant ongoing debate among expert consensus groups as to whether or not the presence of early, isolated Aβ pathology is significant by itself to cause inevitable progression along the biological and clinical AD continuum, as proposed by Alzheimer's Association authors,[7] or is better characterized as a risk factor (the "asymptomatic at risk for AD" stage) as proposed by the International Working Group authors.[6]

CONCLUSION

Advances in the scientific underpinnings of AD have produced diagnostic tools and more effective treatments for AD that are finally crossing the threshold from research to real-world clinical application. Greater access to advanced biomarkers for early AD-related biologic change[7] promises to significantly expedite diagnosis of underlying AD pathology in a way that was impossible in the previous era of clinically-based diagnoses, and improve diagnostic clarity in diagnostically challenging patients. We hope that this review of fundamentals of the general diagnostic approach to AD and the importance of integrating biological and clinical data will aid community providers in informing management decisions this era of expanding diagnostic options. Practitioners considering use of BBM are especially encouraged to become familiar with continually updated practice guidelines for use of this new diagnostic modality.[4,5,24–27]

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Disclosures

None

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