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Dementia

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Dementia

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Dementia at the Crossroads of Prediction and Prevention



Well over a century after the characterization of Alois Alzheimer's eponymous disease, we are still debating its definition. The 2018 publication of a biological framework for the diagnosis of Alzheimer disease (AD) established biomarker-defined criteria independent of clinical findings.¹ The recent proposal from a separate group acknowledges the importance of biomarkers in distinguishing AD from mimickers but espouses a clinical-biological construct that requires compatible cognitive symptoms for the diagnosis.²

There are many areas of agreement between the groups. Both acknowledge the importance and frequency of copathology in patients with dementia, including vascular and other neurodegenerative elements. Both groups emphasize the importance of early recognition and treatment. Both recognize the preclinical AD cascade spanning decades before the development of cognitive impairment.

As debates go, this one is largely a semantic project. No matter how it is ultimately resolved, it elides an inevitable feature of future AD treatments: Groundbreaking prevention of AD will long precede groundbreaking reversal of AD, and robust predictive biomarkers will be necessary prerequisites, notwithstanding the formal definition of disease onset. Therefore, the future of AD therapeutics relies on (1) biomarkers that accurately predict which patients will develop AD-related cognitive decline before they are symptomatic, and (2) interventions that meaningfully prevent cognitive decline. If current biomarkers are imperfect predictors of clinical AD, then we need better biomarkers. If current therapeutics do not meaningfully slow or prevent cognitive decline, then we need better therapeutics.

We sit at a diagnostic and therapeutic crossroads in dementia, so this issue of *Continuum* is timely. Covering everything neurologists need to know to

navigate a complex and dynamic clinical environment, our guest editors Drs Liana Apostolova and Lisa Silbert have put together a remarkable list of topics and the leading experts in the field to address them. Dr Gregory Day leads off the issue with his article on the diagnostic approach to AD. Drs David Jones, Victoria Pelak, and Emily Rogalski follow with their article reviewing the diverse phenotypes of AD. Superb reviews of frontotemporal dementia and Lewy body dementia come next, authored by Drs David Clark and James Galvin, respectively. Dr Silbert, serving in a dual editor-author capacity, provides a definitive overview of vascular causes of dementia. In the era of disease-modifying therapeutics for AD, it is particularly important to recognize amnestic mimickers, and Drs Vijay Ramanan and Jonathan Graff-Radford do just that in their article on limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), hippocampal sclerosis, and primary age-related tauopathy. Dr Gad Marshall covers critical factors in the care of patients with dementia, the recognition and treatment of the neuropsychiatric symptoms seen in patients with cognitive decline.

As specific treatments emerge for patients with dementia, the stakes for accurate diagnosis are even higher. Neuroimaging is thoroughly reviewed by

Dr Shannon Risacher, followed by an in-depth discussion of the dynamic world of fluid biomarkers by Drs Joseph Quinn and Nora Gray, and finally the evolving genetics and neuropathology of neurodegenerative dementias by Drs Sonja Scholz and Inma Cobos.

Articles on treatment follow, crafted from a variety of perspectives. Dr David Geldmacher reviews the full span of treatments for AD. Caring for patients with dementia requires an understanding of the needs and options to support their care partners, thoroughly reviewed by Dr Angelina Polzinelli. Our Selected Topics in Neurology Practice article addresses the daunting implementation challenges that accompany anti-amyloid monoclonal antibody therapies, including everything from designing the clinical model to patient selection and follow-up, elegantly outlined by Dr Ramanan.

As always, after reading this issue, subscribers can obtain up to 20 AMA PRA Category 1 Credits™ toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program [Section 3] of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada with our posttest, written for the issue by Drs Adam Kelly and Joanne Lynn.

Available to all listeners who want to learn more about dementia, *Continuum* Audio provides easily

accessible podcast interviews with one of our guest editors and expert authors. CME for these interviews will be available to American Academy of Neurology (AAN) members at continpub.com/AudioCME. *Continuum* subscribers have access to exclusive interviews not found on the podcast and CME accompanying those interviews. Verbatim audio recordings of each article from this issue are available to subscribers through our *Continuum Aloud* program, found at the article level at ContinuumJournal.com and in the AAN's Online Learning Center at continpub.com/Audio. Listeners can now download *Continuum Aloud* recordings for offline convenience.

When the next issue of *Continuum* dedicated to dementia is published in several years, the landscape will be different. We may have results from clinical trials of anti-amyloid monoclonal AD therapies in patients who are presymptomatic. The range and specificity of available biomarkers for neurodegenerative dementia are likely to improve. No matter how the debate over the definition of AD is resolved, these developments will be welcome progress.

—LYELL K. JONES JR, MD, FAAN
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...groundbreaking prevention of AD will long precede groundbreaking reversal of AD, and robust predictive biomarkers will be necessary prerequisites, notwithstanding the formal definition of disease onset.

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Diagnosing Alzheimer Disease

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ABSTRACT

OBJECTIVE: This article reviews the current understanding of Alzheimer disease (AD), including the natural history, common risk factors, and expected progression of AD neuropathologic change so that neurologists can apply this knowledge to identify patients with symptoms, signs, and findings on common diagnostic tests consistent with AD.

LATEST DEVELOPMENTS: The advent of potential disease-modifying therapies emphasizes the need to develop and deploy a practical and efficient approach to diagnose patients with cognitive impairment due to AD.

ESSENTIAL POINTS: The accumulation and spread of cerebral amyloid plaques and tau tangles in patients with AD leads to synaptic dysfunction, neuronal loss, and the eventual emergence and progression of cognitive impairment. A pragmatic and organized approach is needed to recognize patients with symptomatic AD in clinical practice, stage the level of impairment, confirm the clinical diagnosis, and apply this information to advance therapeutic decision making.

INTRODUCTION

The opening stanza of the memory clinic call and response is well known to clinicians who routinely assess patients with memory disorders: "What's the difference between Alzheimer disease and dementia?" The traditional response, "Dementia is a syndrome characterized by declines in cognition that impair activities of daily living, while Alzheimer disease is the most common cause of these problems," makes clear the close relationship between dementia and Alzheimer disease (AD) while distinguishing the clinical syndrome (dementia) from its cause (AD). Although dementia has many possible causes, AD is the most common cause in older individuals. In the United States, an estimated 6.7 million people are living with AD.^{1,2} Worldwide, closer to 100 million people have AD. If family members and other care partners of individuals with AD are included, the number of people affected by this disease grows exponentially. These statistics emphasize the enormous reach of AD.

AD is an epidemic. Advancing age is the greatest driver of AD risk across the population. The incidence of dementia due to AD doubles every 5 years after age 65,³ climbing from 5.3% between the ages of 65 and 74 years to 32% in individuals older than 85 years.⁴ Accordingly, the number of patients with dementia due to AD is expected to increase with an aging population. In the

KEY POINTS

- Although dementia has many possible causes, Alzheimer disease (AD) is the most common cause in older individuals.
- Advancing age is the greatest driver of AD risk across the population.
- AD is the sixth-leading cause of death in Americans, the fifth-leading cause of death in people 65 years old and older, and the only “top 10” cause of death that cannot be prevented, halted, or cured. Beyond mortality, AD is associated with substantial morbidity, disability, and dependence. A typical 70-year-old person with AD can expect to spend 40% of their remaining life with severe dementia, a stage characterized by decreasing social interactions, quality of life, and mobility and increasing reliance on others, likelihood of nursing home admission, and risk of swallowing difficulties, malnutrition, pressure ulcers, infections, and fatal falls.^{4,11} For these reasons, the most recent Global Burden of Disease classification system identifies AD as the fourth-leading cause of disability-adjusted life-years lost in people 75 years old and older (a composite measure of the number of years lost due to ill health, disability, or death related to an illness or injury).¹²
- The total lifetime cost of caring for someone with dementia was estimated in 2022 to exceed US \$390,000 USD.¹ These costs are disproportionately borne by family members in the form of unpaid labor, a contribution valued to the United States at nearly \$340 billion, and out-of-pocket expenses exceeding \$87 billion, which are nearly double those experienced by nondementia care partners.¹ Despite this substantial investment from family, approximately 75% of patients with AD dementia who are 80 years old or older will be admitted to a nursing home, compared with 4% of the general population.¹¹ This reality contributes to at least \$300 billion in costs for long-term care and hospice services for people 65 years old and older with dementia,⁶ and per-person Medicare and Medicaid payments that are 3 and 22 times higher in patients with AD compared with those without AD or other dementias.¹ As a result, AD is one of the costliest conditions for society.

United States, 73 million people (approximately 20% of the population) are projected to be 65 years or older by 2030.⁵ Sustained increases in the median age of the US population will result in a doubling of cases of AD and other dementias by 2050.⁶ Barring remarkable breakthroughs in AD prevention or treatment, demographic shifts will greatly outpace the modest reductions in age-specific prevalence attributable to improved educational achievement and management of vascular risk factors (eg, hypertension, hypercholesterolemia, diabetes, smoking).^{4,7,8}

AD is deadly. AD is the sixth-leading cause of death in Americans, the fifth-leading cause of death in people 65 years old and older,^{4,9,10} and the only “top 10” cause of death that cannot be prevented, halted, or cured. Beyond mortality, AD is associated with substantial morbidity, disability, and dependence. A typical 70-year-old person with AD can expect to spend 40% of their remaining life with severe dementia, a stage characterized by decreasing social interactions, quality of life, and mobility and increasing reliance on others, likelihood of nursing home admission, and risk of swallowing difficulties, malnutrition, pressure ulcers, infections, and fatal falls.^{4,11} For these reasons, the most recent Global Burden of Disease classification system identifies AD as the fourth-leading cause of disability-adjusted life-years lost in people 75 years old and older (a composite measure of the number of years lost due to ill health, disability, or death related to an illness or injury).¹²

AD is an economic disaster. The total lifetime cost of caring for someone with dementia was estimated in 2022 to exceed \$390,000 USD.¹ These costs are disproportionately borne by family members in the form of unpaid labor, a contribution valued to the United States at nearly \$340 billion, and out-of-pocket expenses exceeding \$87 billion, which are nearly double those experienced by nondementia care partners.¹ Despite this substantial investment from family, approximately 75% of patients with AD dementia who are 80 years old or older will be admitted to a nursing home, compared with 4% of the general population.¹¹ This reality contributes to at least \$300 billion in costs for long-term care and hospice services for people 65 years old and older with dementia,⁶ and per-person Medicare and Medicaid payments that are 3 and 22 times higher in patients with AD compared with those without AD or other dementias.¹ As a result, AD is one of the costliest conditions for society.

The numbers paint a picture of AD as a prevalent disease with enormous social, psychological, and economic costs, which are expected to worsen as the number of people living with AD increases. This framing, although bleak, serves another purpose, which is to call attention to the need to develop and advance strategies to promote early diagnosis, improve the treatment of patients with cognitive impairment attributed to AD, and ultimately prevent AD dementia in at-risk patients. Neurologists are critical to these goals. With this context in mind, this article reviews the current understanding of what AD is, including the natural history, common risk factors, and expected progression of AD neuropathologic change. This knowledge is adapted to improve early recognition of patients with symptoms, signs, and findings on common diagnostic tests that implicate AD as the cause of emergent cognitive impairment. Together with other articles in this issue, readers will be equipped with a pragmatic and organized approach to evaluate patients with symptomatic AD, stage the level of impairment, establish an efficient and accurate diagnosis, and apply this information to advance therapeutic decision making; for more information on

treatment, refer to the article “Treatment of Alzheimer Disease” by David S. Geldmacher, MD, FACP, FANA,¹³ in this issue of *Continuum*.

UNDERSTANDING ALZHEIMER DISEASE

Although the terms *Alzheimer disease* and *dementia* are often used interchangeably, these terms are distinct. AD is a disease state characterized by specific neuropathologic changes, whereas dementia is a clinical syndrome associated with declines in memory and other cognitive domains (eg, executive, visuospatial, language function) that are sufficient to impair daily function. Although AD is the most common cause of dementia (ie, “AD dementia”),¹ patients may develop dementia without AD (ie, there are many other causes of dementia) or may have AD without meaningful cognitive impairment (ie, preclinical disease). What then is AD?

AD is a multistage illness that progresses across decades (**FIGURE 1-1**).¹⁴ The “amyloid cascade” hypothesis posits that the aggregation with subsequent accumulation of amyloid- β (A β) plaques within the brain represents a critical first step in the pathogenesis of AD, triggering the formation and promoting the spread of neurofibrillary (tau) tangles throughout the brain.^{15,16} This hypothesis is supported by studies in patients with AD, which demonstrate that changes in A β metabolism are detectable 20 (or more) years before the emergence of clinical symptoms^{17,18} and by the consistent demonstration of abnormal deposits of

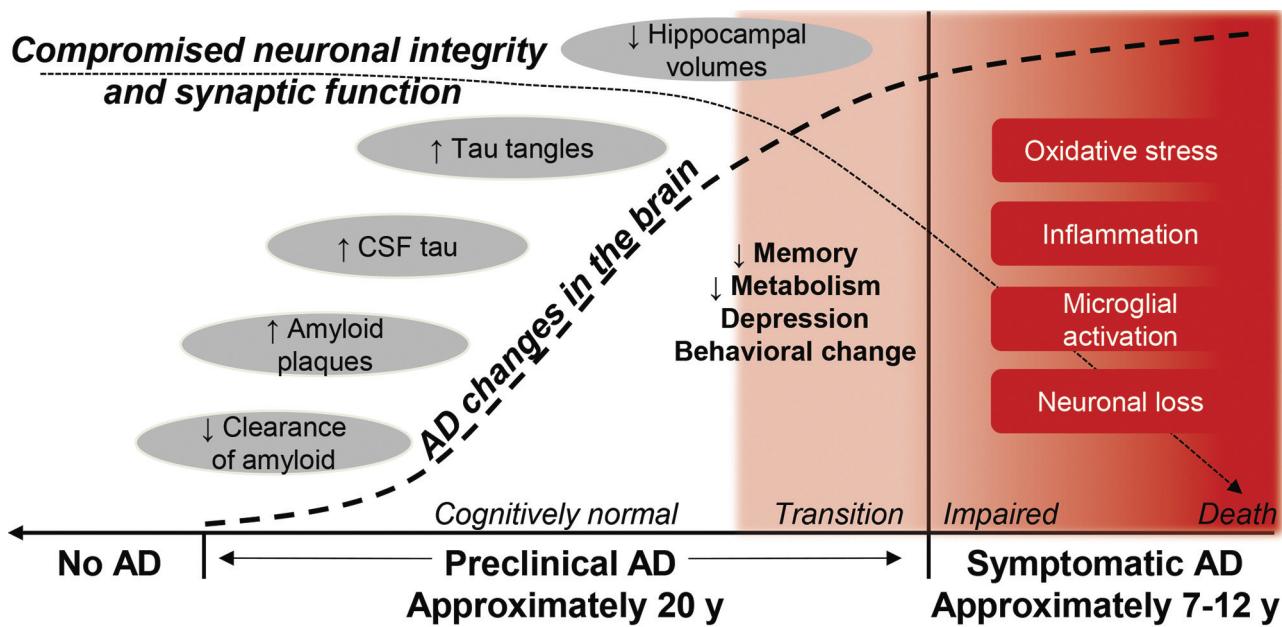


FIGURE 1-1

The lifespan of Alzheimer disease (AD). Inciting pathophysiologic factors lead to the onset of the protracted preclinical phase of AD marked by the formation and accumulation of cerebral (amyloid) plaques, neurofibrillary (tau) tangles, and other changes that compromise neuronal integrity and synaptic function in cognitively normal individuals. Accumulating AD neuropathologic change heralds the emergence of subtle changes in cerebral metabolism, memory, and behaviors (ie, the transition phase) and eventually the onset and progression of cognitive impairment that marks the symptomatic phase of the disease.

Modified with permission from Morris JC, Dana Foundation Newsletter.¹⁴ © 2013 Dana Foundation.

A β -containing plaques and tau-containing neurofibrillary tangles in the brains of patients with AD (FIGURE 1-2).¹⁹ For more information on these topics, refer to the articles “Neuroimaging in Dementia” by Shannon L. Risacher, PhD,²⁰ and “Fluid Biomarkers in Dementia Diagnosis” by Joseph F. Quinn, MD, FAAN, and Nora Gray, PhD,²¹ in this issue of *Continuum*.

$\text{A}\beta$ peptides are produced via sequential cleavage of the large transmembrane amyloid precursor protein by β -secretase and γ -secretase, yielding the 40-amino acid $\text{A}\beta_{40}$ and the 42-amino acid $\text{A}\beta_{42}$ peptides. The amyloid precursor protein is highly expressed in neuronal synapses, with roles in neuronal development, signaling, intracellular transport, and homeostasis.²² Thus, $\text{A}\beta$ peptides are formed as a normal part of cerebral metabolism. Under normal circumstances, $\text{A}\beta$ peptides are cleared from the central nervous system through enzymatic

KEY POINTS

- AD is a disease state characterized by specific neuropathologic changes, whereas dementia is a clinical syndrome associated with declines in memory and other cognitive domains (eg, executive, visuospatial, language function) that are sufficient to impair daily function.

- AD is a multistage illness that progresses across decades.

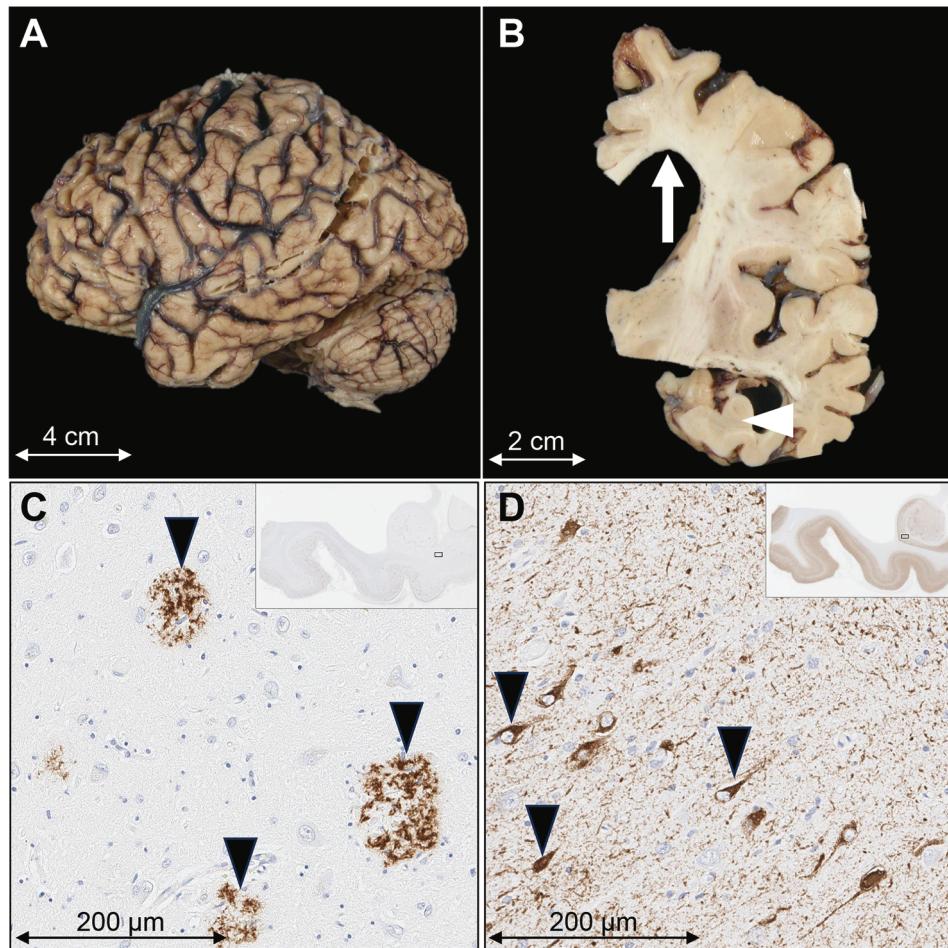


FIGURE 1-2

Typical Alzheimer disease neuropathologic change at autopsy. Macroscopic changes associated with Alzheimer disease include generalized atrophy (A) with thinning of the cortical ribbon, widening of sulci, expansion of the lateral ventricles (B, white arrow), and prominent hippocampal volume loss (B, white arrowhead). Key microscopic changes include abnormal accumulation of amyloid- β ($\text{A}\beta$)-containing cerebral plaques (C, black arrowheads) and tau-containing neurofibrillary tangles (D, black arrowheads). Immunohistochemistry performed on hippocampal sections (C, D, insets) with antibodies directed against $\text{A}\beta_{42}$ (clone 6F/3D) and phosphorylated tau (AT8 phospho tau).

degradation, interstitial fluid bulk flow and CSF absorption, and receptor-mediated transport across the blood-brain barrier.²³ Perturbations influencing the balance between A β production and clearance are associated with A β accumulation and risk of symptomatic AD. This phenomenon is most apparent in families with rare variants in *APP*, *PSEN1*, or *PSEN2* associated with overproduction of A β . Neuropathologic changes emerge in asymptomatic genetic variant carriers in early adulthood, leading to cognitive impairment with a predictable age at symptomatic onset within families.^{18,24} Similar findings are observed in individuals with triplications of the *APP*-containing chromosome 21 (ie, Down syndrome), who develop AD neuropathologic change early in life and remain at increased risk for later-life cognitive decline due to AD.^{25,26} Although less striking, other genetic variants (including *APOE* genotype),^{23,27,28} behaviors (eg, lack of exercise, insufficient sleep), and health comorbidities that are thought to impair A β clearance are associated with higher AD risk (eg, cerebrovascular disease, sleep dysfunction),²⁹⁻³¹ whereas health behaviors that are thought to promote clearance are associated with lower lifetime AD risk (eg, adequate exercise).³² These findings emphasize the close relationship between A β metabolism and AD.

Neurofibrillary tangles are composed of hyperphosphorylated aggregates of the microtubule-associated protein tau, which is encoded by the *MAPT* gene on chromosome 17. Under normal conditions, tau acts like neuronal rebar, stabilizing microtubules and supporting axonal transport, neuronal activity, neurogenesis, and synaptic function.³³ In the presence of accumulating A β , however, tau undergoes hyperphosphorylation and aggregation,^{34,35} decreasing microtubule binding, and leading to mislocalization, misfolding,³⁶ and ultimately to the accumulation and spread of tau neuropathology via seeding of extracellular tau oligomers through functionally connected neurons.³⁷⁻³⁹ The spread of tau neuropathology typically follows a well-choreographed pattern, in which neurofibrillary tangles accumulate within transentorhinal cortices before spreading to the anterior hippocampus, adjacent limbic and temporal cortices, association cortices, and, finally, unimodal cortices (eg, primary sensory and motor cortices).⁴⁰

The accumulation of A β plaques and neurofibrillary tangles in people who are not yet symptomatic marks the preclinical period of AD, a phase during which disease is measurable but clinical consequences are not. The hippocampus and amygdala are privileged structures that are disproportionately involved early in AD. Accordingly, the detection of focal neurofibrillary tangles in the transentorhinal area of asymptomatic research participants identifies individuals with preclinical disease who are presumed to be at the highest risk of developing cognitive impairment due to AD.^{19,41} The continued accumulation of neurofibrillary tangles leads to synaptic failure, neuronal loss, and, eventually, the emergence of symptoms attributed to AD.⁴²⁻⁴⁴

Disruption of neuronal function within the hippocampus and amygdala may herald the onset of subtle behavioral and cognitive concerns in otherwise high-functioning individuals.⁴⁵ New neuropsychiatric symptoms in people 50 years old or older are increasingly recognized as potential early noncognitive manifestations of AD, labeled *mild behavioral impairment*.⁴⁶⁻⁴⁸ Similarly, individuals may present with subjective memory concerns without demonstrable loss of function or declines in performance on objective tests of memory and thinking (ie, subjective cognitive decline).⁴⁹ Whether occurring

KEY POINTS

- The accumulation of amyloid- β plaques and neurofibrillary tangles in people who are not yet symptomatic marks the preclinical period of AD, a phase during which disease is measurable but clinical consequences are not.

- Disruption of neuronal function within the hippocampus and amygdala may herald the onset of subtle behavioral and cognitive concerns in otherwise high-functioning individuals.

- The symptomatic phase of AD represents the final phase of a process that typically evolves across decades.

- Age is the most common nonmodifiable risk factor for AD.

- One-third (or more) of dementia cases worldwide could be eliminated through adequate management of modifiable risk factors.

- Typically, patients with AD have an age at symptomatic onset within or beyond the seventh decade of life.

independently or together, the emergence of behavioral and cognitive symptoms frames the transitional period of AD, a phase of the disease characterized by the emergence of cognitive and behavioral concerns that do not yet result in impairment sufficient to establish a diagnosis of mild cognitive impairment or very mild dementia. With time, the spread of AD neuropathology leads to worsening symptoms and the emergence of objective deficits that typify the symptomatic phase of AD.

The symptomatic phase is the best understood and studied phase of AD with obvious consequences for patients, family members, and health care systems. Yet, the symptomatic phase represents the final phase of a process that typically evolves across decades. By the time symptoms are detected clinically, A β plaques are widely distributed throughout the brain, with the highest density in the frontal and parietal lobes, whereas neurofibrillary tangles are most densely present within the temporal lobes, including the hippocampus, with additional involvement of parietal, precuneus, and visual cortices.⁴² It should come as no surprise, therefore, that the symptomatic phase of AD progresses relatively quickly, with the time from diagnosis to death commonly identified as 4 to 8 years.¹ Typically, cognitive symptoms follow a predictable course that largely mirrors the spread of tau neuropathology and associated synaptic dysfunction and neuronal loss. Short-term memory loss represents the first cognitive symptom in most patients,⁵⁰ reflecting early disruption of hippocampal function. When cognitive deficits begin to disrupt instrumental activities of daily living (but not activities of daily living), a diagnosis of mild cognitive impairment due to AD is appropriate.⁵¹ As AD pathology increases, so does impairment. When cognitive deficits consistently impair activities of daily living, patients meet the criteria for mild dementia.

RISK FACTORS FOR ALZHEIMER DISEASE

Age is the most common nonmodifiable risk factor for AD, with increasing age strongly associated with an increasing prevalence of cerebral plaques and tangles.⁵² The reasons for this are unclear, with most hypotheses incorporating a multitude of age-associated changes that cumulatively result in imbalances in A β production and clearance that promote A β accumulation and downstream consequences. These include age-related declines in cellular repair and mitochondrial function, increasing fragmentation in sleep (potentially altering A β production or clearance), accumulating burden of cerebrovascular disease and associated atherosclerosis that disrupts arterial and venular flow, and cumulative exposures to toxins and oxidative stress.^{29,31,53,54}

Genetics and family history are additional nonmodifiable risk factors. The impact of genetics is most evident in the less than 1% of patients with variants in the genes *APP*, *PSEN1*, or *PSEN2* or triplications of chromosome 21 (trisomy 21, or Down syndrome) associated with the inevitable development of AD, often at a young age.^{25,26} For most patients, however, genetic contributions to AD risk are more complex, arising from an admixture of genes that cumulatively increase risk, and are further influenced by environmental interactions and exposures. Of these, *APOE* polymorphic alleles represent the most common genetic risk factor for AD worldwide, with *APOE** ϵ 4 carriers experiencing an increased risk of AD compared with those carrying the more common *APOE** ϵ 3 allele, and *APOE** ϵ 2 carriers experiencing decreased lifetime risk of AD.^{23,27,28} This association is attributed to the role of apolipoprotein E in lipid shuttling and clearance of A β ,

with *APOE** ϵ 4 isoforms associated with reduced clearance and enhanced aggregation of A β in the brain.²⁸ *APOE** ϵ 4 allele carriers may also experience accelerated accumulation of tau at lower amyloid levels, suggesting that *APOE** ϵ 4 may facilitate early tau spreading across connected brain regions in amyloid-positive patients.⁵⁵

Beyond genetics, the contribution of potentially modifiable dementia risk factors to AD is increasingly recognized, with systematic reviews and meta-analyses suggesting that nearly one-half of dementia cases worldwide could be eliminated through adequate management of modifiable risk factors (FIGURE 1-3).^{30,56-59} The preponderance of mid-life and late-life risk factors emphasizes the role of neurologists in screening, counseling, education, and advocacy concerning the potential to prevent dementia through risk factor modification. Additionally, the overrepresentation of several of these risk factors among Black or African American people and Hispanic or Latino American people may contribute to the 2-times and 1.5-times higher dementia incidence experienced by these communities compared with non-Hispanic White people.⁶⁰⁻⁶⁵ Recognition and quantification of these disparities may support population-level interventions designed to eliminate disparities in dementia risk and improve quality of life among people from communities that remain underresourced by public health services and underrepresented in dementia research.

RECOGNIZING SYMPTOMATIC ALZHEIMER DISEASE IN THE CLINIC

AD is a pathologic state with predictable clinical manifestations and consequences. The typical patient with AD is older, of an age at symptomatic onset within or beyond the seventh decade of life. Patients with AD are more likely to be female and more likely to report a family history of dementia.⁶⁵ These readily discernable clinical features should increase suspicion (or pretest probability) for AD as the cause of cognitive concerns. Short-term memory

concerns predominate and are likely to represent the presenting concern,⁵⁰ most often with little to no loss of longer-term memories. Although perplexing to patients and family members, the short-term/long-term memory paradox points to early involvement of mesial temporal lobe structures that are key to the encoding and recall of newly formed memories.

The strong association between short-term memory loss and symptomatic AD explains the overrepresentation of memory tasks in short-screening instruments designed to identify patients older than 65 years who are at the highest

Early life	Midlife	Late life
Less education (<10 years) ^a	Alcohol consumption (21 units/wk) ^a	
	Depression ^a	Vision loss ^a
		Diabetes ^a
	Hypertension ^a	
	High low-density lipoprotein cholesterol ^a	Air pollution ^a
		Hearing loss ^a
		Physical inactivity ^a
	Obesity ^a	Social isolation ^a
		Traumatic brain injury ^a
	Lifespan	
Atrial fibrillation, cerebrovascular disease, hypothyroidism, nutritional deficits, sleep apnea, smoking, ^a vitamin B ₁₂ deficiency		

FIGURE 1-3

Potentially modifiable dementia risk factors encountered at varying stages of life.⁵⁶⁻⁵⁹

^a Elimination of these 14 risk factors may prevent or delay up to 45% of dementia cases.⁵⁹

risk for symptomatic AD.⁶⁶ Several of these can be reliably administered to patients or their informants in the waiting room, providing an opportunity to adjust pretest probability even before the patient enters the examination room. Of these, the eight-question Ascertain Dementia 8 questionnaire is the best validated and has high positive predictive value (greater than 85%) for meaningful cognitive impairment when informants answer “yes” to two or more questions (**TABLE 1-1**⁶⁷), established validity in multiple languages and health care settings, including primary care and clinic-based practices,^{67,68} and broad accessibility.⁶⁹

Beyond memory concerns, patients with symptomatic AD may present for the evaluation of changes in mood, anxiety, irritability, word-finding difficulty, or “just not thinking straight.” These concerns may frame the presenting symptom, may be disclosed over the course of the visit, or, more problematically, may be mentioned in parting. An accurate assessment of cognitive function requires time, and an accurate assessment is required to recognize early symptoms of AD. Thus, when cognitive or behavioral concerns are raised in passing (or in parting), clinicians are encouraged to recommend a dedicated visit to ensure ample time to elicit a comprehensive history focused on memory and thinking and bedside testing of cognition. Whenever possible, patients should be encouraged to bring a knowledgeable informant to this visit (eg, partner, adult child, close friend), acknowledging that patients with AD are prone to forget what they forget. Indeed, impaired self-awareness (ie, anosognosia) is a common feature in patients with AD that may limit insight into the scope, severity, and impact of symptoms and compromise the diagnostic assessment of unaccompanied patients.^{70,71} For this reason, unaccompanied patients who state, “I don’t know why I’m here,” may represent a far greater concern than patients who zealously endorse memory concerns and then enthusiastically (and ironically) detail all that they have forgotten.

The Ascertain Dementia 8 Questionnaire^{a,b}

TABLE 1-1

Questions administered to a reliable informant

- 1** Is there repetition of questions, stories, or statements?
- 2** Are appointments forgotten?
- 3** Is there poor judgment (eg, buying inappropriate items, poor driving decisions)?
- 4** Is there difficulty with financial affairs (eg, paying bills, monitoring banking statements)?
- 5** Is there difficulty in learning or operating appliances (eg, television remote, microwave oven)?
- 6** Is the correct month or year forgotten?
- 7** Is there decreased interest in hobbies and usual activities?
- 8** Is there overall a problem with thinking and/or memory?

^a Modified with permission from Galvin JE, et al, Neurology.⁶⁷ © 2005 Alzheimer’s Disease Research Center, Washington University.

^b The Ascertain Dementia 8 questionnaire is an eight-question screening tool to detect mild cognitive impairment or very mild dementia in older adults. Positive responses to two or more Ascertain Dementia 8 questions were associated with a high (87%) positive predictive value for impairment (versus no impairment) in research participants (who were 55 years old and older) enrolled within a longitudinal cohort study of memory and aging at a single center.⁶⁷

In the office, the interview should begin at the beginning. Although this may seem intuitive, it is natural for patients and informants to focus on the most prominent symptoms, problematic issues, or active concerns. Establishing the first symptoms is key to appreciating where in the brain pathology began and deciphering the conditions that precipitated symptomatic onset. The gradual onset and progression of short-term memory loss should increase the pretest probability of AD as the cause of cognitive impairment (**CASE 1-1**).

In contrast, prominent perceptual disturbances, including well-formed visual hallucinations, may implicate symptomatic Lewy body dementia (eg, dementia with Lewy bodies⁷²), whereas early changes in personality, social appropriateness, and behaviors may suggest frontotemporal lobar degeneration (behavioral variant frontotemporal dementia⁷³). Identifying the first symptoms is not always easy. Early symptoms may be forgotten by patients or mistaken by informants for changes associated with normal aging, life stage (eg, menopause, retirement), or other critical life events (eg, the death of a spouse). Consequently, symptom onset may be incorrectly linked to specific events that represent an irrefutable change from baseline (eg, unanticipated job loss, medication errors necessitating hospitalization, house fire resulting from an unwatched pot, wandering or getting lost, falling prey to a financial scam). Left unquestioned, these unintentional errors may raise concern for acute conditions (eg, stroke, infectious or autoimmune encephalitis) or rapidly progressive dementia,⁷⁴ leading to unnecessary testing, treatments, and diagnostic delays.

A standardized survey of function may help clarify the onset of cognitive symptoms while also informing the impact of changes on day-to-day function (**TABLE 1-2**⁷⁵). When functional deficits are detected, the clinician should discern when the deficits arose, ensuring that deficits represent changes from baseline that are attributable to declines in cognition, not declines in physical health or mobility. As with the first symptoms, this task may be more difficult than initially assumed. Partners may divide responsibilities across tasks or delegate responsibilities to adult children or other representatives. Additionally, responsibilities may shift with changes in life stages (eg, retirement). When possible, cognitive concerns should be supported by examples, recognizing that patients and families may downplay the influence of symptoms or reflexively answer “no” to a broad question (eg, “Is memory a problem?”) but acknowledge problems with self-administration of medications, management of appointments, and timely bill payments when directly asked. Curiosity is encouraged in history taking, particularly when exploring substantial life changes. Did the patient retire because it was “the right time” or was the retirement prompted by the rollout of a new electronic record system that proved too difficult to learn? Did the patient decline to travel for the holidays because family lived “too far away,” or were there concerns about navigating the airport? Examples and follow-up questions may help codify impairment, clarify the impact on daily activities, and firm up the time of onset and symptomatic progression.

Symptoms attributed to AD should be present consistently. Although patients and informants may report good days and bad days, “normal” days are uncommon in patients with symptomatic AD. A history of prominent fluctuations in cognitive function or alertness should prompt evaluation for Lewy body dementia, which may occur independently of or concurrently

with AD,^{72,76} or autoimmune or toxic-metabolic causes of impairment.^{74,77} However, inconsistent cognitive concerns or deficits may suggest an alternative process, warranting evaluation for disorders that may compromise attention, including mood disorders (eg, depression), sleep dysfunction (eg, obstructive sleep apnea), or chronic pain. Active screening for the use of substances (eg, alcohol, marijuana) or cognitive-impairing and sedating medications is also recommended,⁷⁸ including over-the-counter anticholinergic medications marketed to promote sleep, treat allergies, and manage pruritus (**CASE 1-2**).

The evolution of symptoms may offer additional clues to the diagnosis. Cognitive impairment attributed to AD should progress over time with the spread of AD neuropathology. Typically, memory symptoms that initially appear benign (eg, misplacing items, forgetting unimportant details) gradually become more problematic, often affecting medication management, task completion, shopping, driving, housework, and personal hygiene. As tau neuropathology propagates beyond entorhinal cortices, executive function may be impaired and judgment compromised. Executive dysfunction may result in poor financial decision making, increased susceptibility to scams, and, when severe, errors in social judgment, manifesting as disinhibited or irregular behavior. The involvement of parietal cortices and other posterior cortical areas may manifest with deficits in spatial awareness and wayfinding which, together with executive dysfunction, may result in wandering or elopement behaviors. Although aphasia is often discussed in the context of primary progressive aphasia (a syndrome characterized by prominent loss of language skills), language deficits are common later in the symptomatic course of typical amnestic AD, owing to the spread of neurofibrillary tangles within neuroanatomical structures subserving language. Typical symptoms include word-finding or name-finding difficulty, progressing to impairments in comprehension, speech, sentence recognition, reading (alexia), and spelling and writing (dysgraphia).

Neuropsychiatric symptoms are common in patients with AD. Emotional symptoms, such as dysthymia, depression, anxiety, and apathy, are prevalent early in the symptomatic course and may precede the clinical diagnosis of cognitive impairment (**CASE 1-3**).^{46,48} Other neuropsychiatric symptoms are increasingly likely in the later stages of dementia, including delusions, hallucinations, and agitation.⁴⁸ Active surveillance for neuropsychiatric symptoms at each clinical assessment is recommended, recognizing that behavioral manifestations may accelerate cognitive decline, threaten patient and care partner safety, and substantially increase the burden of care, the risk of institutionalization, and mortality in patients with AD.⁷⁹⁻⁸¹ Early detection and accurate characterization of neuropsychiatric symptoms may provide an opportunity to screen for reversible contributors to behaviors (eg, concurrent medication use, thyroid dysfunction, untreated pain, emerging infection), develop and implement nonpharmacologic approaches to improve behavioral management, and engage available resources to support the patient and care partner. Unfortunately, few effective and safe pharmacologic treatments exist for the management of neuropsychiatric symptoms in AD.^{82,83} The lack of on-label medications indicated for this purpose presents a notable challenge for clinicians, highlighting an important area of need; for more information on this topic, refer to the article “Neuropsychiatric Symptoms in Dementia” by Gad A. Marshall, MD,⁸⁴ in this issue of *Continuum*.

KEY POINTS

- An accurate assessment of cognitive function in the setting of AD requires taking adequate time for the clinical assessment.
- Impaired self-awareness (ie, anosognosia) is a common feature in patients with AD that may limit insight into the scope, severity, and impact of symptoms and compromise the diagnostic assessment.
- The gradual onset and progression of short-term memory loss should increase the pretest probability for AD as the cause of cognitive impairment.
- When possible, cognitive concerns should be illustrated by examples.
- Curiosity is encouraged in history taking, particularly when exploring substantial life changes in the setting of AD.
- Examples and follow-up questions may help codify impairment, clarify the impact on daily activities, and firm up the time of onset and symptomatic progression of AD.
- Cognitive impairment attributed to AD should progress over time with the spread of AD neuropathology.
- Language deficits are common later in the symptomatic course of typical (amnestic) AD.

NEUROLOGIC EXAMINATION IN PATIENTS WITH ALZHEIMER DISEASE

The neurologic examination should be normal early in the symptomatic course of AD. However, as the disease progresses, behavioral changes, aphasia, apraxia, and cortical visual deficits are likely to emerge, reflecting the spread of AD neuropathology to heteromodal association cortices subserving reasoning, abstraction, monitoring of behaviors; language; motor planning; and

CASE 1-1

A 69-year-old retired nurse with managed hypertension and hypothyroidism presented for evaluation of a 1-year history of memory concerns. Her adult daughter noted the gradual onset and progression of repetition of questions and misplacing of items, with emerging difficulties following complex recipes when cooking. Neurologic examination was normal. She scored 28/30 on the Mini-Mental State Examination (MMSE), with points lost for delayed verbal recall (recalling one of three words after a 5-minute delay). Thyroid function tests and serum vitamin B₁₂ levels were normal. Fluid-attenuated inversion recovery (FLAIR) MRI showed diffuse global atrophy, periventricular and subcortical T2 hyperintensities compatible with small vessel disease (**FIGURE 1-4A**), and left more than right hippocampal atrophy (**FIGURE 1-4B**). The patient was diagnosed with mild cognitive impairment, presumed secondary to Alzheimer disease (AD). Her cognitive deficits progressed across follow-up, leading to increased reliance on her daughter to manage medications, finances, and meal preparation. Her performance on the MMSE declined to 23/30. Serial neuroimaging established progressive hippocampal volume loss (**FIGURE 1-4C**). Amyloid positron emission tomography (PET) imaging confirmed increased cortical uptake, suggesting a moderate to severe burden of cerebral (amyloid) plaques.

COMMENT

AD commonly presents with gradual onset and progression of short-term memory deficits in older individuals. Initial deficits may be very mild with limited to no impact on daily life and normal (or near-normal) performance on bedside tests of cognition, particularly in high-functioning individuals. In this case, concerns were substantiated by a reliable collateral source; practical examples clearly indicated that symptoms represented a change from the baseline. Cross-sectional neuroimaging excluded a structural cause of mild cognitive impairment. Longitudinal follow-up (ie, a test of time) showing progressive declines in cognitive function (subjective and objective) with increasing hippocampal atrophy provided strong (albeit indirect) support for the diagnosis of probable AD as the cause of mild dementia. This diagnosis was further supported via a positive amyloid PET scan. The approval of putative disease-modifying therapies for patients with early-symptomatic AD emphasizes the importance of early and accurate recognition of patients with mild cognitive impairment due to AD.

visuoperceptual functions. For these reasons, a comprehensive assessment should include the assessment of abstraction and behaviors, naming (high-frequency, moderate-frequency, and low-frequency items), motor processing and planning, and visual functions (eg, reading, interpretation of a complex visual scene, color discrimination). Various examination findings implicate disruption of higher-order cortical functions and may inform the localization of pathology (**TABLE 1-3**⁸⁵).

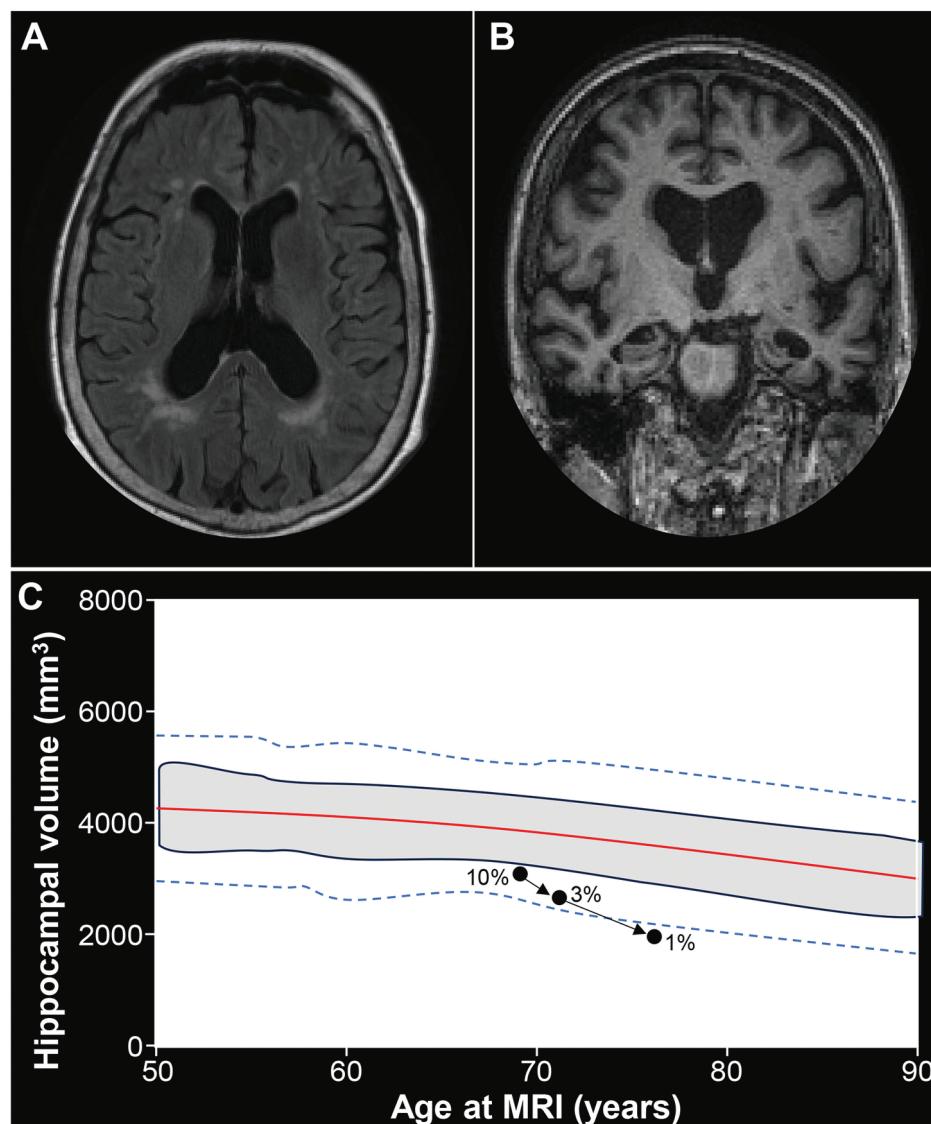


FIGURE 1-4

Imaging studies of the patient in **CASE 1-1**. Axial fluid-attenuated inversion recovery (FLAIR) MRI at the level of the caudates confirms diffuse global atrophy (A), with more pronounced involvement of the hippocampi seen on coronal magnetization-prepared rapid gradient echo (MP-RAGE) (B). Serial imaging confirms progressive decreases in hippocampal volumes (C, black dots) with increasing age. Commercial software was used to quantify volume loss, referencing volumes in age-matched cognitively normal individuals (red line, mean volumes; gray-shaded areas, ± 1 SD; dashed blue lines, ± 2 SD).

TABLE 1-2**Questions to Detect Early Changes in Cognition Affecting Function, Divided by Domains^a**

Functional domain	Example questions to screen for emerging changes
Memory	Are medications forgotten or reminders required to remember daily medications? Are appointments forgotten? Are reminders required? Are stories, statements, or questions repeated?
Orientation	Are there problems remembering dates and times? Is there difficulty navigating in unfamiliar areas (more so than familiar areas, and more so than inside the home)? Have there been changes in perception of time (eg, thinking something that happened 2 weeks ago happened 2 days or 2 months ago)?
Judgment and problem-solving	Is it more difficult to manage household finances? Any change in the ability to make complex decisions (eg, purchasing a new car, having work done on the home)? Any difficulty paying for the bill and calculating a tip when dining out? Any change in social appropriateness?
Community affairs	Has there been a change in your ability to work or volunteer outside of the home? Can you be relied on to purchase a short list of items from the store? Has there been a meaningful change in social engagement (eg, participation at church, service to committees)? Are there concerns regarding driving safety (eg, tickets, near misses, accidents)?
Home and hobbies	Is the home maintained to your usual standards? Any difficulty utilizing appliances? Any difficulty with technology (eg, cell phone, computer, television remote)? Are ingredients forgotten or steps missed when cooking? Any change in interest in hobbies and pursuits? Any change in ability to maintain the home?
Personal care	Have there been any changes in hygiene? Are reminders or prompts required to bathe or brush teeth? Is clothing soiled or the same outfit worn across multiple days?

^a Functional domains include those required to derive the Clinical Dementia Rating.⁷⁵ When assessing function, it is important to ensure that deficits represent a change from baseline and result from impairment in cognition, not physical function.

Word-finding difficulty (anomia) is the most commonly observed sign in patients with AD. Patients with mild impairment may exhibit a reduced use of nouns, appearing to talk around items (eg, “you know, the thing”) or describing items rather than naming them. When asked to name an unknown object, patients may express frustration with their inability to recall the name (eg, “I know what it is; it’s on the tip of my tongue”) and may even accurately describe where the item would be found or how it might be used, demonstrating retained word meaning. When provided with a word list (ie, multiple choice), the word is easily identified, often with some relief at being provided the prompt. As difficulties become more pronounced, patients may exhibit hesitant or interrupted speech, with speech eventually becoming unintelligible or devoid of content. In patients with typical amnestic-predominant AD, signs including apraxia and visual extinction and neglect become more common as AD progresses. The early emergence of these features should raise suspicion for primary progressive aphasia or dysexecutive or visual variant (posterior cortical

CASE 1-2

A 64-year-old man, a recently retired engineer with hypercholesterolemia, presented to the outpatient clinic with his spouse for evaluation of a 9-month history of cognitive concerns. His spouse endorsed increasing forgetfulness, reporting that the patient would forget conversations and the details of television series that they watched together in the evening. His spouse also endorsed intermittent slurring of speech and gait changes (broad-based gait) occurring late in the day. The patient affirmed these observations but denied any limitations in daily function, including medication and financial management. His neurologic examination was normal, with normal performance on a bedside screening test of cognition. Screening blood work was notable for mild elevation in liver enzymes. On direct questioning, the patient acknowledged a long-standing history of alcohol use, with a recent increase in daily intake coinciding with his retirement. A reduction in alcohol intake corresponded to a substantial improvement in cognitive symptoms.

COMMENT

Diurnal variations in cognitive and behavioral symptoms are common in patients with moderate to severe Alzheimer disease, who typically experience exacerbations later in the day (ie, sun-downing), but are uncommon in earlier symptomatic stages. Inconsistent or variable symptoms in a patient with generally maintained function (as in this case) should raise suspicion for potential reversible causes. Metabolic disturbances, sleep disorders, and medication and substance use may all cause variations in cognition, warranting specific questioning and evaluation. In this case, symptoms emerged in the evenings. Slurring of speech, central ataxia, and attentional dysfunction were consistent with inebriation as the cause of cognitive concerns. The clinical response to the reduction in alcohol intake precludes the need for extensive investigations in this case.

atrophy) presentations of AD. For more information on these entities, see the article “Atypical Presentations of Alzheimer Disease” by David Jones, MD, Victoria Pelak, MD, and Emily Rogalski, PhD,⁸⁶ in this issue of *Continuum*.

Unimodal (ie, primary motor and sensory) cortices and deep nuclei (ie, basal ganglia) are spared in the earliest stages of AD, contributing to the relative preservation of motor function. Consequently, the detection of pyramidal signs (eg, pyramidal-pattern weakness, pathologically brisk reflexes, upgoing toes) or gait dysfunction in patients with early symptomatic AD should prompt consideration of other disorders that may occur in association with AD (eg, cerebrovascular disease, normal pressure hydrocephalus), mimic symptomatic AD (eg, frontotemporal lobar degeneration with motor neuron disease), or be

CASE 1-3

A 68-year-old man, a retired executive vice president, presented alone to the outpatient memory clinic for the evaluation of a concern that his “mind sometimes goes blank,” which was exacerbated during periods of stress. Symptoms had minimally improved since he started a low-dose selective serotonin reuptake inhibitor (SSRI) for the treatment of new dysthymia and anxiety. The patient endorsed maintaining all instrumental activities of daily living, although he acknowledged increasing reliance on his smartphone to recall dates and times of appointments, which was a change over the past several months. His neurologic examination, screening blood work, and structural neuroimaging (MRI) were normal. Neuropsychological testing confirmed average immediate recall, with rapid forgetting with increasing delays. Biomarker measures of Alzheimer disease (AD) were recommended, noting objective evidence of short-term memory impairment. CSF analyses confirmed low amyloid- β 42 (A β 42) (697 pg/mL; normal, >834 pg/mL) with elevated phosphorylated tau-181 (pTau181) (71.4 pg/mL; normal, <21.6 pg/mL), consistent with the presence of cerebral (amyloid) plaques and (tau) tangles. The patient was referred for further evaluation and consideration for treatment with anti-amyloid therapies for early symptomatic AD (ie, donanemab and lecanemab).

COMMENT

The emergence of neuropsychiatric symptoms in an older patient with no prior history of psychiatric disease may represent a noncognitive manifestation of underlying AD attributed to disruption of neuronal function within the limbic system. The patient in this case did not endorse limitations in daily function associated with emergent symptoms. However, as the history was not corroborated by a reliable informant, subtle impairment was possibly overlooked. The objective demonstration of domain-specific impairment out of proportion to anxiety or a mood disorder prompted further testing in this case, which ultimately established the diagnosis of AD as the cause of mild behavioral impairment, providing an opportunity to explore emerging disease-modifying treatments for early symptomatic AD.

unrelated to AD but common in older individuals (eg, cervical myelopathy). Similarly, early detection of extrapyramidal findings not attributable to the use of dopamine-suppressing medications (eg, neuroleptics) should prompt consideration of alternative causes or contributors to symptoms, including Lewy body dementia (ie, dementia with Lewy bodies and Parkinson disease dementia), or other parkinsonian conditions, including progressive supranuclear palsy and corticobasal syndrome. As symptomatic disease progresses, extrapyramidal features, tremor, myoclonus, and gait impairment become increasingly common in patients with AD, with motor features detected in 30% to 50% of patients with moderate to severe dementia.⁸⁷ Patients with rare autosomal dominant (inherited) forms of AD present a notable exception to these rules, with motor signs emerging earlier in the symptomatic course, heralding a greater rate of cognitive decline and neuropathologic burden (compared with patients without motor signs).^{88,89}

STAGING SYMPTOMATIC ALZHEIMER DISEASE

AD may be broadly divided into preclinical (asymptomatic) and symptomatic stages. Although there are considerable efforts to identify patients with

Examination Findings That Suggest Higher-order Cortical Dysfunction and Presumed Localization^a

TABLE 1-3

Higher-order cortical function	Findings that suggest dysfunction	Localization
Reasoning, abstraction, monitoring of behaviors	Impaired learning of patterned movements (eg, Luria sequence), difficulty with interpretation of common proverbs or ability to determine similarities, utilization behaviors (eg, sunglasses sign ^{b,87})	Prefrontal cortices and frontoparietal networks (frontal and parietal lobes)
Language	Aphasia (expressive or receptive), echolalia or palilalia, impaired repetition, speech apraxia, surface dyslexia (phonetic pronunciation of irregular words: eg, yacht, pneumonia, colonel)	Dominant frontal and temporal lobes (Broca and Wernicke areas)
Motor planning and execution	Dressing apraxia, ^c motor apraxia (eg, ideational, ideomotor), motor neglect	Supplementary and premotor areas (frontal lobes), sensory association areas (parietal lobes)
Sensory integration	Acalculia, ^d agraphia, ^d finger agnosia, ^d right-left disorientation, ^d astereognosis, graphesthesia, sensory extinction or neglect	Sensory association areas (parietal lobes)
Visuoperceptual function	Oculomotor apraxia, ^e optic ataxia, ^e simultagnosia, ^e impaired color discrimination (eg, Ishihara plates), inability to decipher overlapping items, visual extinction or neglect	Visual association areas (parietal and occipital lobes)

^a Before assessing higher-order cortical functions, it is important to establish that primary sensory (eg, vision, tactile sensation) and motor functions are intact.

^b The “sunglasses sign” may be elicited by placing a pair of sunglasses on a table in front of the patient without further instructions. The sign is considered present if a patient puts on the sunglasses.

^c Dressing apraxia typically localizes to the right parietal lobe.

^d Components of Gerstmann syndrome; when detected together, they localize to deficits within the dominant parietal lobe.

^e Components of Balint syndrome; when detected together, they localize to bilateral parietal or occipital lobes.

preclinical AD to support research,^{19,41} including clinical trials,⁹⁰ by definition, most patients encountered in clinical practice are symptomatic. Several scales have been developed to aid in the accurate staging of cognitive impairment. The Clinical Dementia Rating (CDR) is the most broadly used in clinical trials and multicenter research studies of AD, owing to its high interrater reliability, validity, and reproducibility.⁹¹⁻⁹³ The CDR can be readily operationalized by a trained clinician following a semistructured interview conducted with the patient and a reliable informant. In accordance with published scoring criteria, a score of 0 (no impairment), 0.5 (very mild impairment), 1 (mild impairment), 2 (moderate impairment), or 3 (severe impairment) is assigned across six functional domains: (1) memory, (2) orientation, (3) judgment and problem-solving, (4) community affairs, (5) home and hobbies, and (6) personal care.⁷⁵ The integration of scores via an established algorithm yields a global score indicating a patient with no impairment (global CDR = 0; ie, cognitively normal) or very mild (0.5, also including patients with mild cognitive impairment), mild (1), moderate (2), or severe dementia (3). Increasing global CDR scores closely correlate with progressively increasing disability and dependence on others (FIGURE 1-5).⁷⁵ Other scales may be used alone or in combination to characterize patients with mild, moderate, and severe dementia, including the National Institute on Aging and Alzheimer's Association clinical staging for individuals on the AD continuum (TABLE 1-4), Global Deterioration Scale,⁹⁴ Functional Assessment Staging Tool,⁹⁵ and Dementia Severity Rating Scale.⁹⁶

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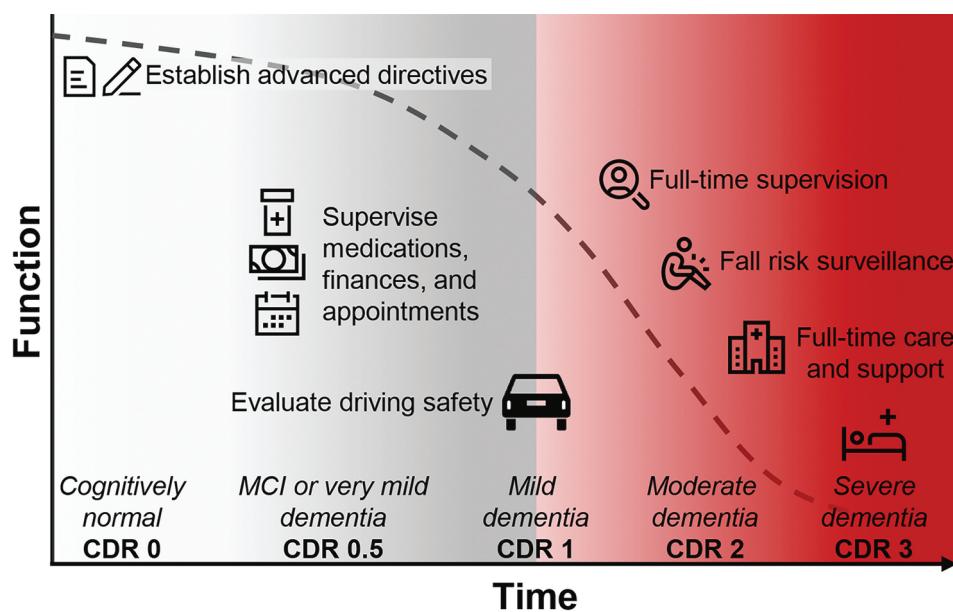


FIGURE 1-5

Expected symptomatic progression and counseling recommendations for patients with typical Alzheimer disease. Stages of impairment are organized left to right, referencing the global Clinical Dementia Rating (CDR). Increasing stages are associated with progressive declines in function necessitating increased supervision and support (red shading). Icons depict stage-appropriate recommendations for surveillance and counseling with the goal of optimizing patient safety while promoting independence.

MCI = mild cognitive impairment.

KEY POINTS

- Behavioral manifestations may accelerate cognitive decline, threaten patient and care partner safety, and substantially increase the burden of care, the risk of institutionalization, and mortality in patients with AD.
- The neurologic examination should be normal early in the symptomatic course of AD.
- Accurate staging of impairment is essential to guide counseling, care, and access to resources for patients with AD and their care partners.

Scores on common batteries of cognitive tests have also been used to stage dementia. Of these, the Mini-Mental State Examination (MMSE),⁹⁷ Montreal Cognitive Assessment (MoCA),⁹⁸ and Saint Louis University Mental Status Examination⁹⁹ are among the most widely recognized and applied. Although these bedside cognitive tests are distinct, all broadly sample memory, orientation, attention, language, and executive and visuospatial functions. Strategies have been proposed to infer dementia stages from absolute scores on cognitive tests (eg, mild dementia: MMSE = 21–25; moderate dementia: MMSE = 11–20; severe dementia: MMSE ≤10).¹⁰⁰ This approach is challenged by difficulties in extrapolating performance on bedside screening tests to day-to-day function and by the inherent potential for pen-and-paper tests to overestimate disability in patients with deficits that directly impair testing, including receptive and expressive aphasia, visuoperceptual dysfunction, or decreased motor function. Thresholds to define patients who are cognitively normal (eg, MMSE ≥24,⁹⁷ MoCA ≥26⁹⁸) versus impaired are equally problematic, recognizing that patients may achieve scores in the normal range (eg, an MMSE score of 27) despite domain-specific impairment indicating early symptomatic AD (eg, 0/3 on tasks of delayed verbal recall; see **CASE 1-1** for a practical example of this). Broader sampling of cognitive function via comprehensive neuropsychological testing may guard against these errors, assuming that patients are motivated to participate in testing and relatively free of visuoperceptual, auditory, speech, and motor impairments. However, cognitive tests may be affected by age, quality of education, acculturation, and primary language, requiring adjustment and interpretation.^{101,102} Together, these limitations emphasize the need for interpretation of test results by experienced clinicians in the context of a comprehensive clinical history and examination.

Accurate staging of impairment is essential to guide counseling, care, and access to resources for patients and their care partners. At the earliest symptomatic stages (ie, prodromal AD, mild cognitive impairment, very mild dementia), patients may require minimal assistance or supervision with daily tasks. Accordingly, medical recommendations may focus on the need for supervision with high-fidelity tasks (eg, medication, financial management), recognizing that minor errors in these areas may have serious consequences. In the mild dementia stages (and beyond), supervision, assistance, and hands-on care become increasingly critical to health and safety, with most patients becoming completely dependent on care partners for all activities of daily living by the moderate stage of impairment (**FIGURE 1-5**).

Safe driving requires complex integration of cognitive (attention, memory, executive function), visuoperceptual, motor, and sensory functions. Progressive compromise of these functions in patients with AD contributes to higher on-road risks,¹⁰³ translating to a greater likelihood of failing a road test¹⁰⁴ and increasing safety risks for patients and others. For these reasons, driving safety should be routinely evaluated in patients with symptomatic AD. This is especially important in patients with mild (or greater) dementia (CDR ≥1) in whom driving cessation (voluntary retirement) may be indicated.¹⁰⁵ Absent driving retirement, a formal on-road driving assessment should be completed and repeated at 6-month intervals. Care partner concerns, restricted driving, a history of crashes, and suspicion of visuoperceptual disturbances by history or examination may identify a patient at even higher risk, warranting reporting to state authorities

TABLE 1-4

National Institute on Aging and Alzheimer's Association Clinical Staging in Patients on the Alzheimer Disease Continuum^a

Stage	Biomarker profile	Clinical features
0	A ± T ± (N)-	Preclinical, asymptomatic with a deterministic (disease-causing) gene ^b No cognitive symptoms Normal performance on objective cognitive tests Maintained function across all domains
1	A+ T- (N)-	Preclinical, asymptomatic (biomarker evidence only) No cognitive symptoms Normal performance on objective cognitive tests Maintained function across all domains
2	A+ T ± ^c (N)-	Preclinical, transitional Subjective cognitive symptoms or mild neurobehavioral changes; may be inconsistent; may be corroborated by an informant Normal performance on objective cognitive tests (subtle declines may be noted on longitudinal testing but patient remains within the normal range) Maintained function across all domains
3	A+ T+ (N)±	Mild cognitive impairment or very mild dementia Consistent cognitive symptoms, corroborated by an informant Impaired performance on objective cognitive tests Maintained activities of daily living; may endorse mild impairment in complex tasks
4	A+ T+ (N)+	Mild dementia Substantial progressive cognitive impairment that affects several domains with or without neurobehavioral disturbance; corroborated by an informant and readily apparent on examination Impaired performance on objective cognitive tests Evident decline in function, impacting daily life and compromising independence
5	A+ T+ (N)+	Moderate dementia Progressive cognitive impairment with or without neurobehavioral disturbance Extensive impact on function resulting in dependence on others
6	A+ T+ (N)+	Severe dementia Progressive cognitive impairment with or without neurobehavioral disturbance Complete dependency with severe functional impairment likely requiring full-time care

± = present or absent; A = amyloid (plaques); (N) = neurodegeneration (volume loss on structural imaging, elevated levels of neurofilament light in blood or cerebrospinal fluid); T = tau (neurofibrillary tangles); + and – denote expected biomarker results (+ = present; - = absent) with available measures.

^a Modified from Jack CR Jr, et al, Alzheimers Dement.¹⁹ © 2024 The Authors.

^b Individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, a decline in functional independence from baseline may be a more appropriate indicator of stage.

^c Tau positron emission tomography (PET) tracer retention is limited to the mesial temporal lobes, if detected.

or mandatory assessment of suitability to drive consistent with state-specific statutes.¹⁰⁵

Accurate staging is also important for treatment. This point is emphasized by the publication of late-phase clinical trials reporting modest disease-modifying effects of anti-A β monoclonal antibodies in patients with early symptomatic AD (ie, mild cognitive impairment and mild dementia due to AD),^{92,106,107} and by stage-dependent recommendations concerning the use of medications for the symptomatic management of AD. Acetylcholinesterase inhibitors (eg, donepezil, rivastigmine, galantamine) are indicated for patients at all stages of dementia,¹⁰⁸ although their use in patients in the prodromal or mild cognitive impairment stage continues to be debated.¹⁰⁹ Conversely, memantine, a partial N-methyl-D-aspartate (NMDA) receptor antagonist, is recommended for use in patients with moderate to severe dementia due to AD,¹¹⁰ with no discernible benefits for patients at earlier stages.¹¹¹

KEY POINT

- Driving safety should be routinely evaluated in patients with symptomatic AD.

DIAGNOSTIC TESTING FOR ALZHEIMER DISEASE

Clinical criteria for probable AD prioritize the clinical history, focusing on symptoms and signs associated with typical AD (**TABLE 1-5**).¹¹² In this context, diagnostic testing is leveraged to exclude potential AD mimics and comorbid conditions that may worsen cognitive impairment. At a minimum, testing should include serum measures of thyroid function and vitamin B₁₂ and screening for depression, recognizing that these reversible conditions are relatively common in older individuals and may contribute to cognitive symptoms.⁵⁷ Screening for medications, exposures, metabolic disturbances, and other potentially treatable conditions that may impair cognition and quality of life (eg, obstructive sleep apnea) should also be considered. Testing for sexually transmitted infections associated with cognitive impairment (namely, human immunodeficiency virus [HIV] and syphilis) should be performed in patients living in endemic areas and those with specific risk factors (including prior infection); this testing is no longer routinely recommended for low-risk patients with typical presentations of dementia.⁵⁷

Structural neuroimaging is indicated in patients with suspected AD to exclude occult lesions or other anomalies that may contribute to or explain impairment, including strokes, subdural hematomas (or other hemorrhages), tumors, and disorders of CSF dynamics (eg, normal pressure hydrocephalus).^{57,112} Although nonenhanced CT of the head will suffice, brain MRI is preferred given its superior discrimination of gray and white matter structures, high sensitivity for cerebrovascular pathology and tumors, and ability to detect microhemorrhages or superficial siderosis associated with cerebral amyloid angiopathy.

Neuroimaging may also support the diagnosis of AD. Although imaging may be normal early in the disease course, hippocampal atrophy is common, with increasing involvement of mesial temporal structures (**FIGURE 1-6**¹¹³), the precuneus, cingulate gyri, and parietal lobes as the disease progresses.¹¹³ Commercial software is available to quantify structural changes and to differentiate atrophy associated with neurodegenerative disease versus normal aging.¹¹⁴ Volumetric imaging is especially valuable when comparing imaging across time, providing standardized measures of structural change within an individual. In the absence of specialized tools, the conscientious clinician may directly examine images for evidence of regional volume loss, including longitudinal increases in the size of the temporal horns of the lateral ventricles

(hydrocephalus ex vacuo), with widening of temporal, parietal, and frontal sulci and thinning of the gyri. Demonstration of progressive atrophy may further increase confidence in the diagnosis of AD, although serial neuroimaging is neither required nor recommended in the longitudinal evaluation of patients with typical AD, absent the emergence of symptoms or signs to suggest a new focal lesion.

Clinical applications of fludeoxyglucose (FDG)-PET neuroimaging in the evaluation of patients with new diagnoses of cognitive impairment are more nuanced. FDG-PET neuroimaging provides a sensitive and reliable measure of synaptic function across brain areas by tracking the metabolism of radionucleotide-tagged glucose, which is the brain's primary energy source. Patterns of hypometabolism in patients with typical presentations of AD (versus other common causes of dementia) are well described (FIGURE 1-7).¹¹⁵ However, clinical applications are limited by overlap in FDG-PET findings and neuropathology in patients with different causes of cognitive impairment, especially AD and Lewy body dementia. For these reasons, typical indications for FDG-PET (and insurance reimbursement in the United States) include the differentiation between AD and frontotemporal lobar degeneration in patients with a recent diagnosis of dementia and documented cognitive decline ongoing for at least 6 months.¹¹⁶

Diagnostic differentiation may be further improved through the judicious use of biofluid and neuroimaging biomarkers with varying sensitivity and specificity for cerebral amyloid and tau neuropathology. The decision to pursue biomarker testing should be made on a case-by-case basis, integrating patient and family input. Clear indications for biomarker measures include the evaluation of patients with confirmed cognitive impairment with a lower pretest probability of

TABLE 1-5

National Institute on Aging and Alzheimer's Association Core Clinical Criteria for the Diagnosis of Probable Dementia Due to Alzheimer Disease^a

- 1 Patient meets criteria for dementia**
- 2 Dementia exhibits the following characteristics**
 - A Insidious (gradual) onset over months to years**
 - B Progressive dysfunction corroborated by a reliable informant or direct observation**
 - C The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories**
 - ◆ Amnestic presentation
 - ◆ Nonamnestic presentation (language, visuospatial, or executive dysfunction)
- 3 Absent evidence of**
 - A Cerebrovascular disease at a level that would explain impairment**
 - B Core features of another neurodegenerative disease (eg, dementia with Lewy bodies)**
 - C A concurrent, active neurologic disease or a non-neurologic comorbidity that could have a substantial effect on cognition**

^a Data from McKhann GM, et al, Alzheimers Dement.¹¹²

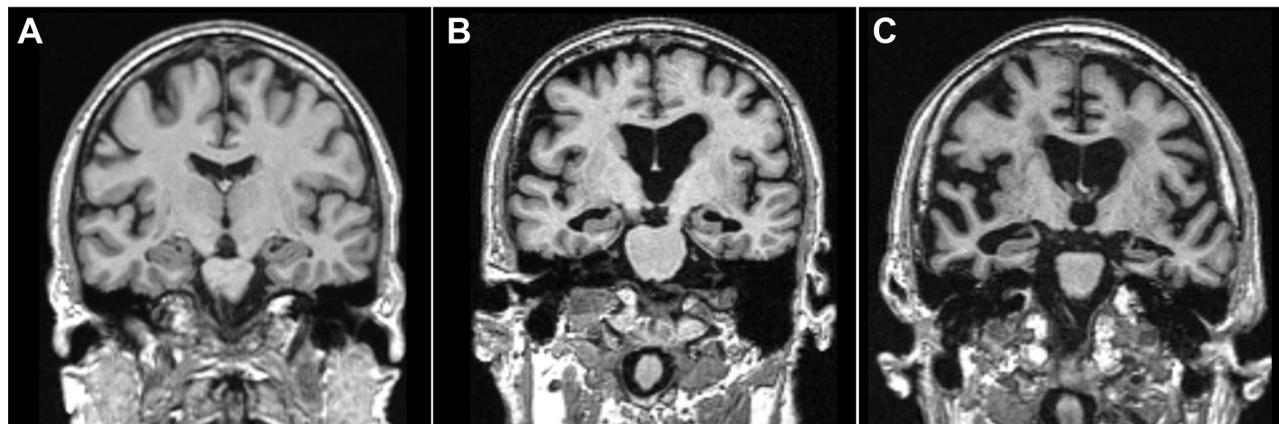


FIGURE 1-6

Common findings on brain MRI in patients with Alzheimer disease. Normal hippocampal and mesial temporal lobe structures in a cognitively normal individual without Alzheimer disease (A) are contrasted against increasing hippocampal and mesial temporal atrophy seen in patients with emergent cognitive impairment (B, amnestic mild cognitive impairment) and mild to moderate dementia (C) due to Alzheimer disease. Coronal T1-weighted images are at the level of the caudate heads.

Modified with permission from Vemuri P and Jack CR Jr, Alzheimers Res Ther.¹¹³ © 2010 BioMed Central Ltd.

AD in whom testing results are more likely to alter management (ie, younger patients and those with atypical disease presentations) and in patients who are considering the use of disease-modifying therapies targeting AD neuropathology (eg, amyloid plaques).¹¹⁷

Genetic testing for disease-causing variants in *PSEN1*, *PSEN2*, or *APP* is not routinely recommended for patients with typical presentations of AD because of the low frequency of causal variants in the general population; for more information about genetic factors in AD, refer to the article “Genetics and Neuropathology of Neurodegenerative Dementias” by Sonja W. Scholz, MD, PhD, FAAN, and Inma Cobos, MD, PhD,¹¹⁷ in this issue of *Continuum*. Exceptions include patients with a history of AD affecting 50% of relatives across two or more generations, patients with one or more first-degree relatives with early-onset AD, and patients with symptomatic onset before 50 years of age who may harbor de novo AD-causing mutations (regardless of family history).^{117,118} Similarly, *APOE* genotyping is not routinely performed in patients with AD because the presence of *APOE** ϵ 4 alleles is neither necessary nor sufficient to cause AD.^{57,119} *APOE* genotyping may be justified for risk stratification in patients considering treatment with monoclonal antibodies targeting A β ,^{120,121} given the strong association between treatment-related amyloid-related imaging abnormalities (including cerebral edema and hemorrhage) and *APOE** ϵ 4 copy number.^{92,106,107,122} Before proceeding with testing, genetic counseling is recommended to ensure ample consideration of the potential implications of test results for medical care, insurance coverage, and employment for the patient and other family members.^{117,119}

AD is a progressive disease. Thus, documented declines across serial evaluations may increase diagnostic certainty, representing a useful diagnostic test. The test of time is an accessible, informative, yet undervalued test in the evaluation of patients with cognitive impairment. Interval clinical follow-up is recommended in patients with new diagnoses of symptomatic AD, providing an

opportunity to reassess deficits, survey day-to-day function, stage dementia severity, assess response to therapies, and screen for associated symptoms (including neuropsychiatric symptoms), care partner burnout, and other issues that may affect patient safety or quality of life.

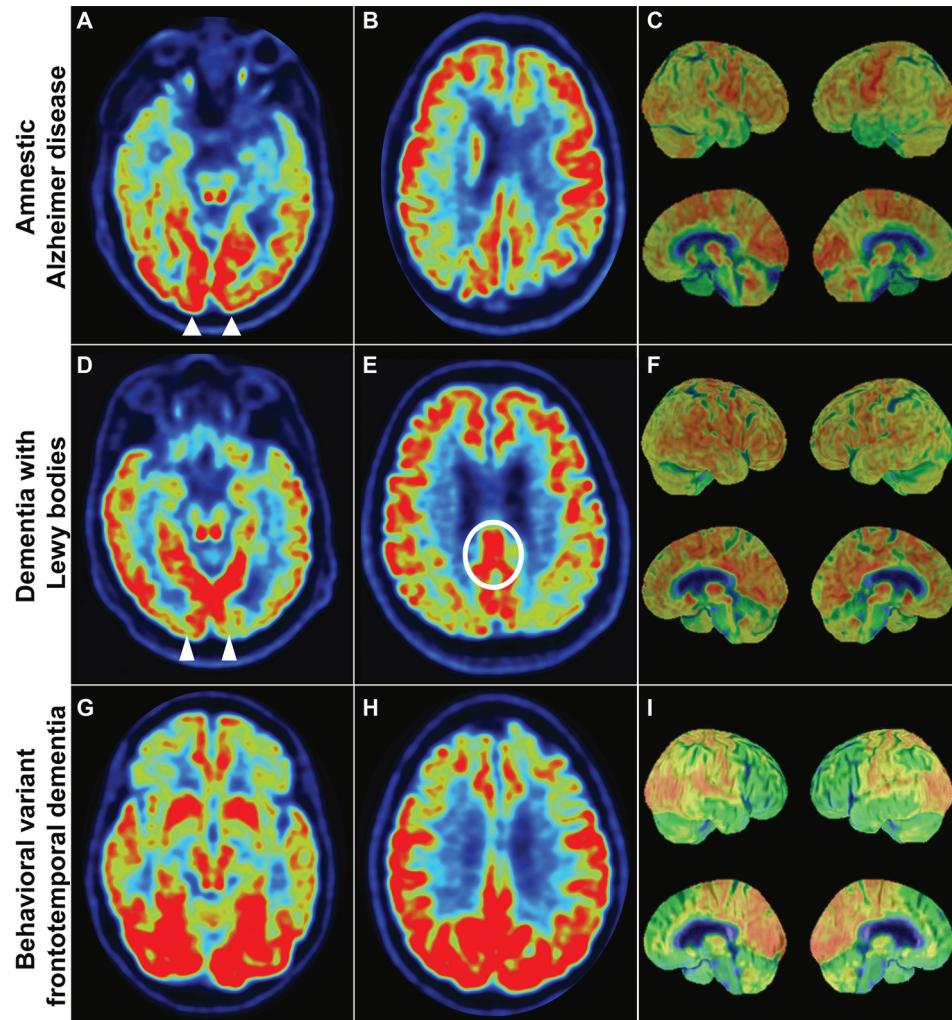


FIGURE 1-7

Expected fludeoxyglucose positron emission tomography (FDG-PET) findings in patients with typical neurodegenerative disease. Patterns of metabolism on FDG-PET are shown in patients with amnestic-predominant (typical) Alzheimer disease (A-C), dementia with Lewy bodies (D-F), and behavioral variant frontotemporal dementia (G-I). Alzheimer disease is classically associated with bitemporal and biparietal hypometabolism. Relative preservation of occipital metabolism distinguishes patients with typical AD from those with dementia with Lewy bodies (A, D, white triangles), who may also have relative sparing of metabolism within the posterior cingulate (cingulate island sign¹¹; E, white circle). In contrast to Alzheimer disease and dementia with Lewy bodies, FDG-PET in behavioral variant frontotemporal dementia typically shows prominent frontal and temporal hypometabolism with relative preservation of posterior structures. FDG-PET axial images are shown at the level of the midbrain (A, D, G) and caudate heads (B, E, H). Panels C, F, and I depict whole-brain metabolism; warmer colors indicate greater metabolism.

THE VALUE OF ACCURATE DIAGNOSIS

The advent of AD-modifying therapies for patients with early symptomatic disease clearly emphasizes the value of an early and accurate diagnosis of AD. Other benefits include a reduction in unnecessary testing, consultations, and therapeutic trials associated with increased costs, burden, and risks. For patients who remain employed, early diagnosis presents an opportunity to mitigate risks of involuntary termination of employment (“with cause”) and support qualified patients in applying for long-term disability. Early diagnosis also provides an opportunity to reinforce autonomy by engaging patients (and care partners) in meaningful discussions concerning advanced care planning; implementing lifestyle and behavioral changes to promote independence and mitigate risks associated with medication errors, wandering behaviors, financial errors, and driving; and encouraging participation in clinical research, including clinical trials. However, the best argument of all is perhaps the simplest one: Patients and care partners want this information,¹²³ with both parties endorsing reduced anxiety¹²⁴ and increased quality of life¹²⁵ after an accurate diagnosis. Collectively, these advantages emphasize the importance of a coordinated and comprehensive approach to the evaluation of patients with emergent cognitive decline.

KEY POINTS

- Structural neuroimaging is indicated in patients with suspected AD to exclude occult lesions or other anomalies that may contribute to or explain impairment.
- Indications for fludeoxyglucose positron emission tomography (FDG-PET) (and insurance reimbursement in the United States) include the differentiation between AD and frontotemporal lobar degeneration in patients with a recent diagnosis of dementia and documented cognitive decline ongoing for at least 6 months.
- Documented declines across serial evaluations may increase diagnostic certainty, representing a useful diagnostic test for AD.
- The advent of AD-modifying therapies for patients with early symptomatic disease clearly emphasizes the value of an early and accurate diagnosis of AD.

CONCLUSION

AD is a multistage illness characterized by the slow and steady accumulation and spread of A β plaques and neurofibrillary (tau) tangles throughout the brain, resulting in synaptic dysfunction and neuronal loss and leading to increasing cognitive impairment, loss of independence, and substantial morbidity and mortality. Advancing age, genetic variants, and exposures or behaviors that alter A β production and clearance all influence AD risk. A comprehensive history involving the patient and a reliable informant is critical to accurately detect emergent changes in short-term memory that identify typical AD, supported by objective tests of memory and thinking. The neurologic examination should be normal early in the symptomatic course, with aphasia, cortical-localizing signs (eg, apraxia, visuoperceptual deficits), and extrapyramidal signs becoming increasingly common as AD progresses. Structural neuroimaging is indicated to exclude alternative causes and potential (treatable) contributors to cognitive impairment. Confidence in the diagnosis may be increased through the judicious application and interpretation of increasingly sensitive and specific neuroimaging and biofluid biomarkers of AD neuropathology and through longitudinal follow-up confirming clinical progression (the test of time). Accurate diagnosis of AD and staging of impairment is critical for clinical care, informing surveillance for symptoms and behaviors that may compromise patient safety and quality of life and supporting timely access to treatments, resources for patients and their care partners, and clinical research opportunities. The value of an accurate diagnosis is further exemplified by the recent approval of disease-modifying therapies indicated for use in patients with mild cognitive impairment and mild dementia due to AD and the corresponding proliferation of clinical trials enrolling patients at earlier and earlier stages of the disease. Advances in AD therapeutics are expected to increase the demand for clinicians who are prepared to efficiently and expertly diagnose, stage, evaluate, and treat patients with symptomatic AD.

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Atypical Presentations of Alzheimer Disease

By David Jones, MD; Victoria Pelak, MD; Emily Rogalski, PhD

ABSTRACT

OBJECTIVE: This article provides a comprehensive review of the distinct features of four atypical Alzheimer disease (AD) variants: dysexecutive AD, behavioral variant AD, posterior cortical atrophy, and the logopenic variant of primary progressive aphasia. It also elucidates their clinical presentations, underlying pathophysiologic pathways, diagnostic indicators, and management requirements.

LATEST DEVELOPMENTS: Recent research has revealed that these atypical AD forms vary not only in clinical manifestations but in their functional neuroanatomy spanning a common pathophysiologic spectrum. Imaging techniques, such as MRI, fludeoxyglucose positron emission tomography (FDG-PET), and tau PET, have identified distinct abnormalities in specific brain regions associated with each variant. This same variability is less tightly coupled to amyloid imaging. Emerging diagnostic and therapeutic strategies should be tailored to each variant's unique features.

ESSENTIAL POINTS: Atypical forms of AD often present with symptoms that are predominantly nonmemory related, distinguishing them from the more common memory-centric presentation of the disease. Two distinct clinical and pathologic entities, dysexecutive AD and behavioral variant AD, have replaced the outdated term *frontal AD*. Posterior cortical atrophy is another variant that mainly affects higher-order visual functions, which can lead to misdiagnoses because of its atypical symptom profile. Logopenic primary progressive aphasia is marked by difficulties in word retrieval, a challenge that may not be readily apparent if the person compensates by using circumlocution. Modern diagnostic techniques, such as MRI, PET, and biomarker analysis, have proven crucial for the accurate diagnosis and differentiation of these atypical AD variants. In treating these forms, it is critical to use tailored therapeutic interventions that combine pharmacotherapy with nonpharmacologic strategies to effectively manage the disease.

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**UNLABELED USE OF PRODUCTS/
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INTRODUCTION

Alzheimer disease (AD) is typically characterized by a multidimensional cognitive decline, with memory impairment often emerging as the most salient feature. However, other cognitive domains, including language, visuospatial and perceptual abilities, perceptual-motor skills, and executive functions, are not

spared and can display variable deterioration. Beyond these characteristic presentations, certain atypical forms of AD are marked by predominant symptoms in nonmemory cognitive domains.¹ These atypical presentations not only differ in their clinical manifestations but also exhibit unique pathophysiologic pathways, diagnostic indicators (see **FIGURE 2-1** for distinct functional anatomy), and management requirements. These atypical presentations are thought to represent extremes of a common underlying functional spectrum.² This article reviews the distinctive features of four such atypical AD variants: dysexecutive AD, behavioral variant AD, posterior cortical atrophy (PCA), and the logopenic variant of primary progressive aphasia (PPA).

KEY POINTS

- Atypical forms of Alzheimer disease (AD) are defined by predominant symptoms in nonmemory cognitive domains.
- Atypical presentations of AD have unique pathophysiologic pathways, diagnostic indicators, and management requirements.

DYSEXECUTIVE AND BEHAVIORAL VARIANT ALZHEIMER DISEASE

Dysexecutive AD is a subtype of AD in which the primary symptom is executive dysfunction. Another, rarer subtype can show symptoms similar to behavioral variant frontotemporal dementia (FTD).³ However, although it mimics behavioral variant FTD clinically, its underlying cause is AD, as confirmed by biomarkers or autopsy. This subtype is termed *behavioral variant AD* in this context and should be distinguished from dysexecutive AD. Recently proposed criteria for dysexecutive AD⁴ stipulate that the behavioral variant FTD syndrome is exclusionary for diagnosing dysexecutive AD (**TABLE 2-1**). It is important to note that the brain areas responsible for social, emotional, and motivational

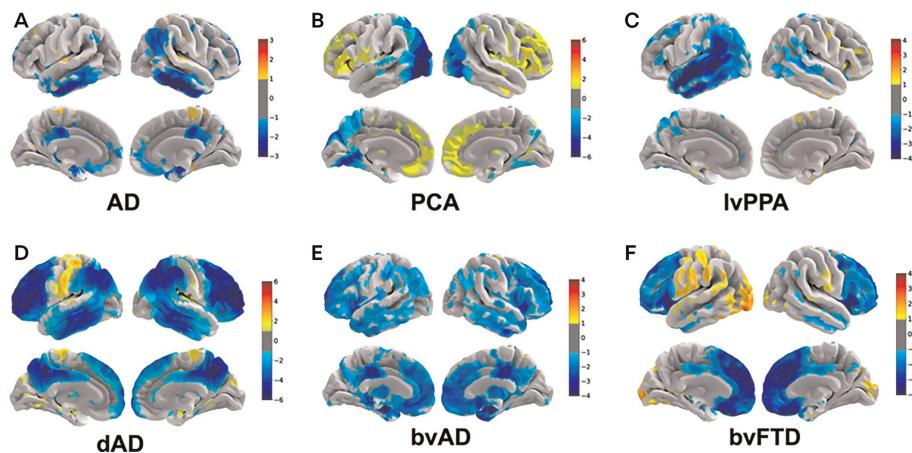


FIGURE 2-1

Brain fluorodeoxyglucose positron emission tomography (FDG-PET) for individual case examples of the clinical phenotypes discussed in this article. These global brain patterns represent the extremes of a common global functional state space or phenotypic spectrum of neurodegeneration.² The individual patient images are displayed on a template brain surface with negative values indicating hypometabolism in blue and positive values indicating hypermetabolism in yellow and red relative to a normative database. **A**, Typical memory predominant Alzheimer disease (AD) showing hypometabolism in temporal and parietal areas. **B**, Posterior cortical atrophy (PCA) showing hypometabolism in occipital and parietal areas and relative hypermetabolism in the frontal lobe. **C**, Logopenic variant of primary progressive aphasia (lvPPA) showing hypometabolism in left temporal and parietal areas. **D**, Dysexecutive AD (dAD) showing hypometabolism in the heteromodal association cortex and hypermetabolism in primary sensory and motor cortices. **E**, Behavioral variant of AD (bvAD) showing hypometabolism in frontal, medial temporal, and cingulate cortices. **F**, Behavioral variant frontotemporal dementia (bvFTD) showing hypometabolism in the frontal lobe and hypermetabolism in occipital and parietal areas.

functions are different from those involved in executive functions.^{5,6} As a result, the clinical manifestations of diseases affecting these areas are distinct. This section delves into the differences in clinical presentations, underlying causes, diagnosis, and management of these two distinct AD subtypes that are often confused.

Clinical Presentations

The progressive dysexecutive syndrome that defines dysexecutive AD represents a unique challenge in the spectrum of AD subtypes.⁴ This clinical syndrome typically occurs at a younger age than other phenotypes, and most patients are still actively engaged in the workforce and have parental responsibilities. Patients diagnosed with dysexecutive AD predominantly face challenges in areas requiring planning, organization, and decision making. Their cognitive abilities, especially those related to the executive functions of working memory and

TABLE 2-1

Proposed Diagnostic Criteria for Progressive Dysexecutive Syndrome and Dysexecutive Alzheimer Disease

	Clinical criteria	Evidence	Exclusions
Progressive dysexecutive syndrome	Persistent, predominant, and progressive decline for 6 months in core executive functions: working memory, cognitive flexibility, or inhibition in the absence of predominant behavioral features (ie, would not meet criteria for the clinical syndrome of behavioral variant frontotemporal dementia)	Evidence of impaired executive functions is obtained by patient or informant reports in conjunction with formal evaluation of cognitive performance on mentally effortful tasks that require conscious active manipulation of abstract or simultaneous information streams	History of sudden onset or other medical conditions severe enough to account for related symptoms (eg, primary psychiatric, cerebrovascular, infectious, toxic, inflammatory, or metabolic disorders)
Progressive dysexecutive syndrome with Alzheimer disease (AD) neuropathologic change (possible dysexecutive AD)	Meets criteria for progressive dysexecutive clinical syndrome	Must have evidence of Alzheimer pathophysiology with one of the following: Decreased CSF amyloid- β 1 (A β 1)-A β 42 or A β 42/A β 40 ratio; or Abnormal tracer retention on amyloid-PET	None
Progressive dysexecutive syndrome due to Alzheimer disease (definite dysexecutive AD)	Meets criteria for possible dysexecutive AD	Must have evidence of one of the following: Increased CSF phosphorylated tau Abnormal tracer retention on tau PET Alzheimer disease autosomal dominant genetic variation present Postmortem diagnosis of AD, high likelihood	

cognitive flexibility, are noticeably compromised. This often manifests in their daily activities, and tasks that require some executive faculties are markedly impaired whereas more automatic activities are entirely preserved. This manifests in a striking disconnect; multitasking and simple tasks involving sequences and spatial manipulations (eg, making a sandwich, learning a new software program or process at work, or mentally manipulating numbers) are markedly impaired, but more complex processes that are well learned and automatic (eg, driving) continue to be performed with seemingly less difficulty.

There is variability in how much an individual can compensate for executive dysfunction by relying on well-learned behaviors. Therefore, some individuals may be able to continue in their jobs for years without noticeable impacts on their performance. However, once a new process, procedure, or software program is introduced, they are unable to perform their work duties, and their cognitive difficulties become apparent to themselves and their employers and family. A similar phenomenon occurs when learning a new process or procedure introduced into the home (eg, new technology such as a smartphone or television), playing a new board game, or assembling toys or furniture. Other cognitive domains that depend on executive abilities related to working memory and cognitive flexibility can also be impaired (eg, language, visuospatial, and memory) leading to logopenic-type language dysfunction (eg, anomia and impaired repetition) or apparent topographagnosia and episodic memory loss. For some individuals, memory loss can be the focus of the reported clinical symptoms as patients and care partners may be unfamiliar with the broader impact of executive function for tasks that are being performed daily. Many of these difficulties are referred to as “forgetting” how to do the task or procedure, which can lead to a mistaken focus on memory encoding and retrieval as the primary cognitive deficit.

People with dysexecutive AD may become more irritable and anxious because they can no longer perform simple tasks and become overwhelmed with multitasking. This may also lead to a withdrawal from activities that were previously enjoyable but are now too difficult to engage in and raises clinical concern for apathy or other emotional disturbances. These circumstances can also understandably produce a depressed mood in many individuals with this type of executive dysfunction. The various combinations of these psychiatric symptoms (eg, irritability, anxiety, apathy, poor attention, and depressed mood) often lead to several psychiatric diagnoses before the diagnosis of dysexecutive AD (eg, major depressive disorders, anxiety disorders, and attention deficit hyperactivity disorders). However, the root cause of these social, emotional, and motivational disturbances is secondary to the primary executive dysfunction. Over time, their ability to solve problems and perform simple tasks becomes increasingly compromised, leading to job loss and increased dependence on care partners or family members for nonautomatic daily functions.

In contrast, behavioral variant AD paints a different clinical picture. People with behavioral variant AD typically undergo noticeable shifts in their personality and behavior with root causes stemming from social, emotional, and motivational disturbances. It is not uncommon for them to behave inappropriately in social contexts, making interactions challenging for both the patient and those around them. Their emotional landscape also changes, with many displaying a diminished emotional response or a blunted affect as the leading clinical symptom. A pronounced lack of motivation becomes evident and is the driving

KEY POINT

- Dysexecutive AD and behavioral variant AD are distinct presentations, and the term *frontal AD* should no longer be used.

source of clinical impairment in some patients with behavioral variant AD, just as it is for some individuals with behavioral variant FTD. Activities that were once pursued with enthusiasm are now met with indifference. This decline in interest can extend to essential daily tasks including basic hygiene. Obsessive, compulsive, and repetitive behaviors can also occur and be indistinguishable from those of behavioral variant FTD. Memory and executive dysfunction may or may not occur but are not the prominent or driving force of the clinical disturbances. Therefore, clinically there is little difference in the syndromes of behavioral variant FTD and behavioral variant AD, but this is an area of ongoing study as behavioral variant AD is not routinely distinguished from dysexecutive AD, with some suggesting they are on one continuum⁷ and others suggesting they are on a multidimensional spectrum (**TABLE 2-2**).⁶

Pathophysiology

Dysexecutive AD stands out not only for its clinical symptoms but also for the specific brain changes causing these symptoms. Although the term *mechanism* is often used to describe such causes, *causal explanation* is used in this article to better capture the broader interplay of anatomy and dynamic physiology behind the deterioration of mental functions in the setting of dysexecutive AD and behavioral variant AD.⁸ All AD subtypes share common causal explanations such as misfolded proteins and the accumulation of amyloid- β (A β) and tau. However, the causal explanations for the distinct clinical symptoms of each subtype relate

TABLE 2-2

Clinicopathologic Features of Dysexecutive Alzheimer Disease, Behavioral Variant Alzheimer Disease, and Behavioral Variant Frontotemporal Dementia

Clinicopathologic feature	Dysexecutive Alzheimer disease	Behavioral variant Alzheimer disease	Behavioral variant frontotemporal dementia
Clinical	Progressive dysexecutive syndrome with younger age of onset (typically between 45 and 70 years old)	Progressive behavioral syndrome with variable age of onset	Progressive behavioral syndrome with younger age of onset (typically between 40 and 65 years old)
Neuropsychological testing	Typically, very abnormal with executive dysfunction affecting performance on most tests (performance validity testing may be falsely indicative of poor validity)	Can demonstrate normal to variable memory and executive dysfunction	Can demonstrate normal to variable memory and executive dysfunction
Social, emotional, and motivational	Minor and secondary feature that may not be present	Major and primary feature that must be present	Major and primary feature that must be present
Imaging and neuroanatomy	Heteromodal association cortex, but parietal dominant focus with frontal involvement is typical; sparing of the hippocampus is common but not always present	Frontotemporal that typically extends to inferior temporal and parietal	Frontotemporal
Alzheimer disease biomarkers	Positive	Positive	Negative

to the degeneration of specific functional brain regions and systems, leading to observable behavioral differences.

Executive functions are key mental skills that are affected in patients with dysexecutive AD.⁵ These skills include working memory (holding and working with information in your mind), cognitive flexibility (switching between tasks or thoughts), and inhibition (controlling impulses). Common models of working memory refer to a few different parts: the phonologic loop (dealing with sounds and words), the visuospatial sketch pad (handling visual and spatial information), and the episodic buffer (linking information across domains to form integrated units of visual, spatial, and verbal information with time sequencing).⁹

Recent research points to a system in the brain where there is a general space for short-term memory. This space is spread across different brain areas, but the main operations, particularly those related to working memory, happen mainly in the parietal and frontal regions. Put simply, the left side of the brain handles information step by step, which helps with logical thinking. However, the right side of the brain can juggle multiple pieces of information quickly, aiding in pattern recognition and abstraction.¹⁰

The symptoms seen in patients with dysexecutive AD, such as trouble with new tasks, planning, or organizing, come from problems in these working memory areas or how these areas communicate with each other. Researchers using brain imaging to study these areas use various names such as *executive control networks*, *working memory networks*, *parietofrontal networks*, *task-positive networks*, and *multidemand networks*, among others.¹¹⁻¹⁶

In contrast, behavioral variant AD presents a different pathophysiologic profile. Although it shares the foundational causal explanations of misfolded proteins and the accumulation of A β and tau, the clinical manifestations of behavioral variant AD are more closely tied to the degeneration of brain regions responsible for behavior, emotion, motivation, and personality. Specifically, the anterior temporal lobes and certain frontal regions play pivotal roles in motivation, social behavior, and emotional processing, and are more affected in behavioral variant AD.

The behavioral changes observed in patients with behavioral variant AD, such as impulsivity, social inappropriateness, apathy, and personality shifts, can be attributed to the degeneration of the anterior temporal lobes and affected frontal lobe regions. Moreover, the overlap in symptoms of behavioral variant AD and behavioral variant FTD can be explained by the similar brain systems affected in both conditions. However, the underlying molecular pathology distinguishes the two, with behavioral variant AD rooted in AD pathology.

Functional neuroimaging studies have highlighted various networks disrupted in behavioral syndromes, including the salience network, default mode network, and emotional processing circuits. These networks, when compromised, can lead to the characteristic motivational, behavioral, and emotional symptoms of behavioral variant AD. Understanding the distinct pathophysiologic underpinnings of dysexecutive AD and behavioral variant AD is crucial for accurate diagnosis and targeted counseling and therapeutic interventions.

Diagnosis

Diagnosing dysexecutive AD demands a comprehensive approach, emphasizing the differential diagnosis of a progressive dysexecutive syndrome. It is essential to recognize features indicative of degenerative etiologies, such as a gradual and

KEY POINTS

- Patients with dysexecutive AD have impaired planning, organization, and decision making.
- Compromised working memory and cognitive flexibility manifest in impairments of cognitively effortful tasks while automatic activities are more preserved in patients with dysexecutive AD.
- In the setting of dysexecutive AD, memory loss can be the focus of the reported clinical symptoms as many are unfamiliar with the role of executive function for daily tasks.
- For patients with dysexecutive AD, changes in behavior are secondary to the impact of impaired executive function and are not themselves the primary driver of dysfunction.
- In behavioral variant AD, changes in behavior are the root cause of impaired daily functioning, similar to behavioral variant frontotemporal dementia (FTD).
- Amyloid and tau biomarkers are positive in dysexecutive AD and behavioral variant AD, but the spatial distribution of tau positron emission tomography (PET), fludeoxyglucose (FDG)-PET, and MRI changes more closely align with the unique functional anatomy of these two syndromes.
- Function of parietal and frontal regions related to working memory is commonly abnormal in patients with dysexecutive AD.

insidious progression. The process begins with a thorough history and physical examination, considering nondegenerative causes of executive dysfunction. Although many of these features are common to all degenerative syndromes and are discussed elsewhere, it is crucial to manage nondegenerative factors influencing executive functioning. These often include sleep disorders, medications, vascular diseases, CSF dynamics disorders, and psychiatric conditions.

Neuropsychological testing is vital to determine the exact nature and severity of executive dysfunction. The Trail Making Test Part B, for instance, is particularly sensitive to various forms of executive dysfunction. However, interpreting these tests requires caution. Most tasks demand some level of executive function, leading to a profile of impairment across multiple domains for individuals with a progressive dysexecutive syndrome. Furthermore, poor performance on validity measures can mistakenly suggest malingering or psychiatric causes.¹⁷ This misinterpretation is especially problematic for working-age patients with dysexecutive AD undergoing testing because of job loss, which can appear as a motivation for secondary gain. Additionally, psychiatric symptoms resulting from lost executive function can lead to misdiagnoses of primary psychiatric disorders.

Structural neuroimaging plays a dual role: excluding specific nondegenerative causes and providing evidence of degenerative changes in working memory systems. Atrophy in the heteromodal association cortex, particularly the parietal lobe, is common. The frontal lobe may be involved but always to a lesser degree than the parietal lobe. The term *frontal AD* is anatomically incorrect and syndromically ambiguous, so this term should not be used for dysexecutive AD or behavioral variant AD. A normal-appearing hippocampus might mislead clinicians to rule out AD, but the hippocampus is commonly spared in dysexecutive AD. Functional imaging, such as fludeoxyglucose positron emission tomography (FDG-PET), can offer more definitive insights, helping differentiate dysexecutive AD from other degenerative conditions and even subtyping dysexecutive AD.^{2,5,10} Even when changes are relatively mild on structural imaging, they are often clearly abnormal on FDG-PET. These imaging patterns guide further testing, medical counseling, staging, prognosis, and management.

Despite comprehensive clinical assessments, neuropsychological testing, and neuroimaging, some conditions can mimic dysexecutive AD, leading to diagnostic uncertainty. Therefore, additional AD biomarker data, preferably from CSF, are indispensable.¹⁸ However, interpreting CSF phosphorylated tau (pTau) levels requires caution, because some patients with dysexecutive AD might present with normal levels.⁴ Tau PET imaging in dysexecutive AD usually demonstrates the highest magnitude of signal increases of any AD subtype.⁴ The parietal and frontal regions show the most characteristic increase in tau PET signal alongside inferior temporal signal changes seen in most AD clinical phenotypes. This regional information informs phenotypic characterization, but this information is also present in FDG-PET and to a lesser degree in structural imaging. From a diagnostic perspective, tau PET may be helpful only when diagnostic uncertainty remains or other AD biomarkers are not feasible.^{4,18} Apart from diagnosis, tau PET may have an emerging role in staging.

Behavioral variant AD is relatively less common and presents its own diagnostic challenges. Clinically, behavioral variant AD can resemble behavioral variant FTD, making differentiation based solely on symptoms challenging. The distinction between the disorders is in the underlying pathology. Although the

clinical presentation might echo behavioral variant FTD, biomarkers will indicate AD pathology. Autosomal dominant genetic etiologies are relatively common in the setting of behavioral variant FTD, but this is not a common consideration in behavioral variant AD. However, genetic counseling and consideration of genetic testing should be done for all patients with a younger onset and individuals with a strong family history of multiple affected relatives, especially first-degree relatives with a younger age of onset. Neuropsychological testing, although not diagnostic, remains essential for documenting severity, strengths, and weaknesses. It may reveal varying degrees of executive and memory impairments in both behavioral variant FTD and behavioral variant AD. Functional neuroimaging, such as FDG-PET scans, can be invaluable for diagnosis and staging, potentially showing patterns in the temporal and frontal regions indicative of behavioral variant AD. Differentiating between behavioral (ie, behavioral variant FTD and behavioral variant AD) and executive (dysexecutive AD) syndromes on neuroimaging requires recognizing distinct functional neuroanatomic patterns, with dysexecutive AD typically sparing the medial frontal region relative to parietal and dorsal lateral prefrontal regions, unlike the behavioral syndromes.

In diagnosing these subtypes, a combination of clinical assessments, neuropsychological testing, structural and functional imaging, and AD biomarkers is paramount. This multifaceted diagnostic approach ensures accurate identification and differentiation among dysexecutive AD, behavioral variant AD, behavioral variant FTD, and other etiologies, guiding patients toward the most appropriate care, interventions, and clinical trials.

Management

The management of dysexecutive AD and behavioral variant AD combines pharmacologic with nonpharmacologic approaches. Cholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists, traditionally used in the treatment of other forms of AD, likely offer similar benefits to patients with dysexecutive AD and behavioral variant AD. However, their efficacy in affecting executive and behavioral features in this setting has not been specifically evaluated. Similarly, amyloid-lowering monoclonal antibodies have not been specifically evaluated in these clinical phenotypes. Appropriate use recommendations suggest that this absence of treatment-related information for atypical AD is not a contraindication for amyloid-lowering monoclonal antibody use, but they do suggest this limitation should be acknowledged in discussions with therapy candidates and their care partners.¹⁹ Data in 2023 suggested that patients with high tau levels may not benefit from anti-amyloid therapy.²⁰ Therefore, further research is necessary to evaluate the possibility that there may be less of a benefit in certain patients with dysexecutive AD who commonly have very high tau levels measured with PET imaging.^{4,5,11} Future clinical trials should emphasize the importance of detailed phenotyping that includes functional neuroimaging, such as FDG-PET (**FIGURE 2-1**), to provide a better understanding of phenotypic variability in responses to therapeutics. This approach will facilitate the shared decision-making process when clinicians are considering the risks and benefits of different therapeutic strategies.

The social, emotional, and motivational symptoms, whether primary in behavioral variant AD or secondary in dysexecutive AD, may respond to

KEY POINTS

- Function of medial frontal regions related to behavior is commonly abnormal in patients with behavioral variant AD and behavioral variant FTD.
- Failure on performance validity testing commonly leads to misinterpretations of neuropsychological testing in the setting of dysexecutive AD.
- In patients with dysexecutive AD, the hippocampus is commonly spared and appears normal on MRI.

typical pharmacologic strategies for these symptoms (eg, antidepressants, antipsychotics, and anxiolytics), but this has not been systematically investigated, and vigilance for over-medicating should be maintained throughout the disease course.

Alongside medications, nonpharmacologic strategies should also be emphasized. Tailored counseling to enhance executive function performance (eg, simplifying environments, avoiding multitasking, and emotion control) or relying on well-learned behaviors to compensate can equip patients with strategies to cope with daily tasks, improving their quality of life and reducing care partner burden. Behavioral redirection and distraction can also help with problematic behaviors just as they can in behavioral variant FTD. Structured routines, environmental modifications, and care partner training can all contribute to managing executive and behavioral challenges.

Regardless of the subtype, care partner education remains a cornerstone of management. Given the unique challenges posed by both dysexecutive AD and behavioral variant AD, it is essential for care partners to understand the nuances of these conditions. Providing them with the knowledge and tools to manage symptoms, handle behavioral challenges, and offer emotional support can significantly enhance the care provided to patients, ensuring their well-being and dignity are maintained (**CASE 2-1**).

POSTERIOR CORTICAL ATROPHY SYNDROME

PCA syndrome due to AD can be difficult to recognize and diagnose without a keen awareness of the higher-order visual deficits that dominate this atypical presentation. PCA is characterized by prominent cortical visual dysfunction with relative sparing of memory, language, executive functions, behavior, and personality at presentation or early in the course. It is defined by its clinical features, and the diagnosis is supported by abnormal posterior brain imaging findings as reviewed later in this section.

The term *posterior cortical atrophy* was coined by Benson and colleagues²¹ when they described five patients who developed progressive dementia after presenting with higher-order visual dysfunction and relative sparing of memory, insight, and judgment in association with predominant parieto-occipital cortical atrophy. Autopsies were not performed. Controversy then ensued about whether PCA was a unique neurodegenerative disease or simply an atypical syndrome of AD. In 1993, Levine and colleagues²² published a clinicopathologic case study of a patient, similar to those described by Benson and colleagues, with postmortem examination that revealed AD pathology, leading to naming the condition the *visual variant of AD*. The term *posterior cortical atrophy* is now favored, particularly after the publication of the PCA consensus criteria by Crutch and colleagues²³ in 2017, which are reviewed later in this article, and with the discovery that non-AD pathologies can also present with PCA syndrome including dementia with Lewy bodies, corticobasal degeneration, Creutzfeldt-Jakob disease, and copathology of Lewy bodies and AD.

Clinical Presentation

Frequently, individuals experiencing PCA-related symptoms attribute their visual issues to ocular causes and first seek the expertise of ophthalmologists or optometrists. A common scenario is for a patient to receive multiple prescriptions for eyeglasses or undergo cataract extraction without alleviation of

their symptoms. In these instances, patients remain undiagnosed for an extended duration, often spanning many months or even years, until advanced higher-order visual impairments occur or with the apparent onset or worsening of memory deficits or other cognitive impairments.

TABLE 2-3 lists examples of initial patient concerns and their evolution over time. Symptoms may initially manifest as ordinary visual blurriness, gradually evolving into difficulty reading and problems perceiving objects that are conspicuously within view. Eventually, patients report poor performance with tasks that are visually demanding or require oculomotor coordination, and even at that stage, some cognitive screening batteries, such as the Mini-Mental State Examination (MMSE), do not capture visual brain dysfunction. After 1 to 2 years, symptoms can extend beyond the visual realm to include difficulty with calculations, writing, and praxis. An exception to this pattern occurs in patients with dominant biparietal dysfunction, who initially have limited visual symptoms related to spatial awareness but have prominent symptoms consistent with impaired praxis (eg, difficulty with object manipulation such as using a computer mouse), dysgraphia, and dyscalculia. Descriptions of variations in the PCA presentation include the biparietal (or dorsal) variant as noted, an occipital variant, and an occipitotemporal (or ventral) variant, although the majority of patients express mixed characteristics.²⁴

Onset of PCA generally occurs at an early age, usually between 50 and 64 years, although late-onset (at 65 years or older) presentations can occur in up to 15% of people with PCA.^{25,26} The atypical nature of the initial symptoms (ie, visual and not memory), the young onset, satisfactory performance on screening measures of global cognition, and preserved insight can lead to a mistaken diagnosis of anxiety or depression as the underlying cause of symptoms. Although it is common for patients to experience symptoms of anxiety or depression, attributing all symptomatology to a mood disorder may result in diagnostic delays, potentially continuing until patients reach a point at which they can no longer engage in activities such as driving, reading, or working.

Diagnostic Criteria and Classification

In 2017, an international PCA work group published consensus criteria for PCA syndrome as well as a PCA classification framework that incorporates underlying pathology and other syndromes that can occur alongside PCA (eg, corticobasal syndrome) (**TABLE 2-4**).²³ In brief, a patient must have 3 of the 16 core cognitive features as an early or presenting sign. Features include alexia, space and object perception impairment, all elements of Balint syndrome (oculomotor apraxia, optic ataxia, simultanagnosia) and Gerstmann syndrome (left-right disorientation, dysgraphia, finger agnosia, acalculia), environmental agnosia, impaired praxis (limb, dressing, and constructional), apperceptive prosopagnosia, and a homonymous visual field defect. Neuroimaging findings that support the diagnosis include atrophy of posterior cortical structures on MRI, hypometabolism on FDG-PET, and hypoperfusion on single-photon emission computed tomography (SPECT). The treating or consulting neurologist should personally review the brain images because subtle, disproportionate posterior findings are not always reported. Patients with PCA are classified as having PCA-pure when they have no other associated syndromes or PCA-plus when PCA occurs in association with another clinical syndrome such as corticobasal syndrome.²⁷ Further classification can occur when biomarkers or tissue confirmation is available. For

KEY POINTS

- The management of dysexecutive AD and behavioral variant AD combines pharmacotherapy with tailored nonpharmacotherapeutic approaches.
- AD is the most common underlying pathology accounting for posterior cortical atrophy (PCA) syndrome.
- PCA is characterized by higher-order visual dysfunction with relative sparing of memory and other cognitive domains, judgment, and insight early in the presentation.
- People with PCA often present to an eye care provider with significant visual concerns that can go unaccounted for in the presence of a normal eye examination.
- Difficulty reading is a common presenting concern for patients with PCA.
- Delays in diagnosis of PCA can occur because of the nature of initial symptoms (ie, visual and not memory), the characteristic young onset (65 years or younger), preservation of insight, and adequate performance on measures of global cognition at presentation.
- The 2017 PCA consensus criteria specify that 3 of 16 core features must be met for the diagnosis of PCA. Features belong to occipitoparietal and occipitotemporal visual pathways including all elements of Balint and Gerstman syndromes.

instance, if CSF AD biomarkers are present or an amyloid PET study is positive, then the patient can be classified as having PCA-AD. More information about this can be found in the 2017 article by Crutch and colleagues.²³

Evaluation

A targeted history and a tailored neurologic examination are necessary for the detection of several of the core features including environmental agnosia, alexia, dysgraphia, dyscalculia, oculomotor apraxia, optic ataxia, and left-right

CASE 2-1

A 52-year-old woman, a financial analyst, presented with a year-long history of increasing difficulties in tasks requiring planning and organization. Both her husband and colleagues observed a marked decline in her performance, particularly when adapting to new software programs or mentally manipulating numbers. She began struggling with the sequential steps of vacation planning. In general, her challenges often manifested as “forgetting” procedural steps in tasks, and her family blamed these errors on memory loss. This led to frequent frustration with, and subsequent avoidance of, activities she once enjoyed, such as hosting dinner parties. The emotional strain also manifested as increased irritability and anxiety, particularly when confronted with decision making or planning tasks.

An evaluation by her primary care provider led to a brain MRI, which was interpreted as normal age-related changes, and the quantitative volumetrics of the hippocampi were in the normal range. A neuropsychological assessment underscored significant impairments in executive functions, notably in working memory and cognitive flexibility. However, her subpar performance across various tests, including performance validity measures, raised concerns about secondary gain in the setting of work-related issues. In addition, the observed degree of impairment seemed inconsistent with her ability to drive and manage many daily activities without notable difficulties. This discrepancy resulted in a provisional diagnosis of depression and anxiety, with recommendations to destress and reduce her work hours.

Subsequently, she was referred to a subspecialist, who identified mild atrophy in the parietal lobe on the brain MRI and arranged for further testing. Given her young age of onset, executive predominant cognitive dysfunction, normal-appearing hippocampi, and reports of changes in her personality by her family, the differential diagnosis included frontotemporal dementia (FTD). However, it was noted that executive dysfunction could be at the root of her clinical symptoms, and her changes in personality and memory could be understood as a secondary manifestation of the changes in executive abilities. Abnormalities observed on brain fludeoxyglucose positron emission tomography (FDG-PET) supported this interpretation (FIGURE 2-1), demonstrating pronounced hypometabolism, especially in the parietal and frontal regions linked with working memory, but medial frontal regions linked to emotion, personality, and motivations were normal, as was medial temporal lobe

confusion. Other features demand specific assessment tools to enhance their detection, and this necessity extends to formal neuropsychological testing, which is important for an accurate diagnosis. Valuable tools and visual stimuli that can be used during an office visit or formal neuropsychological testing are reviewed in TABLE 2-5.²⁸⁻³⁵ The PCA assessment working group provided practical approaches to the assessment of core features.³⁶ For the detection of a homonymous visual field defect when concern for PCA arises, computerized threshold visual field testing is recommended, which is done routinely in eye

metabolism. Further, spinal fluid analysis revealed low amyloid- β (A β) levels, but phosphorylated tau (pTau) levels remained within the normal range, with an elevated pTau to A β ratio.

Considering her clinical manifestations, neuropsychological findings, spinal fluid analysis, and imaging outcomes, a diagnosis of dysexecutive Alzheimer disease (AD) was established. Therapeutically, she was started on a cholinesterase inhibitor, with discussions about N-methyl-D-aspartate (NMDA) receptor antagonist and amyloid-lowering monoclonal antibodies. Although she believed her driving was unaffected, she was counseled to stop driving given her executive cognitive impairment. The patient and her family were educated regarding available social support resources, genetic counseling, clinical trials, and current research. A social worker also supported her in addressing disability and associated concerns. Additionally, she and her family participated in counseling sessions to arm them with coping strategies tailored to her executive function challenges, encompassing environmental modifications, checklist usage, multitasking avoidance, understanding anxiety's role in executive function impairment, and capitalizing on familiar routines.

This case exemplifies the nuanced nature of atypical AD, specifically dysexecutive AD, by highlighting the importance of nonmemory cognitive symptoms as primary manifestations. The patient's impaired planning, organization, and decision-making abilities, alongside preserved routine functions, illustrate the characteristic executive dysfunction of dysexecutive AD. Her perceived memory loss underscores a common misattribution in which difficulties in daily tasks due to executive dysfunction are mistakenly blamed on memory impairment. This case further demonstrates how behavioral changes, such as increased irritability and anxiety, are secondary to impaired executive function rather than primary behavioral issues as seen in behavioral variant AD and behavioral variant FTD. This case also illustrates the pitfalls of neuropsychological assessment and how performance validity testing can be misinterpreted in the context of dysexecutive AD. Younger age of onset and job loss are also common and contribute to this misinterpretation. The integrated treatment approach aligns with the principles that atypical AD forms such as dysexecutive AD require a comprehensive and individualized management plan.

COMMENT

clinics and is a more sensitive method than confrontation visual fields (ie, finger-counting in each quadrant). Homonymous defects can be detected in up to 62% of patients with PCA.³⁷

As with any cognitive disorder, evaluation for treatable causes and contributing factors should be completed and tailored to the individual patient and to the potential pathologic causes of PCA. CT or MRI of the brain is necessary to rule out structural lesions as the cause of symptoms, and studies such as FDG-PET can reveal focal metabolic changes even in the absence of definitive atrophy. Occipital hypometabolism with relative sparing of posterior cingulate metabolism (ie, the cingulate island sign) is a feature of PCA,³⁸ even in the absence of dementia with Lewy bodies. **CASE 2-2** demonstrates a typical presentation of PCA with the progression of symptoms and signs over time and findings on neuroimaging that support the diagnosis.

CSF AD biomarkers for amyloid and tau in PCA are indistinguishable from those for typical AD, as is true for amyloid PET findings.^{25,39} However, tau PET imaging highlights distinctive posterior regional deposition patterns that can differentiate among various AD clinical phenotypes, which is akin to the regional metabolic variances observed with FDG-PET, as depicted in **FIGURE 2-1**.

TABLE 2-3
Presenting Visual Concerns From Patients With Posterior Cortical Atrophy Syndrome^a

	Patient comments
Early vision concerns, year 1	I can't see clearly. My vision seems blurry. It is getting harder to see while I am reading. I have difficulty seeing things on the computer, such as a spreadsheet.
Subsequent vision concerns, year 1-2	I am still having difficulty reading, even after several pairs of new reading glasses. I can't find things that turn out to be right in front of me. I can't read traffic signs. I have problems seeing when I am using email (or phone or other specific circumstance).
Later-stage vision concerns, year 2 and beyond	My depth perception seems off. I can't read anymore. I can't see to sign my name on a straight line. I might have to stop driving if I can't get to the bottom of what is wrong with my vision.

^a Any of these symptoms can be the first symptom discussed with a neurologist when an ophthalmologist or optometrist finds no ocular cause for the visual concerns.

Progression and Prognosis

All patients with PCA who meet the 2017 criteria will progress to dementia, and the pattern of progression can be heterogeneous. Limited data exist regarding specific longitudinal profiles of progression. However, as a group, impaired posterior functions appear to progress at a faster rate than domains that are initially relatively spared in keeping with the regional progression of cerebral atrophy.⁴⁰ This might explain findings from the limited existing data that reveal a slower progression on measures of global cognitive function (ie, the MMSE) for patients with PCA compared with other atypical AD phenotypes and typical AD. People with PCA are not spared the behavioral changes that occur in the later stages of disease when global impairment and moderate to severe dementia are present. Few studies have evaluated PCA survival, but early evidence shows that survival can range widely with an approximate median survival of 8 to 10 years.³⁶

Management

The mainstay of care is symptom management and patient, family, and care partner education, which should be tailored to meet individual needs and follow the principles of care recommended for patients with AD.⁴¹ Treatment with acetylcholinesterase inhibitors and NMDA receptor antagonists for PCA is a common practice and often recommended,³⁹ but data to guide their use in PCA are not available. Anxiety and depression should be managed appropriately, which can improve daily function. For patients who develop visual hallucinations, rapid eye movement (REM) sleep behavior disorder, parkinsonism, or other signs of Lewy body disease, management and evaluation should be directed appropriately as symptoms emerge. If a patient with PCA qualifies for anti-amyloid therapies, then appropriate treatment with US Food and Drug Administration (FDA)-approved drugs might be indicated. Physicians should follow appropriate use guidelines for decision making regarding anti-amyloid treatment.^{19,42} However, the lack of representation of PCA in clinical trials, compounded by the lack of longitudinal outcome measures for PCA, hinders the ability to thoroughly understand the risks and benefits of anti-amyloid therapy for PCA.

LOGOPENIC PRIMARY PROGRESSIVE APHASIA

PPA is a language-based dementia syndrome caused by neurodegenerative diseases that selectively target and erode the language network, usually located in the left hemisphere of the brain.⁴³ The syndromic name, described by Mesulam⁴⁴ in the 1980s, intuitively embeds the key diagnostic features, that is, the PPA diagnosis is made when neurodegenerative disease causes relatively isolated cognitive impairment (ie, primary) that becomes more severe over time (ie, progressive) in the domain of language (ie, aphasia).⁴⁵ Other syndromes in which neurodegenerative disease can extend into the language network include amnestic-onset AD, PCA, progressive dysexecutive syndrome, and behavioral variant FTD; however, the diagnosis of PPA would not apply here as these syndromes have early prominent deficits in memory, higher-order visual functions, executive function, and behavior, respectively.

PPA has created an elegant model for extending our understanding of the language network. For PPA, neurodegeneration is partial and progressive and can occur outside of the boundaries of vascular inputs resulting in presentations distinct from stroke-based aphasia. As such, the characteristic subtypes of stroke-

KEY POINTS

- Neuroimaging characteristics of PCA are supportive of the diagnosis and include posterior findings of cortical atrophy on MRI, hypometabolism on FDG-PET, or hypoperfusion on single-photon emission computed tomography (SPECT), as are posterior and occipital tau PET abnormalities.
- Patients with PCA are classified as having PCA-pure when they have no other associated syndromes or PCA-plus when PCA occurs in association with another clinical syndrome such as corticobasal syndrome.
- It is important to keep PCA features in mind while conducting a focused history and examination and using specific visual assessment tools in the office and during formal neuropsychological evaluation.
- Recently published recommendations for the clinical assessment of PCA provide several options for assessment tools and visual stimuli for detecting the unique core features of PCA.
- AD CSF biomarkers for PCA are indistinguishable from profiles for typical AD, whereas MRI, FDG-PET, and tau PET can reveal patterns of posterior atrophy, hypometabolism, and tau deposition that reflect the PCA clinical phenotype.

based aphasia do not accurately encompass the language impairment presentations for those with PPA. There are at least three recognized subtypes of PPA, logopenic, agrammatic, and semantic, defined by both the language features that are impaired and those relatively spared. Logopenic PPA is characterized by impairments with word retrieval and relative sparing of word comprehension and grammar, whereas agrammatic PPA is characterized by impairments in grammar but relative sparing of word comprehension. Semantic PPA is characterized by impairments in word comprehension and relative sparing of grammar. Each subtype is associated with clinically concordant distributions of peak cortical atrophy (TABLE 2-6⁴⁶). The tripartite subtyping system allows for the classification of some but certainly not all presentations of PPA. A mixed subtype characterized by a combination of comprehension and grammar impairments has been described, as well as unclassifiable presentations.^{47,48} As the disease progresses over time, additional impairments in language and eventually other aspects of cognition and behavior may emerge, resulting in a PPA-plus syndrome.⁴⁹ At the individual level, variation in the location and severity of neurodegeneration and pace of progressive decline result in a spectrum of deficits. Thus, the ability to

TABLE 2-4

Summary of the 2017 Consensus Posterior Cortical Atrophy Criteria and Classification Framework^a

Core posterior cortical atrophy (PCA) syndrome features (all three must be present)

- ◆ Insidious onset, gradual progression, and prominent early disturbance of visual functions or other posterior cortical functions

Core PCA cognitive features (at least three must be present as an early or presenting feature)

- ◆ Space perception deficit
- ◆ Simultanagnosia^b
- ◆ Object perception deficit
- ◆ Constructional dyspraxia
- ◆ Environmental agnosia
- ◆ Alexia
- ◆ Left-right disorientation^c
- ◆ Acalculia^c
- ◆ Apperceptive prosopagnosia
- ◆ Agraphia^c
- ◆ Homonymous visual field defect
- ◆ Finger agnosia^c
- ◆ Oculomotor apraxia^b
- ◆ Optic ataxia^b
- ◆ Limb apraxia (not limb-kinetic)
- ◆ Dressing apraxia

CONTINUED ON PAGE 1629

identify subtype distinctions tends to be most prominent during a “goldilocks” period in which impairments are neither too mild to detect nor too severe where deficits may be present in multiple aspects of language.

The primary neuropathologies associated with PPA include AD neuropathologic change or frontotemporal lobar degeneration (FTLD), including tauopathy (FTLD-tau) and FTLD transactive response DNA-binding protein 43 (TDP-43) proteinopathy (FTLD-TDP).⁵⁰⁻⁵² The neuropathologic entities have shown probabilistic relationships with specific variants of PPA in which the logopenic variant is most commonly associated with AD neuropathologic change (approximately 70%), the agrammatic variant is most commonly caused by FTLD-tau (approximately 60% to 70%), and the semantic variant is most reliably linked to FTLD-TDP (approximately 80%). Historically, the absence of in vivo biomarkers specific to each neuropathic entity gave subtyping prominence as a proxy for determining underlying pathology. The emergence of in vivo biomarkers, including amyloid and tau PET as well as CSF and blood-based biomarkers,⁵³ is transforming this landscape and allowing for greater precision in understanding drivers of disease progression and intervention.

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Core PCA neuroimaging features (supportive of diagnosis)

- ◆ Prominent parieto-occipital or occipitotemporal atrophy or hypometabolism or hypoperfusion on MRI, fludeoxyglucose positron emission tomography (FDG-PET), or single-photon emission computed tomography (SPECT)

Relatively spared features (all must be evident)

- ◆ Anterograde memory function, speech and nonvisual language functions, executive functions, behavior, and personality

Exclusions

- ◆ No other explanation for symptoms based on the following: afferent visual dysfunction, afferent visual lesions, vascular lesions, brain tumor or other mass lesions, or any other causes

PCA designations using a three-level classification framework

◆ Level 1

- ◆ Designation of PCA

◆ Level 2

- ◆ If the patient meets criteria for PCA and does not meet criteria for other clinical syndromes, the designation is *PCA-pure*; if the patient meets criteria for PCA and meets criteria for other clinical syndromes (eg, dementia with Lewy bodies, corticobasal syndrome, prion disease), the designation is *PCA-plus*

◆ Level 3

- ◆ Designation of disease pathology causing PCA, for example, a patient is designated as having *PCA-AD* when Alzheimer disease (AD) biomarkers are present and as having *definite PCA-AD* with autopsy evidence

^a Data from Crutch SJ, et al, Alzheimers Dement.²³

^b Balint syndrome features.

^c Gerstmann syndrome features.

As highlighted earlier, the logopenic variant is commonly but not exclusively associated with AD neuropathologic change. *Logopenia* refers to a reduced rate of speech output due to word-finding difficulty and was noted as a symptom in the 1982 cases described by Mesulam.⁴⁴ However, it was the last of the three research subtypes to be formally characterized.⁵⁴⁻⁵⁶ As such, the research literature for logopenic PPA lags relative to the other subtypes, and nuances around the diagnosis, clinical, and anatomic features have been the focus of some systematic

TABLE 2-5
Examples of Screening Stimuli and Tools to Capture Core Features of Posterior Cortical Atrophy Related to Higher-order Visual Functions

Screening tools	Format	Targeted posterior cortical atrophy core features	Source
Poppelreuter-Ghent overlapping figures	Images of shapes or objects that overlap each other; the complexity of the figure can increase with more images and images at noncanonical angles	Not specific to one feature but relies on figure-ground discrimination and captures space and object perception impairments	Della Sala et al, 1995 ²⁸
Judgment of line orientation	Two angled lines are shown with a set of lines oriented at different angles within a semicircle; the task is to match the angle of each of the two lines to one of the angled lines arranged in the semicircle	Space perception impairment	Benton et al, 1983 ²⁹
Navon figures	A large letter or shape made up of smaller letters or shapes; the task is to recognize both the global and the local shapes	Simultanagnosia	Morris et al, 2021 ³⁰
Cookie Theft picture	Drawing of a kitchen scene from the Boston Diagnostic Aphasia Examination and used as part of the National Institutes of Health (NIH) stroke scale; of note, first published in 1972, there is a call for retiring this image for a more appropriate image that is inclusive and nonbiased	Space and object perception impairments; simultanagnosia	NIH ³¹
Design copy tests	Simple: intersecting pentagons Complex: Rey-Osterrieth Complex Figure; the task is to copy the design	Constructional apraxia	Simple: Mini-Mental State Examination ³² Complex: Zhang et al, 2021 ³³
Visual scanning or visual search tests	Letters or figures are embedded with other letters or figures; the task is to identify the target letter or figure	Space perception impairments	Kaplan et al, 1991 ³⁴
Fragmented letters	Letters that are visually degraded with missing parts; the task is to identify the letter with the partial information	Object perception impairment	Addenbrooke's Cognitive Examination-III ³⁵

reviews since 2019.⁵⁷⁻⁵⁹ Given that PPA subtypes beyond the logopenic variant can be associated with AD neuropathologic change and because of its later historical description, the remainder of this section provides relevant insights about logopenic PPA, the syndrome of PPA, PPA with elevated amyloid biomarkers, and autopsy-proven PPA due to AD neuropathologic change (sometimes referred to as *the aphasic variant of AD*).

Clinical and Anatomic Features and Disease Progression

Ascertaining the diagnosis of logopenic PPA can be complex and requires clinical acumen rather than strict reliance on test scores. In the milder stages, fluency may appear normal if the individual has identified strategies to use simpler word choices, phrases, or circumlocution. However, when pressed to provide precise labels or words of lower frequency in conversation or on tests of object naming, hesitations and errors become more prominent. Atrophy on MRI may be subtle early on, and hypometabolism on PET may not be appreciated,⁵⁷ which can contribute to uncertainties and delays in making the diagnosis of PPA.

When language impairment is more prominent, it can be challenging for the clinician to accurately assess the presence or absence of impairment in nonlanguage domains (eg, attention, memory, executive functioning) because many neuropsychological instruments rely heavily on intact language processing for their instructions (eg, Wisconsin Card Sorting Test) or in the stimuli or responses themselves (eg, episodic memory tests of word-list recall or story recall). Using assessments with a lower degree of language dependency and careful ascertainment of patient and family reports from daily life can provide important insights into areas of impairment versus preservation.⁶⁰

Although asymmetric atrophy is a characteristic feature of PPA associated with AD, atrophy tends to be more widespread in PPA with elevated amyloid biomarkers than without, and damage to the contralateral hemisphere tends to emerge earlier than in PPA without elevated amyloid biomarkers

(FIGURE 2-6).⁶¹⁻⁶³ More diffuse atrophy in the logopenic variant has been noted by others.⁶⁴ Functional decline parallels the atrophy findings, where impairment of activities of daily living is more prominent and encompasses more aspects of daily living in PPA with elevated amyloid biomarkers than without.⁶⁵ Decline in naming is more closely linked to atrophy than tau PET burden.⁶³ There is still considerable unexplained variability at the individual level for both atrophy and functional decline.⁶¹ For example, there are reports of patients with logopenic PPA with relatively rapid decline in cognition and daily function whereas others can maintain daily living activities that do not depend on language for more than 10 years. Such variation makes it difficult to provide families with precise prognostic information in the clinic.

Amyloid and tau PET imaging, CSF analysis, and emerging blood-based biomarkers provide relevant information for discerning the likelihood of AD neuropathologic change as a contributing factor.^{53,66-68} The spatial patterns of impairment offered by imaging support the diagnostic process and also inform our understanding of selective vulnerability patterns that are unique and shared across neurodegenerative syndromes caused by AD neuropathologic change. For example, the selective vulnerability of the language network relative to the memory network is highlighted by both atrophy (measured by structural MRI) and functional perturbations (measured by resting-state functional MRI [fMRI]).⁶⁹⁻⁷¹ Likewise, both amyloid and tau PET imaging can show relatively

KEY POINTS

- Symptom management for patients with PCA should follow that established for AD and be guided by patient needs. It is unknown whether the risks or benefits of anti-amyloid therapies are different for the PCA phenotype.
- In vivo biomarkers play a key role in the diagnosis of AD because there is no one-to-one relationship between clinical phenotype and underlying neuropathology.
- Logopenic primary progressive aphasia (PPA) is characterized by word retrieval failures, which can occur in spontaneous speech or confrontation naming. These deficits may be obscured if the individual is adept at using simplified words or circumlocution.
- Many neuropsychological instruments developed to assess nonlanguage domains rely on preserved language for successful performance, which can make it challenging for clinicians to ascertain the presence or absence of impairment when aphasia is prominent.

CASE 2-2

A 57-year-old man with 16 years of education presented to his optometrist with difficulty reading for 8 months, particularly when reviewing spreadsheets. A pair of reading glasses was prescribed but did not improve his ability to read. His primary care doctor ordered a head CT without contrast, which was normal. His medical history was remarkable for atrial fibrillation and a pacemaker. Escitalopram 10 mg/d was prescribed and helped with anxiety, but his visual symptoms progressed, and 1 year after the initial presentation, he was sent for further evaluation. At that time, he reported that he relied on others to read important material to him, and he had recently driven up an embankment after he misread a temporary construction road sign indicating a lane merge. His other medications included warfarin 2.5 mg/d. He denied visual hallucinations, symptoms of rapid eye movement (REM) sleep behavior disorder, and tremors. He felt slightly forgetful.

Examination revealed 29/30 points on the Mini-Mental State Examination (MMSE) (missing one point for intersecting pentagon copy, **FIGURE 2-2**). He had normal visual acuities and fundi. He was able to count fingers accurately in all four quadrants but initially struggled. His reading was slow with frequent backtracking. He was unable to identify all four objects on a Poppelreuter-Ghent overlapping figure. The remainder of his neurologic examination was normal. A formal neuropsychological evaluation revealed significant higher-order visual dysfunction with relative sparing of other domains (ranging from normal to mild impairment) with relatively poor performance (moderate to severe) on measures dependent on visual stimuli. A Humphrey threshold visual field test (**FIGURE 2-3**) revealed a left homonymous hemianopia (inferior more than superior) and fludeoxyglucose positron emission tomography (FDG-PET)/CT (**FIGURE 2-4**) revealed right more than left parieto-occipital hypometabolism and a cingulate island sign. A lumbar puncture was not performed because of the risks associated with discontinuing warfarin. He met the 2017 criteria for posterior cortical atrophy (PCA) with the demonstration of 5 of 16 PCA core features (deficits in space perception, object perception, and constructional praxis; alexia; and acalculia). Six years later, CT revealed significant posterior atrophy, and he had developed the remainder of the 11 PCA core features and mild to moderate dementia (**FIGURE 2-5**). Nine years later, he had moderate to severe dementia with no clinical features suggestive of non-Alzheimer disease pathology.

COMMENT

This case exemplifies the early age at presentation, reading difficulty as a common symptom at presentation, and the importance of formal neuropsychological testing that can reveal impairments for posterior functions and relative sparing of memory and other domains. Furthermore, structural brain scans, such as head CT, can appear normal early in the course whereas metabolic scans, such as FDG-PET, can reveal significant abnormalities. As noted in the 2017 PCA criteria, imaging features are supportive of the diagnosis and can include abnormal structural, metabolic, or perfusion findings in the posterior regions.

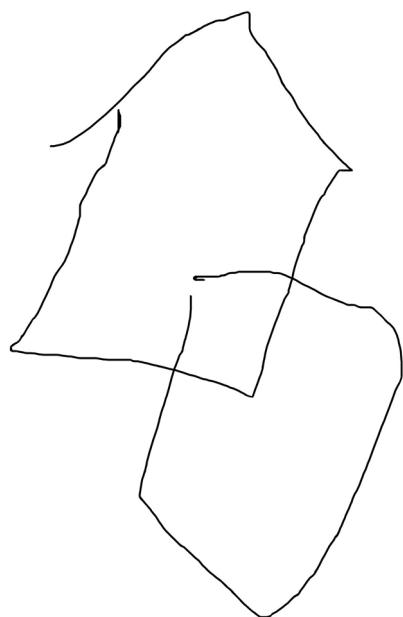


FIGURE 2-2
A copy of intersecting pentagons drawn by the patient in
CASE 2-2.

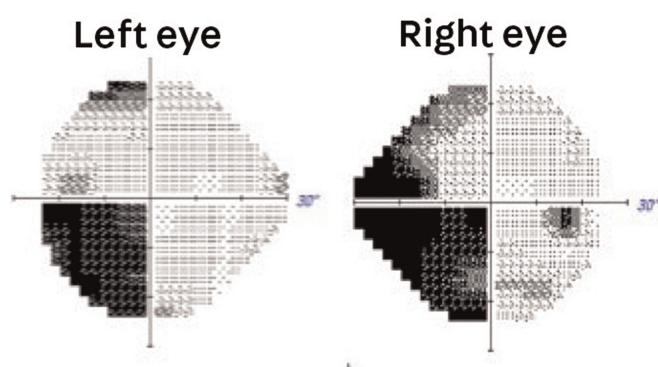
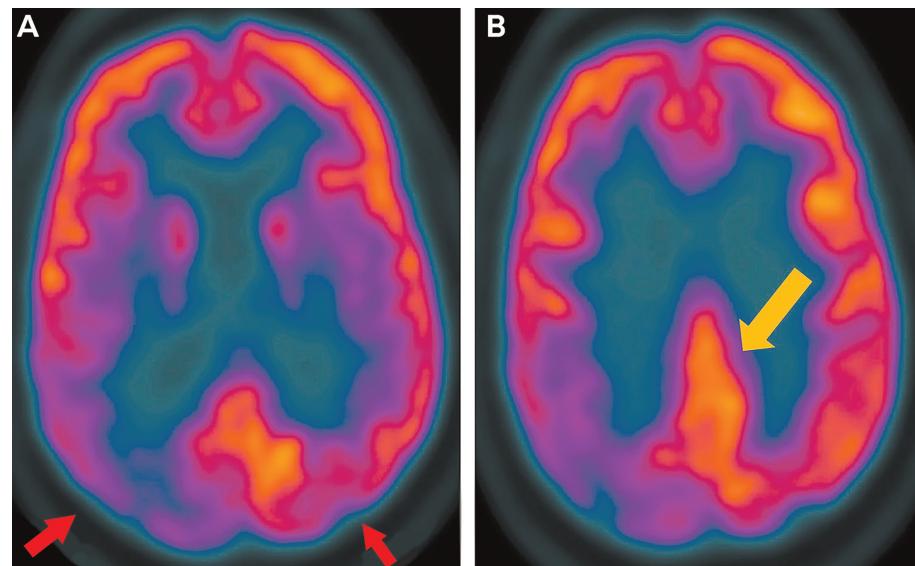
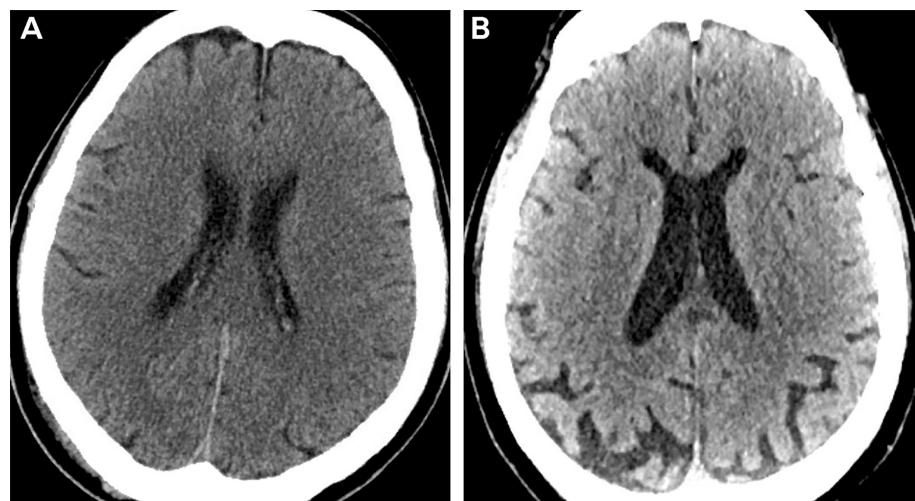


FIGURE 2-3
Visual field testing for the patient in **CASE 2-2**. The patient's left eye and right eye Humphrey 24-2 threshold visual field results show left homonymous hemianopia, inferiorly worse than superiorly.

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CASE 2-2CONTINUED FROM
PAGE 1633**FIGURE 2-4**

Imaging findings for the patient in **CASE 2-2**. Fludeoxyglucose positron emission tomography (FDG-PET)/CT shows right more than left parieto-occipital hypometabolism (A, red arrows) and a cingulate island sign (B, orange arrow).

**FIGURE 2-5**

Imaging findings for the patient in **CASE 2-2**. Head CT at presentation (A) and 6 years later (B), which shows right more than left posterior cortical atrophy.

focal asymmetric burden in the language network (**FIGURE 2-6**).^{62,72,73} These features further distinguish PPA associated with suspected AD neuropathologic change from amnestic AD.

Risk Factors

A full understanding of risk factors for PPA, including logopenic PPA, remains largely elusive. The $\epsilon 4$ allele of *APOE* is an important risk factor for amnestic dementia associated with AD neuropathologic change but does not show the same association with PPA.⁷⁴⁻⁷⁶ A history of learning disabilities for affected individuals or their first-degree family members has been demonstrated to be higher in those living with a diagnosis of PPA than in those with other dementias and a control population, providing a potential hint for selective vulnerability of the language network.^{75,77,78}

Care and Interventions

As a younger-onset dementia (average age of onset is younger than 65 years old) with no definitive cure, PPA brings unique and complex communication, family, and psychosocial challenges with an estimated individual economic burden twice that of AD dementia.⁷⁹⁻⁸¹ A team approach to care including but not limited to neurology, social work, neuropsychology, neuropsychiatry, speech-language pathologists, and occupational therapy may be appropriate with consideration of nonpharmacologic and pharmacologic interventions. The needs and contributions of the care team may shift over time as the disease progresses and brings new profiles of cognitive, behavioral, and daily life challenges.

Nonpharmacologic interventions, care, counseling, and support programs may consider strategies to address care partner burden, family relationships, and communication breakdowns, as well as language impairment, to maximize the quality of life for people with PPA and their care partners. Speech and language

Three Subtypes of Primary Progressive Aphasia^a

TABLE 2-6

Variant	Description
Logopenic	Characterized by loss of fluency due to word retrieval failures in spontaneous speech and commonly in naming, with relative sparing of grammar and word comprehension. Current research criteria list repetition as a core required feature; however, reports of mild impairment question whether it is a better fit as an ancillary feature. Peak atrophy is asymmetric in the language-dominant (usually left) hemisphere including the superior temporal gyrus and may extend to the temporoparietal junction
Agrammatic	Characterized by impairments in grammar in language production, which is commonly accompanied by low fluency; however, single-word comprehension is relatively preserved. Naming, repetition, and comprehension of syntactically complex sentences may be impaired. Peak atrophy commonly includes the language-dominant inferior frontal gyrus
Semantic	Characterized by impairment of single-word comprehension, with relatively preserved grammar and repetition with peak atrophy in the language-dominant anterior temporal lobe

^a Modified with permission from Mesulam MM, et al, *Nat Rev Neurol*.⁴⁶ © 2014 Springer Nature Limited.

interventions have been the most common nonpharmacologic intervention for those living with logopenic PPA but have historically lacked evidence of efficacy.^{82–86} This landscape is changing. One example is the recent completion of the Communication Bridge-2 international, Phase 2, Stage 2, randomized, parallel-group, active-control, clinical trial delivered virtually within a telehealth service delivery model to people with PPA and their communication partners.⁸⁷ The trial enrolled 95 PPA participants, each of the three subtypes were represented, and results are expected in late 2024 or early 2025. The intervention included a custom web application that allowed for asynchronous activities outside of sessions. Additional trials are emerging, including an efficacy trial of a multicomponent and dyadic intervention relative to an impairment-focused intervention.⁸⁸

The National Institutes of Health Phase and Stage model, the Readiness Assessment for Pragmatic Trials tool, and initiatives such as the National

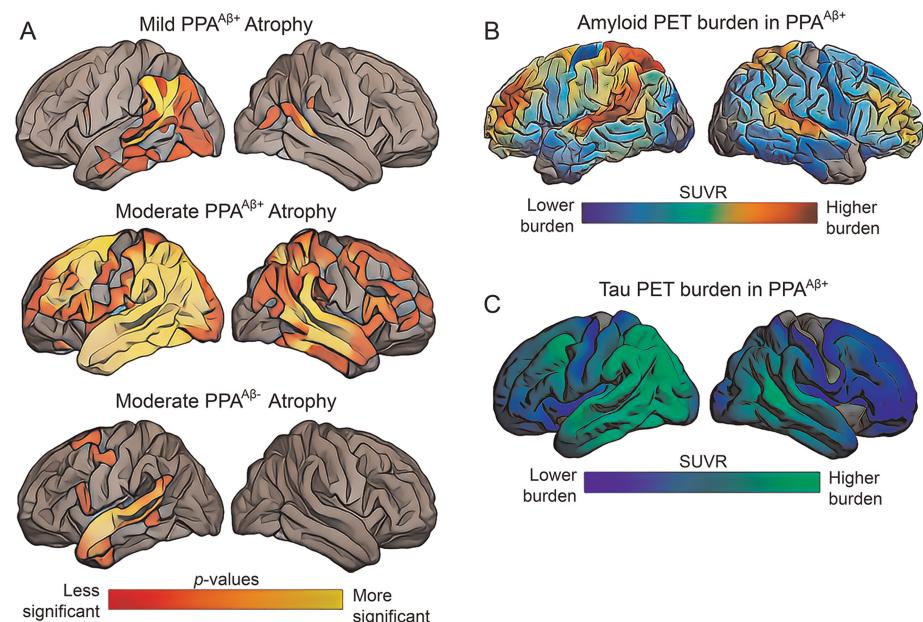


FIGURE 2-6

Asymmetric atrophy and amyloid and tau positron emission tomography (PET) burden in primary progressive aphasia (PPA) associated with biomarker-positive Alzheimer disease neuropathologic change. A (top), An example of asymmetric atrophy patterns when language impairment is relatively mild for PPA with elevated amyloid- β ($A\beta$) biomarkers (PPA $^{A\beta+}$). Note, contralateral right hemisphere involvement may be present. In the moderate to severe stages, atrophy is more diffuse and can include contralateral right hemisphere involvement for patients with PPA $^{A\beta+}$ (A, middle) relative to nonsemantic PPA without elevated $A\beta$ biomarkers (PPA $^{A\beta-}$) (A, bottom). Red and yellow indicate significant cortical thinning patterns for PPA relative to controls, with yellow being more severe than red. A β (B) and tau (C) PET can show relatively focal asymmetric burden in the language network. For amyloid PET, red indicates the most severe amyloid burden. For tau PET, green coloring indicates elevated burden.

SUVR = standardized uptake value ratio.

Panel A (middle and bottom) modified with permission from Rogalski EJ, et al, *Alzheimers Dement*.⁶¹ © 2019 Alzheimer's Association. Panel B modified with permission from Martersteck A, et al, *Acta Neuropathol Commun*.⁶² © 2022 Springer Nature. Panel C modified with permission from Martersteck A, et al, *Alzheimers Dement*.⁶³ © 2021 Alzheimer's Association.

Institute on Aging, IMbedded Pragmatic Alzheimer's disease (AD) and AD-Related Dementias (AD/ADR) Clinical Trials (IMPACT) Collaboratory (impactcollaboratory.org/) deliver key frameworks and resources to assist in developing nonpharmacologic clinical interventions to successful pragmatic clinical trials and eventual dissemination.⁸⁹ Training fellowships, such as the Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD; impact-ad.org/) are creating training opportunities to increase the multidisciplinary expertise in pharmacologic and nonpharmacologic AD-related dementia clinical trials.

PPA has been largely overlooked in the pharmacologic landscape, historically driven by the lack of in vivo biomarkers. For example, cholinesterase inhibitors may have limited benefit for patients with PPA with AD neuropathologic change but require further trials in which patients are allocated by suspected underlying pathology. Limited and inconclusive data also exist for memantine, an NMDA receptor antagonist, and for medications to manage symptoms such as depression. Disease-modifying treatments for AD neuropathologic change have been approved. However, individuals with PPA and elevated AD biomarkers were less frequently included in the trials that led to the approval of these treatments.⁹⁰ Historical contributors to the exclusion of AD-biomarker-positive PPA individuals include the absence of clear guidelines regarding appropriate outcome measures, lack of syndrome awareness, and access to biomarker data. The younger age of onset for logopenic PPA relative to late-onset AD offers unique opportunities to examine the effectiveness of pharmacologic treatments targeting the AD pathophysiologic process in a setting where there is a lower likelihood of copathology and other age-related comorbidities. Advancements over the past decade provide a prime opportunity to advocate for the inclusion of atypical forms of AD in clinical trials through judicious use of in vivo biomarkers. The use of robust pharmacologic or combination (pharmacologic and nonpharmacologic) randomized controlled trials for PPA with AD neuropathologic change offers a promising opportunity for advancing treatment options for PPA.

HEALTH DISPARITIES

Because uncommon dementia syndromes can have a younger age of onset, the diagnostic journey for patients with atypical presentations of AD often requires years rather than months with visits to multiple clinicians who may be nonlocal. This process can require extraordinary persistence, perseverance, and financial resources from the family, which widens the gaps in access to care, especially for those with low literacy, few resources, and different ethnocultural norms. The low diversity in clinical settings also contributes to the exceedingly low diversity in research populations. In the United States, AD is up to twice as likely to occur in non-Hispanic Black people and up to 1.5 times as likely to occur in Hispanic older adults compared with White older adults, yet both populations are far less likely to be included in research than White older adults.⁹¹ Highly educated, White research cohorts are the norm rather than the exception. Calls to action and efforts to increase the diversity of dementia cohorts are mounting, including collaborative efforts from multisite research studies (eg, Longitudinal Early-Onset Alzheimer's Disease Study), the National Institute on Aging–funded Alzheimer's Disease Research Centers, registries, as well as nongovernmental organizations (eg, the Alzheimer's Association and the Association for Frontotemporal Degeneration).

KEY POINTS

- The ε4 allele of APOE is an important risk factor for amnestic dementia associated with AD neuropathologic change but does not show the same association with PPA.
- Nonpharmacologic interventions, care, counseling, and support programs may address care partner burden, family relationships, communication breakdowns, as well as language impairment to maximize quality of life for people with PPA and their care partners.
- The diagnostic journey for patients with PPA tends to take years rather than months.

Addressing these health equity challenges is paramount to obtaining accurate epidemiologic data, understanding of disease, and tailored care plans.

CONCLUSION

Atypical (nonmemory) presentations of AD present distinct clinical challenges that require a heightened level of awareness and a customized approach to both diagnosis and management. Comprehensive diagnostic strategies and targeted clinical interventions for the unique symptoms of atypical AD can ensure prompt diagnosis and the best possible care. Advances in blood-, fluid-, and imaging-based AD biomarkers provide enormous opportunities for early diagnosis and participation in treatment trials for patients with atypical AD.

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Frontotemporal Dementia

By David Glenn Clark, MD

ABSTRACT

OBJECTIVE: This article discusses frontotemporal dementia (FTD) syndromes using a simplified framework of three core syndromes, including details on their pathology and unique genetic variations.

LATEST DEVELOPMENTS: FTD includes at least seven major clinical syndromes. The three core syndromes are behavioral variant FTD and two forms of progressive aphasia, commonly referred to as the nonfluent variant and semantic variant of primary progressive aphasia. Clinical features reflect the involvement of major functional brain networks. Derangements of three proteins account for nearly all underlying pathology for FTD syndromes: transactive response DNA-binding protein 43 (TDP-43) (approximately 50% of cases), MAPT (45% of cases), and FUS (5% of cases). The clinical presentation and imaging provide clues to the underlying pathology. FTD is more heritable than Alzheimer disease, with variations in *C9orf72*, *MAPT*, or *GRN* (which encodes progranulin) occurring in more than 10% of FTD cases.

ESSENTIAL POINTS: The framework described here will provide clinicians with a foundation for understanding the complex and heterogeneous set of FTD syndromes. There are currently no disease-modifying or US Food and Drug Administration (FDA)-approved treatments for FTD, but clinical trials are underway, including some targeting presymptomatic genetic variation carriers. Available FTD treatments address deficits in behavior or language nonpharmacologically or through the off-label use of medications approved for other indications. Improvements in biomarkers will accelerate the discovery of new pharmacologic treatments.

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Dr Clark discusses the unlabeled use of amantadine, amphetamine, aripiprazole, carbamazepine, citalopram, fluoxetine, lamotrigine, olanzapine, paroxetine, quetiapine, risperidone, selegiline, sertraline, and trazodone for the treatment of frontotemporal dementia.

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INTRODUCTION

The term *frontotemporal dementia* (FTD) refers to a heterogeneous group of degenerative brain diseases with the common characteristic of atrophy affecting the frontal and temporal lobes. FTD is the third most common form of degenerative dementia, after Alzheimer disease (AD) and Lewy body dementia, with a prevalence of about 15 per 100,000 people.¹ FTD is the second most common cause of dementia in individuals younger than 65 years old, with only about one-quarter of patients with FTD presenting later.² An analysis of racial factors in a large sample of individuals with clinical evidence of FTD showed greater severity and

neuropsychiatric symptoms in Black patients compared with White or Asian patients.³

The term *frontotemporal lobar degeneration* (FTLD) refers to the highly varied array of histopathologic patterns that may be associated with FTD. The need for separate clinical and pathologic terms hints at the major challenge of FTD: not only are the clinical presentations and pathologic substrates extremely variable, but the mapping from presentation to pathology is not always obvious. Although the standard of diagnosis in the study of neurodegenerative disease is rooted in the study of pathologic tissue, it was only with the recent advent of biomarker tests for AD that diagnosis in living patients became possible. Most clinical trials of AD now only enroll volunteers with biomarker support for the diagnosis. FTD presents the same challenges at an even greater level of complexity because of the clinical and pathologic heterogeneity of the illness. Biomarker tests for FTD are much more limited than for AD.⁴ The process of inferring the histopathology begins with the categorization of the clinical syndrome through the history, exam, and neuropsychological testing.

KEY POINTS

- Frontotemporal dementia (FTD) is the second most common form of degenerative dementia among people younger than 65 years.
- The three core syndromes of FTD are behavioral variant FTD, nonfluent variant primary progressive aphasia (PPA), and semantic variant PPA, with behavioral variant FTD being the most common.
- A common report from family members of patients with behavioral variant FTD is that the patient no longer seems like the same person, but personality changes can be more subtle.
- The key features of nonfluent variant PPA are grammatical omissions, effortful and hesitating speech, and difficulty with articulation.

CLINICAL PRESENTATIONS AND DIFFERENTIAL DIAGNOSIS

As the most common cause of dementia among both late-onset and early-onset populations, AD is almost always an important initial diagnostic consideration when evaluating a patient with cognitive decline and provides a helpful contrast with FTD. Older patients who present with insidious and gradual progression of memory impairment, subsequent involvement of other cognitive domains, and certain typical neuropsychiatric symptoms (such as depression in early stages and delusions of theft or infidelity in later stages) are most likely to have AD. One should weigh the possibility of FTD for patients who deviate from the typical pattern of clinical AD, especially those with negative AD biomarkers, or who are younger than 65 years old.

Three major FTD syndromes were characterized in criteria published in 1998: behavioral variant FTD, progressive nonfluent aphasia, and semantic dementia.⁵

Behavioral Variant Frontotemporal Dementia

The most common of the three is behavioral variant FTD. In much of the literature, the latter two syndromes, which fall into the broad category of primary progressive aphasia (PPA), may be referred to as the nonfluent variant and semantic variant of PPA. Criteria for the clinical diagnosis of these core syndromes were refined in 2011.^{6,7} Memory impairment is less common in FTD than in AD, with two caveats. First, amnestic memory impairment very much like that seen in AD does occur in about 10% of patients with behavioral variant FTD.⁸ Second, deficits in word finding, word recognition, or even face recognition may trigger reports of memory impairment. Clinicians should not assume that patients or family members always mean *episodic* memory when they say there is a memory problem. Patients with behavioral variant FTD are usually accompanied by a spouse or other relative who expresses concerns about the patient's behavior; loss of inhibition, apathy, decline in sympathy or empathy, compulsive or repetitive behavior, and changes in oral behavior, such as dietary compulsions, smoking, or drinking alcohol are all common (**TABLE 3-1**). Changes may be sufficiently severe that family members say the patient no longer seems like the same person. The criteria published in 2011 list

TABLE 3-1**International Consensus Criteria for Behavioral Variant Frontotemporal Dementia With Examples of Behavioral Changes^a**

Criteria	Example
I Neurodegenerative disease	
The following symptom must be present to meet the criteria for behavioral variant frontotemporal dementia (FTD)	
A Shows progressive deterioration of behavior or cognition by observation or history (as provided by a knowledgeable informant)	
II Possible behavioral variant FTD	
Three of the following behavioral and cognitive symptoms (A-F) must be present to meet the criteria; ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events	
A Early behavioral disinhibition (one of the following [A1-A3] must be present)	
A1 Socially inappropriate behavior	The patient touches the breast of his sister-in-law
A2 Loss of manners or decorum	The patient removes his dentures after eating in a restaurant and licks the chewed food off them
A3 Impulsive, rash, or careless actions	The patient gives a bank account number to a stranger over the telephone
B Early apathy or inertia (one of the following symptoms [B1-B2] must be present)	
B1 Apathy	The patient loses all interest in hobbies (eg, reading)
B2 Inertia	The patient spends most of the day lying awake in bed unless strongly encouraged to get up
C Early loss of sympathy or empathy (one of the following symptoms [C1-C2] must be present)	
C1 Diminished response to other people's needs or feelings	The patient makes hurtful comments to his spouse and simply stares when the spouse becomes upset
C2 Diminished social interest, interrelatedness, or personal warmth	The patient no longer seeks the company of friends or hugs her spouse
D Early perseverative, stereotyped, or compulsive or ritualistic behavior (one of the following symptoms [D1-D3] must be present)	
D1 Simple repetitive movements	The patient constantly traces circles on surfaces with fingertips
D2 Complex, compulsive, or ritualistic behaviors	The patient repeatedly attempts to flush large amounts of toilet paper that clog the toilet
D3 Stereotype of speech	The patient compliments everyone she likes by saying, "You are a wonder of the world"

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Criteria	Example
E Hyperorality and dietary changes (one of the following symptoms [E1-E3] must be present)	
E1 Altered food preferences	The patient insists on eating broccoli for every meal
E2 Binge eating, increased consumption of alcohol or cigarettes	The patient routinely eats an entire 16-oz bag of chocolate candy in one sitting
E3 Oral exploration or consumption of inedible objects	The patient stuffs his mouth with pieces from disposable cups
F Neuropsychological profile: executive or generation of deficits with relative sparing of memory and visuospatial functions (all of the following symptoms [F1-F3] must be present)	
F1 Deficits in executive tasks	The patient performs in impaired range on letter fluency and Trail Making Test Part B
F2 Relative sparing of episodic memory	The patient performs at least in the low average range on a standardized test of memory
F3 Relative sparing of visuospatial skills	The patient can still copy line drawings

III Probable behavioral variant FTD

All of the following symptoms (A-C) must be present to meet the criteria

A Meets criteria for possible behavioral variant FTD	
B Exhibits significant functional decline (by care partner report or as evidenced by Clinical Dementia Rating or Functional Activities Questionnaire scores)	The patient can no longer maintain gainful employment, because of cognitive changes consistent with behavioral variant FTD
C Imaging results consistent with behavioral variant FTD (one of the following [C1-C2] must be present)	
C1 Frontal or anterior temporal atrophy on MRI or CT	
C2 Frontal or anterior temporal hypoperfusion or hypometabolism on positron emission tomography (PET) or single-photon emission computed tomography (SPECT)	

IV Behavioral variant FTD with definite frontotemporal lobar degeneration (FTLD) pathology

Criterion A and either criterion B or C must be present to meet criteria

A Meets criteria for possible or probable behavioral variant FTD	
B Histopathologic evidence of FTLD on biopsy or at postmortem	
C Presence of a known pathogenic mutation	

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Criteria	Example
V Exclusionary criteria for behavioral variant FTD	
Criteria A and B must be answered negatively for any behavioral variant FTD diagnosis; criterion C can be positive for possible behavioral variant FTD but must be negative for probable behavioral variant FTD	
A Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders	
B Behavioral disturbance is better accounted for by a psychiatric diagnosis	
C Biomarkers strongly indicative of Alzheimer disease or other neurodegenerative process	

^a Modified from Rascovsky K, et al, Brain.⁶ © 2011 The Authors.

specific manifestations of these categories of behavioral change, as well as the presence of executive dysfunction on standard neuropsychological tests.⁶ In some cases, features of behavioral variant FTD may coexist with features of PPA.

The clinical presentation of behavioral variant FTD overlaps with other central nervous system diseases. AD infrequently presents with a behavioral variant FTD syndrome that cannot be discerned from FTD on clinical grounds alone⁹; for more information, refer to the article “Atypical Presentations of Alzheimer Disease” by David Jones, MD, Victoria Pelak, MD, and Emily Rogalski, PhD,¹⁰ in this issue of *Continuum*. Recurrent strokes affecting the frontal lobes or basal ganglia may manifest with progressive apathy, disinhibition, or executive dysfunction. The similarity to behavioral variant FTD may be most apparent in the setting of vascular dementia caused by cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL).¹¹ Spontaneous intracranial hypotension may present with clinical behavioral variant FTD, usually accompanied by chronic headache, caused by frontotemporal brain-sagging syndrome.¹² It is important to identify these patients, who may improve if the source of CSF hypotension can be identified and addressed. Primary psychiatric disease, such as bipolar affective disorder or axis II disorders, may at times present in midlife and can be difficult to distinguish from behavioral variant FTD.¹³ Many patients with a clinical presentation suggestive of behavioral variant FTD follow a nonprogressive course, a pattern referred to as *FTD phenocopy syndrome*. Patients in this category often have a psychiatric illness and most who have undergone autopsy have not had evidence of neurodegeneration,¹⁴ although cases of very slow FTD progression with proven FTLD pathology have been reported.¹⁵

Nonfluent Variant and Semantic Variant Frontotemporal Dementia

Patients with nonfluent variant PPA exhibit marked agrammatism or difficulty with fluency. Agrammatism refers to the omission of grammatical affixes or

function words, and patients with agrammatism may have deficits in both language output and language comprehension. However, agrammatic comprehension only results in the failure of comprehension for certain complex sentence structures, such as passive voice. Disorders of fluency are characterized by effortful, hesitant language output, often with apraxia of speech, a disorder of the ability to program the articulators to generate a correct sequence of syllables (**TABLE 3-2**).¹⁶ Writing may be relatively preserved, especially in cases where apraxia of speech strongly contributes to the decline in fluency. Although apraxia

TABLE 3-2

Diagnostic Features of Nonfluent or Agrammatic Variant Primary Progressive Aphasia^a

I Clinical diagnosis of nonfluent or agrammatic variant primary progressive aphasia (PPA)

At least one of the following core features must be present

- 1 Agrammatism in language production^b
- 2 Effortful, halting speech with inconsistent speech sound errors and distortions^c

At least two of the three following other features must be present

- 1 Impaired comprehension of syntactically complex sentences^d
- 2 Spared single-word comprehension^e
- 3 Spared object knowledge^f

II Imaging-supported nonfluent or agrammatic variant PPA diagnosis

Both of the following criteria must be present

- 1 Clinical diagnosis of nonfluent or agrammatic variant PPA
- 2 Imaging must show one or more of the following results
 - A Predominant left posterior fronto-insular atrophy on MRI
 - B Predominant left posterior fronto-insular hypoperfusion or hypometabolism on single-photon emission computed tomography (SPECT) or positron emission tomography (PET)

III Nonfluent or agrammatic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present

- 1 Clinical diagnosis of nonfluent or agrammatic variant PPA
- 2 Histopathologic evidence of a specific neurodegenerative pathology (eg, frontotemporal lobar degeneration [FTLD]-tau, FTLD with transactive response DNA-binding protein 43 [TPD-43]-immunoreactive pathology, Alzheimer disease, other)
- 3 Presence of a known pathogenic mutation

^a Modified with permission from Gorno-Tempini ML, et al, Neurology.⁷ © 2011 American Academy of Neurology.

^b Example: The patient omits suffixes and grammatical function words in speech or writing (eg, "She go mall").

^c Example: The patient is unable to repeat the word "catastrophe" five times in a row without making significant phonologic errors.

^d Example: The patient misassigns thematic roles in a picture selection task when given a sentence with an object-relative clause (eg, "The girl that the boy kissed is tall").

^e Example: The patient performs perfectly on a spoken word-picture matching task.

^f Example: The patient answers yes or no questions correctly when presented with pictures of common objects and famous people.

of speech is included in the criteria for nonfluent variant PPA, some patients manifest with progressive apraxia of speech but lack aphasia.¹⁷ The contribution of apraxia of speech to nonfluency in nonfluent variant PPA and the overlap between primary progressive apraxia of speech and PPA are still being explored.

Patients with semantic variant PPA speak fluently, sometimes to the extent that no language disorder is obvious (**TABLE 3-3**). These patients may conceal word-finding deficits by circumlocution, leading to lengthy, but comprehensible

TABLE 3-3

Diagnostic Criteria for the Semantic Variant of Primary Progressive Aphasia^a

I Clinical diagnosis of semantic variant primary progressive aphasia (PPA)

Both of the following core features must be present

- 1 Impaired confrontation naming^b
- 2 Impaired single-word comprehension^c

At least 3 of the following other diagnostic features must be present

- 1 Impaired object knowledge, particularly for low-frequency or low-familiarity items^d
- 2 Surface dyslexia or dysgraphia^e
- 3 Spared repetition^f
- 4 Spared speech production (grammar and motor speech)^g

II Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present

- 1 Clinical diagnosis of semantic variant PPA
- 2 Imaging must show one or more of the following results
 - A Predominant anterior temporal lobe atrophy
 - B Predominant anterior temporal hypoperfusion or hypometabolism on single-photon emission computed tomography (SPECT) or positron emission tomography (PET)

III Semantic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present

- 1 Clinical diagnosis of semantic variant PPA
- 2 Histopathologic evidence of a specific neurodegenerative pathology (eg, frontotemporal lobar degeneration [FTLD]-tau, FTLD with transactive response DNA-binding protein 43 [TPD-43]-immunoreactive pathology, Alzheimer disease, other)
- 3 Presence of a known pathogenic mutation

^a Modified with permission from Gorno-Tempini ML, et al, Neurology.⁷ © 2011 American Academy of Neurology.

^b Example: The patient gives no response or replies "I don't know" when asked to name an object, such as a lapel.

^c Example: The patient is unable to point to an object in response to the name (ie, "Point to a lapel"). The patient may reply, "I don't know what you mean by lapel."

^d Example: The patient cannot recognize familiar or famous faces, animals, or other objects.

^e Example: The patient cannot correctly pronounce the written word "yacht."

^f Example: The patient readily repeats back words she was unable to comprehend, for example, by asking, "What do you mean by 'whistle'?"

^g Example: The patient provides lengthy, fluent replies free of errors in speech or grammar. Circumlocution may be present.

utterances. The key deficit in semantic dementia is a loss of word knowledge, such that the sound pattern of a word (although correctly perceived) is no longer associated with the word's meaning. Patients with semantic variant PPA can repeat single words well but fail at word-picture matching in which the patient is asked to point to an object in response to hearing its name. At times, they may bluntly ask questions about common words, such as, "What is a hamburger?"¹⁸ In addition to the single-word comprehension deficits, it is common for patients with semantic variant PPA to exhibit surface dyslexia, a reading disorder characterized by difficulty reading words with irregular spellings (eg, yacht, island, colonel). This phenomenon may not be evident in patients who speak languages with more predictable grapheme-phoneme mappings, such as Spanish; in Japanese, this disorder manifests as difficulty reading Chinese ideograms (kanji) with preserved ability to read words spelled in either of the two syllabaries (kana).¹⁹ It is common for the semantic deficits of semantic variant PPA to eventually affect nonverbal semantics, resulting especially in prosopagnosia (a deficit of face recognition) or other forms of associative agnosia.²⁰ Patients with these visual associative deficits are sometimes assigned the syndromic diagnosis of semantic dementia, rather than semantic variant PPA, especially if the nonverbal deficits predominate early in the course.

In the simplest terms, one may think of the faculty of language as a capacity for acquiring, retrieving from memory, and sequencing abstract symbols. For language expression, one transforms a mental message into a format that may be shared with others, such as speech, writing, or sign language. Language comprehension consists of an inversion of this transformation, from the physical realization of symbols to a conceptual message. Neither mapping is one-to-one, and ambiguity is the rule.

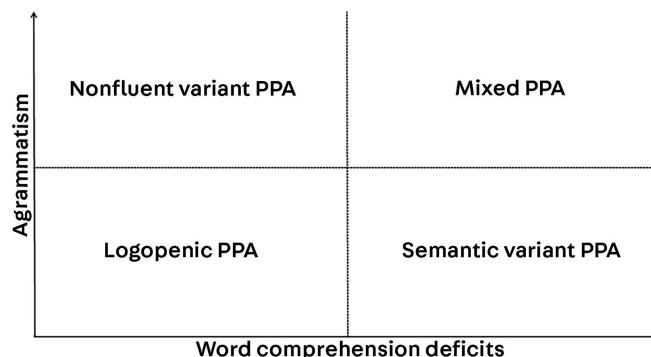
For both nonfluent variant PPA and semantic variant PPA, there are related syndromes, primary progressive apraxia of speech and semantic dementia, respectively, in which the core deficit may arise outside of what is strictly considered the language domain, at least initially leaving intact the fundamental skill of sequencing and processing symbols that is essential for normal language function. In the case of primary progressive apraxia of speech, the deficit is specific to the ability to program the articulators for speech, and, in the case of semantic dementia, the deficit is specific to the representation of knowledge of the world in a nonverbal, conceptual format.

The differential diagnosis for PPA is not as broad as that for behavioral variant FTD. Most patients with aphasia have a nonprogressive form caused by cerebrovascular disease or trauma. Recurrent strokes may give the appearance of progressive disease. Degenerative diseases outside the FTLD spectrum cause some cases of PPA.^{21,22} Most of the time, the history, examination, and brain imaging will differentiate PPA from more acute causes of aphasia. Progressive decline in language in children may indicate acquired epileptic aphasia,²³ and epilepsy may manifest with speech arrest in adults. Encephalitis due to viral infection²⁴ or autoimmune disease²⁵ may result in progressive aphasia, but the deficits are not likely to be restricted to language and the time course is more rapid than the years-long progression of PPA. Rarely, a progressive leukoencephalopathy will present with PPA.²⁶

Mesulam and colleagues²⁷ and Marshall and colleagues²⁸ have advocated approaches to PPA diagnosis that economize effort. Mesulam and colleagues²⁷ suggest beginning with the assessment of word comprehension and grammar,

KEY POINTS

- Typical features of semantic variant PPA are loss of single-word comprehension and deficits of irregular word reading.
- Prosopagnosia is a deficit of face recognition that may occur in the context of a more general object agnosia.
- The most important features for the taxonomy of PPA are agrammatism, word comprehension, and repetition of phrases and sentences.
- About 15% of patients with behavioral variant FTD have amyotrophic lateral sclerosis (ALS) and 30% of patients with ALS have FTD.
- Although not among the core FTD syndromes, corticobasal syndrome and progressive supranuclear palsy syndrome are considered to be part of the FTD spectrum.

**FIGURE 3-1**

A simple approach for categorizing primary progressive aphasia (PPA) based on evaluation of grammar and word comprehension.

rather than fluency, as fluency varies significantly with emotional state and conversation topic. **FIGURE 3-1** shows a schematic for arriving at an approximate PPA diagnosis based on these two features. Most patients with PPA with FTLD pathology exhibit either word

comprehension deficits without agrammatism, placing them in the lower right quadrant of the plane, or grammatical deficits with intact word comprehension, placing them in the upper left quadrant of the plane. Those with both deficits, in the upper right quadrant, are designated as “mixed” PPA. Those with neither deficit are more likely to have *logopenic progressive aphasia*, a PPA syndrome characterized by word-finding pauses in spontaneous conversation and deficits of auditory verbal working memory that result in difficulty repeating sentences in a length-dependent manner.²⁹ Patients with logopenic progressive aphasia usually have AD pathology; for more information, refer to the article “Atypical Presentations of Alzheimer Disease” by David Jones, MD, Victoria Pelak, MD, and Emily Rogalski, PhD,¹⁰ in this issue of *Continuum*.

Based on this taxonomy, there is a possibility that three brief bedside tests could serve to classify most PPA patients: word-picture matching, a test of syntactic knowledge (eg, the Northwestern Anagram Test), and a test of word, phrase, and sentence repetition with progressively lengthier items. Brief tests designed to categorize PPA include the Sydney Language Battery³⁰ and the Mini Linguistic State Examination,³¹ for which accuracies of 80% and 91% have been reported, respectively. Some patients exhibit a mixture of features of behavioral variant FTD and semantic dementia, a syndrome that has been referred to as semantic behavioral variant FTD. Although many of these patients eventually meet the criteria for behavioral variant FTD, certain nonverbal semantic deficits are common.³² Loss of empathy, person-specific semantic impairment, and a deficit of facial affect recognition are prominent features. A specific deficit in knowledge about animals in these patients has also been described (**CASE 3-1**).³³

The spectrum of FTD syndromes has expanded conceptually over the past few decades and includes some clinical presentations that involve motor systems. Amyotrophic lateral sclerosis (ALS) has long been known to occur in conjunction with FTD. The overlap syndrome occurs in approximately 15% of patients with FTD and 30% of patients with ALS.³⁴ The features of ALS are most commonly described in combination with those of behavioral variant FTD but may occur with features of nonfluent variant PPA or semantic variant PPA.³⁵

Corticobasal syndrome and progressive supranuclear palsy syndrome have phenotypic and pathologic overlap with the core FTD presentations but manifest

A 67-year-old, high school-educated, right-handed man presented to the clinic after nearly 4 years of behavior changes. The first thing his wife noticed was a change in the quality of his laugh. His business failed due to awkward interactions with his customers, and he was noted to slap his buttocks or skip in public. Once, he slapped the buttocks of a woman in a social setting. He began to have difficulty recognizing places, spoken words, animals, and foods. He became willing to eat foods he had always disliked and ate large quantities of sweets. He referred to cows in a field as "bears," and could no longer tell the difference between rabbits and squirrels in the yard. Unless his wife insisted, he would not brush his teeth or change his clothes, and when she began to cry about these things, he merely stared at her. She felt that he had become obsessed with feces and weight loss. He went for several walks per day and weighed himself repeatedly. Nevertheless, he would sometimes stay in bed until noon, although he did not appear to be sleeping. With reminders from his wife, he remained capable of paying bills.

He scored 14/30 on the Montreal Cognitive Assessment, missing all three naming items, suggesting that the lion was a deer and the rhinoceros was a cow. The Multilingual Naming Test was discontinued after he missed 19 of the first 29 items. On the American National Adult Reading Test, he correctly pronounced 7/45 irregularly spelled words. Scores on the Trail Making Tests were slightly below average, and he had additional impairments in verbal fluency, syntax construction, irregular word reading, and semantic knowledge, with preserved repetition. MRI revealed bilateral anterior temporal lobe atrophy, worse on the right (**FIGURE 3-2**). The patient was treated with a selective serotonin reuptake inhibitor (SSRI) but, at his most recent visit, was noted by family members to be childish, usually speaking with a high-pitched falsetto voice, and compulsively eating cheeseburgers and candy-coated chocolates.

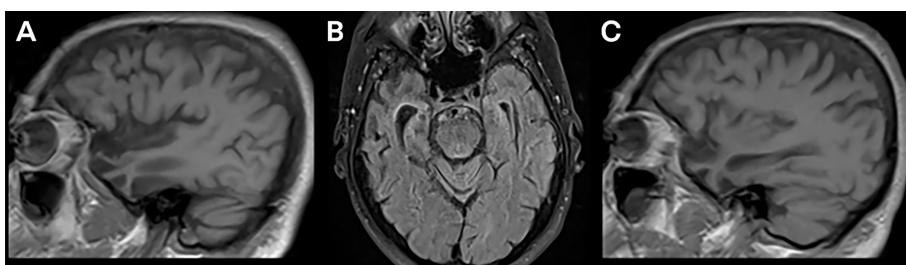


FIGURE 3-2

MRI findings from the patient in **CASE 3-1**. **A**, Sagittal T1-weighted image through the right temporal lobe showing severe anterior temporal atrophy in a patient with semantic behavioral variant frontotemporal dementia. **B**, Axial fluid-attenuated inversion recovery (FLAIR) image showing asymmetry of atrophy in anterior temporal lobes, with right greater than left. **C**, Sagittal T1-weighted image through the left temporal lobe, for comparison with panel **A**.

This case of right temporal lobe frontotemporal dementia (FTD) illustrates many of the typical features of both behavioral variant FTD and semantic variant primary progressive aphasia. This patient appears to have both verbal and nonverbal semantic deficits, especially regarding living things and foods.

COMMENT

with features of atypical parkinsonism (eg, rigidity, bradykinesia). These syndromes will be described briefly to delineate the boundaries of the FTD spectrum.

Corticobasal syndrome results in asymmetric rigidity, often with other movement disorders (eg, dystonia, myoclonus), and deficits referable to cortical dysfunction, including sensory integration deficits, ideomotor apraxia, alien limb phenomenon, and language disturbances.³⁶ Corticobasal syndrome may begin with PPA or patients may develop a nonfluent language disorder during the course of the disease.³⁷ Patients with progressive supranuclear palsy syndrome often present with falls, symmetrically increased tone (especially axially), and a disorder of saccadic eye movements.³⁸ Behavioral changes of apathy and irritability are common, and some patients manifest with a nonfluent language disturbance.³⁹

NEUROIMAGING

Atrophy of the frontal or temporal lobes is typical in FTD and may be visible on MRI early in the disease course. There is some correspondence between regions of apparent atrophy and specific clinical syndromes. Atrophy patterns in these syndromes recapitulate functional networks, possibly because the pathologic changes propagate among neurons that interact with one another (eg, through transneuronal degeneration).^{40,41} Many features of the behavioral variant FTD syndrome are associated with atrophy within a salience network that supports the integration of ambient external and internal stimuli for the deployment of appropriate behaviors.⁴² Clinical features of behavioral variant FTD map to brain regions that overlap this network, which includes the anterior cingulate cortex, anterior insula, striatum, amygdala, hypothalamus, and thalamus.⁹ For example, atrophy in the medial frontal regions, especially the anterior cingulate, has been linked to apathy, although the dorsolateral frontal cortex is also commonly involved.⁴³ Disinhibition in behavioral variant FTD is related to the asymmetry of frontal atrophy, especially in the ventral anterior insula and orbitofrontal regions, and the extent of right-sided atrophy correlates with the severity of disinhibition.⁴⁴ Changes in eating behavior are associated with atrophy in the right insula and orbitofrontal cortex.⁴⁵ Executive deficits on traditional neuropsychological tests are classically associated with damage to circuits involving the dorsolateral frontal cortex and subcortical nuclei.⁴⁶ **FIGURE 3-3** shows examples of the atrophy and hypometabolism seen in behavioral variant FTD.

The syndrome of nonfluent variant PPA is associated with atrophy, hypometabolism, or hypoperfusion centered on the left posterior frontal region and anterior insula.⁴⁷ Other work identifies the left pars opercularis as the epicenter for atrophy in this syndrome.⁴⁸ Concurrent analysis of apraxia of speech and expressive agrammatism in patients with nonfluent variant PPA reveals that the regions of atrophy associated with these two deficits are adjacent to one another in the left inferior frontal lobe. Regions associated with expressive and receptive agrammatism are in the left frontal and temporal lobes, respectively.⁴⁸ **FIGURE 3-4** shows examples of atrophy patterns observed in patients with PPA.

Semantic memory is supported by a bihemispheric network with amodal hubs in the anterior temporal lobes, possibly centered on the perirhinal cortex.⁴⁹ Most cases of semantic variant PPA are associated with asymmetric atrophy within

this network, markedly worse on the left.^{29,50} Over time, the semantic defect may involve nonverbal cognition, resulting in failure to make correct semantic associations between pictures (eg, knowing that eyeglasses are associated with eyes and not a nose).⁵⁰ As noted above, some patients manifest with a pattern of deficits that includes nonverbal semantic features, such as prosopagnosia, and behavioral features, such as loss of empathy, as well as the intersection of these processes—the recognition of emotions in facial expressions.³² These patients typically have predominant right temporal lobe atrophy. One view is that, although the regions supporting semantic memory are amodal, those in the left hemisphere interact more strongly with representations of verbal information,

KEY POINTS

- The clinical features of degenerative diseases reflect the spread of disease within functional brain networks.
- The salience network underpins many behaviors and skills that are disrupted in behavioral variant FTD.
- The hubs of the network underlying grammar and fluency are in the left anterior insula and pars opercularis of the inferior frontal lobe.

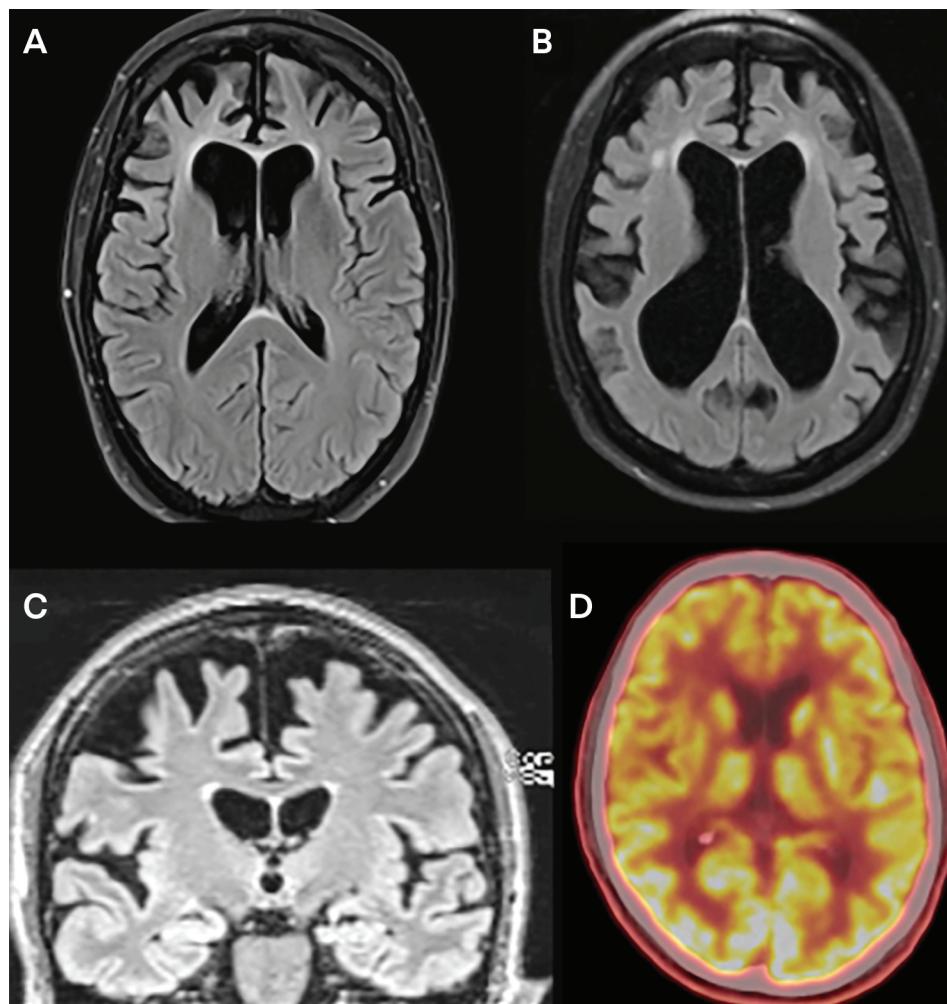


FIGURE 3-3

Imaging characteristics of behavioral variant frontotemporal dementia. A, Axial fluid-attenuated inversion recovery (FLAIR) MRI from a 59-year-old woman with behavioral variant FTD. Note the right greater than left frontal atrophy. B, Axial FLAIR MRI from a 39-year-old woman with a *C9orf72* variation, Asperger syndrome at baseline, and gradual decline after 10 years. Note the global and anterior greater than posterior atrophy. C, Coronal FLAIR MRI from a 58-year-old woman with a *C9orf72* variation and prominent delusions. Note the right greater than left atrophy and frontal greater than temporal atrophy. D, Axial fludeoxyglucose positron emission tomography (FDG-PET) image from a 67-year-old man with a *C9orf72* variation. Note the relative frontal hypometabolism.

and those in the right hemisphere interact preferentially with representations of nonverbal percepts and concepts, including visual, olfactory, tactile, and auditory nonverbal information.^{32,49}

FTD-ALS is associated with a combination of imaging changes typical for each of the two-component syndromes, including bilateral motor and premotor cortices, the middle and inferior frontal gyri, the anterior portion of the superior frontal gyri, the superior temporal gyri, the temporal poles, and the posterior thalamus. Cognitively normal individuals with ALS exhibit less atrophy in the frontal regions in comparison with those with FTD-ALS.⁵¹ Corticobasal syndrome is associated with asymmetric atrophy in the periorolanic region, often

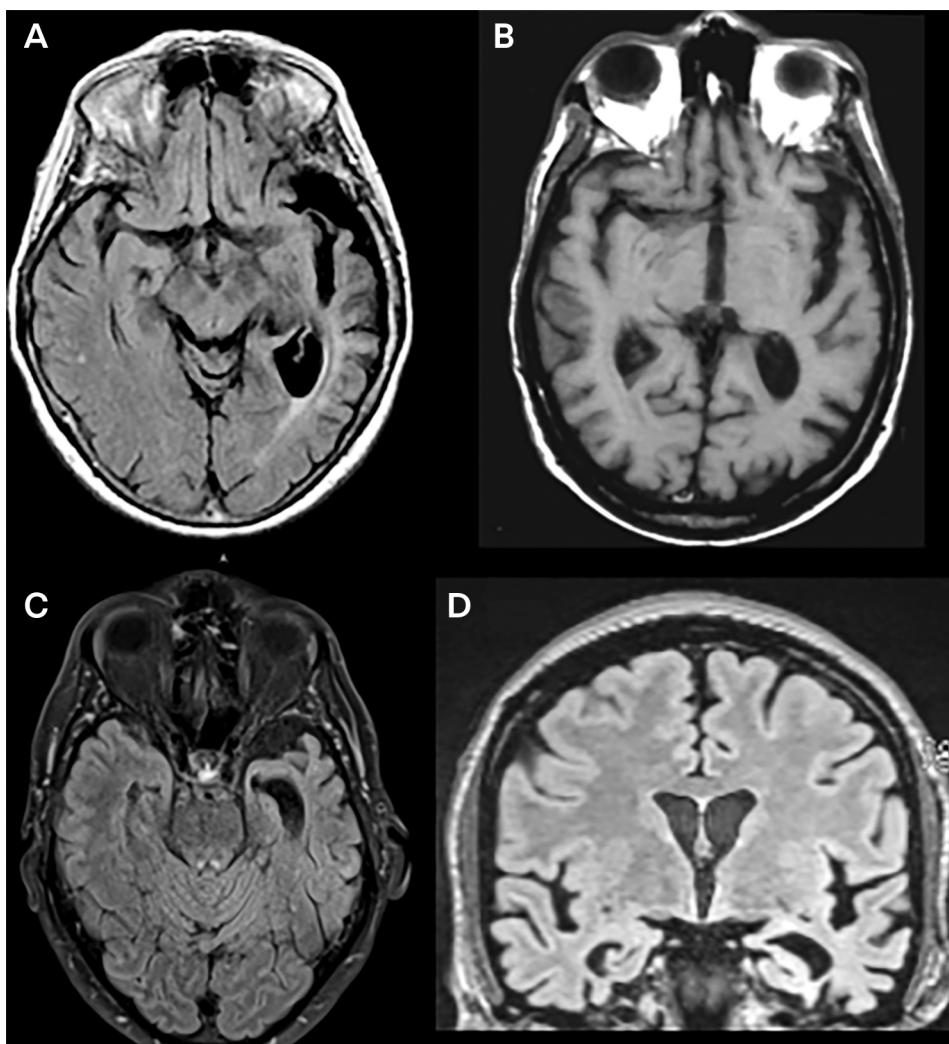


FIGURE 3-4

Imaging characteristics of primary progressive aphasia (PPA). *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI from a woman in her sixties with nonfluent variant PPA. Note atrophy of the insula and perisylvian region on the left. *B*, Axial T1-weighted image from a woman in her sixties with nonfluent variant PPA demonstrating left temporal lobe atrophy and insular atrophy. *C*, Axial FLAIR image from a 60-year-old man with semantic variant PPA. Note the prominent atrophy of the anterior temporal lobe on the left with expansion of the temporal horn. *D*, Coronal FLAIR from a 51-year-old woman with semantic variant PPA showing left greater than right anterior temporal atrophy.

involving a vast swathe of frontal and parietal cortex, as well as the striatum and brainstem.⁵² Patients with greater left hemisphere atrophy may manifest with initial nonfluent variant PPA or apraxia.⁵³ AD pathology frequently underlies corticobasal syndrome and seems to be associated with greater atrophy in posterior regions (eg, parietal lobes) in comparison with cases with FTLD pathology, which is associated with greater posterior frontal atrophy.⁵⁴ In contrast, atrophy in progressive supranuclear palsy syndrome occurs in subcortical structures, including the midbrain and thalamus, with very little involvement of the cortex.⁵²

KEY POINT

- Semantic memory relies on an amodal bihemispheric network with hubs in the anterior temporal lobes, especially the perirhinal cortex.

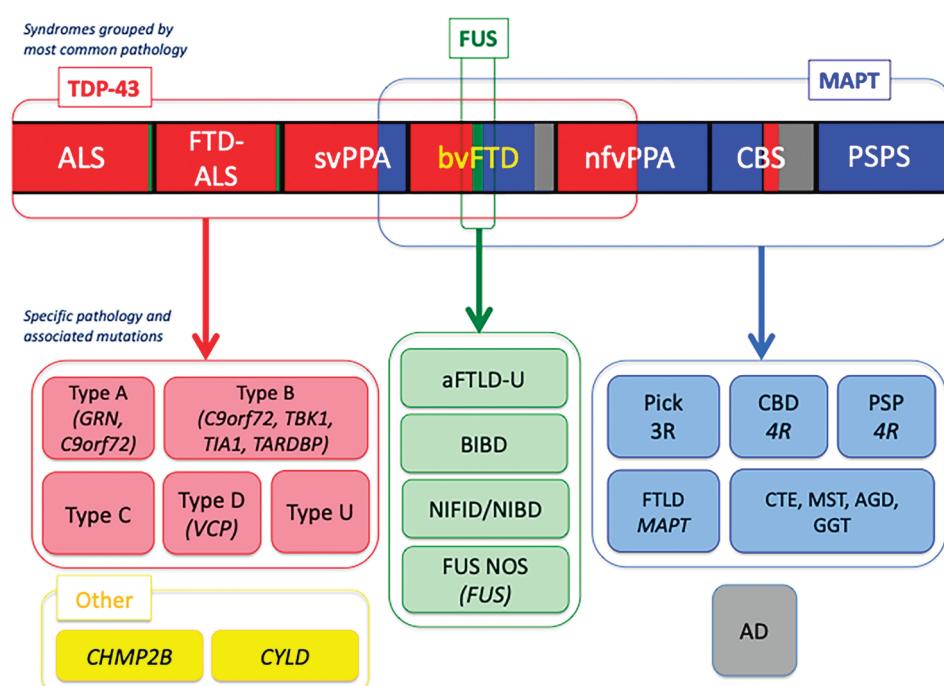


FIGURE 3-5

Relationships among FTD syndromes, frontotemporal lobar degeneration pathologies, and many of the known gene variations. The three types of molecular pathology are TDP-43 (red), FUS (green), and MAPT (blue). Seven clinical syndromes are arranged across the top, with loops identifying which syndromes are associated with each form of pathology. Colored areas within the box for each clinical syndrome reflect the proportion of cases with each type of pathology. Arrows pointing from the loops to collections of boxes identify a subtype of pathology and, in some cases, associated gene variations.

3R = three-repeat tau, 4R = four-repeat tau; aFTLD-U = atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions; AGD = argyrophilic grain disease; ALS = amyotrophic lateral sclerosis; BIBD = basophilic inclusion body disease; bvFTD = behavioral variant FTD; CBD = corticobasal degeneration; CBS = corticobasal syndrome; CHMP2B = charged multivesicular body protein 2B; CTE = chronic traumatic encephalopathy; CYLD = CYLD lysine 63 deubiquitinase; FTD = frontotemporal dementia; FUS = fused in sarcoma; GGT = globular glial tauopathy; GRN = gene for progranulin; MAPT = microtubule associated protein tau; nfvPPA = nonfluent variant primary progressive aphasia; NIBD = neurofilament inclusion body disease; NIFID = neuronal intermediate filament inclusion disease; NOS = not otherwise specified; PSP = progressive supranuclear palsy; PSPS = progressive supranuclear palsy syndrome; svPPA = semantic variant primary progressive aphasia; TBK1 = TANK-binding kinase-1; TIA1 = TIA1 cytotoxic granule associated RNA binding protein; VCP = valosin-containing protein.

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NEUROPATHOLOGY AND GENETICS OF FTD

Nearly all cases of the three core FTD syndromes can be classified into one of three neuropathologic categories at autopsy, based on the primary molecular defect: transactive response DNA-binding protein 43 (TDP-43), MAPT, or FUS.⁵⁵

FIGURE 3-5 summarizes the relationships between FTD syndromes, FTLD pathologies, and causative genetic variations.^{9,55} Approximately 50% of cases exhibit abnormal deposition of TDP-43 protein. TDP-43 pathology is subcategorized into types A through D, based on the morphology and distribution of neuronal cytoplasmic inclusions, dystrophic neurites, and glial cytoplasmic inclusions. Abnormal MAPT protein is identified in 45% of cases. The presence of paired helical tau filaments, as observed in AD, is not typical in FTD. The usual approach to characterizing MAPT pathology is based on the isoforms of tau that are present in the pathologic inclusions. Alternate splicing yields six tau isoforms, which are broadly classified into two groups based on the presence of either three (3R) or four C-terminal repeat domains (4R). Although AD is associated with a mixture of 3R and 4R tau, FTLD manifests as either 3R (Pick bodies) or 4R (seen in both corticobasal degeneration and progressive supranuclear palsy).⁵⁶

Nearly all cases not associated with TDP-43 or MAPT pathology (approximately 5%) are associated with FUS pathology.⁵⁷ In these cases, immunohistochemistry with ubiquitin or FUS reveals neuronal cytoplasmic inclusions mainly in the middle and deeper layers of the neocortex, along with occasional short dystrophic neurites. Neuronal cytoplasmic inclusions are also abundant in the dentate granule cells. **FIGURE 3-6** provides examples of histopathology related to each of these three key molecular derangements.

Among the various FTD syndromes, behavioral variant FTD is the least predictive of underlying pathology. All three of the pathologic defects listed above may result in behavioral variant FTD, and FUS pathology is associated exclusively with the behavioral variant FTD presentation.⁵⁷ TDP-43 pathology occurs in more than 50% of behavioral variant FTD cases, whereas a tauopathy occurs in approximately 40%.⁵⁸ The percentages quoted here refer specifically to behavioral variant FTD with non-AD etiology. The matter is further complicated by the description of patients in the literature who meet behavioral variant FTD criteria but are found to have AD pathology. The prevalence of AD among patients with clinical FTD is unclear, with some pathologic case series estimating approximately 7% and other studies reporting up to 40% AD biomarker positivity.^{58,59}

Certain atypical features may provide an additional clue to the pathology underlying behavioral variant FTD. Concomitant motor neuron disease strongly suggests TDP-43 pathology.⁵⁹ Patients with behavioral variant FTD due to TDP-43 pathology or FUS are more likely to manifest psychotic features, such as delusions and hallucinations.⁶⁰ Tau pathology is more likely to result in one of the forms of atypical parkinsonism.⁶¹ FUS is sometimes associated with very young onset (reported as young as 22 years).^{62,63} Several other features that suggest underlying FUS pathology include an absence of a strong family history, disproportionate atrophy of the caudate nucleus on brain imaging, and behavior characterized by hyperorality, pica, obsessions, rituals, and repetitive behaviors.⁶⁴

Both tau and TDP-43 pathologies commonly underlie nonfluent variant PPA. Tau pathology is more likely to be associated with apraxia of speech, whereas TDP-43 pathology is more likely to result in anomia and agrammatism without apraxia of speech (**CASE 3-2**).⁶⁵ More than 80% of cases of semantic

KEY POINTS

- Atrophy of the right temporal lobe is associated with mixed features of behavioral variant FTD and semantic dementia.
- Nearly all cases of FTD-ALS have underlying transactive response DNA-binding protein 43 (TDP-43) pathology.

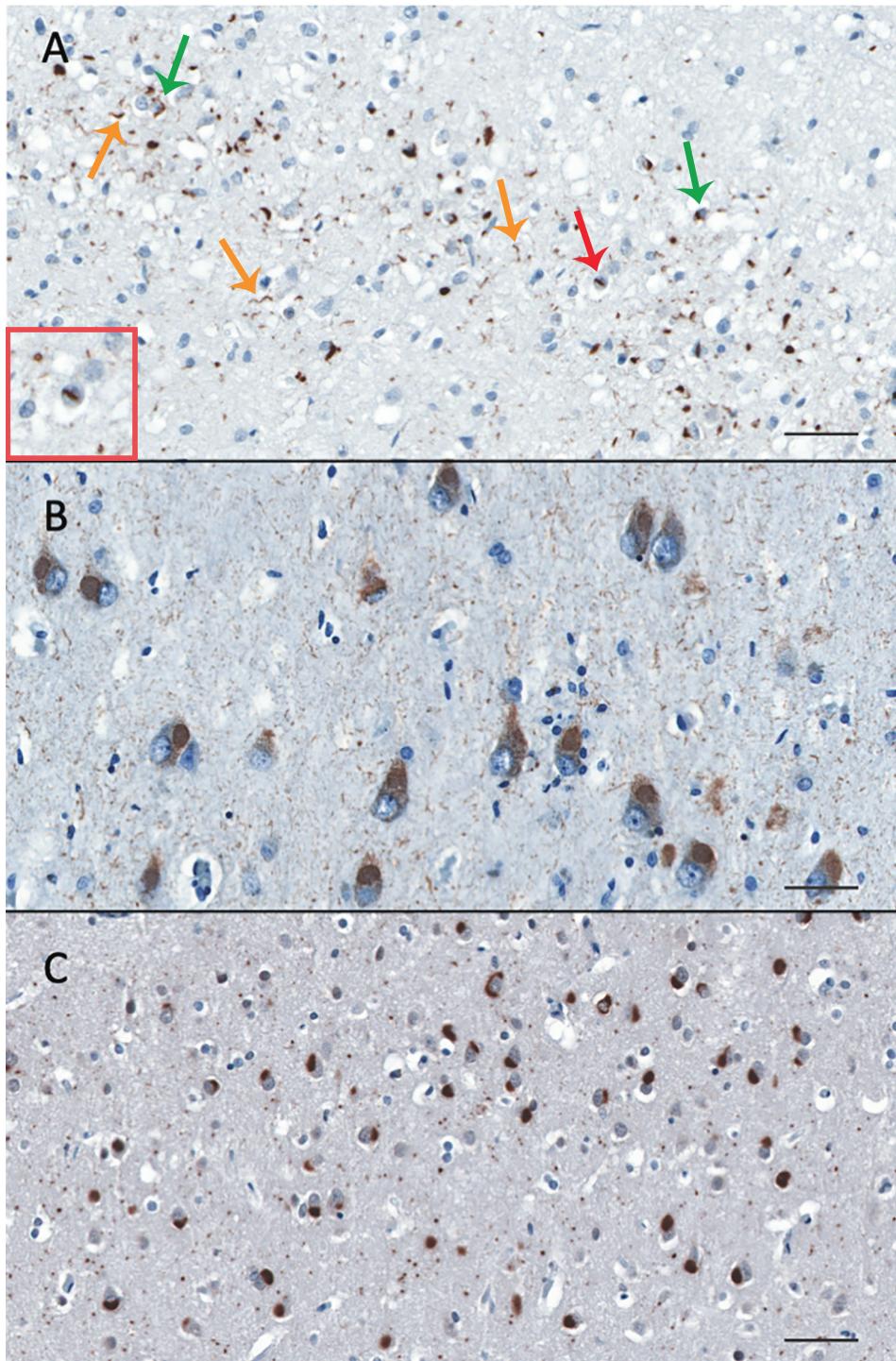


FIGURE 3-6

Immunohistochemically stained micrographs of tissue representing the three major categories of frontotemporal lobar degeneration histopathology. *A*, Immunohistochemical staining in frontal cortex layer 2 using antibodies targeting phosphorylated TDP-43 (pS409/410) showing one intranuclear inclusion (insert, red arrow), several intracytoplasmic inclusions (green arrows), and short dystrophic neurites (orange arrows). The intranuclear inclusion has been magnified in the insert on the lower left. *B*, Staining in the hippocampus using antibodies against tau (AT8). Pick bodies are shown as solid dark brown spheres similar in size to the dark blue nuclei of the pyramidal neurons. *C*, Staining in the cingulate gyrus using antibodies against FUS. Intracytoplasmic inclusions are shown, usually adjacent to the nucleus of the same neuron. Scale bar is 50 μ m for all three panels.

CASE 3-2

A 60-year-old, left-handed woman who worked as a math teacher presented to her neurologist with symptoms of occasionally stuttering or saying the wrong word (eg, "yes" instead of "no") and twitching on the left side of her face. Her family members reported that she seemed more rigid and had developed obsessive-compulsive tendencies. Her mother had carried the diagnosis of Alzheimer disease (not autopsy confirmed) and her younger brother was exhibiting personality changes. She continued to teach algebra and won a teaching award. Her facial jerks resembled hemifacial spasms, had no EEG correlate, and diminished when she was chewing gum. On exam, she was noted to have perseverative tendencies and mild apraxia of speech, which disrupted her ability to repeat the phrase "statistical analysis" several times in a row. Occasionally, she made paraphasic errors (eg, "chinge" rather than "change"). Phrase length was diminished, and when asked to cough she merely repeated the word "cough," but had no apparent oral-buccal or limb apraxia. MRI findings included atrophy of the insula (greater on the right than the left), inferior frontal gyrus, and anterior dorsolateral prefrontal cortex (FIGURE 3-7). Her facial movements improved with levetiracetam. A second neurologist noted that the patient had severe executive dysfunction and labored speech with relatively more nouns and few function words. She occasionally made agrammatic errors (eg, "I am fully function"). Repetition was mildly impaired, and she had difficulty articulating complex words while reading. Serial neuropsychological evaluations revealed consistently intact performance on semantic tasks but declining abilities with sentence repetition, regular word reading, syntax, and action naming. She died 2 years later, and a brain autopsy revealed Pick disease (FIGURE 3-6B and FIGURE 3-8).

COMMENT

The movement disorder, nonfluent variant primary progressive aphasia with apraxia of speech, and asymmetric frontal lobe atrophy are all features suggestive of a tauopathy.

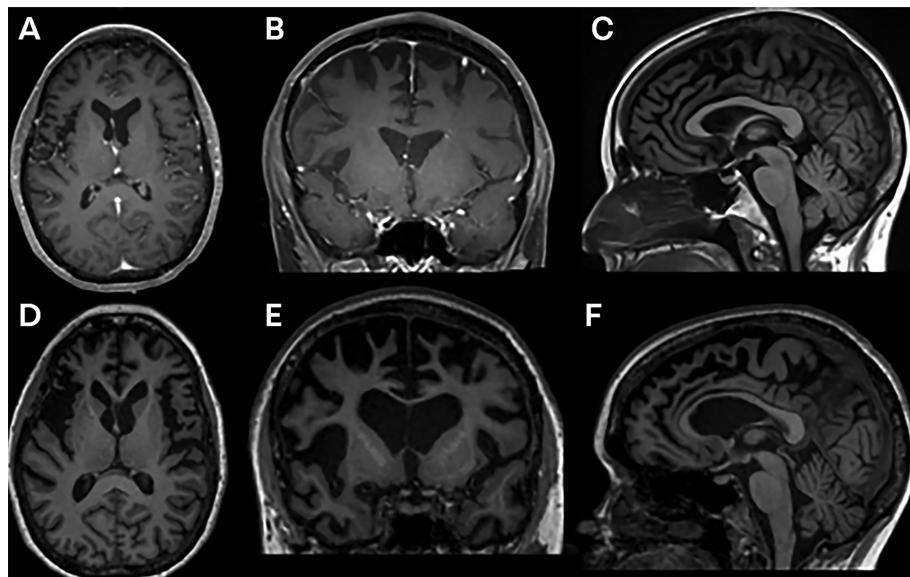


FIGURE 3-7

Imaging of the patient in **CASE 3-2** showing progressive atrophy in Pick disease. The upper series shows axial (A), coronal (B), and sagittal (C) T1-weighted images at presentation. The lower series shows comparable images from a scan performed 4 years later (D, E, and F, respectively). Note the somewhat asymmetric (right greater than left) atrophy involving the insula, anterior cingulate gyrus, superior frontal gyri, and temporal lobes. The scans in the top row are contrast enhanced, but there is no abnormal enhancement.



FIGURE 3-8

Coronal tissue section of the cerebral hemispheres of the patient in **CASE 3-2**. Note the asymmetry of the atrophy, which in this slice involves the left cerebral hemisphere more severely (left side of the image), especially the white matter and superior frontal gyrus. There is also significant striatal atrophy, especially in the caudate nucleus.

variant PPA exhibit TDP-43 pathology (type C).⁶⁴ This type is characterized by long, dystrophic neurites, mainly in the superficial cortical layers, with neuronal cytoplasmic inclusions found in the dentate layer of the hippocampus.⁶⁶ Those without TDP-43 pathology may be found to have a tauopathy, specifically Pick disease, or another atypical tauopathy such as argyrophilic grain disease.^{58,65}

Corticobasal syndrome is pathologically heterogeneous, with many cases found to have AD or Pick disease (3R) pathology at autopsy.⁶⁷ The specific pathology of corticobasal degeneration consists of grossly asymmetrical cerebral atrophy involving the frontal and parietal lobes and basal ganglia. Microscopic evaluation reveals ballooned, achromatic neurons with diffuse phospho-tau immunoreactivity, mainly in the middle and lower neocortical layers.⁶⁸

Progressive supranuclear palsy syndrome is associated with atrophy chiefly of the midbrain and subthalamic nucleus, sometimes including the frontal lobes, although the pattern of gross atrophy varies with the specific clinical subtype. The histopathology of progressive supranuclear palsy syndrome is more homogeneous than that of corticobasal syndrome. Patients with progressive supranuclear palsy syndrome are likely to have the typical histopathology of progressive supranuclear palsy, characterized by globular neurofibrillary tangles mainly located in the vulnerable subcortical nuclei, including the subthalamic nucleus and the substantia nigra. In addition, there is distinctive glial pathology, including tufted astrocytes and oligodendroglial coiled bodies.⁶⁸

Compared with AD, FTD is more likely to be associated with a gene variation. Up to 43% of patients with FTD have a family history of dementia, ALS, or Parkinson disease, and approximately 10% to 20% of patients with FTD carry a variation known to cause disease.^{1,69} Patients with familial origin tend to develop symptoms at a slightly younger age than patients with sporadic origin (53.0 versus 57.8 years).² Occasionally, gene variations are identified in patients with little or no family history suggestive of a heritable form of FTD.⁷⁰ Genetic testing should not be overlooked as a potential means of establishing the diagnosis and it is very important to have access to a genetic counselor.

The majority of variations causing FTD occur in three genes, although at least ten other genes have been implicated.⁷¹ The most common genetic abnormality, and the chief cause of genetically inherited behavioral variant FTD and ALS, is the hexanucleotide repeat GGGGCC in the noncoding portion of the gene *C9orf72*, which results in abnormal inclusions containing TDP-43.⁷² Patients with the *C9orf72* variation exhibit more psychotic features than have typically been described in FTD, especially delusions of a persecutory or somatoform type.¹³ Parkinsonism may arise late in the course.⁵⁹ Of the four subtypes of TDP-43 histopathology, *C9orf72* variations are most frequently associated with type A, type B, or a mixture of the two.⁷³ Type A is characterized by neuronal cytoplasmic inclusion chiefly in layer II of the neocortex, along with short, thick dystrophic neurites. Type B is characterized by diffuse granular neuronal cytoplasmic inclusion throughout the layers of the neocortex and in the dentate lamina of the hippocampus.⁶⁶ Variations in the gene *GRN*, which encodes the protein progranulin, also result in TDP-43 pathology. The most common phenotype in these patients is behavioral variant FTD, followed by nonfluent variant PPA.⁷⁴ However, patients with *GRN* variations with primary language impairment may exhibit logopenic progressive aphasia⁷⁵ or mixed

features of the canonical PPA syndromes (ie, agrammatism and semantic deficits) (**CASE 3-3**).⁷⁶

Occasionally, patients with variations in *GRN* manifest with features of posterior cortical atrophy.⁷⁷ The phenotypes associated with *GRN* variations vary widely both between and within kindreds.⁷⁸ Thus, when assessing the family history of a patient with any possible FTD syndrome, it is worth considering the possibility that relatives with very different presentations could be expressing a common variation (eg, a patient with PPA whose father had parkinsonism). Despite having some histopathologic features in common with those with *C9orf72* variations, patients with *GRN* variations do not present with motor neuron disease. The most common pattern of TDP-43 pathology in these cases is type A.⁶⁶ Patients with variations in *MAPT* tend to manifest with symptoms at a younger age (mean 49.5 years) than those with *GRN* or *C9orf72* variations (58.2 and 61.3 years, respectively).² Early age of onset in the setting of a positive family history should raise concern for a *MAPT* variation.⁷⁷ *MAPT* and *GRN* variations tend to present with different behavioral issues, with patients with *MAPT* variations exhibiting more disinhibition and patients with *GRN* variations exhibiting more apathy.² As with *GRN* variations, some degree of phenotypic variability occurs within related individuals with *MAPT* variations.⁷⁸ For example, carriers of the P301L variation have been described as manifesting with disinhibition, abulia, or obsessive-compulsive behavior within the same family.⁷⁹ Semantic impairment is common in patients with *MAPT* variations and anomia may be detectable in presymptomatic stages.⁸⁰

Histopathologically, variations in *MAPT* are associated with abundant filamentous tau inclusions in neurons and glia, especially in the hippocampus and cortex.⁵⁶ Some inclusions may resemble Pick bodies⁸¹ or globular glial tauopathy.⁸² Risk for both corticobasal degeneration and progressive supranuclear palsy is imparted by the presence of a specific haplotype (H1) of the *MAPT* gene, consisting of a 900 kb inversion.⁸³ These three types of variations are associated with characteristic patterns of atrophy on imaging. The atrophy in *GRN* variations is typically very asymmetric and involves the frontal, temporal, and parietal lobes. The side with greater atrophy varies within families.⁷⁷ Both *MAPT* and *C9orf72* variations are associated with relatively symmetric atrophy, with *MAPT* being associated with greater temporal lobe atrophy and *C9orf72* with greater frontal lobe atrophy.⁸⁴

BIOMARKERS

The development of specific biomarkers for FTLD pathology could greatly accelerate the discovery of effective disease-modifying treatments. Available biomarkers are currently limited and nonspecific. Neurofilament light chain may be detected in blood or CSF and signals the presence of neuroaxonal loss from neurodegenerative disease.⁸⁵ Elevated plasma neurofilament light chain indicates a worse prognosis in both AD and FTD, but does not discriminate well between the two conditions.⁸⁶ Neurofilament light chain appears to be particularly useful for differentiating FTD from primary psychiatric disease.⁸⁷ Biomarkers show different patterns of longitudinal change in presymptomatic individuals with known variations. For example, plasma neurofilament light chain levels in patients with *C9orf72* variations begin to exceed normal levels 30 years before the onset of symptoms. In patients with *GRN* variations, neurofilament light chain levels rise later but more sharply, deviating from control levels about 15 years

KEY POINTS

- More than 80% of cases of semantic variant PPA or semantic dementia have underlying TDP-43 type C pathology.
- Consider a hereditary form of frontotemporal lobar degeneration in any patient with a family history suggestive of FTD phenotypes in other relatives.
- Striking asymmetry of atrophy should raise the question of a variation in the gene *GRN*. Variations in the gene *MAPT* are associated with greater temporal atrophy than variations in the gene *C9orf72*, which are associated with greater frontal atrophy.

CASE 3-3

A 67-year-old man reported a four-month history of progressive word-finding difficulty. There was concern for a positive family history, as both of his parents had suffered from unknown neurologic diseases later in life. The patient initially reported improvement with the discontinuation of his statin. However, his wife noted that he was sometimes unable to make himself understood in conversation but was unaware of the problem. He underwent a trial of a cholinesterase inhibitor but quit the medication due to cardiac rhythm disturbance. His language skills gradually worsened, and after 2 years his speech was noted to be "telegraphic," although he continued to score in the high 20s on the Mini-Mental State Examination. Clinicians who evaluated him alternately categorized his aphasia as nonfluent or semantic. Neuropsychological testing revealed deficits in object naming, word selection, word comprehension, object and person knowledge, and repetition. There was no surface dyslexia or dysgraphia. In addition, there was grammatical simplification and effortful, halting speech. On a test of question repetition, he consistently transformed more complex object-relative constructions into simpler subject-relative constructions (eg, "Who is the woman kissing?" became "Who is kissing the woman?"). Written language showed a progressive decline in grammar (**FIGURE 3-9**). He became apathetic and developed right-sided apraxia and a tendency to hold his right arm in unusual postures, especially while walking. MRI showed left anterior temporal and perisylvian atrophy with expansion of the frontal and posterior horns of the lateral ventricle (**FIGURE 3-10**). Lumbar puncture for Alzheimer disease (AD) biomarkers was indeterminate, as it revealed a low amyloid-tau index of 0.63 (less than 0.8 is supportive of AD) but also a low phosphorylated tau of 39.4 (greater than 68 is supportive of AD). Apolipoprotein E testing was negative for ε4. At his final clinic visit, he had developed incontinence and a severe gait disorder. Nevertheless, he remained cooperative and was on no medications for psychiatric or cognitive symptoms. The patient died 7 years after presentation. His brother subsequently underwent genetic testing and was positive for a GRN variation.

COMMENT

This case illustrates two features typical of patients with GRN variations: progressive aphasia with mixed semantic and grammatical deficits, and marked asymmetry of atrophy on MRI.

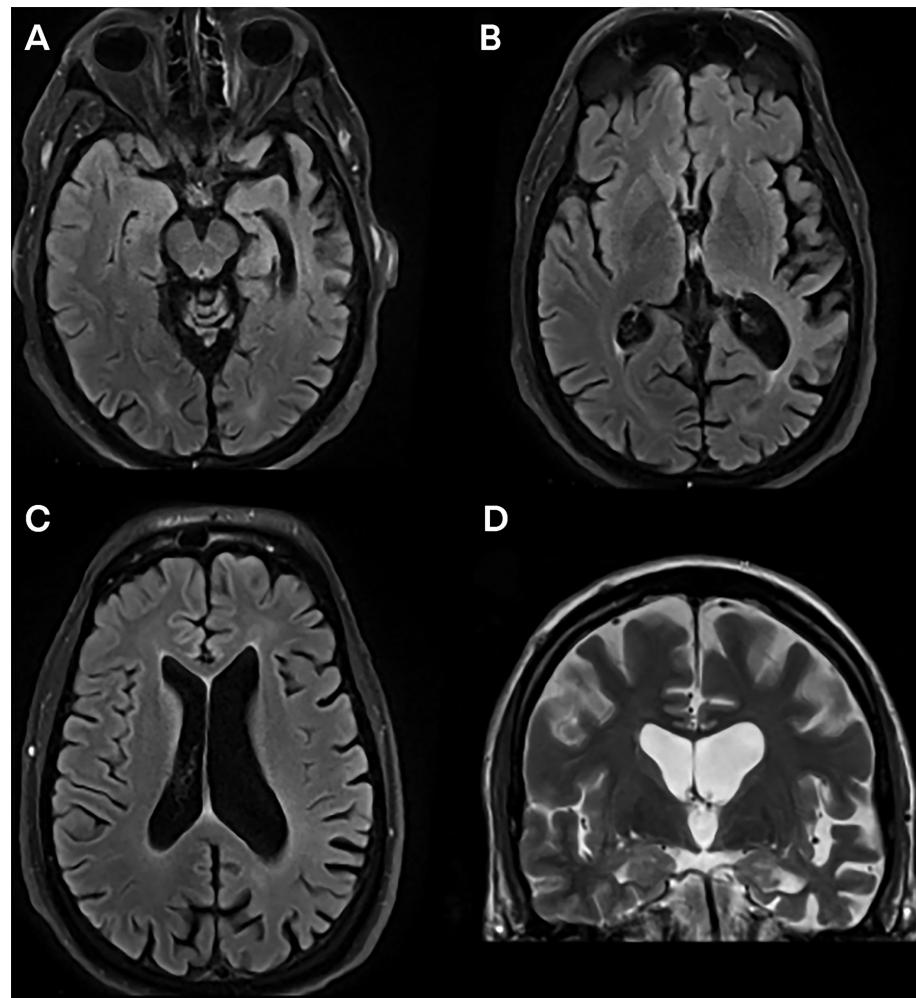
At presentation MMSE 26	This is a great area in Indiana University.
2 months MMSE 27	The Pug Dog we have had over eight years.
1 year MMSE 30	We have a dog, his name is Pogi.
1.75 years MMSE 28	A dog came today for his play.
2.25 years MMSE 29	Dog will be here today.
2.5 years MMSE 25	This is a dog.
2.75 years MMSE 23	Mine sentence would be OK.
3.25 years MMSE 20	For the store.
3.75 years MMSE 17	The The
4.25 years MMSE 13	I nee paper.
5 years MMSE 4	(nothing written)

FIGURE 3-9

Testing results for the patient in **CASE 3-3** showing sentences written during serial administrations of the Mini-Mental State Examination (MMSE) over a 5-year interval. To the left of each sentence is the approximate length of time after presentation and the global MMSE score at that time. Sentences up to 2.75 years after presentation are adequate to receive the point on the test and grammar is mildly affected. After that time, the patient failed to write a complete sentence. The sentence at 4.25 years after presentation was meant to read, "I need paper."

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**FIGURE 3-10**

Imaging of the patient in **CASE 3-3**. MRI scan shows asymmetric, left hemisphere-predominant atrophy. **A, B, and C**, Three different axial fluid-attenuated inversion recovery (FLAIR) images. **D**, Coronal T2-weighted image showing marked left temporal greater than frontal atrophy.

before the onset of symptoms, but greatly exceeding levels in the other variation groups among symptomatic patients.⁸⁸ Real-time quaking-induced conversion, a technique originally applied to the diagnosis of prion disease, may prove to be valuable for detecting TDP-43⁸⁹ or tau⁹⁰ pathology but requires a sample of CSF.

In the appropriate clinical context, the identification of a known pathogenic variation is considered proof of definite FTLD pathology.^{6,7} Because of the relatively high frequency of variations among patients with FTD, genetic testing can help establish a diagnosis. However, there are ethical and legal concerns, and the author only undertakes such testing with support from a genetic counselor. Laws, testing parameters, and cultural attitudes toward this practice may vary widely and should be given careful consideration. Apart from genetic testing, some genetic variations result in abnormal levels of proteins that may be measured in biofluids and may become relevant for diagnosis or treatment.^{91,92} Although brain imaging is not likely to be widely adopted for presymptomatic screening in individuals with no apparent genetic risk, structural MRI may permit the detection of changes before the onset of FTD symptoms among variation carriers. Among individuals with *C9orf72* variations, temporal lobe volumes begin to differ from those of controls around 6 years before symptom onset. Reductions in both frontal and temporal volumes precede the onset of symptoms from *GRN* variations by a little more than 1 year, and a decline in medial temporal lobe volume occurs nearly 2 years before the onset of symptoms from *MAPT* variations.⁸⁸ Atrophy and hypometabolism due to *GRN* variations tend to be much more asymmetric than those occurring in the setting of *MAPT* variations, and this asymmetry may be reflected in the clinical presentation.⁷⁷

Patterns of hypometabolism identified using fludeoxyglucose positron emission tomography (FDG-PET) differ starkly between FTD and AD, and these scans are commonly employed to help differentiate between the two diagnoses in ambiguous cases.⁹³ Amyloid PET also serves to discern between these two patient groups.⁹⁴ Although one might expect PET scans developed for the detection of tau to have value in the setting of FTLD, the only tau tracer currently approved for clinical use exhibits off-target binding in patients with suspected TDP-43 pathology.^{95,96} PET tracers specific for TDP-43 or the forms of tau that occur in FTLD are still needed.

TREATMENT

Treatments for FTD are primarily focused on behavioral and environmental strategies, care partner education, and pharmacologic intervention targeting symptoms that disrupt quality of life for the patient or care partner. Currently, no US Food and Drug Administration (FDA)-approved disease-modifying treatments are available, but several clinical trials are underway.

FTD syndromes, especially behavioral variant FTD, impose a significant burden on care partner, who experience more stress and depression and decreased health-related quality of life compared with AD care partners.^{97,98} Moreover, they tend to feel that their greatest needs, those of support and education about the dementia and its trajectory, are not adequately met.⁹⁹ Nonpharmacologic therapeutic interventions show potential for reducing care partner burden with a minimum of side effects or other unintended negative consequences.^{59,100} Behaviors in FTD may respond to interventions tailored to a patient's specific needs by following the describe-investigate-create-evaluate

KEY POINTS

- Levels of neurofilament light chain mark the severity of neuroaxonal loss in neurodegenerative diseases and may be measured in plasma or CSF.
- Behavioral interventions for FTD can be tailored to an individual patient's needs.
- Serotonergic medications are the main pharmacologic agents with utility in FTD.

(DICE) model.¹⁰¹ The components of this model include a description (D) of the circumstances leading to problem behaviors, an investigation (I) of potential inciting factors, the creation (C) of an action plan to alleviate factors that exacerbate behavior, and a subsequent evaluation (E) of the need for further interventions. Transcranial direct current stimulation may ameliorate behavioral symptoms in FTD.¹⁰² Speech therapy might have value for the treatment of PPA, although some studies suggest that gains are transient and do not generalize to untrained material.^{100,103} However, script training, an approach commonly employed in stroke aphasia, may offer sustained benefit for patients with nonfluent variant PPA.¹⁰⁴

Pharmacologic interventions are often necessary when behavioral symptoms of FTD disrupt functions of daily life. No medication has FDA approval for symptomatic FTD treatment, but pathophysiologic rationale and limited evidence may guide the off-label use of some compounds. The neurotransmitter underpinnings of behavioral symptomatology support pharmacologic intervention. The clearest evidence for neurotransmitter alterations with functional or symptomatic manifestations in FTLD points to serotonergic and dopaminergic hypofunction.¹⁰⁵ Serotonergic function is reduced in FTD,¹⁰⁵ and serotonergic dysfunction correlates with behavioral symptoms such as impulsivity, irritability, and abnormal eating behaviors.¹⁰⁶ Thus, there is interest in using agents that increase serotonergic activity.¹⁰⁷ Small clinical trials have supported the use of selective serotonin reuptake inhibitors (SSRIs), such as sertraline, paroxetine, fluoxetine, and citalopram, for the treatment of behavioral symptoms in FTD, including disinhibition, irritability, compulsions, and depression.¹⁰⁸ Trazodone, another drug with serotonergic effects, may be beneficial for irritability, agitation, depression, and disordered eating in behavioral variant FTD.¹⁰⁹

Reductions in mesolimbic and mesocortical dopaminergic function driven by the loss of both dopaminergic neurons and postsynaptic receptors may underlie behavioral symptoms in FTD. These findings have led to interest in compounds that trigger dopamine release or otherwise enhance dopaminergic transmission, such as amphetamines, selegiline, and amantadine, for the treatment of apathy or other neuropsychiatric consequences of FTD.^{45,110} Somewhat counterintuitively, antipsychotic medications (which typically block dopamine receptors) may be used off-label to treat certain behavioral symptoms in FTD. This approach is based in part on the beneficial behavioral effects observed in other dementias and psychotic disorders.¹¹¹ Because patients with FTLD pathology are more sensitive to extrapyramidal side effects of antipsychotic medication, atypical agents are preferable to typical agents,¹¹² and it is generally recommended to use the lowest effective dose, weaning and discontinuing the medication as soon as possible. Peer-reviewed evidence for antipsychotic use specifically in FTD is limited.¹¹³ One 24-month open-label trial of olanzapine demonstrated a beneficial effect on psychosis, anxiety, and agitation in patients with FTD, AD, Lewy body diseases, and vascular dementia with only mild and transient hemodynamic and postural adverse effects and no recognized anticholinergic adverse effects.¹¹⁴ Case reports suggest potential benefits of aripiprazole¹¹⁵ and risperidone.¹¹⁶ Although cholinergic neuron loss occurs in some nuclei, cholinergic projections are largely intact, and cholinergic function is considered to be preserved in FTD.^{105,117} Cholinesterase inhibitors

are not recommended in patients with FTD and may be associated with cognitive and behavioral worsening.^{113,118}

Other agents considered for behavioral management in FTD include memantine and mood stabilizers. Memantine is well tolerated but does not seem to be beneficial.¹¹⁹ Anticonvulsants, specifically carbamazepine and lamotrigine, have been reported to ameliorate problematic sexual behavior¹²⁰ and physically violent behavior,¹²⁰ respectively. Case reports suggest a benefit of topiramate in patients with FTD for hyperorality.¹²¹

CONCLUSION

FTLD comprises a complex array of neurodegenerative diseases whose diagnosis is rendered difficult by the imprecise mapping from heterogeneous clinical presentation to equally heterogeneous neuropathology, the paucity of disease-specific biomarkers, and the phenotypic overlap with psychiatric conditions. Attention to clinical details, such as motor syndromes and neuropsychiatric features, and patterns of atrophy or hypometabolism on brain imaging can aid the clinician in developing an informed list of potential underlying causes for any given FTD syndrome. Tau PET has limited utility in FTD but there is interest in developing new tracers for detecting specific molecular defects. Genetic testing is the only method currently available for establishing a definite diagnosis without a sample of brain tissue, although there is interest in developing specific biomarkers or in making nonspecific biomarkers (such as neurofilament light chain) more available in the clinical setting. Recent advances in treatment have chiefly been nonpharmacologic, consisting of speech therapy or behavioral modification techniques, but several available medications have off-label uses. Some current clinical trials focus on specific gene variations, whereas others focus on syndromes with greater pathologic predictability (eg, semantic variant PPA, progressive supranuclear palsy syndrome). The development of specific biomarkers for sporadic FTD syndromes will permit greater precision in the search for effective treatments.

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Lewy Body Dementia

REVIEW ARTICLE

By James E. Galvin, MD, MPH



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ABSTRACT

OBJECTIVE: *Lewy body dementia (LBD) is an umbrella term describing two closely related conditions: Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB). LBD is the second most common cause of neurodegenerative dementia but is often underrecognized in clinical practice. This review covers the key epidemiologic, clinical, cognitive, behavioral, and biomarker features of LBD and discusses current treatment options.*

LATEST DEVELOPMENTS: *Indicative biomarkers of LBD improve the ability to make a diagnosis and include single-photon emission computed tomography (SPECT) of the dopamine system (brain) and the noradrenergic system (cardiac), and polysomnography. α -Synuclein-specific biomarkers in spinal fluid, skin, plasma, and brain imaging are in active development with some available for clinical use. Prodromal stages of PDD and DLB have been contextualized, and diagnostic criteria have been published. An emerging theme is whether an integrated staging system focusing on protein aggregation, rather than clinical symptoms, may advance research efforts.*

ESSENTIAL POINTS: *LBD is a common cause of cognitive impairment in older adults but is often subject to significant delays in diagnosis and treatment, increasing the burden on patients and family care partners. Understanding key features of disease and the use of biomarkers will improve recognition. Earlier detection may also facilitate the development of new therapeutics and enrollment in clinical trials.*

INTRODUCTION

*L*ewy body dementia (LBD) is an umbrella term that encompasses two related clinical diagnoses, Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB), that share a common pathologic substrate of α -synuclein aggregation in the form of Lewy bodies and Lewy neurites.¹ LBD is the second most common cause of neurodegenerative dementia after Alzheimer disease (AD) and similar in prevalence to vascular dementia.² The Lewy Body Dementia Association estimates that approximately 1.4 million Americans are living with LBD.¹ No one sign or symptom definitively distinguishes PDD from DLB. Rather, the current clinical criteria distinguish DLB from PDD only by the temporal requirement that the dementia manifests more than 12 months after the onset of motor signs in the setting of PD. If dementia precedes or is concurrent with parkinsonism, then DLB is diagnosed.³ Movement disorder and cognitive disorder researchers

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RELATIONSHIP DISCLOSURE:

Dr Galvin has received personal compensation in the range of \$500 to \$4999 for serving on a scientific advisory or data safety monitoring board for Passage Bio, Inc; in the range of \$10,000 to \$49,999 for serving as a consultant for GE HealthCare and F. Hoffmann-La Roche Ltd; in the range of \$50,000 to \$99,999 for serving as a consultant for Biogen, Eisai Co, Ltd, and Lilly; and in the range of \$100,000 to \$499,999 for serving as a consultant for Cognivue, Inc. Dr Galvin has noncompensated relationships on the boards of directors of the Alzheimer Association
Continued on page 1698

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Galvin discusses the unlabeled use of carbidopa/levodopa, clonazepam, clozapine, donepezil, droxidopa, fludrocortisone, galantamine, melatonin, memantine, midodrine, mirabegron, olanzapine, pimavanserin, quetiapine, risperidone, and rivastigmine, for the treatment of dementia with Lewy bodies and for the treatment of Parkinson disease dementia.

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have challenged the clinical meaningfulness of this 1-year rule. Regardless of the timing of the movement disorder compared with the onset of cognitive or behavioral symptoms, multiple studies support that DLB and PDD share many features, and differentiation between them may have more to do with the sites of early α -synuclein aggregation and its subsequent spread.

Clinically, LBD can be distinguished from AD or other neurodegenerative dementias by (1) early and prominent deficits in visuospatial, executive, and attentional domains as opposed to the marked episodic memory impairment that characterizes AD or language deficits of the progressive aphasias, (2) spontaneous parkinsonism, (3) visual hallucinations, (4) rapid eye movement (REM) sleep behavioral disorder (RBD), and (5) cognitive fluctuations.³⁻⁵ Additional suggestive features of LBD that may assist in the diagnosis include depression, anxiety, apathy, hallucinations in other modalities (eg, auditory, olfactory, tactile), frequent falls, syncope, unexplained loss of consciousness, hyposmia, hypersomnia, constipation, orthostatic hypotension, and sensitivity to classic neuroleptic medications.³ Although these suggestive features are common in DLB and PDD, they lack the sensitivity and specificity to establish a diagnosis of LBD on their own; however, when collectively considered, they may increase the suspicion of LBD. The signs and symptoms of LBD may resemble the more widely recognized dementia syndrome of AD (particularly in the early stages), but with careful evaluation, LBD can be distinguished from AD by using consensus criteria for DLB³ or PDD^{4,5} and indicative biomarkers. **TABLE 4-1** describes the most common signs and symptoms that patients with LBD may experience.

There is a movement to recategorize LBD as neuronal α -synuclein disease using a biological definition rather than relying on the clinical syndromes of DLB and PDD.⁶ Neuronal α -synuclein disease would be defined by the presence of pathologic α -synuclein in neuronal cell bodies (Lewy bodies) and neuronal processes (Lewy neurites). This proposed integrated staging system needs to be further validated and remains controversial at the time of writing. It is not without merit, however, and this proposed biological definition is expanded on later in this article, weighing both its advantages and disadvantages for research and potential extension to clinical practice. For this review, *LBD* is used when describing the spectrum of conditions with α -synuclein pathology and common aspects of disease. *DLB* and *PDD* are used to highlight specific differences and when citing specific experimental and clinical data.

EPIDEMIOLOGY OF LEWY BODY DEMENTIA

The exact number of individuals living with LBD is unknown, although estimates of prevalence and incidence for PDD and DLB are available. For PDD, the point prevalence of dementia in patients with PD is approximately 30%, and the incidence rate is fourfold to sixfold compared with healthy controls.⁷

Approximately 75% of individuals with PD for 10 or more years are likely to develop dementia^{6,8} with a mean onset of 10 years.^{4,5} However, there is considerable variation from patient to patient, with some individuals developing cognitive symptoms soon after diagnosis. Risk factors for PDD include older age, more severe motor symptoms (eg, gait and postural instability), visual hallucinations, and cognitive changes at the time of diagnosis.

For DLB, prevalence is estimated at 0.02 to 63.5 per 1000 (up to 5% of the general population and up to 30% of patients with dementia) with older age and

Common Signs and Symptoms Associated With Lewy Body Dementia^a

TABLE 4-1

Cognitive features

- ◆ Delayed recall and retrieval that improves with cueing
- ◆ Visual tracking and attention
- ◆ Visuospatial and perceptual
- ◆ Verbal and motor initiation
- ◆ Clock-drawing and block design (construction)
- ◆ Timed attention tasks
- ◆ Executive tasks

Movement features

- ◆ Bradykinesia^b
- ◆ Rigidity^b
- ◆ Postural instability with repeated falls^b
- ◆ Slow, shuffling gait
- ◆ Myoclonus
- ◆ Resting tremor less common but may have postural or action tremor

Behavioral features

- ◆ Visual hallucinations^b
- ◆ Hallucination in other modalities
- ◆ Delusions
- ◆ Depression
- ◆ Anxiety
- ◆ Apathy
- ◆ Rapid eye movement (REM) sleep behavior disorder^b
- ◆ Cognitive fluctuations^b

Autonomic and constitutional features

- ◆ Loss of smell
- ◆ Constipation or obstipation
- ◆ Urinary incontinence
- ◆ Drooling
- ◆ Runny nose
- ◆ Gastroparesis
- ◆ Dizziness and lightheadedness
- ◆ Abnormal sweating
- ◆ Sexual dysfunction
- ◆ Oily or flaky skin

^a These signs and symptoms can assist with differential diagnosis. Not all features will be present in all patients.

^b Core feature.³

male sex as strong risk factors. The incidence of DLB is estimated at 0.5 to 1.6 per 1000 person-years (up to 0.1% of the general population and up to 3% for new dementia cases).² Per Medicare claims data, the overall incidence of LBD (53% DLB and 47% PDD) is estimated to range from 0.18% to 0.21% with a prevalence rate of 0.83% to 0.90%.⁷ The age of onset for LBD tends to be younger than that seen in AD, more commonly in the late fifties to early seventies compared with AD, which is more commonly seen in the mid-seventies to mid-eighties.^{2,3} LBD appears to be a more rapidly progressive disease than AD with a median course of 8.5 years.² LBD is a male-predominant disease with a 1.6:1 ratio of men to women.⁹ The reasons for this difference are unknown. The majority of research and clinical series in the United States have been in predominantly non-Hispanic White individuals.¹⁰ LBD appears to be common in Asian populations and is particularly well described in Japan. However, far fewer cases of LBD are described in Black and Hispanic populations. This could be due to ascertainment bias, caused by more limited access to health care and specialty centers, or that minoritized individuals get dementia diagnoses at later stages when it may be more difficult to establish etiology. However, case series of AD suggest that Black and Hispanic people have a higher risk of dementia, most likely due to vascular burden. Further research is needed to determine the disparity in LBD detection and risk factors across different sex, gender, racial, and ethnic groups.^{9,10}

CLINICAL SYNDROMES

Although the pathologic substrate of PDD and DLB is shared, each is considered separately here.

Parkinson Disease Dementia

Parkinson disease (PD), one of the most common movement disorders in older adults, affects 1 in 100 individuals older than 60 years and 4% to 5% of adults older than 85 years (approximately 1.5 million Americans). PD is characterized by the cardinal motor features of rigidity, bradykinesia, and tremor at rest with postural instability usually presenting later in the course. Historically, cognitive problems were not considered to be important features of PD. In his famous text, James Parkinson (1755-1824) stated, “by the absence of any injury to the senses and to the intellect that the morbid state does not extend to the encephalon.”¹¹ Cognitive symptoms in PD were first characterized by Charcot, but the nonmotor components of PD were not fully appreciated until the late 20th century. It is now well recognized that cognitive changes may be present very early in PD and that dementia is common, representing some of the most debilitating aspects of the disease.¹² Furthermore, proposed revisions to the diagnostic criteria for PD consider the possibility of eliminating dementia as an exclusion criterion for PD.¹³ There is strong evidence that dementia not only has significant clinical consequences for patients with PD regarding increased disability, risk for psychosis, reduced quality of life, and increased mortality but also results in greater stress and burden of caring for patients with PDD and higher disease-related costs due to increasing chances of nursing home admission.¹⁴ According to clinical diagnostic criteria, PDD is a dementia syndrome that develops in the context of established PD.^{4,5} Like AD, PDD has an insidious onset with slow progression and is defined as impairment in more than one cognitive domain, representing a decline from prior levels. The deficits must

be severe enough to affect daily social or occupational functioning or personal care, and the deficits must be independent of the impairment resulting from motor or autonomic symptoms.

Dementia With Lewy Bodies

DLB is the second most common cause of neurodegenerative dementia in older adults. An international consortium on DLB resulted in revised criteria for the clinical and pathologic diagnosis of DLB, incorporating new information about the core clinical features and improved methods for their assessment.³ DLB is characterized by a progressive decline in cognitive functioning that is often indistinguishable from PDD.¹⁵ The core features of DLB include fluctuating cognition, recurrent well-formed visual hallucinations, spontaneous parkinsonism, and RBD.³ However, not all patients will manifest all core features, and some core features (hallucinations, fluctuations) may be transient or inconsistent throughout the course. The inclusion of indicative biomarkers may improve diagnosis.⁶ Extrapyramidal signs, including bradykinesia, rigidity, and postural instability are the most frequent signs of parkinsonism and can vary in severity. Resting tremor is less common, but postural and action tremors can occur, as well as myoclonus. Parkinsonism is usually bilateral at onset with more axial rigidity than idiopathic PD. RBD may precede cognitive decline by more than a decade. Supportive features are those that commonly occur but lack specificity and include neuroleptic sensitivity, postural instability, falls, syncope, hypersomnia, hyposmia, autonomic dysfunction, anxiety, apathy, and depression.³ Many patients with DLB and PDD report chronic constipation.⁶ According to the revised DLB consortium criteria, dementia and the presence of two core features or one core feature and one indicative biomarker are sufficient for a diagnosis of probable DLB; one core feature or one or more supportive features suggest a diagnosis of possible DLB (**CASE 4-1**).³

A definitive diagnosis of DLB relies on brain autopsy following death. These criteria permit 83% sensitivity and 95% specificity for the presence of neocortical Lewy bodies. However, the criteria fail to reliably differentiate between pure DLB (approximately 10% to 20% of cases) and the more common mixed forms of DLB and AD (approximately 80% of cases).^{2,3}

BIOMARKERS OF LEWY BODY DEMENTIA

Revisions to DLB diagnostic criteria in 2017 recognized the move to incorporate biomarkers to increase the specificity of clinical diagnoses defined as indicative biomarkers and supportive biomarkers. Although proposed as part of DLB criteria, these same biomarkers can help diagnose PD and PDD. Low dopamine uptake in the striatum on dopaminergic imaging (**FIGURE 4-1**) was a suggestive feature of DLB in the third consensus report but was upgraded to an indicative biomarker in the fourth consensus report.³ There is now a US Food and Drug Administration (FDA)-approved indication of this study for the diagnosis of PD, PDD, and DLB.¹⁶ Other indicative biomarkers include evidence of REM sleep without atonia during polysomnography, supporting the presence of RBD, and low uptake on iodine-123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy. Abnormal MIBG imaging results from the reduction in noradrenergic innervation of the myocardium in LBD; however, this may also be seen in other conditions that affect the autonomic nervous system, such as diabetes, and is rarely used in the United States.¹⁷

KEY POINTS

- Lewy body dementia (LBD) is common but underrecognized and underdiagnosed in routine clinical practice.
- LBD is an umbrella term that encompasses two related clinical diagnoses: Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB).
- Although initial clinical presentations may differ between PDD and DLB, the common underlying pathology of α -synuclein aggregation may present an opportunity to uniformly describe both clinical and pathologic progressions.
- LBD is a male-predominant disorder with a slightly earlier age of onset than Alzheimer disease (AD).
- Criteria for the diagnosis of PDD and DLB exist, with high specificity when applied in clinical and research settings.

CASE 4-1

A 75-year-old man presented with a 2-year history of progressive cognitive decline and behavioral issues. Cognitive testing revealed difficulty with memory with word recall, which improved with recognition and cueing, executive function tasks, visual construction (ie, clock-drawing), and fluctuating attention. Mild mood changes (depression and apathy) were also present. There were frequent visual misperceptions, such as mistaking furniture for people, but it was unclear from the medical history whether there were overt visual hallucinations. On physical examination, there was some mild bradykinesia, but no other parkinsonian features (eg, resting tremor, rigidity) were detected. Given the nonamnestic cognitive presentation, fluctuations, and behavioral changes, a diagnosis of probable dementia with Lewy bodies (DLB) was suspected clinically.

Dopamine transporter single-photon emission computed tomography (SPECT), an indicative biomarker to assist in determining the diagnosis, showed asymmetric decreased uptake of the tracer with evidence of dopaminergic degeneration involving the putamen (**FIGURE 4-1**). The presence of dementia, one core feature (cognitive fluctuations), and no clear presence of another core feature but the presence of an indicative biomarker (positive dopamine transporter SPECT) supported a diagnosis of DLB in alignment with consensus criteria.

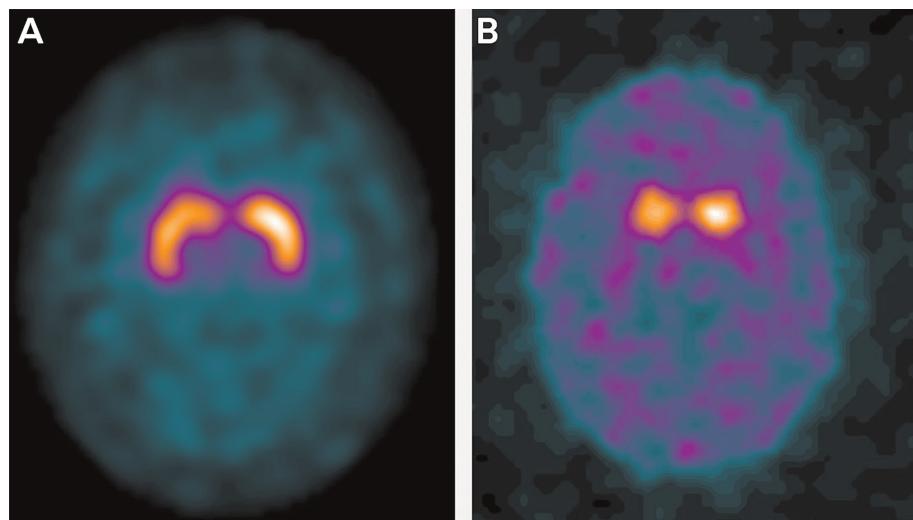


FIGURE 4-1

Dopamine transporter single-photon emission computed tomography (SPECT) from a healthy control patient (A) and a patient with Parkinson disease dementia (B). Note the loss of dopamine transporter uptake in the posterior putamen consistent with dopaminergic degeneration.

COMMENT

This case emphasizes the value of an indicative biomarker when clinical suspicion is high, but the lack of clear core features lessens the clinician's confidence in the diagnosis.

Supportive biomarkers were also proposed that lack sensitivity but offer reasonable specificity. Imaging modalities include MRI and fludeoxyglucose positron emission tomography (FDG-PET). Cortical atrophy is found in both LBD and AD, but relative preservation of the hippocampus and medial temporal lobe structures in LBD can be a helpful sign (FIGURE 4-2).³ For FDG-PET, hypometabolism in the posterior parietal and temporal lobes can be seen in both LBD and AD. However, in LBD, two other markers are helpful when present. Reduced occipital metabolism is more common in patients with LBD than in those with AD, especially in patients experiencing visual hallucinations. This may be accompanied by relative preservation of FDG activity in the posterior cingulate area leading to the cingulate island sign (FIGURE 4-3).¹⁸ Another supportive biomarker is prominent slow-wave activity on EEG. Incorporating biomarkers along with core features increases the confidence of an LBD diagnosis. However, the presence of an abnormal biomarker alone, in the absence of core clinical features, is not sufficient to diagnose probable LBD. Each of these indicative and supportive biomarkers is an indirect measure of disease.³ Biomarkers that specifically target α -synuclein have become available and are discussed later in this article (CASE 4-2).

KEY POINT

- Indicative biomarkers greatly improve the reliability of LBD diagnosis but are largely indirect measures of neuronal injury and neurodegeneration.

MILD COGNITIVE IMPAIRMENT FORMS OF LEWY BODY DEMENTIA

A wide variety of cognitive impairments have been reported in PD early in the course of the disease and, with careful testing, may be present at the time of diagnosis of the movement disorder. The relationship between the onset of initial deficits and subsequent decline to dementia has not been clearly established; however, criteria now exist for defining mild cognitive impairment (MCI) due to PD.¹⁹ Accumulating evidence suggests MCI due to PD is associated with prominent visuospatial, attention, working, and executive impairments that may exist for up to 5 years before formal diagnosis, whereas tests focusing on episodic memory may not be sufficient to detect and quantify the very early cognitive deficits in PD.²⁰ The International Parkinson and Movement Disorders Society reported that MCI due to PD, older age, male sex, and more severe PD motor signs increase the future risk of developing PDD (CASE 4-3).²¹

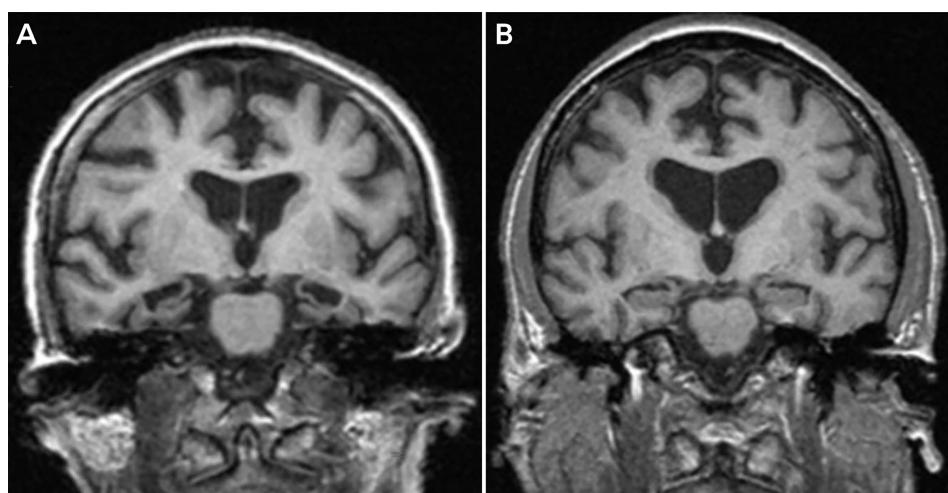


FIGURE 4-2

Coronal MRI views from patients with Alzheimer disease (A) and dementia with Lewy bodies (B). Although cortical atrophy and ventricular dilation are seen in both images, there is less hippocampal atrophy in the patient with Lewy bodies.

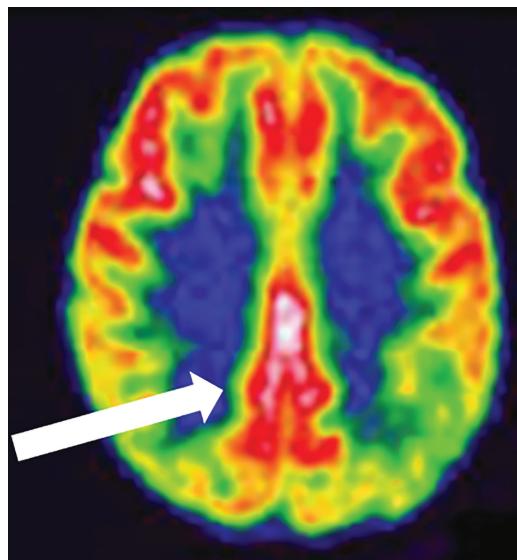


FIGURE 4-3
Fludeoxyglucose positron emission tomography (FDG-PET) from a patient with dementia with Lewy bodies. Note the areas of hypometabolism in the bilateral occipital lobes with preservation of uptake in the posterior cingulate representing a cingulate island sign (arrow).

Prodromal DLB refers to a predementia stage with signs or symptoms indicative of future DLB and encompasses not only cognitive deficits but a mixture of noncognitive clinical features including motor features, sleep disorders, autonomic dysfunction, and neuropsychiatric disturbance.²² Evidence suggests these prodromal features can occur 15 or more years before dementia onset, making it extremely difficult to distinguish early-stage DLB from the first manifestations of other dementias, particularly AD. Identification of prodromal DLB is critical to enabling early detection and advance care planning, using appropriate symptomatic medications, avoiding iatrogenic adverse events, and initiating early intervention with emerging disease-modifying therapies before clinical symptoms become debilitating.²³ The research criteria for prodromal DLB have been operationalized for several subtypes with the most common being an MCI form. Less commonly proposed presentations may include behavioral-onset, delirium-onset, and autonomic-onset forms. MCI due to DLB is characterized by a cognitive concern that can be expressed by the patient, an informant, or the clinician with objective evidence of impairment in one or more cognitive domains and minimally affected activities of daily living. One or more of the core features of DLB are present, and many indicative biomarkers may also be positive at this stage.²²

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CLINICAL FEATURES OF LEWY BODY DEMENTIA

The cognitive features of LBD are typically accompanied by other clinical features, which can serve as useful diagnostic clues.

Neuropsychological Features of Lewy Body Dementia

Neuropsychological profiles of cognitive strengths and weaknesses help define LBD and can distinguish LBD from AD or other forms of cognitive impairment. Cognitive symptoms in patients with LBD include a combination of cortical and subcortical impairment; this is contrasted with a classic cortical profile of impairment predominant in AD. TABLE 4-2 summarizes the neuropsychological deficits differentiating LBD from AD, but each domain is briefly described in the following sections.

EXECUTIVE FUNCTION. Early frontal and executive dysfunction may be predictive of incident LBD and is a core feature of both DLB³ and PDD.^{4,5} Executive functions

KEY POINTS

include cognitive skills such as planning, abstraction, conceptualization, mental flexibility, insight, judgment, self-monitoring, and regulation. The executive dysfunction seen in patients with LBD includes impaired judgment, organization, and planning and may begin in PD up to 5 years before overall cognitive decline²⁰ and can similarly be seen in prodromal DLB.²² Patients with LBD are also more susceptible to distraction and have difficulty engaging in a task and shifting from one task to another. Patients with LBD tend to perform more poorly on Stroop color-word, card-sorting, and phonemic verbal fluency tasks than patients with comparably staged AD.²⁴

ATTENTION. Marked attentional disturbance in patients with LBD may serve as the basis of fluctuating cognition that is characteristic of DLB and PDD.² Consistent group differences are seen in more complex attentional tasks, such as those requiring mental control, visual search and set-shifting, and visual selective attention. On cancellation tasks, patients with LBD perform more poorly than patients with AD. Additionally, patients with LBD tend to perform worse on timed tasks than untimed tasks in similar domains.²⁴

VISUOSPATIAL AND CONSTRUCTION. Visuospatial deficits are common in patients with LBD and represent a very early and sensitive marker.²⁵ Visuospatial changes are varied and can manifest across measures of facial recognition, spatial memory, spatial planning, object-form perception, visual attention, visual orientation, and constructional praxis with greater impairments in LBD than AD on visuospatial and constructional tasks, even brief tests such as pentagon-copying.²⁶ On complex figure-copy tests, performance may be affected by disrupted visuospatial perception and reduced frontal lobe-mediated skills such as organization, planning, and working memory. Furthermore, impairment on constructional tasks likely reflects more than just the motor demands of the tasks and the motor impairment of LBD because these patients also show greater impairment than patients with AD on visual perceptual tasks without significant motor demands, even after controlling for the motor-slowing characteristic in PDD.²¹ Because visual hallucinations are among the strongest predictors of DLB and PDD,^{2,6} the neuropsychological assessment of visual perceptual and constructional functions is important in suspected DLB and PDD and their differentiation from AD.

MEMORY. Patients with LBD generally perform better on episodic memory tasks than patients with AD. Memory may be spared early in LBD and decline as the disease progresses. Memory deficits are the presenting problem in 67% of patients with PDD, which is less than in patients with DLB (94%) and AD (100%).²⁶ The memory deficit in LBD differs from AD in that it tends to be one of retrieval rather than encoding or consolidation and storage, with significant improvement noted with cueing in LBD relative to AD. The more severe amnestic deficits in patients with AD relative to LBD likely reflect the greater burden of neurofibrillary tangles in the entorhinal cortex and surrounding medial temporal lobe regions in patients with AD. Patients with mixed AD and LBD tend to have worse performance in memory tasks than individuals with pure LBD pathology.²⁵ Examples are presented in **CASE 4-1** and **CASE 4-2**.

- Prodromal stages of PDD and DLB exist, and diagnostic criteria are available to assist in their recognition.

- Patients with LBD tend to perform more poorly on Stroop color-word, card-sorting, and phonemic verbal fluency tasks than patients with comparably staged AD.

- The memory deficit in LBD differs from AD in that it tends to be one of retrieval rather than encoding or consolidation and storage, with significant improvement noted with cueing in LBD relative to AD.

- The cognitive and neuropsychiatric profile of LBD is distinct from AD and can assist in the diagnosis.

LANGUAGE. Patients with DLB generally show milder deficits than patients with AD on measures of confrontation naming, which become more severe with disease progression. Patients with AD are more likely to make semantic errors on confrontation naming testing than patients with DLB. Measures of generative fluency have also proven to be useful in differentiating AD from DLB. Patients with DLB are equally impaired in category and letter fluency, whereas patients with AD perform significantly better with letters than categories.²⁴ This may be related to underlying mechanisms: Whereas patients with AD have degraded semantic networks or retrieval difficulties affecting semantic networks, attentional and executive impairments likely contribute to the difficulties with word search and retrieval in patients with DLB. The language impairments in PDD also tend to be mild, with aphasia being a rare occurrence. Verbal and semantic fluency impairments are reliably observed in patients with PDD; however, they may not manifest until after other cognitive domains show clinically detectable decline.²⁰ Additional features of speech and language

CASE 4-2

An 80-year-old woman presented with a 3-year history of progressive memory decline, originally diagnosed by her primary care provider as Alzheimer disease (AD) who started her on donepezil. During a brief hospitalization for treatment of a urinary tract infection, she experienced an episode of delirium and hallucinations, which was treated with low-dose haloperidol. Although her neurologic examination was reported as nonfocal, after the second dose of haloperidol, the patient developed significant parkinsonism. Haloperidol was discontinued, and the delirium and parkinsonism resolved over 3 days. On referral to the neurologist, there was no parkinsonism present, but her blood pressure changed from 136/84 mm Hg sitting to 110/78 mm Hg standing with some complaints of dizziness and lightheadedness. Mental status testing revealed moderate episodic memory impairment without benefits from cueing, mild deficits in orientation to date and day of the week, mild executive dysfunction, and impaired clock-drawing. The family was interested in a potential treatment with monoclonal antibodies against amyloid- β protein that was recently approved for the treatment of AD, but the recent events and the findings from the office visit raised suspicion of dementia with Lewy bodies (DLB) rather than AD as a diagnosis. A skin biopsy detected the presence of α -synuclein pathology and showed phosphorylated α -synuclein deposition in two of three sites, supporting a DLB diagnosis (**FIGURE 4-4**). This finding enabled the neurologist to have an informed discussion about the diagnosis and assist in treatment decisions.

COMMENT

This case provides an example of how newly emerging biomarkers can increase confidence in a DLB diagnosis. Although the original diagnosis was AD, the neurologist suspected possible DLB given the presence of many supportive features (ie, orthostatic hypotension, neuroleptic sensitivity) with the absence of clear core features.

impairment in patients with PDD include decreased content of spontaneous speech, impaired naming, shorter phrase length, and hypokinetic dysarthria.²

Behavioral and Neuropsychiatric Features

Neuropsychiatric features such as hallucinations and delusions, elicited primarily via informant interviews, are common in patients with LBD. Approximately 61% of patients with PD exhibit neuropsychiatric disturbances. The most common features are depression (38%), hallucinations (27%), delusions (6%), anxiety (40%), sleep disturbances (60% to 90%), and sexual disorders (5% to 10%).^{2,27} The presence of visual hallucinations is the strongest single predictor of developing dementia in patients with PD and increases the risk of developing dementia 20-fold.^{2,27} Visual hallucinations tend to be well formed and detailed and most commonly involve anonymous people (often described by the patient as dysmorphic or small), although they may also involve family members, animals, body parts, and machines. Hallucinations can occur in other modalities,

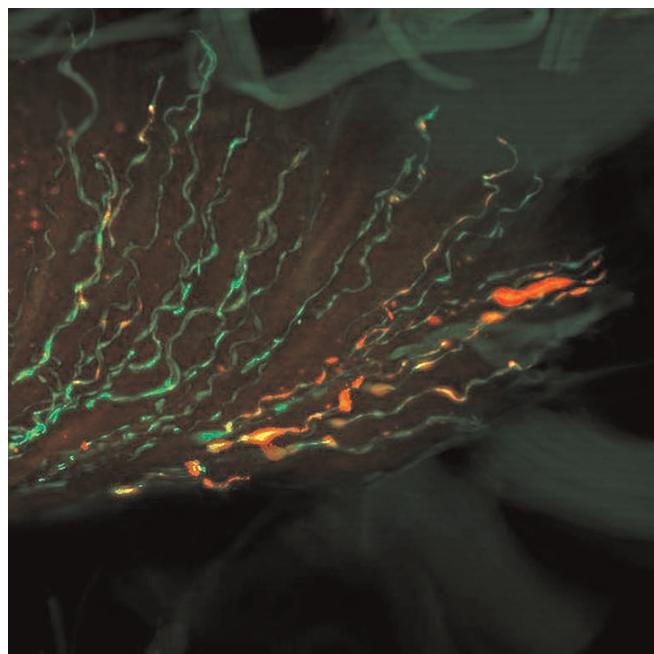


FIGURE 4-4
A skin biopsy from a patient with dementia with Lewy bodies. The fluorescent green signals depict peripheral nerves with the fluorescent red signal representing positive staining for phosphorylated α -synuclein indicating a positive biopsy.

including auditory, tactile, and olfactory. Patients with DLB are more likely to show psychiatric symptoms and have more functional impairment at the time of initial evaluation than patients with AD. Visual hallucinations are typically present early in the disease and do not diminish in later periods. Hallucinations and delusions are generally more frequently present in individuals with pure Lewy body pathology or mixed Lewy body and AD pathology than pure AD

CASE 4-3

A 61-year-old man with a 2-year history of mild motor slowing and gait abnormalities and more recent cognitive change was diagnosed with mild cognitive impairment (MCI) by his primary care physician. He had a long-standing history of constipation and several years of changes in olfaction. His wife reported that he had night terrors (shouting and thrashing in his sleep) that occurred several times per month, which on further questioning raised suspicion of rapid eye movement (REM) sleep behavior disorder (RBD) for the past 5 years. His mild memory issues did not interfere with his everyday functioning. The patient and his wife read about Lewy body dementia on the internet and wondered whether he might have this and if he would be eligible for a new clinical trial offered at the local university.

On neurologic examination, he had a decrease in spontaneous facial expression and blink rate, mild asymmetric bradykinesia, left-sided increased tone without cogwheeling, and a decreased arm swing on the left. There was no resting tremor or postural instability. On mental status testing, the patient scored 25 on the Montreal Cognitive Assessment (MoCA), missing 2 of 5 words on delayed recall, had trouble with the clock-drawing and cube-drawing, and had one mistake in serial subtraction. Given that the movement disorder began approximately 2 years before the cognitive symptoms and that symptoms of RBD, constipation, and anosmia began before the movement disorder, there was a high suspicion of a diagnosis of MCI due to Parkinson disease. Dopamine transporter single-photon emission computed tomography (SPECT), ordered to assist in the confirmation of dopaminergic degeneration, showed bilateral putamen decreased uptake. A polysomnogram, ordered to evaluate for RBD, demonstrated REM sleep without atonia, confirming RBD. Confident of a diagnosis of MCI due to Parkinson disease and after discussion with the patient, the neurologist initiated treatment for the movement disorder with carbidopa/levodopa and RBD with melatonin and chose to wait to address the mild cognitive symptoms at the follow-up visit.

COMMENT

Although MCI was the diagnosis the patient was referred for, on careful evaluation, both parkinsonism and RBD were suspected. The presence of two indicative biomarkers confirmed the diagnoses and guided treatment decisions. Because the movement disorder was the more disabling symptom and the cognitive symptoms were mild and not interfering with everyday functioning, a patient-centered treatment approach was made possible.

pathology at autopsy when presenting at their initial clinical evaluation.²⁴ Delusions also occur in 56% of patients with DLB at first presentation and 65% at some point in their illness. Delusions tend to be more common in patients with DLB than in those with PDD or AD. Paranoia, Capgras phenomenon (believing individuals are replaced by an identical imposter), and phantom boarder (unseen individuals residing in one's home) are among the most common content of the delusions.^{2,3} Capgras syndrome usually accompanies visual hallucinations and anxiety in patients with DLB. Misidentification syndromes appear to be particularly prevalent in LBD, occurring in up to 40% of patients, compared with 10% in patients with AD. Depression is common in patients with LBD, and there is equivocal evidence as to whether base rates of depressed mood and major depression differ between these disorders and AD.² A history of depression has been reported in 58% of people with PDD, 50% of patients with DLB, and 14% of patients with AD at autopsy.²⁸ The incidence of depression appears to be unrelated to the presence or absence of dementia or the severity of motor impairment.³ Anxiety and apathy co-occur with depression in 40% and 15%, respectively, of patients with LBD.

Cognitive Fluctuations

Fluctuations in cognition are one of the hallmarks of DLB, present in 15% to 80% of patients with DLB.²⁹ Cognitive fluctuations are also common in patients with PDD and may be as frequent as in DLB.² Fluctuations are uncommon in patients with AD. These fluctuations often involve the waxing and waning of cognition, attention, concentration, functional abilities, or arousal in the

Cognitive Test Performance in Patients With Lewy Body Dementia Compared With Alzheimer Disease

TABLE 4-2

Domains	Level of impairment	
	Lewy body dementia	Alzheimer disease
Episodic memory		
Free recall	Moderate	Marked
Recognition	None or minimal	Marked
Prompts or cues	Benefit	No benefit
Intrusions	Marked	Marked
Semantic memory	Mild	Moderate
Procedural memory	Mild	None or minimal
Working memory	Marked	Moderate
Insight	Mild	Marked
Attention	Marked	Moderate
Executive function	Marked	Moderate
Visuospatial skills	Marked	Moderate

absence of any clear precipitant. They are often described as episodes of behavioral confusion, inattention, hypersomnolence, and incoherent speech alternating with episodes of lucidity and capable task performance. Patients may be described as staring into space or dazed, and the episodes can last minutes to days, varying from alertness to stupor. In an extreme form of these fluctuations, patients are found mute and unresponsive for a few minutes. Several scales have been developed, including the Clinician Assessment of Fluctuation³⁰ and the Mayo Fluctuations Questionnaire.²⁹

Autonomic Dysfunction

Autonomic dysfunction is a common clinical sign in patients with LBD.⁶ Autonomic features can occur at any point in the course of LBD. Symptomatic orthostasis is probably the most serious manifestation of autonomic dysfunction, observed in approximately 15% of patients. Other features include decreased sweating, excessive salivation (sialorrhea), seborrhea, heat intolerance, gastroparesis and urinary dysfunction, constipation or diarrhea, and erectile dysfunction or impotence. Constipation may precede any cognitive or motor symptoms by more than a decade. Patients with LBD also have a higher frequency of carotid hypersensitivity than older patients or patients with AD. An example of an autonomic checklist is highlighted in **CASE 4-2**.

Sleep Disorders

Many patients with LBD have parasomnias. The most common is RBD, which tends to begin concurrently with or after the onset of parkinsonism or dementia.³¹ RBD is marked by a lack of normal muscle atonia that prevents movements (other than eye movements) during REM sleep in the presence of excessive activity while dreaming; this can result in vocalizations and sometimes wildly violent behavior. Patients may be unaware of the disorder, and the history is, therefore, often dependent on the patient's bed partner. RBD is most commonly found in men in their fifties and may precede the clinical signs associated with LBD by many years. Other sleep disturbances reported include excessive daytime sleepiness, periodic leg movements of sleep, and restless leg syndrome.^{6,31} It is advisable to also assess for symptoms of obstructive sleep apnea as snoring, choking, or other symptoms can be mistaken for RBD. RBD as a presenting symptom is demonstrated in **CASE 4-3**.

Neuroleptic Sensitivity

Neuroleptic sensitivity is very common in patients with DLB; reactions are observed in 30% to 50% of these patients and are characterized by a sudden onset of impaired alertness, acute confusion, psychotic episodes, and an exacerbation of parkinsonism symptoms such as rigidity and immobility.³ In some cases, these reactions can lead to death within several days. There is a reported 58% frequency of neuroleptic sensitivity to olanzapine, with lower rates with clozapine (11%) and thioridazine (6%) in patients with DLB and in up to 40% of patients with PDD.³² These data support the notion of unacceptable neuroleptic safety in patients with LBD. An example is discussed in **CASE 4-2**.

IMPROVING THE CLINICAL DIAGNOSIS OF LEWY BODY DEMENTIA

At present, LBD remains a challenge to diagnose, particularly outside of specialty centers. This leads to long delays in diagnosis resulting in significant burden

on patients and their families and care partners, increases the probability of inappropriate treatments, and hinders research. Although the DLB and PDD consensus criteria have excellent specificity, until recently, there has been no easy standardized way to assess signs and symptoms or assist clinicians and researchers in making LBD diagnoses. This has changed with the creation and publication of several measures: the Lewy Body Composite Risk Score,³³ the LBD module for the Uniform Data Set of the National Institute of Aging Alzheimer Disease Center program,⁶ and the assessment toolkit for Lewy body dementia (from the DIAMOND Lewy study) created in the United Kingdom.³³ The Lewy Body Composite Risk Score was validated against the Clinical Dementia Rating and gold standard measures of cognition, motor, function, and behavior with scores of 3 or greater suggesting that Lewy body pathology is a likely cause of cognitive impairment (**TABLE 4-3**).³¹ The LBD module (LBD-MOD) was designed to evaluate the clinical, cognitive, and behavioral symptoms associated with DLB. Both the Lewy Body Composite Risk Score and the LBD-MOD differentiate (1) LBD from AD; (2) LBD from other dementias; and (3) MCI due to LBD from MCI due to AD. LBD differs from AD in extrapyramidal symptoms, hallucinations, activities of daily living, apathy, autonomic features, REM sleep behaviors, daytime sleepiness, cognitive fluctuations, timed attention tasks, episodic memory, and visual perception. MCI due to LBD differs from MCI due to AD in extrapyramidal features, mood, autonomic features, fluctuations, timed attention tasks, and visual perception.⁶ The DIAMOND Lewy toolkits are two complementary instruments to assist in the recognition and diagnosis of PDD (designed for non-neurologists) and DLB

Lewy Body Composite Risk Score^a

TABLE 4-3

Please rate the following symptoms as being present or absent at least 3 times over the past 6 months. Does the patient...		Yes	No
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?			
Have rigidity (with or without cogwheeling) on passive range of motion in any of the four extremities?			
Have a loss of postural stability (balance) with or without frequent falls?			
Have a tremor at rest in any of the four extremities or head?			
Have excessive daytime sleepiness or seem drowsy and lethargic when awake?			
Have episodes of illogical thinking or incoherent, random thoughts?			
Have frequent staring spells or periods of blank looks?			
Have visual hallucinations (ie, see things not really there)?			
Appear to act out his or her dreams (eg, kick, punch, thrash, shout, or scream)?			
Have orthostatic hypotension or other signs of autonomic insufficiency?			
Total Score^b			

^a Modified with permission from Galvin JE, Alzheimers Dement (Amst).³³ © 2015 The Author.

^b One point is scored for each "Yes," with a total score of 3 or greater consistent with an increased risk of Lewy bodies being present and contributing to the clinical picture.

(designed for nonpsychiatrists) in clinical settings.³⁴ In a pilot randomized controlled trial, the introduction of these assessment toolkits was associated with increased diagnostic rates of DLB but not PDD.³⁵ These LBD tools can identify patients with an increased diagnostic probability that Lewy body pathology is contributing to the dementia syndrome and should improve clinical detection, diagnosis, and treatment, as well as case ascertainment to enhance enrollment for clinical trials.

NEUROPATHOLOGY

There is no pathologic distinction between PDD and DLB. The core pathologic features of LBD are Lewy bodies and Lewy neurites (FIGURE 4-5). These can occur in the brainstem nuclei, amygdala, limbic-paralimbic cortices, basal ganglia, and cerebral cortex but also may be found in the peripheral nervous system, such as the sympathetic chain and enteric nerve plexus.³⁶ The primary building block of Lewy bodies is the presynaptic protein α -synuclein, although other constituents have been described. From a morphologic perspective, Lewy bodies can be

divided into two types: brainstem and cortical. Brainstem Lewy bodies are spherical intraneuronal cytoplasmic inclusions characterized by a hyaline eosinophilic core, concentric lamellar band, and a pale halo and are typically easy to identify by standard histologic methods. Cortical Lewy bodies occur in limbic and neocortical regions and are more difficult to detect, requiring specific immunohistochemistry with antibodies against the α -synuclein protein. A substantial proportion of patients with LBD (DLB more than PDD) also have concomitant amyloid pathology, with many fulfilling pathologic criteria for AD. Neurofibrillary tangles, however, tend to be less common in patients with LBD than AD.³ Many patients with LBD also have microvascular changes that could contribute to symptom presentation.³⁷

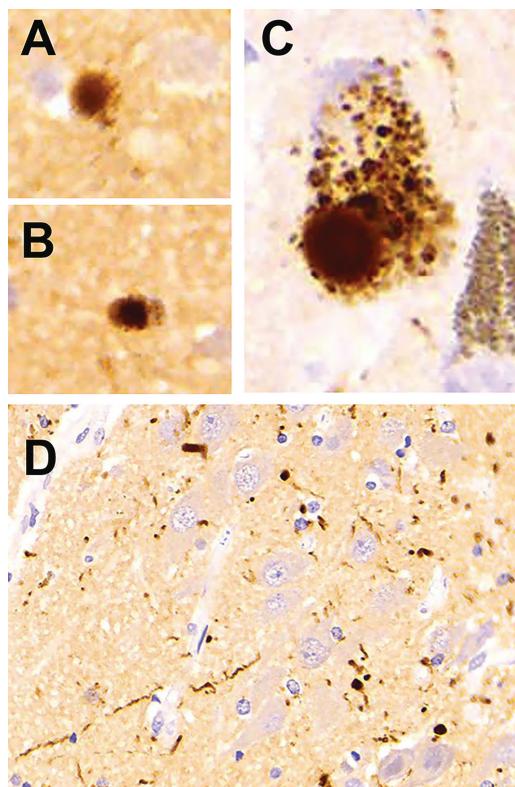


FIGURE 4-5
Lewy body dementia pathology and biomarkers.
A, B, Photomicrographs of cortical Lewy bodies with antibodies against α -synuclein (40x magnification). **C,** A nigral Lewy body within a dopaminergic neuron with antibodies against α -synuclein (40x magnification). **D,** A lower field view of Lewy neurites in the CA2/CA3 region of the hippocampus with antibodies against α -synuclein (20x magnification).

GENETICS

As with many other adult-onset diseases, LBD is commonly labeled as sporadic even if the disease is mendelian, simply

because affected family members have either died or have not reached the age of onset. In DLB, there is, however, the added component of how difficult an accurate diagnosis can be, often leading to familial forms not being recognized because family members receive different diagnoses. In early studies with discordant twin pairs, DLB was thought not to have a strong genetic component, whereas more than 90 genetic loci play a role in PD. Many patients with variations in SNCA (the gene that encodes α -synuclein) show neurologic features beyond typical idiopathic PD, such as cognitive decline, dementia, hallucinations, or autonomic dysfunction. Two genes have been shown to be risk factors for LBD: *APOE* and *GBA*. The β_4 allele of *APOE* has an intermediate frequency in DLB when compared with PD and AD. The *GBA* gene encodes the lysosomal enzyme glucocerebrosidase, responsible for breaking down the chemical glucocerebroside, an intermediate in glycolipid metabolism. Homozygous variations in *GBA* cause the lysosomal storage disorder Gaucher disease, whereas heterozygous variations were shown to increase the risk for PD and DLB by about fivefold.^{38,39} A more recent study focusing on LBD replicated the same three signals (*APOE*, *GBA*, and *SNCA*) and found evidence for two additional loci: *BIN1* and *TMEM175*.⁴⁰

KEY POINT

- Although they are not specifically diagnostic, autonomic and constitutional symptoms of LBD are less common in patients with AD and can assist in the diagnosis.

PET IMAGING

To date, there are no PET tracers that bind to α -synuclein aggregates available for clinical use, but several companies are developing ligands. However, there is interest in conducting PET studies using ligands that characterize AD pathology commonly found in LBD.

Amyloid imaging has emerged as an important neuroimaging tool in studies of brain aging and dementia. Three commercially available tracers (florbetapir, florbetaben, flutemetamol) are available. These PET ligands do not significantly bind to other protein aggregates such as neurofibrillary tangles or Lewy bodies and, hence, may be useful for diagnostically discriminating between AD and non–amyloid- β (A β) dementias. Cortical A β burden tends to be higher in DLB than in PDD but slightly lower than in AD. A β PET imaging may prove to be useful to distinguish AD from PDD but less so AD from DLB because of frequent comorbid pathology.⁴¹ A β PET imaging is likely less useful than dopamine SPECT in MCI due to PD and DLB.⁴²

More recently, tau ligands for PET have become available. Although tau burden tends to be lower in DLB and PDD, it is commonly observed at autopsy. A 2023 study of cognitively healthy controls, patients with AD, and patients with DLB found that 43% of DLB cases with amyloid were tau positive, whereas 8% of DLB cases without amyloid were tau positive with flortaucipir.⁴³ An earlier cross-sectional study demonstrated that tau imaging in individuals with DLB was highly variable but greater than that seen in controls, most notably in the inferior temporal gyrus and precuneus.⁴³ Less tau binding was seen in patients with PDD than in patients with DLB but in the same regions. The imaging in patients with PD without dementia was similar to controls.

α -SYNUCLEIN BIOMARKERS

There is currently great interest in developing biomarkers characterizing α -synuclein aggregation. Several potential sources of samples include CSF, skin, plasma, and PET.

CSF

In patients with LBD, CSF levels of α -synuclein are typically reduced, whereas in patients with AD, they are elevated. However, elevated levels of CSF α -synuclein have also been described in patients with DLB when compared with controls and patients with AD, which may represent a competitive state between aggregation of α -synuclein into Lewy bodies and release of the protein from degenerating synapses.⁴⁴ Additionally, the fact that current α -synuclein assays measure total amounts of the protein and not Lewy body–specific forms further complicates the use of this protein as a biomarker for LBD, as does the fact that α -synuclein is expressed in red blood cells, suggesting that sample collection methods and efficacy may play an important role in the assessment of α -synuclein.⁴⁴⁻⁴⁶

CSF SEEDING STUDIES. α -Synuclein can spread from cell to cell and accumulate in a prionlike fashion.⁴⁷ This capacity for self-propagation has enabled the development of seed amplification assays that can detect α -synuclein aggregates in various biospecimens including brain tissue, CSF, skin, and olfactory mucosa. Real-time quaking-induced conversion and protein-misfolding cyclic amplification assays have evolved as ultrasensitive, specific, and relatively practical methods for detecting aggregated forms of α -synuclein from patients with LBD.⁴⁵ An FDA-cleared commercial assay has become available with reported sensitivities from 92% to 95% and specificities from 95% to 97% in distinguishing LBD from non–Lewy body disorders.^{48,49} Recent evidence suggests the commercial assay works very well in cases with a high burden of cortical and limbic Lewy bodies but with lower sensitivity in amygdala-only and brainstem-only cases.⁵⁰ The seeding assays may have lower sensitivity and specificity in the prodromal stages such as RBD.⁵¹ At present, these assays are largely qualitative, but there are efforts to develop quantitative measures that could be used to track progression and response to medications.

Skin

Another potential source of tissue to detect α -synuclein is the skin. A dermal biopsy provides sweat and sebaceous gland tissue as well as intraepidermal and subdermal nerve fibers. Immunohistochemical approaches using antibodies against α -synuclein and phosphorylated α -synuclein can show colocalization of Lewy pathology in glandular tissue and nerve fibers (**FIGURE 4-4**).^{52,53} An FDA-cleared commercial assay now available examines phosphorylated α -synuclein at serine 129 with 80% sensitivity and specificity approaching 100%.⁵⁴ An example of the potential utility of the skin biopsy is demonstrated in **CASE 4-2**.

Plasma

Several platforms are being developed to measure α -synuclein and phosphorylated α -synuclein in plasma using immunohistochemical, mass spectrometry, and immunomagnetic reduction techniques. Several publications show immunomagnetic reduction approaches to measuring plasma α -synuclein and phosphorylated α -synuclein to discriminate patients with LBD from healthy controls and other neurodegenerative diseases that overcome challenges of interference from other plasma components, including hemoglobin with a level of detection in the femtomolar range.^{55,56} Plasma levels of total α -synuclein and

phosphorylated α -synuclein were significantly higher in patients with PD compared with controls, as was the ratio of phosphorylated to nonphosphorylated synuclein. Phosphorylated α -synuclein levels were higher with more advanced Hoehn and Yahr motor stages and correlated with International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale part III scores. Preliminary evidence suggests that total α -synuclein predicts cognitive decline whereas phosphorylated α -synuclein predicts motor progression. However, most other laboratories have had difficulty developing blood-based α -synuclein markers, so it will likely be some time before these markers are available clinically.

PET

There are currently no clinically available PET ligands for α -synuclein, but 2023 research reports suggest that several possible tracers look promising and show good in vitro affinity and specificity for pathologic forms of α -synuclein in neurons from patients with PD and oligodendrocytes in patients with multiple system atrophy.^{57,58} The PET ligand [¹⁸F]ACI-12589 demonstrated good binding in the cerebellar white matter of patients with multiple system atrophy with limited binding in patients with PD.⁵⁷ Other libraries of PET tracers are being developed with early evidence for selective binding to α -synuclein pathology and the ability to cross the blood-brain barrier.⁵⁸

THERAPEUTIC APPROACHES

There are few medications specifically approved for the treatment of LBD; however, treatment decisions (often off-label) can be guided by evidence of efficacy in the literature. These symptomatic approaches can help manage symptoms, but clinical benefits must be weighed in consideration of commonly occurring adverse effects.

Cognitive Symptoms

Acetylcholinesterase inhibitors may be especially useful in the treatment of LBD. These medications, including donepezil, rivastigmine, and galantamine, block the breakdown of acetylcholine within the synapse, thereby prolonging its effect on postsynaptic receptors. Acetylcholinesterase inhibitors are generally well-tolerated at their standard dosing and may be more effective in patients with LBD than those with AD because of early and prominent central nervous system cholinergic dysfunction in this group.³ Independent clinical studies, as well as meta-analyses, of acetylcholinesterase inhibitor treatment using donepezil, galantamine, and rivastigmine suggest that acetylcholinesterase inhibitors can improve cognitive and neuropsychiatric measures, without significant increases in extrapyramidal symptoms.⁵⁹ Acetylcholinesterase inhibitors are FDA approved in the United States for the treatment of PDD and are often used off-label in the treatment of DLB. The primary side effects of acetylcholinesterase inhibitor treatment are gastrointestinal (eg, nausea, vomiting, diarrhea, anorexia, and weight loss). Other side effects can include insomnia, vivid dreams, leg cramps, and urinary frequency. The N-methyl-D-aspartate (NMDA) antagonist memantine, another medication approved for use in the treatment of AD, has not yet been tested in large, randomized, controlled studies in patients with PDD or DLB. Reported results have been variable in a few case reports or case series in patients with PDD and DLB.⁵⁹

Motor Symptoms

Carbidopa/levodopa is commonly used to treat the motor symptoms of PD and is frequently continued in patients with PDD, although the dose may need to be adjusted for behavioral symptoms and psychosis. Although there are no controlled clinical trials for the treatment of motor features in patients with DLB, case series suggest improvement of motor symptoms with levodopa.³ Both carbidopa/levodopa and dopamine agonists can be associated with drug-induced psychosis.⁵⁹ Carbidopa/levodopa is almost universally used in patients with PD and continued as cognitive impairment develops. However, in patients with DLB, given the increased risk of psychosis and because the motor impairments may be mild, clinicians often treat parkinsonism only if the motor symptoms interfere with function. Other PD medications such as amantadine, catechol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists with high selectivity for the D₂ receptor, and anticholinergics tend to exacerbate cognitive and behavioral impairment and should ideally be avoided.⁵⁹

Behavioral Symptoms

Behavioral symptoms such as hallucinations, delusions, mood disorders (eg, anxiety, depression, apathy), and agitation or aggression frequently occur in patients with LBD. Nonpharmacologic treatment approaches should be considered first, including evaluating for physical ailments that may be provoking behavioral disturbances (eg, fecal impaction, pain, or decubitus ulcers).⁶⁰ Avoidance or reduction of doses of other medications that can potentially cause agitation should also be attempted. When medications are needed to modify behaviors, they should be used at the lowest dose for the shortest duration possible. Benzodiazepines should be avoided given their risk of sedation and paradoxical agitation. Tricyclic antidepressants should be avoided because of their anticholinergic effects. It is worth noting that hallucinations that are nonthreatening to the patient and do not disturb function may not require any pharmacologic intervention.^{59,60} Classic neuroleptics (such as haloperidol) are best avoided in patients with LBD as they may worsen motor function and even potentially result in life-threatening neuroleptic sensitivity.³

Experience with atypical antipsychotics in patients with LBD has been mixed. Quetiapine is often used as the first line of therapy although the literature supporting this option is weak. Clozapine has long been used for PD psychosis and may benefit patients with LBD; however, requirements for close monitoring for hematopoietic effects make it difficult to use. Risperidone and olanzapine at low doses are usually well tolerated; however, motor deterioration may occur with higher doses and in more advanced cases. Pimavanserin, a novel 5-hydroxytryptamine, serotonin receptor 2A inverse agonist, reduces delusions and hallucinations in patients with PDD⁶¹ and has been approved by the FDA for the treatment of psychosis in patients with PD. Its efficacy in treating neuropsychiatric symptoms in patients with DLB has, however, not been confirmed.⁶² Aripiprazole and brexpiprazole have not been well studied in LBD. Although several case reports and small series suggest possible benefits,⁶³ because of high antagonist or partial agonist action on dopamine receptors, these agents may not be well tolerated given their high risk for extrapyramidal side effects. As a class, antipsychotics may be poorly tolerated due to excessive sedation, orthostatic hypotension, and paradoxical responses.

Sleep Disturbances

RBD is a core feature of LBD. Melatonin is usually the first line of treatment at 3 mg to 9 mg nightly with maximal doses of 15 mg to 20 mg.⁶⁴ Clonazepam, a long-acting benzodiazepine is the second-line therapy usually started at the lowest dose possible because of its negative impact on falls, dizziness, drowsiness, and confusion.⁶² Most evidence supporting the use of melatonin and clonazepam comes from case studies rather than placebo-controlled trials.^{59,65} Other sleep disorders that can be present and should be managed concurrently include obstructive sleep apnea (which sometimes can be confused for RBD-like motor activity), restless leg syndrome, and periodic leg movements of sleep.³¹

Autonomic Dysfunction

Autonomic dysfunction is usually treated with standard approaches depending on the symptom and extent of discomfort in the patient. Orthostatic hypotension occurs in about 45% of patients with DLB⁶⁶; midodrine, droxidopa, and fludrocortisone are the most used medications.⁶⁷ For urinary symptoms, such as overactive bladder, β_3 agonists such as mirabegron can reduce symptoms with fewer adverse cognitive effects compared with antimuscarinic medications (ie, trospium, oxybutynin), which should be avoided because they tend to exacerbate cognitive deficits.^{59,68}

EMERGING CONTROVERSIES

Both PDD and DLB are defined by their clinical features and initial presentations with α -synuclein pathology used as a gold standard to determine the definitive diagnosis. Similar to movements in AD to define the disease by the underlying proteinopathy, a 2024 article has suggested redefining PD, PDD, and DLB based on biology as neuronal α -synuclein disease rather than as clinical syndromes.¹⁵ An integrated staging system has been proposed that considers neuronal α -synuclein pathology (S) defined by CSF seeding studies as the primary anchor with dopaminergic degeneration (D) defined by abnormal dopamine transporter SPECT as the secondary anchor. This staging paradigm proposes S and D anchors and degree of functional impairment to define nine stages (0, 1A, 1B, 2A, 2B, and 3 through 6).

This staging paradigm recognizes that although many individuals develop changes in the D anchor before functional impairment, symptoms may be present in individuals with only the S anchor. Further, the staging recognizes that the D anchor is not specific for neuronal α -synuclein disease.¹⁵

Advantages of this proposed research staging system is to provide a research framework for testing hypotheses and therapeutic development much in the way the amyloid-tau-neurodegeneration framework has advanced efforts in AD.⁶⁹ Using an integrated staging system might also reduce heterogeneity in clinical trials by requiring a biological definition rather than clinical phenotypes that can introduce variability and imprecision.¹⁵ A major disadvantage is that individuals with DLB, especially in the prodromal stages, may not have parkinsonism and up to 25% never have abnormal dopamine transporter SPECT.⁷⁰ Under the current proposed staging structure, a patient with dementia, hallucinations, and fluctuations could be quite impaired clinically and functionally but be rated as 2B or less, inconsistent with the obvious clinical picture. Further validation of these research criteria is needed with consideration of dropping the D anchor or replacing it with a

KEY POINTS

- Biomarkers specific for α -synuclein pathology are currently available in CSF and skin and are being developed in plasma and positron emission tomography (PET).
- In patients with LBD, hallucinations that are nonthreatening to the patient and do not disturb function may not require any pharmacologic intervention.
- There are no specific approved treatments for most symptoms of LBD, but clinical experience and case series inform off-label use of medications for individual symptoms.

more LBD-specific marker of neuronal injury and neurodegeneration. A similar call for validation was highlighted in a 2024 perspective article by the Movement Disorder Society.⁷¹

CONCLUSION

Lewy body disorders are the second most common cause of neurodegenerative dementia after AD and are characterized by a distinctive clinical picture of cognitive, behavioral, affective, movement, and autonomic symptoms. PDD and DLB have very similar neuropsychological profiles that better distinguish them from AD than from each other. PDD and DLB share common pathology with accumulation of α -synuclein pathology in the form of Lewy bodies and Lewy neurites in neocortical, limbic, subcortical, and brainstem regions that explain, in part, the core features of LBD. There is ongoing controversy as to whether PDD and DLB should continue to be considered separate conditions whose differences in presentation reflect the emergence of regional pathology versus grouping them as neuronal synuclein diseases. Although these debates linger, continued use of the 1-year rule is still useful, both in research and in clinical practice. At some point, the 1-year rule may be replaced by a more objective integrated staging system. Development of staging systems combined with deep phenotypic characterization of prodromal stages of disease (eg, anosmia, RBD) will likely lead to advances in understanding the disease mechanisms and open new avenues for drug development. There is emerging research on the use of indicative biomarkers to improve the diagnosis of LBD, but each indicative biomarker is an indirect measure of neuronal injury and neurodegeneration. Recent advances in direct measurement of α -synuclein in CSF, skin, plasma, and PET may be transformative. These advances, along with the use of standardized measurement tools, will help improve diagnosis rates in clinical practice, enrich clinical trial recruitment, and aid in the development, testing, and validation of new therapeutics.

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USEFUL WEBSITES

The following websites contain useful patient and care partner information and resources that are content specific for LBD. Some sites also provide lists of providers with expertise in LBD.

ALZHEIMER DISEASE EDUCATION AND REFERRAL CENTER
alzheimers.gov

AMERICAN PARKINSON DISEASE ASSOCIATION
apdaparkinson.org

LBD RESEARCH CENTERS OF EXCELLENCE
lbda.org/research/research-centers-of-excellence

LEWY BODY DEMENTIA ASSOCIATION
wlbda.org

LEWY BODY DEMENTIA RESOURCE CENTER
lewybodyresourcecenter.org

MICHAEL J. FOX FOUNDATION
michaeljfox.org

PARKINSON FOUNDATION
parkinson.org

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DISCLOSURE

Continued from page 1673

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Vascular Cognitive Impairment

REVIEW ARTICLE



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By Lisa C. Silbert, MD, MCR, FAAN

ABSTRACT

OBJECTIVE: Vascular cognitive impairment is a major contributor to age-associated cognitive decline, both independently and as a contributor to mixed dementia syndromes. This article reviews the current understanding of how vascular dysfunction contributes to cognitive impairment and dementia risk in older individuals and includes updated diagnostic criteria and treatment recommendations.

LATEST DEVELOPMENTS: Clinical and research criteria have been evolving to more accurately determine the full prevalence of vascular cognitive impairment. The Boston Criteria version 2.0 for cerebral amyloid angiopathy now includes multiple punctate MRI T2 white matter hyperintensities and MR-visible perivascular spaces in addition to previously described T2* hemorrhagic signatures. MR-visible perivascular spaces are associated with both vascular cognitive impairment and Alzheimer disease, potentially linking cerebrovascular dysfunction to neurodegenerative disorders through its role in brain waste clearance. The American Heart Association's goal for cardiovascular health promotion, "Life's Essential 8," has been updated to include sleep health and acknowledges psychological well-being and social determinants of health as fundamental components necessary to achieve optimal cardiovascular health for all adults.

ESSENTIAL POINTS: Vascular cognitive impairment is a common and often underrecognized contributor to cognitive impairment in older individuals, with heterogeneous etiologies requiring individualized treatment strategies. Effective cerebrovascular disease risk factor modification starting in midlife is critical to reducing the risk of Alzheimer disease and related dementias, with the goal of preventing vascular brain injury and maintaining cognitive reserve in the presence of nonvascular age-related brain pathologies.

INTRODUCTION

The term *atherosclerotic dementia* was coined by Kraepelin in 1896 to describe most older-onset dementias. To this day, vascular contributions to cognitive impairment and dementia are recognized as playing a significant role in age-related cognitive impairment, both independently and as a component of mixed-etiology dementia syndromes. This article reviews the terminology, prevalence, common clinical

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UNLABELED USE OF PRODUCTS/ INVESTIGATIONAL USE

DISCLOSURE:

Dr Silbert discusses the off-label use of memantine and donepezil for the treatment of vascular dementia.

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presentations, imaging findings, and etiologies of vascular cognitive impairment, as well as the current understanding of how dysfunction of the cerebral vasculature may relate to the risk of neurodegenerative disease. Finally, this article reviews current recommendations to prevent cerebrovascular disease with the goal of maximizing brain reserve and cognitive health in advanced age and in the presence of other common comorbidities.

EPIDEMIOLOGY AND CLINICAL IMPACT

Vascular dementia has been estimated to account for approximately 20% of all dementia cases¹; however, the lack of standardized diagnostic criteria, the underestimation of nonstroke-related vascular cognitive impairment, and the exclusion of mild vascular cognitive impairment and mixed-etiology dementia in the reporting of vascular dementia diagnoses create a likely considerable underestimation of the true contribution of vascular disease to cognitive impairment in older populations. The more widespread use of neuroimaging in the evaluation of age-related cognitive decline has resulted in a greater appreciation of the prevalence of “silent” small vessel ischemic disease and its impact on cognitive function. Pathologically, community-based autopsy series have demonstrated that mixed pathologies are more common than any single pathology alone, with Alzheimer disease (AD) and cerebrovascular disease (with or without other neurodegenerative pathologies) being the most commonly observed combination.² In a community-based autopsy series from the Religious Orders Study and Rush Memory and Aging Project, vascular pathology accounted for 32% of the association between age and dementia.³ Importantly, the presence of significant cerebrovascular disease has been shown to decrease the amount of both AD and α -synuclein pathology necessary for the clinical expression of dementia,^{4,5} particularly when the total AD pathology burden is low.⁶ Moreover, having multiple pathologic diagnoses increases the likelihood and severity of dementia compared with just one pathology.^{7,8}

TABLE 5-1

Mechanisms Linking Vascular Function to Neurovascular Unit Function^a

Mechanisms	Capillary function	Function within the neurovascular unit	Effects of vascular disorders
Hemodynamic flow	Hemodynamic pressure gradients (osmotic and hydrostatic)	Nutrient delivery to organ and tissue	Ischemia, infarction, capillary rarefaction
Structural integrity	Tight junctions	Blood-brain barrier integrity	Solute leakage
Neurovascular coupling	Astrocyte function, pericyte function, vascular distensibility, etc	Autonomic innervation and functional hyperemia	Decoupling of vascular function and neuronal activity
Nutrient extraction point and trophic support	Diffusion, facilitate transport and maintain the vascular-neuron trophic coupling	Nutrient delivery (eg, oxygen, glucose, ketone bodies) and sensing of carbon dioxide and pH changes	Impaired metabolism and functional response
Drainage	Collection site	Facilitates solute clearance	Solute aggregation

^a Reprinted with permission from Zlokovic BV, et al, Alzheimers Dement.¹¹ © 2020 The Alzheimer's Association.

Accordingly, it is now appreciated that the total number of pathologies present may be more important than any single pathology alone in the development of cognitive decline and that each subsequent vascular insult serves to decrease both brain resilience and one's threshold to manifest clinical expression of other brain pathologies, such as AD.⁹ Cerebrovascular disease is associated with modifiable risk factors, so it is potentially preventable. Therefore, it is critical that cerebrovascular health be emphasized as a means of preventing dementia of all causes, including that from neurodegenerative disease.

KEY POINTS

- Community autopsy studies show that mixed pathologies are more common than any one pathology in older individuals. The most common combination is Alzheimer disease (AD) and cerebrovascular pathology.

- Cerebrovascular disease lowers the threshold for manifesting cognitive impairment when other pathologies are present. Treatment goals include the maintenance of cognitive reserve with advancing age when copathologies are likely to be present.

- The term *vascular cognitive impairment* includes a wide range of cerebrovascular-related cognitive decline, including those with mild impairment but preserved function, vascular dementia, and mixed-*etiology* dementias.

TERMINOLOGY AND DIAGNOSTIC CRITERIA

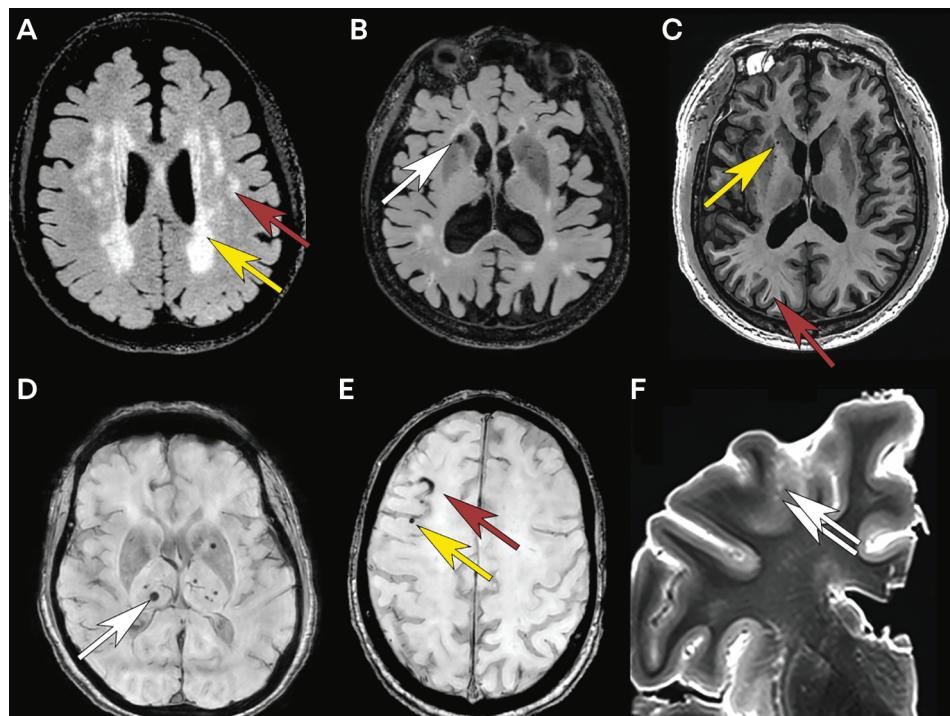
In 1993, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché l'Enseignement en Neurosciences established criteria for vascular dementia that were sensitive to the detection of poststroke dementia but excluded more slowly progressive and chronic manifestations of vascular-related cognitive impairment.¹⁰ Subsequent efforts continued to refine the terminology and diagnostic criteria for vascular dementia but also resulted in disparate standards that made comparisons among studies difficult. It is now recognized that vascular dysfunction contributes to a wide range of clinical syndromes, including milder forms of cognitive impairment and mixed dementias. There is additional need to further define biological mechanisms that lead to disruption of the neurovascular unit and subsequent cognitive decline, including those described in TABLE 5-1.¹¹ The term *vascular cognitive impairment* is inclusive of all forms of vascular-related cognitive impairment, including those resulting in cognitive decline that does not meet criteria for dementia (ie, preserved daily function) and those resulting from mixed pathologies (eg, AD and vascular disease).¹²

The Vascular Impairment of Cognition Classification Consensus Study used a Delphi approach that included a multinational group of clinicians and researchers to update and harmonize research and clinical criteria for vascular cognitive impairment.¹³ In this revised conceptualization, mild vascular cognitive impairment is defined by the presence of impairment in at least one cognitive domain and mild to no functional decline in instrumental activities of daily living (ADL) or basic ADL. A diagnosis of major vascular cognitive impairment (vascular dementia) requires deficits in at least one cognitive domain and severe disruption to instrumental ADL or basic ADL that are independent of stroke-related motor or sensory impairment. Major vascular cognitive impairment is further composed of the following subtypes: (1) poststroke dementia (cognitive decline within 6 months of stroke); (2) subcortical ischemic vascular dementia; (3) multi-infarct (cortical) dementia; and (4) dementias due to mixed pathologies. The Vascular Impairment of Cognition Classification Consensus Study consensus criteria also include the recommendation that neuroimaging evidence of cerebrovascular disease be required for the diagnoses of probable vascular cognitive impairment, with MRI being the preferred modality because of its increased sensitivity to small vessel ischemic disease.

POSTSTROKE COGNITIVE IMPAIRMENT

Acute worsening of cognitive function after a clinical stroke represents the traditional form of vascular dementia, with a classic abrupt or stepwise pattern of decline following each vascular event being distinct from that of the insidious

onset and slowly progressive decline commonly observed in most neurodegenerative diseases, such as AD. Stroke is a major risk factor for vascular cognitive impairment, with poststroke cognitive impairment occurring in up to 60% of poststroke survivors in the first year, mostly within the first 6 months.¹⁴ Stroke doubles the risk of dementia, with hemorrhagic stroke conferring higher dementia risk than ischemic stroke.^{15,16} Greater age, stroke volume, MRI evidence of chronic small vessel ischemic disease (FIGURE 5-1), brain atrophy, the presence of diabetes, low education, and worse prestroke performance on cognitive testing have all been shown to increase the risk of dementia after stroke.¹⁷ Although the presence of more than one stroke increases the risk for vascular cognitive impairment,¹⁸ cognitive impairment can also occur after a single large or small vessel vascular event. This is referred to as a *strategic infarct*, with the left frontotemporal lobe, left thalamus, and right parietal lobe being strongly associated with poststroke cognitive impairment.¹⁹ Risk factors for stroke include hypertension, hypercholesterolemia, diabetes, heart and renal disease, smoking, sedentary behavior, unhealthy diet, moderate and severe obstructive sleep apnea, and obesity.²⁰ Although poststroke cognitive

**FIGURE 5-1**

MRI features of small vessel ischemic disease. *A*, Axial fluid-attenuated inversion recovery (FLAIR) image of periventricular (yellow arrow) and deep or subcortical (red arrow) white matter hyperintensities. *B*, Axial FLAIR image of subcortical lacunar infarct (white arrow). *C*, Axial T1-weighted image of basal ganglia (yellow arrow) and posterior white matter (red arrow) MR-visible perivascular space. *D*, Axial susceptibility-weighted image (SWI) of basal ganglia cerebral microbleeds (white arrow). *E*, Axial SWI of cortical superficial siderosis (red arrow) and cortical cerebral microbleeds (yellow arrow). *F*, Axial T2-weighted 7 T postmortem image demonstrating cerebral microinfarcts (white arrows).

impairment is common, some degree of recovery of cognitive function can occur, most commonly within the first 6 months after stroke.

KEY POINTS

- More than one-half of patients who have a clinical stroke will have poststroke cognitive impairment. Stroke doubles the risk of dementia, with hemorrhagic stroke conveying a higher dementia risk than ischemic stroke.
- MRI features of small vessel ischemic disease associated with vascular cognitive impairment include lacunes, microinfarcts, microhemorrhages, enlarged perivascular spaces, and white matter hyperintensities.
- Subcortical infarcts, or lacunes, are seen on MRI in up to 23% of older individuals. Lacunar infarcts located in the basal ganglia and thalamus have the greatest association with cognitive impairment.
- Pathologically, MRI white matter hyperintensities are associated with myelin pallor, demyelination, axonal loss, inflammation, vacuolization, microinfarcts, and gliosis. Vascular features associated with MRI white matter hyperintensities include cerebral amyloid angiopathy (CAA), arteriolosclerosis, and venous collagenosis.
- Executive dysfunction has the greatest association with MRI white matter hyperintensities, although impairment in other areas, including memory, can be observed. Greater white matter hyperintensity burden is associated with increased risk for stroke, dementia, and overall mortality.

SMALL VESSEL ISCHEMIC DISEASE

Whereas previous diagnostic criteria focused on dementia due to multiple strokes, advances in neuroimaging have resulted in greater recognition of more chronic progressive forms of vascular cognitive impairment as major contributors to age-related cognitive decline, largely due to small vessel ischemic disease. MRI features of small vessel ischemic disease that are associated with vascular cognitive impairment in the absence of a clinical stroke include subcortical lacunar infarcts, cerebral microinfarcts, microhemorrhages, MR-visible perivascular spaces, and white matter hyperintensities (FIGURE 5-1). Evidence of small vessel ischemic disease is extremely common with increasing age. Small subcortical infarcts (ie, lacunes) are observed on MRI in up to 23% of older individuals, with more than 90% occurring in those without a history of transient ischemic attack (TIA) or stroke.²¹ Lacunar infarcts occurring within the basal ganglia and thalamus are associated with worse global cognitive function than those located in the deep white matter.²²

MRI T2 white matter hyperintensities are nonspecific but are seen in more than 90% of older individuals and commonly reflect white matter injury associated with small vessel ischemic disease.²³ White matter hyperintensities on MRI can be distinguished by their location as being directly adjacent to the ventricle, known as periventricular white matter hyperintensities. They may also be surrounded by normal-appearing white matter and distal from the ventricle wall, termed *subcortical*, or *deep*, white matter hyperintensities. Pathologically, white matter hyperintensities have been associated with myelin pallor, demyelination, axonal loss, inflammation, vacuolization, microinfarcts, and gliosis.²⁴⁻²⁷ Relevant vascular findings include cerebral amyloid angiopathy (CAA), arteriolosclerosis, and venous collagenosis.^{28,29} MRI white matter hyperintensities are highly associated with older age, and larger baseline lesion volume, hypertension, and smoking are predictors of faster white matter hyperintensity progression over time.^{30,31} What is clearly visible as T2 hyperintensity on MRI is thought to represent just a fraction of the total volume of actual damaged tissue, with surrounding normal-appearing white matter demonstrating microstructural integrity disruption on diffusion tensor imaging and diminished cerebral blood flow on arterial spin labeling sequences predicting future white matter hyperintensity expansion.³² MRI white matter hyperintensities and stroke share common vascular risk factors, including hypertension, cardiovascular disease, diabetes, and smoking.^{33,34}

Although impairments in executive function and processing speed are the primary cognitive domains affected by white matter hyperintensities,^{35,36} decline across a range of cognition domains, including global cognition and memory, has also been observed.³⁷⁻³⁹ Importantly, greater white matter hyperintensity volume has been associated with increased risk of stroke, dementia, and all-cause mortality.⁴⁰ Although common manifestations of subcortical vascular dysfunction are visually apparent on MRI as T2 hyperintensities and T1 hypointensities (ie, lacunes), more widespread deleterious effects, including global cortical atrophy, are now appreciated as being sequelae of subcortical ischemic disease, contributing to observed associations with cognitive decline.⁴¹ Other mechanisms contributing to white matter hyperintensity-related cognitive impairment include associated regional brain atrophy,³⁷ thinning of distal

cerebral cortex in regions with tractography and network-based connectivity to white matter hyperintensities,^{42,43} and disruption of cholinergic pathways.⁴⁴ It is important to note that MRI T2 white matter hyperintensities, particularly in the parietal and occipital lobes, can be an early feature of AD and associated with AD pathology.^{28,45,46} Accordingly, some component of age-related MRI white matter hyperintensities is likely a reflection of wallerian degeneration from neurodegenerative disease in those with cortical AD pathology in addition to, or in place of, an ischemic etiology.^{46,47} Small vessel ischemic disease begins to develop as early as midlife, with greater lesion size being associated with increased cognitive impairment and dementia risk.^{48,49} Such findings highlight the early nature of small vessel ischemic disease development and the need to address risk factors in young to middle-aged individuals, before more severe white matter damage occurs, for the preservation of cognitive health with advanced age.

CEREBRAL MICROINFARCTS

The contribution of cerebral microinfarcts to vascular cognitive impairment is significant, albeit challenging to fully assess. Cerebral microinfarcts are defined as microscopic ischemic lesions invisible on gross tissue examination. Difficulties in studying the effects of cerebral microinfarcts on cognition include the lack of focal motor or sensory correlates and poor or no visibility on in vivo neuroimaging, as well as variability in pathologic criteria, tissue sampling methods, and participant populations studied. Previously described cerebral microinfarcts have ranged in size from 50 µm to several millimeters. Cerebral microinfarcts on the larger end of the size spectrum can be visibly apparent on high-resolution in vivo MRI as being hypointense on T1 and hyperintense on T2 sequences. Pathologically, they are described as small foci with neuronal loss, gliosis, pallor, or cystic lesions. Some studies describe cerebral microinfarcts as



FIGURE 5-2

Schematic of likely widespread consequences of cerebral microinfarcts beyond local tissue damage. Perilesional deficits are caused by secondary effects of ischemic injury. Remote deficits can occur when microinfarcts damage white matter fibers or occur in areas that are connected to the function of other brain regions.

BBB = blood-brain barrier.

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being evenly distributed throughout the brain, with others reporting higher frequencies in the parietal occipital lobes and in watershed regions.⁵⁰ Given that current autopsy sampling methodologies include the microscopic examination of less than 0.01% of total brain tissue, total cerebral microinfarct lesion burden is likely to be significantly underestimated, with one model predicting approximately 550 to 1100 actual cerebral microinfarcts for every 1 to 2 observed on standard pathologic dissection.⁵¹ In a review of 32 autopsy studies that included more than 10,500 individuals, cerebral microinfarcts were observed most frequently in patients with vascular dementia (62%), followed by patients with AD (43%) and dementia-free older adults (24%).⁵⁰ In the 90+ Study of the oldest adults, 51% had at least one cerebral microinfarct at autopsy, and the risk for dementia for those with three or more cerebral microinfarcts was similar to that observed for individuals with high (Braak stages V to VI) neurofibrillary tangle burden.⁵² A review of seven community-based autopsy studies determined the prevalence of cerebral microinfarcts to range from 16% to 48%, with a pooled dementia risk of people with cerebral microinfarcts being more than twice that of those without cerebral microinfarcts.⁵³

Cerebral microinfarct–related global cognitive impairment has been shown to be independent of concurrent AD pathology⁵⁴ and, therefore, represents an underappreciated but important contributor to cognitive decline in older individuals. Pathologically, cerebral microinfarcts are associated with a greater severity of arteriolosclerosis and atherosclerosis, as well as the presence of CAA.⁵⁵ Cognitive impairment is thought to result from focal and perilesional neuronal and white matter tract injury, with mechanisms that include neuronal death, astrogliosis, and blood-brain barrier leakage.⁵⁶ In an animal model, occlusion of a single penetrating cortical vessel resulted in injury to the contralateral hemisphere, thought to be mediated via microglia and macrophage migration along white matter tracts.⁵⁷ Accordingly, cerebral microinfarcts may have a similar widespread impact on cerebral function due to remote cortical injury and impaired long-range signaling (**FIGURE 5-2**).⁵⁶

CEREBRAL AMYLOID ANGIOPATHY

CAA incidence increases with age and is defined by the presence of amyloid- β (A β) protein deposition in the tunica media and adventitia of small arteries and arterioles of the cortex and leptomeninges. It is associated with both apolipoprotein E ϵ 4 (*APOE** ϵ 4) and apolipoprotein E ϵ 2 (*APOE** ϵ 2) allele status.⁵⁸ Although *APOE** ϵ 4 has been associated with more severe CAA,^{58,59} *APOE** ϵ 2 is thought to result in vasculopathic changes resulting in an increased risk for hemorrhage.⁶⁰ Although both A β 40 and A β 42 peptides are implicated in CAA, A β 40 is the predominant species. This is in contrast to neuritic plaques found in sporadic AD, which are composed primarily of A β 42. In a 2022 meta-analysis of 170 studies that included more than 73,000 participants, the prevalence of moderate-severe CAA pathology was 48% in patients with AD and 23% in population-based cohorts of older individuals.⁶¹

Over time, progressive damage of the vessel wall can lead to rupture and hemorrhage, with evidence of local vascular remodeling at the site of bleeding thought to be due to blood-brain barrier leakage and subsequent perivascular inflammation.⁶² This can take the form of symptomatic hemorrhagic stroke, which is most likely to occur in lobar and, less commonly, cerebellar brain regions. This is in contrast to hypertension-related hemorrhagic strokes, which

KEY POINTS

- MRI indicators of small vessel ischemic disease are observed in midlife and are associated with later cognitive decline, highlighting the need to address vascular risk factors early in adulthood, before vascular brain injury.
- Cerebral microinfarcts are common in older populations, particularly in people with vascular dementia. The presence of cerebral microinfarcts increases the risk of dementia independently of AD pathology.
- Cerebral microinfarcts are associated with arteriolosclerosis, atherosclerosis, and CAA. Mechanisms leading to cognitive impairment include both focal and long-range tissue injury occurring via associated white matter tracts.
- CAA is characterized by the deposition of amyloid- β 40 (A β 40) in walls of cortical and leptomeningeal arterioles and small arteries and occurs in the presence or absence of parenchymal AD pathology.
- The Boston Criteria version 2.0 for CAA includes MRI white matter hyperintensity in a multispot pattern and MR-visible perivascular spaces within the centrum semiovale, in addition to hemorrhagic features on susceptibility-weighted images (SWI) and T2* sequences.

are more commonly found in the basal ganglia, thalamus, and pons.⁶³ Small regions of hemorrhage, often subclinical in nature, can also be observed. These consist of (1) lobar cerebral microbleeds and (2) bleeding into the cortical sulci resulting in acute convexity subarachnoid hemorrhage or its more chronic form, cortical superficial siderosis.

The Boston Criteria for the clinical diagnosis of CAA were revised in 2022 and are described in TABLE 5-2 and TABLE 5-3.⁶⁴ Current MRI criteria include the presence of white matter hyperintensities in a multispot pattern (more than 10 in both hemispheres, typically symmetrical) and multiple (more than 20 in each hemisphere) MR-visible perivascular spaces within the white matter of the centrum semiovale.⁶⁴ Evidence of intracerebral hemorrhage (ICH), convexity subarachnoid hemorrhage, cerebral microbleeds, and cortical superficial siderosis is visible on susceptibility-weighted imaging (SWI) or T₂* gradient echo (GRE) MRI, which show areas of the blood breakdown product hemosiderin as areas of low signal (FIGURE 5-3).⁶⁵ Most cases of CAA are sporadic; however, autosomal dominantly inherited CAA (ie, Dutch, Italian, Arctic, Iowa, and Flemish genetic variations) caused by point variations in the amyloid precursor protein exist and result in younger-onset stroke and cognitive decline and greater severity of CAA on histologic examination compared with sporadic forms of the disease.⁶⁶

Clinically, CAA can manifest as acute neurologic decline after a lobar intracerebral hemorrhage. Other transient, chronic, or subacute clinical expressions exist, however, and include transient focal neurologic episodes, cognitive decline and dementia, and subacute neurologic decline due to CAA-related inflammation. Transient focal neurologic episodes usually last less than 30 minutes, are stereotyped, and consist of either positive or negative symptoms. Symptoms often gradually evolve across contiguous areas of the body, thought to be the result of spreading cortical depolarization, and transient focal neurologic episodes are associated with an increased risk of clinical hemorrhagic stroke (TABLE 5-4).⁶⁷ Accordingly, it is important that T₂* or SWI sequences be obtained as part of a workup of transient neurologic symptoms, because common interventions for similarly presenting stroke and TIAs, such as thrombolytics and antiplatelet therapies, can increase the risk of hemorrhage in patients with CAA-

TABLE 5-2

Boston Criteria Version 2.0 Cerebral Amyloid Angiopathy MRI Features^a

White matter lesions (T2-weighted images)

- ◆ Severe perivascular spaces (>20 in one hemisphere) in the centrum semiovale
- ◆ White matter hyperintensities (>10 in both hemispheres) in a multispot pattern

Lobar hemorrhagic lesions

- ◆ Intracerebral hemorrhage
- ◆ Cerebral microbleeds (susceptibility- or T₂*-weighted images)
- ◆ Superficial siderosis (susceptibility- or T₂*-weighted images)
- ◆ Convexity subarachnoid hemorrhage

^a Data from Charidimou A, et al, Lancet Neurol.⁶⁴

associated transient focal neurologic episodes. CAA is associated with an increased risk of AD and greater rate of decline in perceptual speed, episodic and semantic memory, and global cognition, with findings remaining after controlling for AD, dementia with Lewy bodies, and non-CAA vascular pathologies.⁶⁸

CAA-related inflammation presents as subacute cognitive decline, headaches, focal neurologic deficits, or seizures and may be responsive to immunosuppressive therapies, as demonstrated in **CASE 5-1**.⁶⁹ It is associated with younger age at clinical presentation and the presence of the *APOE*ε4* allele and is the greatest in *ε4/ε4* homozygotes, although cases have also been reported in *APOE*ε2* allele carriers.^{70,71} Neuroimaging features consist of asymmetric corticosubcortical or deep MRI T2 white matter hyperintensities and the presence of at least one other CAA-associated imaging feature (eg, cerebral microbleeds, cortical superficial siderosis, or lobar hemorrhage).⁷² White matter hyperintensities in CAA-related inflammation are thought to represent inflammation-mediated vasogenic edema and frequently colocalize with cerebral microbleeds and cortical superficial siderosis, similar to that seen in amyloid-related imaging abnormalities of edema (ARIA-E) and hemorrhage (ARIA-H) after treatment with anti-amyloid monoclonal antibody therapies. These similarities indicate a common mechanism between the two clinical phenomena, possibly related to an overwhelmed perivascular waste clearance system.^{62,73}

Boston Criteria Version 2.0 Cerebral Amyloid Angiopathy Clinical Criteria^a

TABLE 5-3

Clinical presentation

- ◆ 50+ years of age
- ◆ Spontaneous intracranial hemorrhage, or
- ◆ Transient focal neurologic episodes, or
- ◆ Cognitive impairment or dementia

Probable cerebral amyloid angiopathy

- ◆ Clinical presentation, and
- ◆ At least two lobar hemorrhagic lesions, or
- ◆ One lobar hemorrhagic lesion plus one white matter feature

Possible cerebral amyloid angiopathy

- ◆ Clinical presentation, and
- ◆ One lobar hemorrhagic lesion, or
- ◆ One white matter feature

Other criteria

- ◆ Absence of other causes of bleeding
- ◆ Absence of deep hemorrhagic lesions

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HEREDITARY AND RARE ETIOLOGIES OF CEREBRAL SMALL VESSEL DISEASE

Many rarer causes of small vessel ischemic disease are associated with cognitive decline and MRI white matter injury that, in some cases, should be considered in the workup for vascular cognitive impairment. The most common of these is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is an autosomal dominant disease resulting from a variant in the cysteine residue in an epidermal growth factor-like repeat domain of the *NOTCH3* gene expressed in endothelial smooth muscle cells, with the location of the mutation being related to disease severity.^{74,75} This alteration eventually results in vascular smooth muscle cell degeneration, fibrosis, and vessel stenosis.⁷⁶ Clinically, CADASIL is characterized by migraine, subcortical strokes, and generally young-onset vascular cognitive impairment, as illustrated in **CASE 5-2**.

The average age of patients with ischemic stroke in the setting of CADASIL is 49 years, but it has a fairly wide range (20 to 70 years).⁷⁷ MRI features include subcortical lacunes, cerebral microbleeds, and enlarged perivascular spaces.⁷⁷ Characteristic confluent MRI T2 white matter hyperintensities can begin in early adulthood and often involve the superior frontal, external capsule, and anterior temporal lobes, a pattern generally distinct from that observed in more common age- and vascular risk factor-related cerebral small vessel ischemic disease.⁷⁸ Although randomized controlled trials in CADASIL are lacking, treatment considerations include valproic acid for migraine prophylaxis, low-dose aspirin in those with a history of ischemic stroke, and trials of memantine, donepezil, or both for cognitive symptoms.^{77,79} Use of beta-blockers for migraine prophylaxis should be avoided because of the greater incidence of reported side effects.⁷⁷ CADASIL and other rarer etiologies of vascular cognitive impairment should be considered in patients presenting with greater than expected MRI white matter

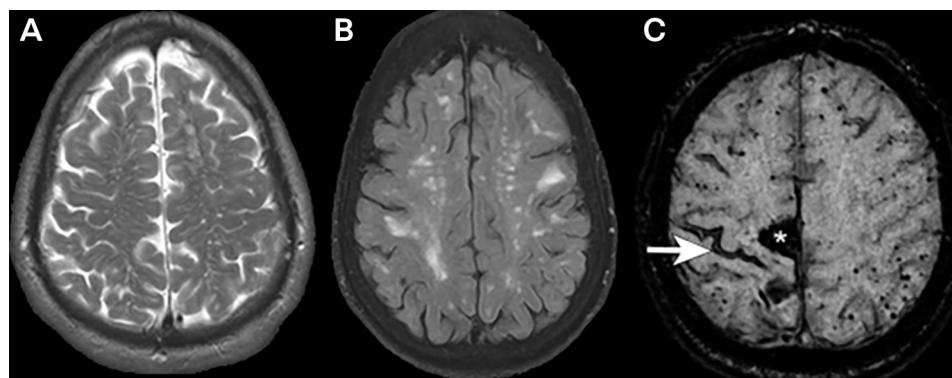


FIGURE 5-3

MRI markers included in the Boston Criteria version 2.0. **A**, Severe centrum semiovale perivascular spaces identified on axial T2-weighted image (>20 in one hemisphere). **B**, A multispot white matter hyperintensity pattern (>10 fluid-attenuated inversion recovery [FLAIR] small circular or ovoid hyperintense lesions in the subcortical white matter of both hemispheres). **C**, Susceptibility-weighted image of cerebral microbleeds (multiple hypointense foci) including right parasagittal cerebral amyloid angiopathy-related spontaneous lobar intracerebral hemorrhage (asterisk) and area of cortical superficial siderosis (arrow).

Panels A and B reprinted with permission from Charidimou A, et al, Lancet Neurol.⁶⁴ © 2022 Elsevier Ltd. Panel C reprinted with permission from Greenberg SM and Charidimou A, Stroke.⁶⁵ © 2018 Wolters Kluwer Health.

injury for the number and severity of their vascular risk factors, particularly if a family history of a similar disease process or significant MRI white matter injury is present (**TABLE 5-5**).⁸⁰

HEART DISEASE AND CAROTID STENOSIS

Among cardiovascular disorders, atrial fibrillation and congestive heart failure have the most evidence of association with cognitive impairment, independent of clinical stroke or shared vascular risk factors. Atrial fibrillation is associated with cognitive decline and increased dementia risk and is strongest in younger individuals with longer atrial fibrillation duration.^{81,82} Congestive heart failure is associated with mild cognitive impairment (MCI) and dementia, conferring a 60% increase in dementia risk that is likely vascular in nature.^{83,84} Coronary artery disease has been associated with a 27% increase in dementia risk,⁸³ with myocardial infarction being associated with an increased risk of vascular, not AD, dementia.⁸⁵ One 2023 study, pooling data from six longitudinal cohort studies, found incident myocardial infarction not to be associated with acute cognitive decline but rather with an increased rate of progressive cognitive decline over time.⁸⁶ Presumed mechanisms linking cardiac disease to dementia include associated microinfarcts, global hypoperfusion, inflammation, and microhemorrhages.^{81,86} In the Rotterdam Study, which followed more than 4500 dementia-free adults for approximately 7 years, decreased cerebral perfusion was associated with an increased rate of cognitive decline and greater risk of dementia, a finding most pronounced in those with greater MRI white matter hyperintensity burden.⁸⁷

High-grade carotid stenosis, in particular, has been found to negatively affect cognition, with potential mechanisms that include embolization and hypoperfusion. Findings from CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) demonstrated that individuals with 70% or greater asymptomatic carotid stenosis and no stroke history perform worse on cognitive testing, particularly in memory,⁸⁸ and improved cerebral blood flow and cognition after carotid endarterectomy have been reported.⁸⁹ Proposed mechanisms linking chronic cerebral hypoperfusion

Clinical Characteristics of Cerebral Amyloid Angiopathy-related Transient Focal Neurologic Episodes^a

TABLE 5-4

- ◆ Focal neurologic symptoms; these are often unilateral motor, sensory, or both, sometimes including other symptoms such as dysarthria or aphasia
- ◆ Usually resolve within 30 minutes (nearly always within 3 hours)
- ◆ Often spread from one body part to another represented by contiguous cortex
- ◆ Often recurrent in a stereotyped or similar pattern over days or weeks
- ◆ Age 55 or older
- ◆ MRI evidence of probable or possible cerebral amyloid angiopathy by Boston Criteria version 2.0
- ◆ Absence of acute infarction consistent with thromboembolism

^a Modified with permission from Smith EE, et al, Neurology.⁶⁷ © 2021 American Academy of Neurology.

CASE 5-1

A 57-year-old woman presented with 2 years of forgetfulness. She was independent in all activities of daily living. Her mother died of a stroke at age 62, and her father had dementia beginning at age 71. A maternal aunt and cousin were diagnosed with dementia due to Alzheimer disease. On examination, her blood pressure was 150/90 mm Hg, and there were no focal neurologic abnormalities. Neuropsychologic testing demonstrated mostly average performance, with low average story recall and mild impairment in executive function. Workup included normal thyroid-stimulating hormone (TSH), vitamin B₁₂, and vitamin D. Brain MRI revealed periventricular and scattered fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities and extensive foci of susceptibility-weighted imaging (SWI) cerebral microbleeds consistent with a diagnosis of cerebral amyloid angiopathy (CAA) (**FIGURE 5-4**). A diagnosis of mild vascular cognitive impairment due to CAA was determined. The patient was counseled regarding CAA-related risk of hemorrhagic stroke and strict blood pressure management, and avoidance of antiplatelet and anticoagulant therapies was recommended. Stable cognitive performance was noted on serial testing over the next 2 years with no change on MRI.

Three years after her initial evaluation, the patient had several weeks of headaches and more notable cognitive decline, followed by her first seizure. She was started on levetiracetam 750 mg 2 times a day. Serial brain MRIs 1 month apart showed increasing cerebral microbleeds and white matter hyperintensity lesions, particularly over the left parietal lobe. A diagnosis of CAA-related inflammation was established, and the patient was started on methylprednisolone 1000 mg IV daily for 5 days followed by a prolonged oral prednisone taper, with improvement in cognition. Posttreatment MRI showed decreased left parietal FLAIR white matter hyperintensities (**FIGURE 5-4D**). Additional workup included apolipoprotein E genetic testing, which showed the patient to be homozygous for the apolipoprotein E ε4 (*APOE**ε4) allele.

COMMENT

This case demonstrates mild vascular cognitive impairment due to CAA followed by subacute cognitive decline and seizures, consistent with CAA-related inflammation, which is more common in *APOE**ε4 homozygotes. Neuroimaging revealed typical CAA findings of cerebral microbleeds and white matter hyperintensities and subsequent development of asymmetric white matter hyperintensity lesions consistent with CAA-related inflammation. In this case, the patient was responsive to high-dose steroids. Long-term treatment with anticonvulsive therapy, strict blood pressure control, and avoidance of antiplatelet medications were recommended.

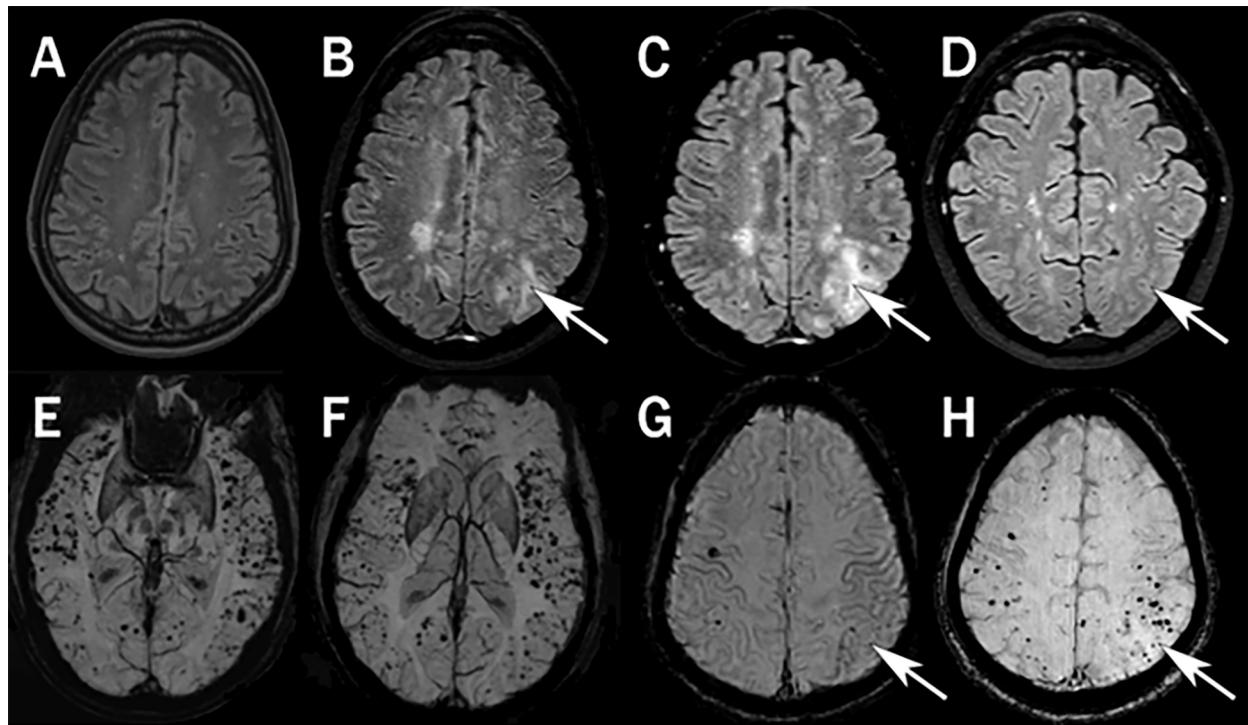


FIGURE 5-4

Cerebral amyloid angiopathy-related inflammation in the patient in **CASE 5-1**. **A**, Baseline axial fluid-attenuated inversion recovery (FLAIR) MRI. **B**, Postseizure axial FLAIR MRI 3 years after the baseline MRI showing new asymmetric left more than right parietal white matter hyperintensities (white arrow). **C**, Postseizure axial FLAIR MRI 1 month later showing enlarged left parietal white matter hyperintensities (arrow). **D**, Axial FLAIR MRI after steroid treatment for presumed cerebral amyloid angiopathy-related inflammation showing resolution of white matter hyperintensities (arrow). Cerebral microbleeds observed on baseline axial susceptibility imaging (SWI) at the level of the temporal-occipital lobes (**E**), the basal ganglia (**F**), and frontal-parietal lobes (**G**) and an increased number of cerebral microbleeds observed at the level of the frontal-parietal lobes after seizure (**H**) (arrow in panel **H** compared with arrow in panel **G**).

Images courtesy of Aimee Pierce, MD.

to vascular cognitive impairment include chronic inflammation, oxidative stress, neurodegeneration, and brain atrophy.⁹⁰

LINKS WITH ALZHEIMER DISEASE

A greater increase in cardiovascular risk factors over time has been shown to be associated with a greater risk of both AD and vascular dementia.⁹¹ As previously

CASE 5-2

A 63-year-old man presented with a 3-year history of progressive cognitive impairment. His family reported worsening day-to-day function over the past year, requiring more help with instrumental activities of daily living. His past medical history included multiple small vessel ischemic strokes and progressive motor decline starting in his early fifties and mild hypertension and hypercholesterolemia well controlled with medication management. He had no history of atrial fibrillation, and previous ECG, transthoracic echo, and workup for hypercoagulable state were normal. He had a long-standing history of migraine with aura that ran in his family on his mother's side. His mother died in her early sixties after having multiple strokes, and a maternal aunt had a diagnosis of multiple sclerosis. His medications included low-dose aspirin for stroke prevention and a beta-blocker for migraine prophylaxis.

Cognitive testing demonstrated significant deficits in executive function, attention, and memory. Mild left hemiparesis with positive bilateral Babinski responses and frequent word-finding difficulties were observed on examination. Brain MRI showed multiple lacunes, cerebral microbleeds, and confluent white matter hyperintensities greater than expected for his age and vascular risk factors (FIGURE 5-5). Based on imaging findings and his family history of migraines, stroke, and MRI white matter lesions, a diagnosis of hereditary arteriopathy was suspected. After undergoing genetic counseling, the patient was diagnosed with a *NOTCH3* variation consistent with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). He continued treatment with low-dose aspirin, and a trial of memantine was started for cognitive impairment. The beta-blocker was discontinued, and valproic acid was started for migraine prophylaxis. Genetic counseling was subsequently offered to the patient's two asymptomatic adult children.

COMMENT

This patient presented with typical features of CADASIL, including multiple small vessel ischemic strokes and early-onset cognitive decline. MRI showed extensive small vessel ischemic disease, including T2 white matter hyperintensities involving the anterior temporal poles. Low-dose aspirin can be considered for ischemic stroke prevention, but the use of a beta-blocker was not the optimal treatment for CADASIL-related migraine prophylaxis because of a greater risk of side effects. Hereditary arteriopathy should be considered in patients with evidence of extensive small vessel ischemic disease out of proportion to stroke risk factors and a family history of stroke and MRI T2 white matter hyperintensities.

mentioned, the presence of cerebrovascular disease lowers the threshold for the clinical expression of dementia when combined with other pathologies. Whether the effects of cerebrovascular disease on cognition are additive but independent of AD pathology⁹² or synergistic with AD pathology⁹³ remains an active area of study. Results from several investigations support a link between cerebrovascular disease risk and AD pathology, including an association between

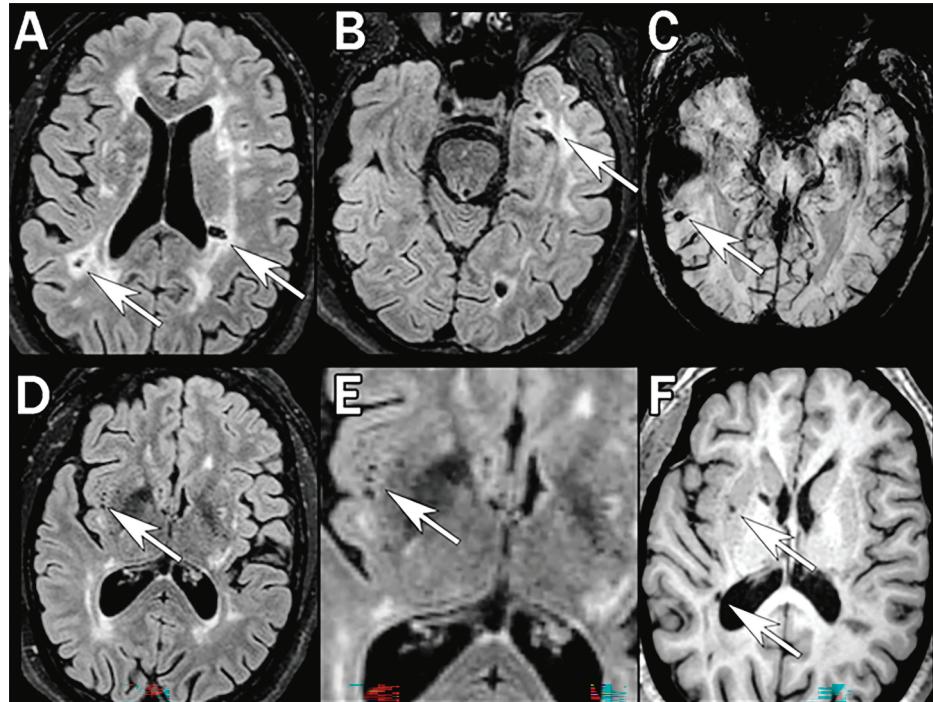


FIGURE 5-5

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in the patient in **CASE 5-2**. Axial MRI shows confluent fluid-attenuated inversion recovery (FLAIR) periventricular white matter hyperintensities and multiple subcortical lacunar infarcts (A, arrows), FLAIR white matter hyperintensities involving the anterior temporal pole (B, arrow), susceptibility-weighted image (SWI) of a cerebral microbleed (C, arrow), multiple FLAIR MR-visible deep subcortical perivascular spaces (D, arrow; magnified in E, arrow), and multiple T1-hypointense subcortical lacunar infarcts (F, arrows).

Images courtesy of Helmi Lutsep, MD.

midlife elevation of triglycerides and CSF findings of decreased A β and higher phosphorylated tau later in life.⁹⁴ In the Framingham Heart Study, midlife vascular risk factors were not associated with AD pathology at autopsy, although greater late-life vascular risk was associated with a higher Braak neurofibrillary tangle score.⁹⁵ Associations between pathologically confirmed vascular disease and AD pathology have also been described, including a

TABLE 5-5

Rare Etiologies of Cerebral Small Vessel Disease^a

Genetic

- ◆ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (*NOTCH3*)
- ◆ Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (*HTRA1*)
- ◆ Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) (*MT-TL1*)
- ◆ Fabry disease (*GLA*)
- ◆ Type IV collagen mutation-related cerebral small vessel ischemic disease (*COL4A1* or *COL4A2*)
- ◆ Retinal vasculopathy with cerebral leukoencephalopathy (*TREX1*)
- ◆ Hereditary cerebral hemorrhage with amyloidosis (Dutch, Italian, and Flemish: amyloid precursor protein gene; Icelandic type: cystatin gene)
- ◆ Multi-infarct dementia of the Swedish type (3'UTR variation of *COL4A1*)

Immune-mediated

- ◆ Primary angiitis of the central nervous system
- ◆ Antineutrophil cytoplasmic antibody-associated vasculitis
- ◆ Hypersensitivity vasculitis
- ◆ Systemic lupus erythematosus central nervous system vasculitis
- ◆ Sjögren syndrome-associated vasculitis
- ◆ Rheumatoid vasculitis
- ◆ Mixed connective tissue disease-associated vasculitis
- ◆ Behçet vasculitis

Infection-mediated

- ◆ Meningovascular neurosyphilis
- ◆ Varicella-zoster virus
- ◆ Cytomegalovirus
- ◆ Hepatitis B and C
- ◆ Human immunodeficiency virus (HIV)
- ◆ Fungus
- ◆ Schistosomiasis
- ◆ Cerebral malaria

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relationship between a greater circle of Willis atherosclerosis score and higher neuritic plaque density, neurofibrillary tangle density, and CAA severity.⁹⁶ In one brain autopsy series, arteriolosclerosis in posterior, but not anterior, watershed regions was associated with higher tau burden.⁹⁷ In this same population, the relationship between cerebrovascular disease (CAA and arteriolosclerosis) and cerebral microinfarcts was stronger in the presence of greater AD pathology, indicating that the presence of AD pathology may lower the threshold for microvascular injury.⁹⁸

A greater number of midlife vascular risk factors has been associated with an increased likelihood of having elevated amyloid on positron emission tomography (PET) imaging more than 20 years later,⁹⁹ although the contributions from midlife vascular risk factors and cerebral amyloid on dementia risk in this same population were independent of each other, without evidence of synergistic effects.¹⁰⁰ Midlife dyslipidemia, in particular, has been found to be associated with greater later-life amyloid deposition on Pittsburgh Compound B-PET.¹⁰¹ Although not directly associated with amyloid, other vascular risk factors examined in this study, such as obesity, smoking, diabetes, hypertension, and cardiac and metabolic conditions, were associated with decreased cortical thickness in areas affected early in the course of AD, implicating vascular risk factors to be associated with AD-independent cortical neurodegeneration. Investigations into the relationship between neuroimaging measures of regional white matter hyperintensities and AD pathology have largely supported an association between posterior more than anterior white matter hyperintensities and AD pathology on PET, and as mentioned previously, posterior MRI white matter hyperintensities are found on MRI in patients with autosomal dominant AD.^{45,102} These findings are consistent with pathologic studies demonstrating frontal white matter lesions to be associated with both vascular and AD pathologies and posterior white matter lesions to be more often associated with AD.^{46,47}

THE PERIVASCULAR SPACE

Much recent attention has focused on the perivascular space as being a mediating factor in the interaction between cerebrovascular dysfunction and the development and progression of neurodegenerative pathology. The perivascular space consists of the space within or between the endothelial basement membrane and surrounding astrocytic end-feet (FIGURE 5-6).¹⁰³ Previous work, mainly in animal models, supports the role of the para- or intramural vascular space as an integral component of the brain waste clearance system (ie, the “glymphatic” or intramural periarterial drainage [“IPAD”] pathways).^{104,105} Although the precise pathways are still to be determined, CSF influx from the subarachnoid space is thought to enter the brain parenchyma via the perivascular spaces, where it combines with interstitial fluid and toxic solutes (eg, soluble A β and tau) before reentering the perivascular space for egress out of the central nervous system through dural and then peripheral lymphatics, a process potentially facilitated during sleep.^{103,106,107} Perivascular spaces observed on clinical strength MRI sequences are presumed to be enlarged, and a higher number of MR-visible white matter perivascular spaces within the centrum semiovale is associated with increased dementia risk.¹⁰⁸ Greater MR-visible perivascular space burden has been observed in relation to vascular cognitive impairment and AD as well as imaging and pathologic

KEY POINTS

- CAA can present clinically as acute neurologic decline after hemorrhagic stroke, transient focal neurologic episodes, gradual cognitive decline and dementia, or subacute cognitive decline due to CAA-related inflammation.

- The most common hereditary form of vascular cognitive impairment is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The NOTCH3 variation location partially explains the difference in disease severity across patients.

- CADASIL is characterized by migraine, subcortical strokes, and young-onset vascular cognitive impairment. MRI features include subcortical lacunes, SWI and T2* cerebral microbleeds, and fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities involving the anterior temporal poles.

- Cardiac dysfunction, including atrial fibrillation, congestive heart failure, and coronary heart disease, increases the risk for vascular cognitive impairment. Acute myocardial infarction is associated with cognitive decline years later. Presumed mechanisms include associated microinfarcts, global hypoperfusion, inflammation, and microhemorrhages.

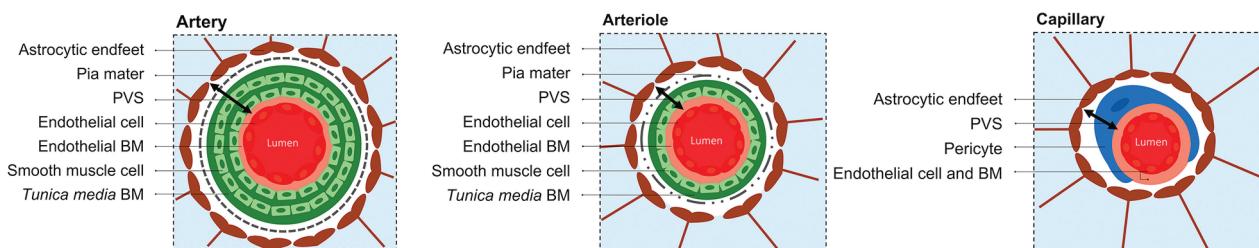


FIGURE 5-6

Schematic representation of the perivascular space (PVS). Arrows point to the internal endothelial basement membrane (BM) and external astrocytic end-feet boundaries of the PVS at each level of an artery, arteriole, and capillary.

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features of cerebrovascular disease (ie, white matter hyperintensities, lacunes, cerebral microbleeds, CAA).^{107,109,110} Regional differences in MR-visible perivascular space exist between disease states, with greater MR-visible basal ganglia perivascular space burden being associated with cerebrovascular disease, and greater MR-visible centrum semiovale perivascular space burden more associated with AD and CAA.^{64,111} Although the exact mechanisms remain undetermined, fluid drainage via the perivascular space waste clearance system may be facilitated by cardiac-related vascular pulsations or vascular smooth muscle cell-generated vasomotor activity and potentially affected by age, CAA, and vascular risk factor–related cerebrovascular dysfunction.^{112,113}

VASCULAR CONTRAINDICATIONS TO ALZHEIMER DISEASE MONOCLONAL ANTIBODY THERAPY

Advancements in AD therapeutics include the US Food and Drug Administration (FDA) approval of monoclonal antibodies for the treatment of MCI or mild dementia due to AD; for more information on this, refer to the article “Treatment of Alzheimer Disease” by David S. Geldmacher, MD, FACP, FANA,¹¹⁴ in this issue of *Continuum*. Common monoclonal antibody–associated treatment side effects include ARIA-E and ARIA-H. As stated earlier in this article, individuals with CAA can present with acute or subacute clinical decline due to CAA-related inflammation, with features similar to ARIA-E and ARIA-H. Accordingly, patients with MRI findings consistent with CAA-related inflammation and CAA are likely to be at increased risk for monoclonal antibody–related ARIA and would, therefore, not be good candidates for this type of anti-amyloid therapy. Other vascular-related exclusion criteria used in the Phase 3 lecanemab study included history of TIA or stroke within the past 12 months, greater than four cerebral microbleeds or any macrohemorrhages greater than 10 mm in diameter, superficial siderosis, significant FLAIR white matter hyperintensities, multiple lacunar strokes, or any major vascular territory stroke.¹¹⁵ Specific MRI exclusion criteria for monoclonal antibody AD therapy are reviewed in the article “Neuroimaging in Dementia” by Shannon L. Risacher, PhD,¹¹⁶ in this issue of *Continuum*.

CLINICAL EVALUATION

Vascular cognitive impairment should be considered in all patients presenting with a history of cognitive impairment (progressive, stepwise, or a

combination of both) that is a change from previous levels of performance. A history of stroke or TIA with stepwise decline in cognitive abilities is consistent with a multi-infarct type of vascular dementia, with focal neurologic findings being additionally supportive. As stated previously, vascular cognitive impairment due to worsening small vessel ischemic disease and chronic hypoperfusion can present with a more slowly progressive course of declining cognition, similar to that observed in neurodegenerative disease, and mixed pathologies that include cerebrovascular disease are common. Although focal neurologic deficits may not be present, patients with severe small vessel ischemic disease can present with motor slowing, gait and balance difficulties, and urinary urgency or incontinence.¹¹⁷ Potential behavioral manifestations of vascular cognitive impairment include depression, apathy, and emotional lability.¹¹⁸

Neurologic evaluation in these patients should include an assessment of multiple cognitive domains (eg, executive function, attention, memory, visuospatial skills, language, and orientation). Focal cortical damage from stroke may result in corresponding region-specific areas of cognitive impairment, whereas progressive accumulation of small vessel ischemic disease is most likely to affect executive function and processing speed. When available, neuroimaging with MRI (including T₁, FLAIR, and T₂* or SWI sequences) is recommended as part of a workup for patients presenting with new-onset cognitive impairment, particularly in those with multiple stroke risk factors in whom cerebrovascular disease is a possible contributor. Additional investigations into stroke or hypoperfusion-related vascular cognitive impairment (eg, carotid ultrasonography, cardiac echocardiography, ECG) and rarer etiologies of vascular cognitive impairment (**TABLE 5-5**) should be considered along with more typical contributors to cognitive impairment (eg, thyroid values, vitamin B₁₂, and vitamin D), as indicated.

PREVENTION AND TREATMENT

Even modest improvements in individual cerebrovascular disease prevention may significantly reduce vascular cognitive impairment burden at the population level.¹ Two randomized controlled trials, the Syst-Eur (Systolic Hypertension in Europe) study and PROGRESS (Perindopril Protection Against Recurrent Stroke Study), found that lowering blood pressure in older individuals decreased the risk of cognitive decline in those with or at risk for cerebrovascular disease.^{119,120} SPRINT (the Systolic Blood Pressure Intervention Trial) was terminated before its anticipated end date because of significant early demonstration of decreased major cardiovascular events and overall mortality in patients assigned to an intensive (systolic blood pressure less than 120 mm Hg) versus standard (systolic blood pressure less than 140 mm Hg) treatment group.¹²¹ The subsequent SPRINT-MIND study further demonstrated intensive blood pressure lowering to be associated with reduced risk for MCI and combined rate of MCI and dementia.¹²² Notably, intensive blood pressure treatment was associated with increased, rather than decreased, cerebral blood flow, as determined by arterial spin labeling MRI.¹²³

The randomized controlled FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial investigating multidomain interventions targeting cerebrovascular disease risk, including diet, exercise, vascular risk factor management, and cognitive training, demonstrated benefits

KEY POINTS

- A greater increase in cardiovascular risk factors over time raises the risk for both AD and vascular dementia. Whether cognitive effects from cerebrovascular disease are independent of, or synergistic with, AD pathology has not been resolved.
- Midlife cardiovascular risk factors have been associated with amyloid pathology on positron emission tomography (PET) in later life, as well as cortical neurodegeneration occurring independently of AD pathology.
- Pathologically, posterior white matter lesions are associated with AD pathology, consistent with *in vivo* findings demonstrating greater posterior MRI T₂ white matter hyperintensities in patients with autosomal dominant AD.
- The perivascular space plays a role in waste clearance from the brain. MR-visible perivascular space in the basal ganglia has greater associations with cerebrovascular disease and vascular cognitive impairment, whereas centrum semiovale perivascular space is more associated with AD and CAA.
- Vascular cognitive impairment treatment and prevention should focus on stroke risk factors, including blood pressure control. For patients with a history of stroke or transient ischemic attack, individualized secondary stroke prevention measures are warranted.

of intervention in reducing cognitive decline in older adults.¹²⁴ However, two other multidomain lifestyle intervention studies, MAPT (the Multidomain Alzheimer Prevention Trial) and PreDIVA (the Prevention of Dementia by Intensive Vascular Care), failed to show beneficial effects of treatment on primary cognitive outcomes. Study differences possibly explaining these discrepancies in outcomes include the average age of enrolled participants as well as the intensity of and adherence to the implemented intervention.^{125,126}

One randomized controlled trial investigating memantine for the treatment of vascular dementia found significant beneficial effects on cognitive function in patients with vascular cognitive impairment due to small vessel ischemic disease,⁷⁹ and there is additional evidence of treatment efficacy of donepezil on cognition in those with vascular dementia.¹²⁷ For patients who have already had a clinical stroke or TIA, individualized stroke prevention measures are indicated to preserve cognitive function and prevent new vascular brain injury, as outlined in the 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines for secondary stroke prevention.¹²⁸ The AHA/ASA presidential advisory has additionally published guidelines regarding the maintenance of cognitive health for all adults, optimizing cardiovascular risk factors that are thought to parallel relationships with cerebrovascular health.¹²⁹ Recommendations include following the AHA's "Life's Simple 7," which targets four modifiable health behaviors (healthy diet, participation in physical activity, avoidance of nicotine, and healthy weight) and three health factors (healthy levels of blood lipids, blood glucose, and blood pressure) that have previously been shown to reduce incidence of cognitive impairment.^{130,131} These guidelines were updated in 2022, resulting in the new "Life's Essential 8," which now includes sleep health and additionally identifies two cardiovascular health foundations: (1) psychological health and well-being and (2) social determinants of health. These metrics of optimal cardiovascular health can be found in **TABLE 5-6.**¹³² The overall goals for vascular cognitive impairment prevention include not only the prevention of cognitive decline due to direct vascular brain

TABLE 5-6**Metrics for Optimal Cardiovascular Health: "Life's Essential 8"^a**

Metric	Ideal Cardiovascular Health Definition
Diet	Dietary Approaches to Stop Hypertension (DASH)-style diet adherence
Physical activity	150 minutes or more of moderate-or-greater-intensity activity per week
Nicotine exposure	Nonsmoker
Sleep health	Average of 7-9 hours of sleep per night
Body mass index	<25 kg/m ²
Blood lipids	Non-high-density lipoprotein cholesterol <130 mm/dL
Blood glucose	Fasting blood glucose <100 mg/dL or hemoglobin A _{1C} <5.7%
Blood pressure	<120/<80 mm Hg

^a Data from Lloyd-Jones DM, et al, Circulation.¹³⁰

injury but also the preservation of cognitive reserve so that cognitive function may be better maintained in the presence of other abnormal brain pathologies common in older age.

HEALTH DISPARITIES IN VASCULAR COGNITIVE IMPAIRMENT

Black and Hispanic or Latino adults are disproportionately affected by AD and related disorders and have 1.5 to 2 times the risk of AD and other dementias compared with non-Hispanic White adults.^{133,134} Although research regarding the impact of health disparities on the incidence of vascular cognitive impairment specifically is currently lacking, it is recognized that much of the observed difference in AD and related dementia risk can be attributed to an increased prevalence of cardiovascular risk factors in historically marginalized and underserved populations.¹³⁴ Older Black adults have a greater incidence of recurrent stroke and stroke mortality compared with White adults, and they have a higher prevalence of stroke risk factors, including hypertension, diabetes, and smoking.^{20,135} In the WHICAP (Washington Heights-Inwood Columbia Aging Project) study, older Black participants had greater MRI T2 white matter hyperintensity burden than older White and Latino participants.¹³⁶ Furthermore, neuropathologic data from the National Alzheimer's Coordinating Center has demonstrated greater mixed pathologies at autopsy, including cerebrovascular disease, in Black and Hispanic compared with White decedents who died with dementia.¹³⁷ Contributors to health disparities in vascular cognitive impairment are varied and complex. They include such factors as lack of social support, lower educational attainment and socioeconomic status, limited health care access (including preventative care, health maintenance, and acute care), differences in health literacy and cultural norms, and implicit and explicit bias in disease management.^{17,133,138} Social determinants of health are now recognized by the AHA as a fundamental consideration in the evaluation of cardiovascular health. Addressing health disparities and lack of health care equity is a critical component of realizing successful vascular cognitive impairment prevention and treatment in all older adults.¹³²

KEY POINTS

- The American Heart Association's "Life's Essential 8" recommendations for optimal cardiovascular health include a healthy diet and weight; physical activity; nicotine avoidance; glucose, lipid, and blood pressure control; and adequate sleep.
- Older Black and Hispanic or Latino adults are disproportionately affected by AD and related dementias, largely because of health care disparities in the management of stroke and vascular risk factors.
- Contributors to health disparities in vascular cognitive impairment include lack of social support, limited health care access, and implicit and explicit bias in disease management. Addressing health care inequities is fundamental in vascular cognitive impairment prevention.

CONCLUSION

Vascular cognitive impairment is extremely common and heterogeneous, with etiologies of vascular brain injury ranging from cardiac dysfunction hypoperfusion syndrome and large vessel territorial infarcts to more chronic and insidious manifestations of cumulative small vessel ischemic disease due to venous collagenosis, arteriolosclerosis, cerebral microinfarcts, and CAA. The diagnosis of vascular cognitive impairment should be made in individuals with cognitive impairment due to cerebrovascular dysfunction, including those with MCI and mixed-etiology dementias. Brain injury due to cerebrovascular disease contributes to cognitive impairment both independently and as part of mixed-pathology syndromes. Vascular cognitive impairment has links to AD in shared risk factors and a possible role in pulsatility-related impairment in the clearance of toxic solutes from the brain. Treatment and intervention recommendations are individualized to specific causal mechanisms leading to vascular cognitive impairment, with preventative measures targeting cardiovascular risk factors recommended for all adults starting in midlife. Goals for cerebrovascular disease prevention include not just the deterrence of direct brain injury from vascular

insults but also the preservation of cognitive reserve in the presence of common nonvascular age-related cortical pathologies. The largely preventable nature of vascular cognitive impairment makes it a critical target for treatment and prevention efforts aimed at preserving cognitive function in older adults.

ACKNOWLEDGMENT

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LATE, Hippocampal Sclerosis, and Primary Age-related Tauopathy

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ABSTRACT

OBJECTIVE: Although Alzheimer disease (AD) is the most common neurodegenerative cause of dementia, neurologists must be aware of other etiologies that can mimic the amnestic-predominant syndrome and medial temporal brain involvement typically associated with AD. This article reviews recent updates surrounding limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), hippocampal sclerosis, and primary age-related tauopathy.

LATEST DEVELOPMENTS: LATE neuropathologic change occurs in approximately 40% of autopsied older adults, including occurrences in isolation in some older individuals with amnestic cognitive impairment. LATE neuropathologic change is often, but not always, associated with hippocampal sclerosis (neuronal loss and gliosis in the hippocampus and associated structures) and frequently coexists with AD and other neurodegenerative pathologies. Although there is no direct clinical biomarker for TDP-43 pathology, recent studies suggest that a clinical diagnosis of LATE can be achieved through the integration of multiple data points. Primary age-related tauopathy refers to the pathologic finding (in some cognitively unimpaired older adults as well as some individuals with cognitive impairment) of medial temporal-predominant neurofibrillary tangles in the absence of amyloid- β (A β) plaques. Recent consensus frameworks have attempted to resolve ambiguities of nomenclature and diagnosis for these entities, and efforts toward in vivo biomarkers are ongoing.

ESSENTIAL POINTS: LATE, with or without hippocampal sclerosis, and primary age-related tauopathy belong in the differential diagnosis (along with AD, argyrophilic grain disease, and other disorders) for slowly progressive amnestic-predominant cognitive impairment, particularly in individuals older than 75 years. Accurate recognition of clinical and diagnostic test features supportive of these non-AD entities is vital to optimize patient counseling, therapeutic selection, and novel biomarker development.

INTRODUCTION

The clinicopathologic spectrum of neurodegenerative diseases is wide, including heterogeneity in disease-associated proteins, brain topographical involvement, clinical features, and rates of symptomatic progression. Alzheimer disease (AD) is the most common neurodegenerative cause of mild cognitive impairment and dementia in older adults and typically results in progressive amnestic-predominant cognitive decline. However, data from a 2021 study indicate that approximately 15% of individuals diagnosed clinically with probable AD dementia do not have biological evidence for AD (ie, they do not have evidence for amyloid- β [A β] plaques and tau neurofibrillary tangles), implying an alternative cause for dementia in those cases.¹ In the initial Phase 3 trials of solanezumab, more than 20% of patients with a clinical diagnosis of mild AD were amyloid positron emission tomography (PET) negative.² These findings highlight the prevalence of mimics, even within a carefully phenotyped trial, and the necessity of biomarkers for trial enrollment and treatment decisions.³

Among older individuals with amnestic impairment, additional important elements of the differential diagnosis include limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) with or without hippocampal sclerosis and primary age-related tauopathy. Current limitations to the accurate diagnosis of these entities include a lack of awareness outside of subspecialty clinic and research settings, an evolving understanding of potentially distinguishing signs and symptoms in the absence of established clinical criteria, and the high prevalence of neurodegenerative copathology in older adults with cognitive impairment. Particularly with the emergence of disease-modifying treatment options, which are specific to underlying etiology,⁴ it is vital for neurologists to accurately recognize these and other potential mimics of AD to optimize clinical decision making and patient counseling. This article examines clinically relevant concepts of LATE, hippocampal sclerosis, and primary age-related tauopathy, with a particular focus on postmortem pathologic definitions, recent terminology updates, commonly encountered syndromic features, insights from existing diagnostic tools, and active and future developments in antemortem biomarkers.

LATE AND HIPPOCAMPAL SCLEROSIS

Studies of LATE and hippocampal sclerosis represent one of the most dynamic areas of neurodegenerative research. *LATE neuropathologic change* refers to the pathologic accumulation of aberrantly localized and phosphorylated TDP-43 primarily within the limbic system in older adults (FIGURE 6-1).⁵ It is increasingly recognized that some older individuals with amnestic dementia syndromes and little or no AD pathology may instead be found at autopsy to have LATE neuropathologic change.⁶ Similarly, LATE neuropathologic change may co-occur with AD pathology and play a role in the phenotypic expression of the disorder. In 2019, a consensus workgroup proposed diagnostic criteria for LATE (the disease entity associated with LATE neuropathologic change), which often coexists with hippocampal neuronal loss and gliosis referred to as *hippocampal sclerosis*.⁷ The complex and evolving nosology around these historically pathology-defined entities contributes to ongoing debate around the accuracy

KEY POINTS

- Alzheimer disease (AD) is the most common neurodegenerative cause of dementia and typically manifests with amnestic-predominant cognitive decline.
- As many as 15% to 20% of individuals diagnosed clinically with probable AD dementia lack biological evidence of the disease, highlighting the importance of awareness of potential AD mimics.
- Limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) is an increasingly recognized cause of slowly progressive amnestic impairment, particularly among individuals older than 75 years.
- LATE neuropathologic change is marked by aberrantly localized and phosphorylated TDP-43 primarily within the limbic system.

of diagnosis, precision of communication among neurologists and other clinicians, and investigation of underlying mechanisms, all of which have implications for current clinical care and future treatment trials. Adding to this nuance, although LATE and hippocampal sclerosis commonly coexist, neither is necessary nor sufficient for diagnosis of the other, and there remains debate on the intersections and boundaries among LATE, hippocampal sclerosis, AD, frontotemporal lobar degeneration (FTLD) associated with TDP-43 (FTLD-TDP), and mixed-pathology scenarios.

Relationships Among LATE, LATE Neuropathologic Change, and Hippocampal Sclerosis

Widespread neuronal loss and gliosis in the hippocampus can be observed in a variety of clinical settings, including via anoxic or ischemic injury, focal epilepsy, and trauma, among others. However, in older individuals, hippocampal sclerosis is common (found in 10% to 20% of adults older than 85 years) and is associated with slowly progressive amnestic cognitive impairment, which can mimic the clinical syndrome of AD.^{8,9} The term *hippocampal sclerosis of aging* is sometimes used to describe this context, namely, the observation of characteristic hippocampal sclerosis pathology in an older individual without other risk factors (eg, temporal lobe epilepsy) to account for the histologic findings. By most definitions, the typically striking neuronal loss and gliosis observed in hippocampal sclerosis is not explained by the burden of AD pathology, which can be absent in many cases.^{9,10} In addition, after age 85, the prevalence of hippocampal sclerosis increases while the prevalence of severe AD neuropathologic change decreases,¹¹ further suggesting that hippocampal sclerosis in the oldest individuals represents an outcome of a clinically and pathologically distinct neurodegenerative disorder.

A growing body of research has implicated TDP-43 as a central feature in hippocampal sclerosis. Among older individuals who were confirmed by

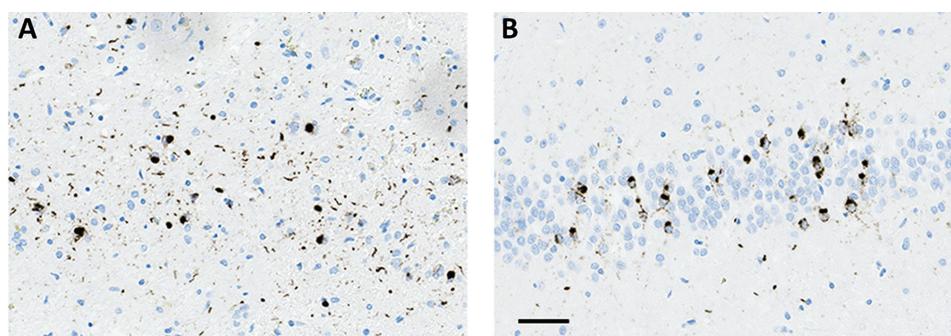


FIGURE 6-1

Formalin-fixed, paraffin-embedded tissue sections (5- μ m thick) were immunostained for phosphorylated transactive response DNA-binding protein 43 (TDP-43) (pS409/410, mouse monoclonal; 1:5000) and analyzed at 20x magnification. A, Frequent TDP-43 immunoreactive inclusions (denoted by dark staining within neurons in the field) were observed in the entorhinal cortex, consistent with limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathologic change by consensus criteria. B, Moderate burden of TDP-43 immunoreactive inclusions was additionally observed in the dentate gyrus, consistent with advanced LATE neuropathologic change. Of note, in vivo biomarkers and postmortem neuropathologic findings in this patient were also consistent with admixed Alzheimer disease.

postmortem neuropathology to have hippocampal sclerosis, abnormal TDP-43 proteinopathy (defined by a loss of normal nuclear localization, presence of TDP-43-positive neuronal cytoplasmic inclusions, and accumulation of aberrantly phosphorylated TDP-43 in neurons and glial cells)³ has been identified in up to 90% of cases.^{8,9} Several studies have demonstrated that the presence of TDP-43 pathology is associated with greater hippocampal atrophy and more severe cognitive impairment, including independent effects of TDP-43 even in the presence of coexistent AD, Lewy body disease, or cerebrovascular disease pathology.¹²⁻¹⁵ In addition, limbic-predominant TDP-43 immunostaining is almost always bilateral in cases of hippocampal sclerosis even when routine histology shows only unilateral findings of hippocampal neuronal loss and gliosis.^{7,9} Further, antemortem imaging studies of individuals with confirmed TDP-43-positive hippocampal sclerosis have reported atrophy and hypometabolism outside of the hippocampus proper.^{16,17} Collectively, these findings point to TDP-43-related processes as potentially being mechanistically upstream of observed hippocampal sclerosis in older individuals. This background has served as motivation for efforts to refine the terminology applied in this space to enhance awareness, implement frameworks for clinical diagnosis and pathologic staging, and facilitate antemortem biomarker development.

The proposed terms of *cerebral age-related TDP-43 with sclerosis*¹⁸ and subsequently *LATE*⁷ have placed TDP-43 pathology as the signal element of an underlying disease entity that can in many (but not all) cases result in findings of hippocampal sclerosis and clinical symptoms. Within this context, staging criteria for LATE neuropathologic change have been developed based on the stereotyped topographic pattern of TDP-43 proteinopathy observed in most cases, first affecting the amygdala (stage 1), then the hippocampus (stage 2), and then more broadly the neocortical regions including the middle frontal gyrus (stage 3).⁵ In this model, it has been suggested that stage 1 LATE neuropathologic change may represent a preclinical or incipient state compatible with normal cognition or early memory symptoms, whereas stages 2 and 3 LATE neuropathologic change have more robust associations with amnestic-predominant cognitive impairment.^{5,7,19}

LATE neuropathologic change is highly prevalent in the general population; it has been found in approximately 40% of older adults overall at autopsy and in isolation in up to 20% of individuals older than 85 years who had amnestic cognitive impairment.⁶ Of note, criticisms of the LATE framework have argued for additional research before more widespread use. These criticisms include the use of *encephalopathy* when LATE neuropathologic change can be present without cognitive impairment, the competing hypothesis that TDP-43 pathology itself may represent an end-stage product of other degenerative processes, the lack of clarity in differentiating LATE from FTLD-TDP (discussed in more detail later in this article) and other settings in which TDP-43 pathology may be identified, and the concept of LATE being a semantic construct in nature rather than a settled distinct disease entity.²⁰ Nevertheless, there is a growing consensus on the potential value of establishing criteria for a clinical diagnosis of LATE to maximize awareness for clinical decision making, equity for patients receiving care in settings with varying expertise and technology access, and development of novel biomarkers and therapeutics.²¹

KEY POINT

- In older individuals, findings of hippocampal sclerosis (neuronal loss and gliosis in the hippocampus) are typically the result of neurodegenerative disease, with LATE being the most commonly associated entity.

Clinical Features

The typical clinical syndrome of LATE is characterized by insidiously progressive amnestic-predominant cognitive decline.⁷ As can be reported in patients with early AD, the history may include asking repeated questions or forgetting recent conversations or events (**CASE 6-1**).

On examination, patients may struggle with tasks of verbal learning and memory, such as those involving word lists or story recall. In the appropriate clinical context, features suggestive of LATE (compared with AD) include presentation at an older age (typically older than 75 years), a longer symptomatic course with milder intensity, concomitant mild semantic deficits (eg, difficulties recalling major world events and other emotionally salient historical information) reflecting amygdalar and hippocampal

CASE 6-1

A 78-year-old woman was seen in neurology clinic for 5 years of gradually progressive short-term memory difficulties, manifesting with her frequently repeating questions and forgetting recent conversations and events. Over a similar timeframe, she was noted by her family to be less patient and more irritable. She had retired from her job 12 years before and had remained medically healthy, mentally and physically engaged, and independent with daily activities in the years since. She had good insight into her symptoms. At initial evaluation, she scored 35/38 on the Short Test of Mental Status, including 1/4 on delayed word recall. Laboratory testing revealed low-normal vitamin B₁₂ (226 ng/L) and normal thyroid-stimulating hormone (TSH) levels. After brain MRI, she was diagnosed with clinically probable Alzheimer disease (AD) and was started on donepezil.

At follow-up 2 years later, her family felt that memory difficulties had become somewhat more prominent, necessitating occasional reminders for medication adherence. She scored 34/38 on the Short Test of Mental Status, including 0/4 on delayed recall, and had a normal general neurologic examination. Neuropsychological testing revealed mild impairments in verbal memory assessed by the Rey Auditory Verbal Learning Test (5 words learned, with 0 words recalled at a 30-minute delay), along with a relatively normal cognitive profile otherwise. Brain MRI showed hippocampal volume loss, and brain fludeoxyglucose positron emission tomography (FDG-PET) showed medial temporal hypometabolism (**FIGURE 6-2**). Amyloid PET was negative, indicating no evidence of abnormal amyloid- β (A β) plaque deposition. She was diagnosed clinically with amnestic mild cognitive impairment due to probable limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE). She was counseled on lifestyle modifications to promote brain health, pursued daily adaptations and oversight strategies given her memory difficulties, and discontinued donepezil. At autopsy 10 years later, she was confirmed to have LATE neuropathologic change with coexisting hippocampal sclerosis and no evidence of AD neuropathology.

dysfunction, and a lack of prominent neocortical signs (eg, apraxia).²¹ Autopsy-based studies with antemortem clinical evaluations support that individuals with isolated LATE neuropathologic change have a later age of onset of cognitive decline, lesser degree of impairment, and longer overall lifespan than individuals with AD, highlighting the prognostic value of differentiating these distinct etiologic diagnoses.²² Importantly, individuals with LATE neuropathologic change may perform within the normal range on cognitive testing (particularly office-based screening tools such as the Mini-Mental State Examination or the Short Test of Mental Status) at early time points but nevertheless be at risk for future declines, with implications for case-control research studies and therapeutic trial enrollment.²²

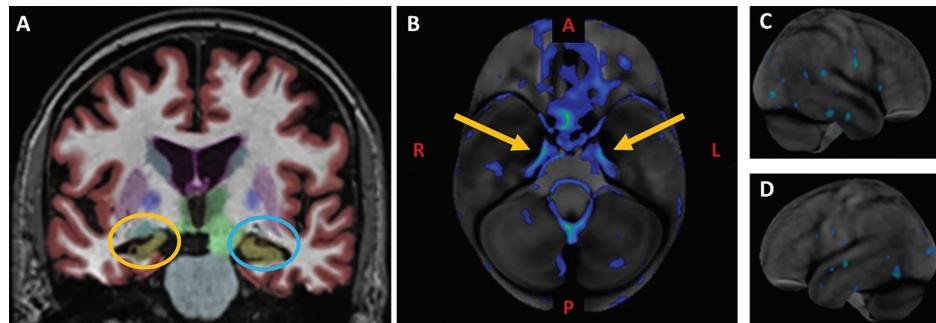


FIGURE 6-2

Neuroimaging findings for the patient in **case 6-1**. **A**, Coronal T1-weighted brain MRI shows bilateral right (orange oval) slightly worse than left (blue oval) hippocampal volume loss. **B**, Inferior view from brain fluorodeoxyglucose positron emission tomography (FDG-PET) where blue color denotes regions of diminished metabolism relative to an age-matched normal population. Medial temporal hypometabolism (arrows) was observed in this patient, a finding that can in the right context support a clinical diagnosis of limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE). **C, D**, Surface maps of the right and left hemispheres from the same brain FDG-PET show an absence of parietal or lateral temporal hypometabolism, arguing against Alzheimer disease as the etiologic diagnosis in this patient.

This case illustrates a characteristic clinical presentation of LATE, an entity that belongs in the differential diagnosis (along with AD, argyrophilic grain disease, primary age-related tauopathy, and other etiologies) for slowly progressive amnestic-predominant syndromes in individuals older than 75. Although there is no known direct clinical biomarker of TDP-43 pathology, the pattern of medial temporal atrophy and hypometabolism without involvement of other cortical areas (parietal and temporal lobes) has been described in patients with LATE and coexisting hippocampal sclerosis. Therefore, the combination of the clinical presentation (memory-circumscribed syndrome at a later age), slowly progressive course, and imaging findings in the absence of AD pathology (negative amyloid PET) points to LATE as the probable etiologic diagnosis.

COMMENT

Despite the presence of hippocampal sclerosis in some cases with temporal lobe seizure disorders, there is no evidence that concomitant hippocampal sclerosis in the setting of LATE neuropathologic change is associated with increased seizure prevalence.²³ More broadly, hippocampal sclerosis associated with LATE neuropathologic change is distinguished from the hippocampal sclerosis associated with seizures by the age of onset (older adults), association with TDP-43, and slowly progressive amnestic presentation. Pathologic studies have identified a limbic-predominant form of AD with a similar clinical phenotype, highlighting a situation in which AD biomarkers may be useful.²⁴ Of note, most studies of LATE have involved cohorts mainly comprising non-Hispanic White individuals.²⁵ The largest known community-based study of older Black individuals showed similar prevalence (approximately 40%) and clinical features (association with amnestic-predominant cognitive decline) with LATE neuropathologic change compared with White individuals.²⁶ There remains a pressing need for additional research in diverse cohorts, including efforts to address existing data gaps on the intersection of lifelong structural and social determinants of health, cerebrovascular disease, and TDP-43 and AD pathology toward cognitive functioning in the broader population.²⁷

Biomarkers

Although there is no direct antemortem biomarker for LATE (with or without hippocampal sclerosis), neuroimaging in conjunction with the clinical scenario can be useful in prioritizing LATE against other elements of the differential diagnosis. Compared with AD, amygdalar and hippocampal atrophy on MRI with LATE (particularly when hippocampal sclerosis is coexistent) may be striking and out of proportion to the clinical scenario (ie, the atrophy occurs in the setting of mild or circumscribed impairment as opposed to more extensive multidomain impairment of clinically typical AD). A 2023 study of cognitively unimpaired older adults found that longitudinal hippocampal volume loss was associated with cognitive decline independent of A β or tau PET burden,²⁸ further pointing to non-AD pathologies (including TDP-43) as potentially important contributors to cognitive decline mediated by hippocampal dysfunction and degeneration. The relative lack of neocortical volume loss observed in inferior or lateral temporal and parietal regions on MRI can also indirectly support LATE as the etiologic diagnosis over AD in the right clinical setting. Some studies suggest that anterior-medial temporal lobe atrophy reflects TDP-43 pathology while posterior hippocampal atrophy is more associated with tau related to AD pathology.²⁹

Isolated medial temporal and posterior cingulate hypometabolism on fludeoxyglucose (FDG)-PET in the absence of inferior or lateral temporal, precuneus, or parietal hypometabolism may also be a supportive marker for LATE as opposed to AD (**FIGURE 6-2**), and the ratio of inferior to medial temporal hypometabolism has been proposed as a potential indicator of tau negativity (and therefore higher likelihood of LATE and hippocampal sclerosis) in cases of amnestic dementia.¹⁷ It is not yet known how sensitive FDG-PET is for the detection of neuronal dysfunction or degeneration due to LATE in the absence of hippocampal sclerosis, and FDG patterns may reflect the cases with symptomatic LATE and hippocampal sclerosis rather than LATE in isolation. Nevertheless, when integrated with the finding that tau PET positivity is very unlikely in the setting of amyloid negativity,¹ these observations highlight the potential value of

FDG-PET as a complementary biomarker in the evaluation of amnestic dementia syndromes. Research in 2023 also demonstrated the ability to extrapolate tau PET imaging patterns based on FDG hypometabolism,³⁰ which could heighten the importance of FDG-PET in clinical evaluations, particularly given that tau PET imaging is not currently available widely in clinical practice and the fact that some tau tracers have demonstrated a degree of off-target binding hypothesized to relate to TDP-43.³¹ Another motivation for the development of biomarkers specific to LATE and hippocampal sclerosis involves the fact that AD and TDP-43 pathologies commonly coexist in older adults, where the presence of dual pathology is associated with more global cognitive impairment and faster clinical declines (**CASE 6-2**).^{22,32}

In the presence of AD neuropathologic change, individuals with a high burden of TDP-43 pathology have faster rates of brain atrophy (within and outside of the hippocampus) early in the symptomatic course compared with those with lower stages of TDP-43 pathology.³³ The finding that individuals with AD and low TDP-43 burden exhibit acceleration of brain atrophy late in the disease course correlates most strongly with the development of advanced tau pathology (higher Braak stage),³³ further highlighting the challenge in distinguishing among patients with AD, LATE, or AD and LATE early in the clinical course. These distinctions will become even more important with the clinical availability of symptomatic medications (eg, cholinesterase inhibitors, memantine) and emerging disease-modifying treatment options (eg, anti-amyloid monoclonal antibody therapies) for AD,⁴ none of which have indications for use in isolated LATE and for which relative risks and benefits may be dramatically influenced by the presence of dual pathology as opposed to isolated AD.

Attempts to develop fluid biomarkers for TDP-43 pathology remain ongoing, although without clear successes to date. Thus far, no antibody-based assays have been able to reliably detect phosphorylated TDP-43 in the CSF.³⁴ Blood-based measures represent an attractive option for future biomarker development, but challenges with dynamic range for detection seen with other neurodegenerative conditions may be exacerbated with LATE and hippocampal sclerosis because of the molecular structure of TDP-43 and limitations in detecting brain-enriched shorter protein fragments by immunoassay on blood samples.²⁵ Blood-based astrocyte-derived extracellular vesicles measuring TDP-43 appear to be an emerging technique requiring additional studies for confirmation.³⁵ Developing seed amplification assays similar to those used for prion disease are being investigated for application with olfactory mucosa samples in FTLD-TDP, although additional validation remains critical.³⁶

Distinctions Between LATE and FTLD-TDP

TDP-43 accumulation represents the primary proteinopathy in approximately 50% of patients with frontotemporal dementia (FTD), as well as most cases of amyotrophic lateral sclerosis (ALS).³⁷ Pathologic subtypes of FTLD-TDP have been defined based on the specific brain topographic pattern of TDP-43 accumulation and other histologic features, such as the laminar involvement in neocortical regions, the presence of neuronal versus glial cytoplasmic inclusions, and the appearance of dystrophic neurites.³⁷ As with frontotemporal degenerative diseases more broadly, there is informative but incomplete correlation of clinical phenotypes with pathologic subtypes of TDP-43; for

KEY POINTS

- Compared with people with AD, individuals with LATE typically have a longer clinical course with milder intensity of functional impairment and a lack of prominent neocortical signs.
- Currently, there are no direct antemortem imaging or fluid biomarkers of LATE, although several approaches are in active development.
- Amygdalar and hippocampal atrophy is often striking in LATE, out of proportion to the degree of impairment or extent of neocortical atrophy observed.
- Preferential volume loss (on MRI) and hypometabolism (on FDG-PET) in the medial temporal regions with a relative absence of parietal or inferior or lateral temporal involvement may serve as supportive biomarkers for LATE in the appropriate clinical context.
- Among individuals with an amnestic dementia and amyloid PET positivity, the ratio of inferior to medial temporal metabolism on FDG-PET may serve as a surrogate to detect tau PET negativity and a resulting high likelihood of LATE and hippocampal sclerosis.

example, FTLD-TDP type B accounts for the majority of FTD and ALS cases, and most cases of semantic dementia are related to FTLD-TDP type C.³⁸

There remains active debate on the optimal boundaries between LATE or LATE neuropathologic change and FTD or FTLD-TDP. From a purely pathologic standpoint, stage 3 LATE neuropathologic change and FTLD-TDP may be challenging to discriminate in some cases and could be influenced by the cerebral hemisphere sampled for autopsy analyses. Nevertheless, frameworks for distinguishing LATE neuropathologic change from FTLD-TDP have been proposed and largely rely on differences in the regional distribution and relative burden of phosphorylated TDP-43.^{5,25} Data-driven

CASE 6-2

An 83-year-old man was referred to a neurologist for 2 years of progressive cognitive decline, primarily observed by his family, with the patient himself not convinced of any substantive change. Particularly over the preceding year, he had been observed to repeat questions, misplace objects, have difficulty recalling recent family activities, display word-finding troubles in conversation, and require assistance with navigation in his hometown. His spouse began to manage the home finances after he left two bills unpaid and miscalculated tip amounts at restaurants. On examination, he scored 16/38 on the Short Test of Mental Status, was tangential but redirectable, was unable to complete the Luria (fist-edge-palm) hand sequence, had ideomotor apraxia, and had difficulties providing substantive details about major historical events (eg, September 11, 2001, or the worldwide coronavirus pandemic). Neuropsychological assessment included diffuse impairment with verbal learning and memory most severely affected but with no cognitive domain spared. Laboratory studies revealed normal vitamin B₁₂ and thyroid-stimulating hormone (TSH) levels.

Brain MRI showed volume loss in the left worse than right parietal regions along with the appearance of disproportionate atrophy involving the hippocampi (FIGURE 6-3). Brain fludeoxyglucose positron emission tomography (FDG-PET) showed parietotemporal hypometabolism most prominent in the left cerebral hemisphere, along with left medial temporal hypometabolism (FIGURE 6-3). CSF biomarker testing revealed an abnormal phosphorylated tau to amyloid-β (Aβ) ratio (0.047; normal, ≤0.028) as well as abnormal CSF phosphorylated tau (28.6 pg/mL; normal, ≤21.6 pg/mL) and CSF Aβ (565 pg/mL; normal, >834 pg/mL) concentrations. The patient was diagnosed with Alzheimer disease (AD) dementia, with suspicion for admixed limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE). He was treated with a cholinesterase inhibitor and memantine. Over the following 3 years, the disease continued to progress clinically, and he was transitioned to a memory care facility before dying at age 86. Postmortem neuropathology confirmed the presence of LATE neuropathologic change coexistent with advanced AD neuropathology.

approaches based on machine learning have similarly been able to discriminate most cases of LATE neuropathologic change from FTLD-TDP, but overlap across late-stage LATE neuropathologic change and early-stage FTLD-TDP remained problematic in those models.³⁹ In general, clinical differentiation is less fraught based on the distinctive syndromes described for LATE (amnestic-predominant cognitive decline at older ages) versus FTD (predominant behavioral and language impairment at relatively younger ages).^{40,41} Analyses of community-dwelling adults support the accuracy of clinical distinction between these entities.³² For clinical settings where LATE and FTLD are considerations in the differential diagnosis, it may therefore be

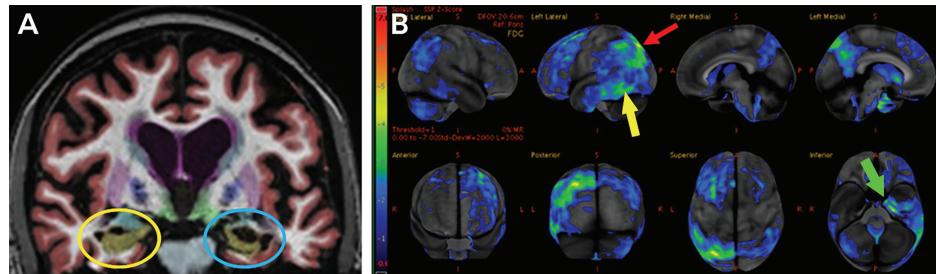


FIGURE 6-3

Neuroimaging findings for the patient in **case 6-2**. **A**, Coronal T1-weighted brain MRI shows substantial bilateral but left (blue oval) worse than right (yellow oval) hippocampal volume loss. **B**, Brain fludeoxyglucose positron emission tomography (FDG-PET) shows regional hypometabolism (indicated by areas of color, with higher colors on the scale denoting more severe hypometabolism) relative to an age-matched normal population. FDG hypometabolism was observed in the parietal (red arrow) and inferior and lateral temporal (yellow arrow) regions in a pattern highly consistent with underlying Alzheimer disease. Additional hypometabolism was observed in the left medial temporal region (green arrow). Given the clinical syndrome, pattern of parietotemporal FDG hypometabolism, and relatively disproportionate atrophy and metabolic disturbance in the medial temporal regions in a patient older than 80 years, the clinical diagnosis was suspected to involve mixed Alzheimer disease and limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE).

This case illustrates a common scenario among older adults with cognitive decline, particularly those at a later age, specifically the presence of multiple neurodegenerative etiologies (ie, copathology). Clues to the potential presence of admixed LATE in this patient included the clinical presentation of progressive multidomain impairment with a relatively faster clinical trajectory (in contrast to **CASE 6-1**) and the disproportionate hippocampal atrophy alongside other imaging and fluid biomarkers supportive of AD.

COMMENT

practical to consider that LATE would be favored among older individuals (eg, those older than 70 to 75 years) and in the absence of archetypal clinical syndromes (eg, behavioral variant FTD, semantic dementia, agrammatic or nonfluent primary progressive aphasia) or genetic mutations (eg, *GRN*, *C9orf72*) pointing to FTLD-TDP.

PRIMARY AGE-RELATED TAUOPATHY

The presence of tau-containing neurofibrillary tangle pathology represents a nearly ubiquitous finding among the oldest adults (ie, individuals older than 90 to 100 years).⁴² Although the majority of such cases reflect underlying AD neuropathologic change (ie, amyloid positive and tau positive), approximately 20% of centenarians display hippocampal neurofibrillary tangles without evidence of A β plaques.⁴³ This finding of medial temporal–predominant AD-type neurofibrillary tangles in the absence of A β plaque accumulation has been more recently designated as primary age-related tauopathy.⁴⁴ The concept of primary age-related tauopathy is meant to encompass a continuum ranging from the medial temporal–predominant neurofibrillary tangle deposition in cognitively normal older adults through what has been previously described as “tangle-predominant dementia” or “tangle-only dementia” in some older individuals with cognitive impairment. As it is currently understood, primary age-related tauopathy includes areas of overlap and distinction in relation to AD, FTLD associated with tau, and normal cognitive aging, highlighting the need for further study and greater precision to guide clinical practice and evolving research frameworks.

Neuropathology

The defining postmortem histologic trait of primary age-related tauopathy involves hyperphosphorylated three-repeat (3R) and four-repeat (4R) tau isoforms aggregated into paired helical filament structures within neurons.⁴⁴ In primary age-related tauopathy, neurofibrillary tangles are predominantly found in the medial temporal (and associated subcortical) regions. With more advanced primary age-related tauopathy pathology, there can be an extension of neurofibrillary tangle accumulation to the lateral temporal and cingulate

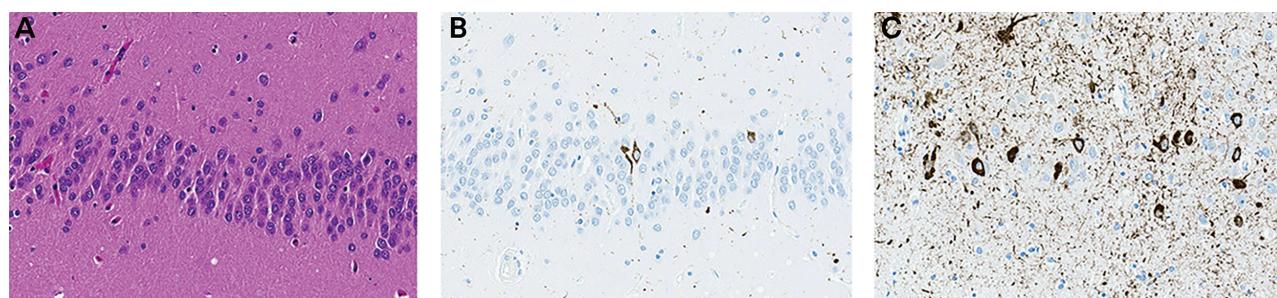


FIGURE 6-4

Formalin-fixed, paraffin-embedded tissue sections (5- μ m thick) are displayed at 20x magnification. **A**, Hematoxylin and eosin (H&E) staining shows mild neuronal loss in the dentate gyrus. **B**, A representative section from the dentate gyrus shows mild immunostaining for phosphorylated tau (AT8; 1:1000). **C**, More extensive phosphorylated tau staining is observed in the entorhinal cortex, which in the context of a lack of amyloid- β (A β) plaques (not displayed) and no evidence for tau deposition in the temporal neocortex, is consistent with primary age-related tauopathy in this patient.

regions. This focal distribution, as opposed to more widespread extratemporal involvement, and the lack of concomitant evidence for cortical amyloid plaques distinguish primary age-related tauopathy from AD pathologically (**FIGURE 6-4**).

Criticisms of the primary age-related tauopathy framework have proposed that it may not represent a distinct disease entity but rather that pathologic findings of primary age-related tauopathy are best viewed within the spectrum of biologically defined AD (wherein amyloid and tau are each necessary but neither is sufficient).⁴⁵ The concept of primary age-related tauopathy and AD representing a single mechanistic process is challenging to align with their distinct demographic and clinical profiles (discussed in more detail later in this article). Neuropathologic differences exist, as well, including higher Braak stage⁴⁶ and more frequent coexistence of TDP-43 accumulation⁴⁷ in AD than primary age-related tauopathy. In addition, genetic studies have consistently revealed robust relationships of the apolipoprotein E (*APOE*) gene with cerebral amyloidosis⁴⁸ and clinically diagnosed AD dementia⁴⁹ but have demonstrated no convincing association of *APOE* with primary age-related tauopathy.⁵⁰ Some imaging studies have also confirmed the presence of distinct spatial and temporal patterns of tau deposition in AD (including limbic-predominant and hippocampal-sparing patterns)⁵¹ compared with amyloid-negative settings⁵² and have suggested that at least moderate levels of cortical amyloid burden are necessary for detectable tau burden beyond the entorhinal cortex.⁵³ Collectively, these areas of divergence support the concept of primary age-related tauopathy being a clinically and mechanistically separate entity from AD, acknowledging the need for additional research in this area.

Clinical Features

There are no established criteria for a clinical diagnosis of primary age-related tauopathy. One barrier to developing robust diagnostic criteria involves the fact that many individuals with pathologically definite primary age-related tauopathy (approximately 70% in one large autopsy cohort)⁵⁴ have no evident cognitive syndrome at the time of death. Nevertheless, several studies have described an association of primary age-related tauopathy pathology at autopsy with antemortem cognitive impairment that is typically mild, slowly progressive, and amnestic-predominant.^{44,55-57} Recent analyses also suggest that nonamnestic (eg, executive function, language) impairment may be more frequent in patients with primary age-related tauopathy than was previously thought,^{57,58} including that deficits on measures of processing speed (eg, Trail Making Test A) and task switching (eg, Trail Making Test B) may be selectively affected in primary age-related tauopathy compared with AD.⁵⁷ Some studies have reported that the Braak stage in primary age-related tauopathy is associated with the degree of cognitive impairment observed.^{43,44,55,57} These findings are largely consistent with data on the relationship of the severity and topography of tau deposition to cognitive impairment in AD.⁵⁹ One large autopsy-defined series indicated that cognitive symptoms were only evident at Braak stages III and IV,⁵⁷ suggesting that differences in the extent of tau pathology may account for the heterogeneity in cognitive profiles among individuals with primary age-related tauopathy. However, additional work has cast doubt on whether the Braak stage alone is sufficient for characterizing the phenotypic spectrum of primary age-related

KEY POINTS

- AD and LATE commonly coexist in older adults with cognitive impairment and, when present concomitantly, are associated with faster rates of clinical decline and brain atrophy.
- LATE neuropathologic change is associated with distinctive clinical presentations and postmortem histologic features of TDP-43 pathology compared with frontotemporal lobar degeneration associated with TDP-43.
- The presence of neurofibrillary tangle pathology involving tau is a nearly ubiquitous finding among the oldest adults (ie, individuals older than 90 to 100 years).
- Primary age-related tauopathy refers to the finding of medial temporal-predominant AD-type neurofibrillary tangles in the absence of amyloid-β (Aβ) plaque accumulation.

KEY POINTS

- Individuals with primary age-related tauopathy may be cognitively unimpaired or may have a mild, amnestic-predominant syndrome.
- The severity and topographic distribution of neurofibrillary tangles in primary age-related tauopathy influence the likelihood of incident cognitive impairment.
- At this time, the presence of definite primary age-related tauopathy can be determined only through postmortem neuropathologic studies.
- Hippocampal atrophy (on MRI) and medial temporal hypometabolism (on FDG-PET) can be seen in patients with primary age-related tauopathy, but these findings are not specific to that diagnosis.
- Tau PET using newer-generation tracers represents an emerging biomarker for identifying primary age-related tauopathy, in the context of a lack of evidence for brain amyloidosis.

tauopathy,⁵⁴ with disruptions to larger-scale functional brain networks proposed as an alternative mechanism.⁶⁰

Another challenge in defining the clinical spectrum associated with primary age-related tauopathy relates to the high frequency of comorbid non-AD neuropathologies in the population (the oldest adults) in whom primary age-related tauopathy is most commonly identified. For example, in one study of patients meeting pathologic criteria for primary age-related tauopathy, approximately 25% also had TDP-43 accumulation, the presence of which was associated with greater medial and anterior temporal atrophy on MRI.⁶¹ Nevertheless, the aggregate of clinical outcome data supports that individuals with primary age-related tauopathy display less severe cognitive and functional impairment, later age of onset, and slower rates of decline than people with AD and other related neurodegenerative diseases.⁶²⁻⁶⁴ These findings highlight that primary age-related tauopathy should be an element of the differential diagnosis in appropriate clinical settings, particularly among older individuals with persistently mild impairment that seems clinically atypical for AD and has no specific features to suggest Lewy body disease (eg, parkinsonism, rapid eye movement [REM] sleep behavior disorder), FTD (eg, prominent behavior and personality changes), or other alternative etiologic diagnoses.

Biomarkers

Currently, the presence of definite primary age-related tauopathy can be determined only through postmortem neuropathology. Antemortem neuroimaging in cases with definite primary age-related tauopathy has demonstrated hippocampal atrophy on MRI and medial temporal hypometabolism on FDG-PET, indicative of focal neurodegeneration and neuronal metabolic dysfunction.^{55,65} However, these findings in isolation are not specific for primary age-related tauopathy and could be seen in limbic-predominant AD, LATE (with or without hippocampal sclerosis), argyrophilic grain disease (a 4R tau neurodegenerative disease characterized by spindle- or comma-shaped silver-staining lesions in the neuropil of predominantly medial temporal structures), or some temporal-predominant cases of FTLD.^{66,67}

It has been hypothesized that some tau PET tracers, thought to be specific for AD-like neurofibrillary tangles with mixed 3R and 4R tau in paired helical filament morphology, may be able to provide evidence for tau pathology in primary age-related tauopathy. Most existing studies involving flortaucipir have not provided evidence to support this hypothesis,^{68,69} and knowledge gaps remain regarding off-target tracer binding in both AD and non-AD settings.⁷⁰ A recent study of cognitively unimpaired individuals using a newer-generation tau PET tracer (¹⁸F-RO948) demonstrated an association of higher age with higher regional tau PET burden in the medial temporal lobes, as well as some extratemporal neocortical regions, after adjusting for amyloid PET burden.⁷¹ Subgroup analyses showed similar results among individuals who were amyloid PET negative, suggesting that ¹⁸F-RO948 tau PET could be useful in ascertaining amyloid-independent tau accumulation, including detection of tau accumulation outside the medial temporal lobes in some cases of primary age-related tauopathy.⁷¹ Additional work is needed to confirm no evidence of confounding by off-target tracer binding and to assess for validation in other samples, including those consisting of individuals with cognitive impairment. Further, it is not yet known how CSF or blood biomarkers measuring tau isoforms, most often

used in the context of determining the presence of cerebral amyloidosis for suspected AD,⁷² would perform in cases of primary age-related tauopathy, understanding that technical advances remain ongoing. In summary, existing knowledge and tools suggest that *in vivo* biomarker evidence supportive of primary age-related tauopathy in the future may involve both positive (ie, measures demonstrating tau deposition) and negative (ie, the absence of amyloidosis and other neurodegenerative pathologies) data points integrated into specific clinical scenarios. Further identification of molecular or conformational differences in primary age-related tauopathy-associated versus AD-associated tau could alter this landscape.

A RATIONAL APPROACH TO PATIENTS WITH AMNESTIC COGNITIVE IMPAIRMENT

It is broadly understood that there is no single test result or other data point that is uniformly sufficient for etiologic diagnosis of neurodegenerative diseases affecting cognition and behavior. Among older individuals with insidiously progressive cognitive impairment, it can sometimes be challenging to distinguish specific underlying causes by history and examination alone, particularly in early and mild stages where there can be heavy syndromic overlap. Although AD is the most common neurodegenerative cause of mild cognitive impairment and dementia in older adults and typically presents with amnestic-predominant impairment, LATE (without or with hippocampal sclerosis), primary age-related tauopathy, argyrophilic grain disease,^{66,67} and other etiologies remain important

Considerations Among Potential Etiologic Diagnoses for Amnestic Syndromes

TABLE 6-1

	AD	DLB	FTLD	LATE/HS	PART	AGD	CVD	Copathology
Age								
<65 years	+++	++	++++	NA	NA	+	+	+
>75 years	++++	+++	++	++	+	NA	++	++
>85 years	++	+	+	+++	++	+	++	+++
>95 years	+	+	+	++	++++	+	++	++++
Multidomain impairment								
Amnestic-only impairment	++	+	+	+++	++	+	NA	NA
Neuropsychiatric features								
Motor symptoms	NA	+++	++	NA	NA	NA	+	+++
Very slow progression								
Hippocampal atrophy	+++	NA	++	++++	++	++	NA	++++

+ = rarely present; ++ = sometimes present; +++ = often present; ++++ = very often present; AD = Alzheimer disease; AGD = argyrophilic grains disease; CVD = cerebrovascular disease; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar degeneration; HS = hippocampal sclerosis; LATE = limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy; NA = not applicable; PART = primary age-related tauopathy.

KEY POINTS

- A systematic clinical approach integrating syndromic features and appropriate use and interpretation of biomarkers can help to distinguish among AD and common mimics in older adults.
- With new disease-modifying therapies for AD, high-confidence etiologic diagnoses will be critical to maximize treatment benefits for those eligible and minimize unnecessary treatment-related complications in individuals with non-AD diagnosis or multi-etiology dementia.

to consider in the differential diagnosis. Integration of clinical and demographic features with biomarker testing can help to prioritize elements of this differential to guide systematic counseling and management (**TABLE 6-1**). A complicating factor in clinical evaluation and management is that copathology is increasingly common with age, particularly among AD, LATE (with or without hippocampal sclerosis), cerebrovascular disease, and Lewy body disease.⁷³ This copathology has implications for the appropriate use of emerging disease-modifying therapies, where treatment mistargeted to the etiology would result in unnecessary exposure to potential side effects (without anticipation of benefit) and where future regimens may involve individualized combination therapy approaches.

Another challenge in this space involves inequities in care, including those related to varying access to specialist clinicians and technologies used for diagnosis and treatment. These existing disparities place a high premium on enhancing awareness among nonspecialists, patients, and care partners regarding AD mimics, leveraging tools that are currently more widely available (such as structural imaging techniques for the detection of cerebrovascular disease),⁷⁴ addressing structural and social determinants of brain health in communities, and enhancing trust and entry to care among historically underserved populations. Developments in cost-effective, infrastructure-efficient blood-based biomarkers and digital cognitive assessments hold promise in helping ameliorate some of these challenges, but these will require education and expertise among clinicians around appropriate use and interpretation.^{34,75,76}

CONCLUSION

LATE neuropathologic change, hippocampal sclerosis, and primary age-related tauopathy are increasingly recognized essential components of the differential diagnosis of late-life progressive amnestic disorders. The recent introduction of disease-modifying therapies for AD highlights the importance of recognizing these mimics to avoid unnecessary treatment-related complications. Specific biomarkers to identify LATE neuropathologic change and hippocampal sclerosis during life are not yet available. Tau PET in the context of a negative amyloid PET scan is an emerging biomarker for identifying primary age-related tauopathy. Overall, a systematic clinical approach with appropriate application of biomarkers allows clinicians to identify these mimics with more confidence.

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Neuropsychiatric Symptoms in Dementia

By Gad A. Marshall, MD

ABSTRACT

OBJECTIVE: This article discusses the prevalence, pathophysiology, assessment, and management of neuropsychiatric symptoms in patients with dementia.

LATEST DEVELOPMENTS: There is a growing body of evidence localizing neuropsychiatric symptoms in dementia to frontal circuits in the brain, as well as relating them to pathologic changes seen in different dementias. Although very few medications have been approved by the US Food and Drug Administration (FDA) for the treatment of neuropsychiatric symptoms in dementia, there are more clinical trials showing the benefit of antidepressants, stimulants, and antipsychotics. In line with that trend, in 2023, the FDA approved the use of brexpiprazole, an atypical antipsychotic, for the treatment of agitation in Alzheimer disease dementia.

ESSENTIAL POINTS: Neuropsychiatric symptoms are a core feature of all dementias and often emerge before cognitive symptoms manifest. They are highly clinically significant symptoms that disrupt the lives of patients and care partners and greatly influence the decision to place patients in long-term care facilities. The first line of treatment for neuropsychiatric symptoms in dementia is nonpharmacologic behavioral modification, but clinicians often must supplement this intervention with medications using an empiric approach.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Marshall discusses the unlabeled use of alprazolam, amphetamine, aripiprazole, bupropion, buspirone, citalopram, clonazepam, dextroamphetamine, diazepam, escitalopram, fluoxetine, gabapentin, lamotrigine, lorazepam, methylphenidate, mirtazapine, olanzapine, paroxetine, quetiapine, risperidone, sertraline, trazodone, and valproic acid for the treatment of neuropsychiatric symptoms in dementia.

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INTRODUCTION

Dementia is often considered to be primarily a cognitive disorder accompanied by a decline in activities of daily living (ADLs). However, a core feature of all dementias, and sometimes a leading feature, is the development of neuropsychiatric symptoms, also referred to as *behavioral and psychological symptoms of dementia*. Depending on the type of dementia and stage of disease, a variety of neuropsychiatric symptoms may be present, some preceding cognitive symptoms and some occurring after the development of cognitive symptoms. Therefore, when assessing patients with cognitive concerns, it is always important to ask about neuropsychiatric symptoms as well. A key red flag to keep in mind is the development of late-life neuropsychiatric symptoms (eg, in a patient's sixties or seventies) that were not previously present during young adulthood (eg, in a patient's twenties or thirties); this is usually an indicator of a

neurodegenerative disease manifesting with neuropsychiatric symptoms.¹ However, a 2023 large population-based study examining depression diagnosed in early, middle, and late life showed an increased risk of incident dementia for all timeframes of depression diagnosis,² illustrating the complex nature of these associations.

Neuropsychiatric symptoms are prevalent in dementia and its precursor, mild cognitive impairment (MCI). In some cases, these symptoms even precede MCI and the development of cognitive impairment.^{3,4} Different dementias, such as Alzheimer disease (AD) and frontotemporal dementia (FTD), usually manifest with different neuropsychiatric symptoms, particularly in the early stages. Neuropsychiatric symptoms are highly clinically meaningful and are strongly associated with disease progression, decline in ADLs, reduced quality of life, increased care partner burden, and long-term placement, often more so than cognitive symptoms.⁵⁻⁷ Various assessments have been developed to measure neuropsychiatric symptoms in dementia, some assessing multiple neuropsychiatric symptoms and some focusing on individual neuropsychiatric symptoms. Many studies have tried to elucidate the underlying pathophysiology of neuropsychiatric symptoms in dementia by using multimodal imaging and postmortem samples, with a particular focus on symptoms of apathy, depression, agitation, anxiety, and delusions. Treatment of neuropsychiatric symptoms in dementia consists of nonpharmacologic or behavior modification approaches, often coupled with pharmacologic approaches. However, there are very few US Food and Drug Administration (FDA)-approved medications indicated for the treatment of neuropsychiatric symptoms in dementia, and therefore, treatment is usually empiric. This article discusses these topics, making use of illustrative clinical cases, with the goal of providing practical information for clinicians assessing and treating patients with dementia.

PREVALENCE OF NEUROPSYCHIATRIC SYMPTOMS

Over the course of the disease, nearly all patients with dementia will experience one or more neuropsychiatric symptoms.³ The prevalence of specific neuropsychiatric symptoms depends on the source of information (eg, population-based study versus convenience academic center research sample), type of dementia, and severity. In patients with AD dementia, based on epidemiologic studies and similarly convenience-based studies, the most prevalent neuropsychiatric symptoms are irritability, anxiety, depression, apathy, sleep disturbances, and agitation.^{3,8,9} In patients with MCI, based on epidemiologic studies, the most prevalent neuropsychiatric symptoms are depression, apathy, irritability, sleep disturbances, agitation, and anxiety,^{3,10} whereas in convenience-based studies, the most prevalent neuropsychiatric symptoms are irritability, depression, agitation, anxiety, and apathy.^{8,11}

In recent years, the construct of mild behavioral impairment has been introduced and validated.¹² Mild behavioral impairment is meant to capture individuals who do not yet meet the criteria for dementia but have neuropsychiatric symptoms in late life that may mildly affect their instrumental ADLs but not basic ADLs as we see with MCI. Therefore, similar to MCI, it serves as a prodrome for dementia but with a focus on neuropsychiatric symptoms. From a cognitive standpoint, individuals with mild behavioral impairment can have normal cognition, subjective cognitive decline, or MCI, but not dementia. Therefore, mild behavioral impairment often overlaps with

KEY POINTS

- A core feature of all dementias, and sometimes a leading feature, is the development of neuropsychiatric symptoms.
- The development of late-life neuropsychiatric symptoms that were not previously present during young adulthood is usually an indicator of a developing neurodegenerative disease.
- Over the course of dementia, nearly all patients will experience one or more neuropsychiatric symptoms.
- In patients with Alzheimer disease dementia, the most prevalent neuropsychiatric symptoms are irritability, anxiety, depression, apathy, sleep disturbances, and agitation.

cognitive diagnoses. It is not meant to replace them but rather provide a different approach for identifying individuals at risk for dementia based on the presence of neuropsychiatric symptoms. By using the Mild Behavioral Impairment Checklist,¹³ five domains of neuropsychiatric symptoms have been identified: (1) apathy and lack of motivation, (2) mood and anxiety, (3) agitation and irritability, (4) disinhibition and lack of empathy, and (5) delusions and hallucinations. Mild behavioral impairment has been shown to predict future cognitive decline and progression to dementia and has been associated with markers of AD pathology and neurodegeneration.¹⁴ Currently, mild behavioral impairment is primarily a research construct and is only starting to be integrated into clinical care as the acceptance of the importance of neuropsychiatric symptoms grows.

There is limited information about the role of race and ethnicity in neuropsychiatric symptoms in dementia. However, a 2023 study of nearly 7000 cognitively healthy older adults showed that among Hispanic, Black, and Asian people, compared with non-Hispanic White people, the presence of neuropsychiatric symptoms, was associated with greater development of cognitive decline over time.¹⁵

DIFFERENT PRESENTATIONS OF NEUROPSYCHIATRIC SYMPTOMS BY DEMENTIA TYPE

Neuropsychiatric symptoms may manifest differently depending on the type of dementia a patient has. Early in AD, patients usually present with depression, anxiety, apathy, and irritability. They later develop agitation, sleep disturbances, and delusions, and as they enter the later stages of dementia, develop hallucinations, disinhibition, and aberrant motor behavior.³ In the setting of vascular dementia, patients present with irritability, depression, and sleep disturbances and later develop anxiety and apathy⁹; for more information about vascular cognitive impairment, refer to the article “Vascular Cognitive Impairment” by Lisa C. Silbert, MD, MCR, FAAN,¹⁶ in this issue of *Continuum*. Patients with Lewy body disease present with well-formed and colorful visual or auditory hallucinations, apathy, depression, anxiety, and a variety of sleep disturbances including rapid eye movement (REM) sleep behavior disorder and increased daytime sleeping; they also may develop delusions, irritability, agitation, aberrant motor behavior, and appetite changes⁷; for more information about Lewy body dementia, refer to the article “Lewy Body Dementia” by James E. Galvin, MD, MPH,¹⁷ in this issue of *Continuum*. Patients with behavioral variant FTD present with apathy, lack of empathy, disinhibition, aberrant motor behavior, and increased eating, particularly of sweets and carbohydrates (**CASE 7-1**); at later stages, they also develop agitation, depression, and anxiety^{18,19}; also refer to the article “Frontotemporal Dementia” by David Glenn Clark, MD,²⁰ in this issue of *Continuum*. Patients with primary progressive aphasia (PPA) may manifest different neuropsychiatric symptoms depending on the variant. Patients with semantic variant PPA often present with similar neuropsychiatric symptoms to that of behavioral variant FTD with disinhibition and compulsive behavior being prominent early on and depression developing later.²¹ Patients with logopenic variant PPA usually present with significant anxiety, depression, and apathy.²² Patients with nonfluent agrammatic PPA present with anxiety and depression initially and later develop disinhibition.²¹ Finally, patients with posterior cortical atrophy are often thought to present with

limited neuropsychiatric symptoms, but a 2023 study showed that, in fact, they often present early on with anxiety, depression, and apathy.²² For more information about logopenic variant PPA and posterior cortical atrophy, refer to the article “Atypical Presentations of Alzheimer Disease” by David Jones, MD, Victoria Pelak, MD, and Emily Rogalski, PhD,²³ in this issue of *Continuum*.

CLINICAL RELEVANCE OF NEUROPSYCHIATRIC SYMPTOMS

Neuropsychiatric symptoms are highly clinically relevant symptoms and often have a greater influence on clinical outcomes than cognitive symptoms in dementia. Several neuropsychiatric symptoms have been associated with disease progression. Studies have shown that particularly depression, apathy, anxiety, and agitation have predicted the development of MCI among cognitively healthy

CASE 7-1

A 54-year-old right-handed man with a history of osteoarthritis and gastroesophageal reflux disease presented to the behavioral neurology clinic with a recent diagnosis of bipolar disorder treated with valproate by a psychiatrist for the past year. When questioned about his mood, behavior, and cognitive function, the patient said that there was nothing wrong with him and that he came to the appointment only because his wife made him. However, his wife said that she no longer recognizes her husband and that he is a different man from the loving, conscientious, and level-headed man she married 25 years earlier.

She said that she cannot remember exactly when things changed, but about 3 years ago, a few striking incidents occurred. First, her sister who lived near them was diagnosed with pancreatic cancer. When the patient's wife told him the news, he did not seem to care and went on watching a basketball game on the television. Second, the patient, who had always made sound financial choices, decided without consulting with his wife to use his retirement funds to purchase several hundred thousand dollars' worth of paintings despite never being an art lover. Third, the patient, who had always been health-conscious and adhered to a strict Mediterranean diet and a daily 3-mile walk, started eating cookies and ice cream every night and gained 9 kg (20 lb) in 3 months. The patient's wife also noted that he had become more apathetic and disinhibited, he was making errors in paying the bills, he was having difficulties sorting the mail, his home office was in disarray, and he was wearing stained and foul-smelling clothes more frequently. On examination, the patient was noted to have impaired divided attention and working memory, poor abstract reasoning, worse performance on phonemic than semantic verbal fluency, and mild encoding and retrieval memory difficulties with intact storage. An MRI of his brain showed bilateral (right greater than left) anterior temporal and medial frontal atrophy.

This is a case of behavioral variant frontotemporal dementia, which is often mistaken for a primary psychiatric condition because of the prominent neuropsychiatric symptoms and its earlier age of onset than more common dementias such as Alzheimer disease.

COMMENT

older adults, as well as progression from MCI to dementia.^{2,4,8,11} At the stage of MCI, apathy has been associated with impairment in instrumental ADLs.²⁴ At the stage of dementia, overall neuropsychiatric symptom burden, and particularly agitation, hallucinations, apathy, appetite changes, aberrant motor behavior, depression, disinhibition, and sleep disturbances, have been associated with impairment in instrumental ADLs and basic ADLs.⁷ Furthermore, neuropsychiatric symptoms may be a significant source of frustration, distress, and burden for patients with dementia and their care partners; for more information about this, refer to the article “Care Partner Burden and Support Services in Dementia” by Angelina J. Polzinelli, PhD, ABPP-CN,²⁵ in this issue of *Continuum*. A 2023 study showed that greater frequency and severity of overall neuropsychiatric symptoms in patients with MCI and AD dementia were associated with multiple care partner outcomes including care partner depression, distress, and reduced quality of life, as well as greater informal care time.⁶ Finally, greater overall neuropsychiatric symptoms have been associated with an increased rate of placement of patients with dementia in assisted living facilities and nursing homes.⁵

ASSESSING NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA

When assessing a patient with dementia in the clinic, it is important to ask about neuropsychiatric symptoms. Often, this is done in an unstructured fashion. To systematically capture the presence of neuropsychiatric symptoms, it is preferable to use a validated assessment tool. The most widely used assessment for determining the presence and progression of multiple neuropsychiatric symptoms in dementia is the Neuropsychiatric Inventory in which the questions are typically addressed to the care partner.²⁶ The Neuropsychiatric Inventory consists of 12 neuropsychiatric symptoms items and has several screening questions for each item. If it is determined that a neuropsychiatric symptom item is present based on the screening questions, it is further rated for frequency and severity, as well as care partner distress. The 12 items include delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and appetite. An abbreviated version, the Neuropsychiatric Inventory brief questionnaire form, which includes only a single screening question per item, severity score, and care partner distress, has been used widely, as well.²⁷ As mentioned earlier, preceding the stage of dementia, the Mild Behavioral Impairment Checklist, which is administered to both the patient and care partner, can be used to assess five domains of neuropsychiatric symptoms.¹³

Many assessments focus on individual neuropsychiatric symptoms in dementia. For depression, the most widely used instruments include the Geriatric Depression Scale,²⁸ Beck Depression Inventory,²⁹ and Patient Health Questionnaire (Depression)-9.³⁰ All these depression scales are administered to the patient or self-completed by the patient, which introduces a reliability challenge as dementia advances. In those cases, the Cornell Scale for Depression in Dementia,³¹ which is administered to both the patient and care partner, resulting in a clinician rating, may be used.

For anxiety, commonly used assessments include the Geriatric Anxiety Inventory,³² Beck Anxiety Inventory,³³ and Generalized Anxiety Disorder 7-item.³⁴ All these anxiety scales are administered to the patient or self-completed by the patient. For more impaired patients, the care partner-reported Rating Anxiety in Dementia scale³⁵ may be administered. For apathy, many

scales have been developed and used over the years, including the Apathy Evaluation Scale,³⁶ Apathy Inventory,³⁷ and Lille Apathy Rating Scale.³⁸ These apathy scales include patient, care partner, and clinician ratings. Finally, for agitation, the most widely used instrument has been the Cohen-Mansfield Agitation Inventory,³⁹ which is administered to care partners.

When seeing patients in the clinic, especially for the first time, an overall screening tool for neuropsychiatric symptoms such as the Neuropsychiatric Inventory brief questionnaire form is recommended. Depending on which items are endorsed and the severity of symptoms, unstructured questions may be asked or structured assessments for specific symptoms described earlier may be used. These assessments may then be repeated periodically to determine the progression of symptoms or responses to treatment.

PATOPHYSIOLOGY OF NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA

Various studies have attempted to examine the underlying pathophysiology of neuropsychiatric symptoms in dementia and preceding stages, particularly in AD. Most studies have focused on one of the following neuropsychiatric symptoms: apathy, depression, agitation, anxiety, or delusions. Most studies have used various imaging modalities to explore the underlying mechanisms of the symptoms. To a lesser extent, studies have also focused on pathologic changes seen at autopsy. Although considerable variability has been reported in the localization of neuropsychiatric symptoms, some patterns have emerged, such as the involvement of frontal-subcortical networks, particularly at the stage of dementia.⁴⁰

Overall neuropsychiatric symptom burden in patients with AD at the stage of dementia has been associated particularly with medial frontal changes such as anterior cingulate neurofibrillary tangle burden (signifying tau pathology) seen at autopsy.⁴¹ More recently, another postmortem study showed an association between the total number of neuropsychiatric symptoms and Parkison disease Braak stage for Lewy body disease (signifying α -synuclein pathology) and Braak stage for AD (signifying tau pathology); moreover, hallucinations were particularly associated with Lewy body disease pathology, and depression and agitation were associated with AD tau pathology.⁴² Before progressing to dementia, patients meeting the criteria for mild behavioral impairment had lesser amyloid- β , greater phospho-tau, and greater total tau in their CSF, consistent with greater AD risk.⁴³ A cluster of affective symptoms, including apathy, depression, anxiety, sleep, and appetite, has been associated with frontal and parietal reduced connectivity and greater entorhinal and precuneus tau in early-stage AD.^{43,44}

Apathy is the most widely assessed neuropsychiatric symptom in terms of brain localization. Across multiple types of dementia, including AD, FTD, and vascular dementia, apathy was associated with anterior cingulate atrophy.⁴⁵ In patients with AD, apathy has been associated with atrophy, hypoperfusion, hypometabolism, reduced connectivity, reduced fractional anisotropy, and greater amyloid and tau burden in vivo and at autopsy across different regions in the brain.^{41,43,45-50} At the stage of AD dementia, apathy has been most consistently associated with reward pathways and medial frontal dysfunction and pathology, whereas at earlier stages in preclinical AD and MCI, apathy has been associated with regions affected early in AD, such as inferior temporal, medial, and lateral parietal regions.⁵¹

KEY POINTS

- Mild behavioral impairment is a new clinical construct that represents a prodrome for dementia, similar to mild cognitive impairment, but with a focus on neuropsychiatric symptoms.
- Behavioral variant frontotemporal dementia is often mistaken for a primary psychiatric condition because of the prominent neuropsychiatric symptoms and its earlier age of onset than more common dementias such as Alzheimer disease.
- Neuropsychiatric symptoms are highly clinically relevant symptoms and often have a greater influence on clinical outcomes than cognitive symptoms in dementia.
- The most widely used assessment for determining the presence and progression of neuropsychiatric symptoms in dementia is the Neuropsychiatric Inventory in which the questions are typically addressed to the care partner.
- Although considerable variability has been reported in the localization of neuropsychiatric symptoms, some patterns have emerged, such as the involvement of frontal-subcortical networks, particularly at the stage of dementia.

Depression in MCI and AD dementia has been associated with dorsolateral prefrontal atrophy.⁵² In patients with preclinical AD, depressive symptoms have been associated with hippocampal atrophy, temporoparietal hypometabolism, cortical amyloid, and entorhinal and inferior temporal cortical tau.⁵³⁻⁵⁶ Furthermore, the interaction of depressive symptoms and cortical amyloid burden predicted cognitive decline over time.⁵⁷

Agitation in the setting of AD dementia has been associated with insula, anterior cingulate, and dorsolateral prefrontal atrophy; frontal, cingulate, and temporal hypometabolism; and medial frontal tau burden.^{52,58-60}

Anxiety in AD dementia has been associated with medial and lateral temporal and insula hypometabolism, anterior hyperperfusion, and parietal atrophy.^{61,62} Moreover, worsening anxiety has been associated with greater cortical amyloid burden and has been shown to moderate the association between amyloid and cognitive decline in preclinical AD.^{54,63}

Delusions in AD dementia have been associated with frontal atrophy and dorsolateral prefrontal, medial frontal, and temporal hypometabolism.^{58,64}

TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS

Various neuropsychiatric symptoms occur at the stage of MCI and later at the stage of dementia depending on the type of dementia. Some neuropsychiatric symptoms gradually worsen over time, some diminish, some come and go, and some are situational. Some neuropsychiatric symptoms are mild and not disruptive, whereas some are severe and highly disruptive for both the patient and the care partner. When episodic, neuropsychiatric symptoms may be short lived (eg, minutes or hours) or long lasting (eg, days or weeks). Therefore, when treating neuropsychiatric symptoms, it is critical to obtain a detailed history considering these many variables.

The first-line treatment for neuropsychiatric symptoms in dementia is a nonpharmacologic or behavior modification approach. If that is unsuccessful, a pharmacologic approach alone or in combination with a nonpharmacologic approach may then be attempted cautiously because patients with dementia are usually older and more susceptible to adverse effects than patients with primary psychiatric conditions. Moreover, very few medications are indicated by the FDA for the treatment of neuropsychiatric symptoms in dementia. Therefore, an empiric treatment approach is undertaken, again warranting further caution.

FIGURE 7-1 provides an overview of the treatment of neuropsychiatric symptoms in dementia.

Nonpharmacologic or Behavior Modification Approaches

The first step in a nonpharmacologic or behavior modification approach to treating neuropsychiatric symptoms in dementia is a careful review and identification of the target symptoms and their potential triggers with the patient and care partner, as well as the patient's environment. Sometimes the intervention is as simple as education. For example, a patient with Lewy body disease reports to his spouse vivid colorful visual hallucinations of little purple people walking in their house. The spouse is very distressed by this and brings it up to the patient's neurologist, inquiring about potential pharmacologic treatment. On further questioning, it appears that the patient is not distressed and is even entertained by the visual hallucinations. Consequently, the neurologist educates the patient and his spouse that this is a common manifestation of Lewy body disease and that, if it

is not distressing to the patient, no additional action is necessary, thus avoiding potential treatment with an antipsychotic.

Another common example of an education intervention is instructing care partners not to point out to patients with dementia or MCI that they already told them something and that they do not remember because it may exacerbate feelings of low self-esteem, depression, and irritability and does not help the patient. Sometimes it is more challenging to find the trigger of the neuropsychiatric symptoms, particularly in patients with advanced dementia who cannot express themselves well. These patients are often very stimulus bound, and small stimuli can result in excitability or agitation. For example, if the patient needs help transferring from a bed to a chair by an aide at a facility, touching them quickly without a warning or explanation may be a trigger. Sometimes even mild knee pain or having a full bladder can be a source of agitation. Therefore, taking the time to explore these potential triggers and then systematically testing behavior modifications, most often by the care partner, are crucial. It is also important to make sure that the proposed behavior modification can be carried out by the care partner and patient and is not beyond their abilities or circumstances to perform.

Other approaches to behavior modification consist of specific activities that may distract patients, give them pleasure, relax them, or tire them. These include listening to music, watching a show, dancing, exercising, participating in arts and

KEY POINTS

- The first-line treatment for neuropsychiatric symptoms in dementia is a nonpharmacologic or behavior modification approach.
- Very few medications are indicated by the US Food and Drug Administration (FDA) for the treatment of neuropsychiatric symptoms in dementia, and therefore, an empiric treatment approach is undertaken, warranting further caution.
- The first step in the behavior modification approach for the treatment of neuropsychiatric symptoms in patients with dementia is a careful review and identification of the target symptoms and their potential triggers with the patient and care partner, as well as a review of the patient's environment.

Thorough review of neuropsychiatric symptoms

- Identify active neuropsychiatric symptoms
- Determine frequency and severity
- Determine if disruptive to patient, care partner, or both
- Determine triggers



First-line treatment

Nonpharmacologic approach or behavior modification

- Patient and care partner education
- Target triggers of neuropsychiatric symptoms
- Ensure patient and care partner can carry out recommendations
- Additional approaches include exercise, music, dance, arts and crafts, massage



If unsuccessful, add

Pharmacologic approach

- Few FDA-approved medications, empiric approach
- Identify cluster of active neuropsychiatric symptoms
- Treat by class of medication (antidepressants, stimulants, mood stabilizers, anxiolytics, antipsychotics) and tailor for potential benefits and side effects
- Start low and go slow
- Monitor for response and side effects
- Reassess regularly the need for ongoing treatment

FIGURE 7-1

Overview of treatment of neuropsychiatric symptoms in dementia.

FDA = US Food and Drug Administration.

crafts activities, receiving a slow massage, aromatherapy, reminiscence therapy, and bright light therapy. These should be tailored to patients depending on their preferences and abilities to participate in the intervention.

Pharmacologic Approaches

As mentioned earlier, there have been almost no FDA-approved medications for the treatment of neuropsychiatric symptoms in dementia. In 2010, the FDA approved dextromethorphan hydrobromide, an *N*-methyl-D-aspartate (NMDA) receptor antagonist that inhibits serotonin reuptake, combined with quinidine, for the treatment of pseudobulbar affect in dementia, a condition in which patients have frequent and usually brief episodes of crying or laughing that are not congruent with their emotional state.⁶⁵ More recently, in 2023, the FDA approved brexpiprazole, an antipsychotic, for the treatment of agitation in Alzheimer disease dementia, a much more common neuropsychiatric symptom.⁶⁶ All other medications used for the treatment of neuropsychiatric symptoms in dementia are used empirically except pimavanserin, which has a narrow indication (described below). Some medications are used based on evidence from clinical trials that have yet to lead to FDA approval and some based on indications for related symptoms in primary psychiatric conditions.

When starting a medication for neuropsychiatric symptoms in patients with dementia, it is recommended to start low and go slow because the patients are usually older and more susceptible to potential medication side effects. Typically the lowest usual starting dose or even half of that dose of a medication is given initially, and then the dose is gradually titrated over weeks or months while side effects and benefits are monitored. As noted earlier, it is recommended to use medications in conjunction with nonpharmacologic approaches. However, sometimes the symptoms are severe, and a more aggressive pharmacologic approach is necessary to avoid hospitalization. For example, a patient with moderate dementia may develop paranoid delusions about people trying to break into their house and consequently may display agitation or increased risk of harm to self or others. In such a situation, the provider may want to initiate a potent antipsychotic, such as risperidone, and increase the dose every few days until the neuropsychiatric symptoms are under control. In more extreme situations, when a patient poses a clear threat to themselves or others, an inpatient admission to a geriatric psychiatry unit is warranted. There, medications may be titrated quickly and safely by providers with expertise in prescribing psychotropic medications to patients with dementia. In addition, the staff is usually well trained in behavior modification, and the environment provides anchoring structure and calmness.

Different classes of medications are used to treat neuropsychiatric symptoms in the setting of dementia. For AD dementia, before using psychotropic medications, it is first recommended to check the response to cholinesterase inhibitors (eg, donepezil, rivastigmine, and galantamine), memantine, or a combination of both, all of which have been approved for the treatment of AD dementia and have been shown to reduce overall neuropsychiatric symptom burden, as well as specific neuropsychiatric symptoms; also refer to the article “Treatment of Alzheimer Disease” by David S. Geldmacher, MD, FACP, FANA,⁶⁷ in this issue of *Continuum*. Rivastigmine has also been approved for the treatment of Parkinson disease with dementia and has been shown to help with neuropsychiatric symptoms in that condition.

If neuropsychiatric symptoms persist during treatment with cholinesterase inhibitors and memantine, alone or in combination, various classes of psychotropic medications may be used depending on the type of neuropsychiatric symptoms present. These include antidepressants, stimulants, mood stabilizers, anxiolytics, and antipsychotics. **TABLE 7-1** lists medication classes used for the treatment of neuropsychiatric symptoms in dementia.

ANTIDEPRESSANTS. The most commonly used antidepressants for the treatment of neuropsychiatric symptoms in dementia are selective serotonin reuptake inhibitors (SSRIs), primarily escitalopram, citalopram, and sertraline. Fluoxetine is used to a lesser extent, and paroxetine is usually avoided because of its anticholinergic properties. SSRIs have been used for the treatment of depression, anxiety, and irritability in dementia (**CASE 7-2**). However, SSRIs have been shown to worsen apathy, which is a common neuropsychiatric symptom in dementia that often co-occurs with mood symptoms, thus sometimes making it challenging to use these medications. Citalopram and escitalopram have both been shown to be effective in the treatment of agitation in dementia.^{68,69} Compared with the side effects of antipsychotics, SSRIs are better tolerated and, therefore, are the preferred treatment for agitation not associated with psychotic symptoms. Bupropion, which is a dual norepinephrine and dopamine reuptake inhibitor, is an activating antidepressant, which is often used to treat depression in the context of apathy. Mirtazapine, which acts on histamine, norepinephrine, and serotonin systems, is often used to treat insomnia at lower doses in which it primarily targets histamine (7.5 mg to 15 mg nightly) and depression at higher doses in which it primarily targets norepinephrine and serotonin systems (30 mg to 45 mg nightly). The aforementioned antidepressants usually take weeks to demonstrate efficacy and may need to be gradually titrated. Finally, trazodone, which acts on multiple neurotransmitter systems (eg, serotonin, norepinephrine, acetylcholine, dopamine, and histamine), is used primarily to treat insomnia at low doses (starting at 50 mg nightly). Sometimes it is also used to treat agitation because it may take effect within 30 to 60 minutes.

STIMULANTS. Apathy is one of the most common neuropsychiatric symptoms across all types of dementia. Several clinical trials have assessed the potential of treating apathy in AD dementia with the stimulant methylphenidate, resulting in some improvement in apathy, as well as global functioning, most recently noted in the ADMET 2 trial (**CASE 7-2**).⁷⁰ The combination of amphetamine and dextroamphetamine is another stimulant that may be used for the treatment of apathy in dementia.

MOOD STABILIZERS. Patients with dementia who have labile mood, agitation, or mania may be treated with mood stabilizers such as lamotrigine, valproic acid and divalproex sodium, or gabapentin. Lamotrigine is generally the best-tolerated mood stabilizer for patients with dementia but requires a slow titration to avoid the rare side effect of Stevens-Johnson syndrome and toxic epidermal necrolysis. Gabapentin may be titrated more quickly but can be too sedating for some patients. Finally, valproic acid and divalproex sodium, although associated with more side effects, have the potential to help both with chronic mood stabilization and more acute symptoms because they can also take effect within 30 to 60 minutes.

KEY POINTS

- It is important to make sure that the proposed behavior modification in patients with dementia can be carried out by the care partner and patient and is not beyond their abilities or circumstances to perform.
- When starting a medication for the treatment of neuropsychiatric symptoms in dementia, it is recommended to start low and go slow because the patients are usually older and more susceptible to potential medication side effects.
- The most commonly used psychotropic medications for the treatment of neuropsychiatric symptoms in patients with dementia are selective serotonin reuptake inhibitors (SSRIs), primarily escitalopram, citalopram, and sertraline.
- When using benzodiazepines to treat neuropsychiatric symptoms in dementia, lorazepam and clonazepam are the preferred choices because they are not as long-acting as diazepam and their effect is not as immediate as diazepam or alprazolam and, thus, are less prone to dependence.

TABLE 7-1**Medication Classes Used for the Treatment of Neuropsychiatric Symptoms in Dementia**

Medication class and preferred medications	Typical dose	Common side effects
Antidepressants		
Escitalopram	5-20 mg/d	Gastrointestinal, headache, sexual dysfunction, appetite change, sleep disturbance, dose-dependent QT interval prolongation
Citalopram	20-30 mg/d	Gastrointestinal, headache, sexual dysfunction, appetite change, sleep disturbance, dose-dependent QT interval prolongation
Sertraline	25-200 mg/d	Gastrointestinal, headache, sexual dysfunction, appetite change, sleep disturbance
Bupropion	75-300 mg/d	Gastrointestinal, headache, insomnia (rare: lowers seizure threshold), increased blood pressure
Mirtazapine	7.5-45 mg/d	Gastrointestinal, headache, increased appetite, drowsiness
Trazodone	50-200 mg/d	Drowsiness, headaches, dizziness, priapism
Stimulants		
Methylphenidate	5-45 mg/d	Insomnia, appetite loss, increased blood pressure and heart rate
Amphetamine and dextroamphetamine	10-30 mg/d	Insomnia, appetite loss, increased blood pressure and heart rate
Mood stabilizers		
Lamotrigine	50-200 mg/d	Headache, blurry vision, dizziness, drowsiness, tremor, toxic epidermal necrolysis, gastrointestinal (rare: Stevens-Johnson syndrome)
Valproic acid and divalproex sodium	250-1000 mg/d	Gastrointestinal, blurry vision, dizziness, tremor, hyperammonemia, elevated liver function tests, weight gain, vitamin D deficiency, blood dyscrasias (eg, thrombocytopenia)
Gabapentin	300-900 mg/d	Drowsiness, weight gain, swollen ankles, dizziness, blurry vision, gastrointestinal
Anxiolytics		
Buspirone	5-45 mg/d	Gastrointestinal, dizziness, headache, drowsiness, blurry vision
Lorazepam	0.5-2 mg/d	Drowsiness, confusion, paradoxical agitation
Clonazepam	0.25-1 mg/d	Drowsiness, confusion, paradoxical agitation
Antipsychotics		
Quetiapine	25-200 mg/d	Drowsiness, weight gain, orthostatic hypotension
Risperidone	0.5-2 mg/d	Gastrointestinal, dizziness, extrapyramidal syndrome (at high doses)
Olanzapine	2.5-10 mg/d	Gastrointestinal, weight gain, drowsiness, extrapyramidal syndrome, orthostatic hypotension
Aripiprazole	2-15 mg/d	Akathisia, drowsiness, dizziness, blurry vision, headache
Pimavanserin	34 mg/d	Gastrointestinal, gait disturbance, QT interval prolongation
Brexpiprazole	0.5-3 mg/d	Drowsiness, dizziness, headache, weight gain

ANXIOLYTICS. Buspirone is a serotonergic medication used specifically to treat generalized anxiety disorder. Like SSRIs, it takes weeks to demonstrate efficacy and must be titrated gradually. Benzodiazepines may be used to treat short-term extreme anxiety, insomnia, or agitation in dementia but must be used with caution because they can lead to worsening cognition or even delirium, both of which are usually short lived for several hours. Moreover, benzodiazepines may result in paradoxical disinhibition or even agitation. When using them, lorazepam and clonazepam are the preferred choices among benzodiazepines because they are not as long-acting as diazepam and their effect is not as immediate as diazepam or alprazolam and, thus, are less prone to dependence.

ANTIPSYCHOTICS. Psychotic symptoms such as delusions and visual and auditory hallucinations may be quite disruptive in patients with dementia and tend to occur early in Lewy body disease and later in other dementias such as AD. In these settings, atypical antipsychotics may be used. Quetiapine is a low-potency (with low affinity to dopamine D₂ receptors) sedating antipsychotic that is used widely to treat psychotic symptoms, agitation, nighttime behavioral

A 75-year-old right-handed woman was recently diagnosed with mild dementia thought to be due to Alzheimer disease (AD). She was started on donepezil, which she tolerated well. As part of her presentation, she developed several neuropsychiatric symptoms, including anxiety, irritability, insomnia, and apathy. Recently, the patient's daughter reported that the patient's anxiety had worsened, which compounded her insomnia because she was staying up late worrying about her family and financial situation. Consequently, the patient's neurologist started her on citalopram at nighttime, aiming to improve her anxiety and irritability, as well as potentially her insomnia because citalopram may be sedating. After 2 months, the patient's anxiety, irritability, and insomnia decreased. However, her apathy worsened, and she stopped painting and playing tennis. The patient was then referred to a geriatric psychiatrist who recommended a trial of methylphenidate to be taken each morning. After titrating the dose up for 6 weeks, the patient's interest and participation in various activities improved. She resumed painting and playing tennis and took up pickleball. However, her appetite was diminished. Despite that, she was not losing weight, and the patient, her daughter, and the geriatric psychiatrist decided to continue the citalopram and methylphenidate and monitor her weight.

CASE 7-2

Neuropsychiatric symptoms that commonly occur in early-stage AD primarily consist of mood symptoms and sleep disturbances. They are often treated empirically with antidepressants, particularly SSRIs, with attempts to tailor the medication also based on its potential side effects. A potential consequence of using SSRIs is the development or worsening of apathy. Clinical trials have shown a potential benefit of treating apathy in AD dementia with stimulants such as methylphenidate.

COMMENT

disturbances, and insomnia in dementia. Risperidone is a high-potency (with high affinity to dopamine D₂ receptors) nonsedating antipsychotic that is used widely in low doses to treat psychotic symptoms and agitation (**CASE 7-3**) but not used as much in higher doses because of the increased risk of extrapyramidal symptoms at higher doses. Olanzapine and aripiprazole are antipsychotics that are used to treat psychotic symptoms and agitation in dementia, as well.

In 2016, the FDA approved the use of the atypical antipsychotic pimavanserin for the treatment of psychosis in Parkinson disease with or without dementia but not for other dementias.⁷¹ Of note, patients with Lewy body disease are

CASE 7-3

An 83-year-old right-handed woman with a 10-year history of mixed dementia secondary to Alzheimer disease and vascular dementia secondary to moderate small vessel ischemic disease was recently noted to have progressed to severe dementia. Her husband had her transferred from an assisted living facility to a nursing home because of worsening neuropsychiatric symptoms that could not be managed by the prior facility's staff with behavior modification approaches. The patient's outpatient neurologist was treating her with galantamine, memantine, and escitalopram. However, the patient had been getting agitated multiple times a day, especially in the afternoon and evening when she also appeared to be interacting with people who were not there and often screamed in a panicked voice. The patient needed help with all of her personal care and had been more and more resistant to bathing and even simple transfers from her bed to a chair or onto the toilet. She started swinging her arms and yelling when the aides at the facility helped her with transfers and actually hit them on a few occasions. The patient's behavior was better in the morning when she was more alert and more cooperative. After moving to the nursing home, the patient was evaluated by a geriatric psychiatrist, who recommended to the husband a trial of low-dose risperidone in the afternoon to treat the agitation, potential visual hallucinations, and overall worsening symptoms in the afternoon and evening. The psychiatrist explained the potential short-term and long-term side effects of risperidone to the patient's husband, who decided to proceed with the treatment. After 2 weeks, the nursing home staff noted some improvement but ongoing agitation. As a result, the risperidone dose was increased leading to a good response and a plan to reassess the need for ongoing treatment on a monthly basis.

COMMENT

In the setting of end-stage dementia, it is common for patients to have very disruptive neuropsychiatric symptoms such as frequent significant situational agitation or agitation secondary to psychotic symptoms. In these situations, if an SSRI does not work, an antipsychotic is often tried. Antipsychotics typically have more significant short-term and long-term side effects than other psychotropic medications and so must be used with caution, at low doses if possible, and potentially discontinued after stabilization of symptoms.

extremely sensitive to antipsychotics, which should be avoided in these patients if possible. More recently, as mentioned earlier, in 2023 the FDA approved brexpiprazole, another atypical antipsychotic, for the treatment of agitation in AD dementia but not for the treatment of psychosis.

When using psychotropic medications to treat neuropsychiatric symptoms in dementia, it is important to monitor for short-term and long-term side effects and to consider the duration of treatment. The most commonly used psychotropic medications, SSRIs, in the short term may cause gastrointestinal side effects, sleep disturbances, appetite changes, headache, and sexual dysfunction. In the long term and especially with higher doses, they may cause cardiac manifestations such as a prolonged QTc interval.

Antipsychotics can lead to sedation early in use, after a few months of use they can result in weight gain, metabolic syndrome, and extrapyramidal symptoms, and after several years of use, they can cause serious cardiac arrhythmias, cerebrovascular disease, and early mortality. Accordingly, the FDA issued a boxed warning for the use of antipsychotics in patients with dementia, focused on the risk of cerebrovascular disease and mortality. As such, there is close monitoring of the duration of antipsychotic use in facilities. Moreover, whenever possible, after a period of stability of neuropsychiatric symptoms, it is recommended to attempt to taper antipsychotics. When prescribing psychotropic medications to patients with dementia, it is important to discuss these consequences with patients and care partners so they can make an informed decision about whether or not they want to start or continue such treatment. In many cases, patients and care partners consider the improvement in quality of life from these treatments worth the risk.

KEY POINTS

- Patients with Lewy body disease are often sensitive to antipsychotics, which should be avoided in these patients if possible.
- Antipsychotics typically have more significant short-term and long-term side effects than other psychotropic medications and so must be used with caution, at low doses if possible, and potentially discontinued after stabilization of symptoms in patients with dementia.
- It is important to work with the patient and care partner in deciding which course of action to take to treat neuropsychiatric symptoms in patients with dementia, and improve the patient's and care partner's quality of life.

CONCLUSION

Neuropsychiatric symptoms are a core feature of all dementias and usually increase in frequency and potentially severity as dementia progresses in patients. Neuropsychiatric symptoms are often localized to frontal-subcortical networks and relate directly to the underlying pathology of different dementias. The first line of treatment for neuropsychiatric symptoms in patients with dementia is nonpharmacologic or behavior modification approaches. However, those interventions are often insufficient, and pharmacologic treatment may be implemented. Because there are very few FDA-approved treatments for neuropsychiatric symptoms in dementia, the approach to using psychotropic medications in this context is usually empiric. Various classes of medications are used cautiously to minimize short-term and long-term side effects. It is important to partner with the patient and care partner in deciding which course of action to take to treat these highly disruptive symptoms and improve the patient's and care partner's quality of life.

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Neuroimaging in Dementia

REVIEW ARTICLE



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By Shannon L. Risacher, PhD

ABSTRACT

OBJECTIVE: This article captures the current literature regarding the use of neuroimaging measures to study neurodegenerative diseases, including early- and late-onset Alzheimer disease, vascular cognitive impairment, frontotemporal lobar degeneration disorders, dementia with Lewy bodies, and Parkinson disease dementia. In particular, the article highlights significant recent changes in novel therapeutics now available for the treatment of Alzheimer disease and in defining neurodegenerative disease using biological frameworks. Studies summarized include those using structural and functional MRI (fMRI) techniques, as well as metabolic and molecular emission tomography imaging (ie, positron emission tomography [PET] and single-photon emission computerized tomography [SPECT]).

LATEST DEVELOPMENTS: Neuroimaging measures are considered essential biomarkers for the detection and diagnosis of most neurodegenerative diseases. The recent approval of anti-amyloid antibody therapies has highlighted the importance of MRI and PET techniques in treatment eligibility and monitoring for associated side effects. Given the success of the initial biomarker-based classification system for Alzheimer disease (the amyloid, tau, neurodegeneration [A/T/N] framework), researchers in vascular cognitive impairment have created similar techniques for biomarker-based diagnosis. Further, the A/T/N framework for Alzheimer disease has been updated to include several pathologic targets for biomarker detection.

ESSENTIAL POINTS: Neurodegenerative diseases have a major health impact on millions of patients around the world. Neuroimaging biomarkers are rapidly becoming major diagnostic tools for the detection, monitoring, and treatment of neurodegenerative diseases. This article educates readers about the current literature surrounding the use of neuroimaging tools in neurodegenerative diseases along with recent important developments in the field.

INTRODUCTION

The clinical diagnosis of dementia is completed primarily through comprehensive clinical and cognitive evaluations to identify primary areas of cognitive, motor, and clinical impairment. Brain imaging can aid with clinical diagnosis, particularly in confirming suspected diagnoses,¹ ruling out alternative causes of cognitive impairment, and

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refining the differential diagnosis. Neuroimaging biomarkers of neurodegenerative conditions are important tools for clinicians looking to provide the most accurate diagnosis for their patients as well as researchers seeking to understand the biological basis of dementias and ultimately their treatment.

MRI is the most commonly used technique in clinical and research imaging of patients with neurodegenerative diseases to evaluate the severity and location of brain volume loss. MRI tools can also help exclude nondegenerative causes of cognitive impairment, such as mass lesions, hydrocephalus, subdural hematomas, or infection. Clinically, the most common MRI tools used include T1-weighted sequences, which broadly allow for the identification and localization of brain atrophy, and T2-weighted or fluid-attenuated inverted recovery (FLAIR) sequences to identify the presence and severity of cerebrovascular lesions. A few other sequences, including diffusion-weighted imaging (DWI) to assess white matter integrity and susceptibility-weighted imaging (SWI) to assess the presence and severity of cerebral microbleeds, may also be used clinically. Numerous other sequences assessing brain function at rest or during a task, blood-brain barrier integrity, and cerebral blood flow, as well as more advanced forms of structural and diffusion sequences, are used widely in research into neurodegenerative conditions.

Another commonly used neuroimaging technique to study neurodegenerative diseases is positron emission tomography (PET), which uses radioactive tracers that bind to a target protein of interest. In the setting of dementia, PET imaging is typically used to measure brain metabolism (ie, fluorodeoxyglucose [FDG]-PET) or protein aggregation, particularly pathologic protein deposition (ie, amyloid, tau, and α -synuclein). Single-photon emission computed tomography (SPECT) is a very similar technique that is used to measure changes in dopaminergic systems in patients with dementia with Lewy bodies (DLB) or Parkinson disease dementia (PDD).

A comprehensive review of neuroimaging in dementias was published in the February 2023 *Continuum* issue on Neuroimaging.² This article reviews neuroimaging findings in multiple dementias, while particularly focusing on areas of new development. It touches on neuroimaging findings in the most common neurodegenerative diseases and dementias, namely Alzheimer disease (AD), vascular cognitive impairment, DLB, PDD, and frontotemporal lobar degeneration (FTLD) spectrum disorders.

One of the biggest developments in the past 2 years is the approval and insurance coverage of anti-amyloid antibody treatments for AD.³ This article also discusses the use of neuroimaging in defining those who meet the criteria for these treatments, as well as the use of MRI in tracking the emergence of amyloid-related imaging abnormalities (ARIA). Revised diagnostic criteria⁴ based on biological markers for AD and related dementias were published in 2024 and updated the original amyloid, tau, and neurodegeneration (A/T/N) criteria for AD from 2016.⁵ In addition, biological-based diagnostic criteria, which largely depend on neuroimaging and other biomarker measures, are being developed for other neurodegenerative conditions beyond AD, including synucleinopathies and cerebral small vessel disease.⁶⁻⁸ These defined diagnostic criteria proposals will help refine the clinical diagnosis of many neurodegenerative conditions by using neuroimaging and other biomarker advancements from the past few decades. Finally, the potential next steps

for the use of neuroimaging tools in the clinical care of dementia are summarized.

KEY POINTS

- One of the biggest developments in the treatment of Alzheimer disease (AD) in the past 2 years is the approval of anti-amyloid antibody treatments.
- Biological-based diagnostic criteria, which largely depend on neuroimaging and other biomarker measures, are being developed for other neurodegenerative conditions beyond AD, including synucleinopathies and cerebral small vessel disease.
- Three monoclonal antibody treatments have been approved by the US Food and Drug Administration (FDA) (ie, aducanumab, lecanemab, and donanemab).
- Imaging with amyloid-specific PET tracers demonstrates widespread amyloid deposition throughout the cortex in patients with AD.

ALZHEIMER DISEASE

AD, the most common age-related dementia, is pathologically characterized by widespread amyloid- β (A β) deposition as extracellular plaques and hyperphosphorylated tau deposition in intracellular neurofibrillary tangles.⁹ Patients with AD generally present with progressive cognitive decline, often with particularly marked impairments in memory, although impairment in other cognitive domains is common. Symptomatic treatments for AD have been available for many years, specifically acetylcholinesterase inhibitors (eg, galantamine, rivastigmine, donepezil) and an N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). Monoclonal antibody treatments targeting A β are also now available for treatment in patients with mild cognitive impairment (MCI), which is considered a prodromal stage of AD in many cases, or mild AD. Three monoclonal antibody treatments have been approved by the US Food and Drug Administration (FDA) (ie, aducanumab, lecanemab, and donanemab).^{10,11}

Neuroimaging tools used to study brain changes in patients with MCI and AD have shown marked brain atrophy, deposition of amyloid and tau, and glucose hypometabolism, which progress as the disease and clinical symptoms worsen.¹²

Interestingly, studies in patients in preclinical stages of AD, namely older adults who have abnormal amyloid deposition, suggest a long course of development and a temporal ordering of brain changes. Specifically, current literature suggests that abnormal amyloid and tau accumulation, neurodegeneration, and cognitive decline occur over decades. Jack and colleagues¹³ suggested that the first abnormalities are seen in amyloid measures (in CSF or on PET), followed by tau (in CSF or on PET) and functional brain changes. Then, as the disease progresses and patients begin to show cognitive impairments, abnormal brain atrophy is observed, followed by further worsening of clinical symptoms and finally clinical dementia.

In 2024, the diagnostic staging scheme for characterizing older adults at risk for AD was updated.⁴ The original scheme focused only on amyloid, tau, and neurodegeneration, and thus, was called the *A/T/N staging system*.⁵ The previous system categorized patients by their amyloid status (positive or negative CSF A β or amyloid PET scans), tau status (positive or negative CSF phosphorylated tau or tau PET scans), and neurodegeneration (positive or negative FDG-PET or structural MRI). The new system alters this staging slightly by generally separating findings from fluid and PET biomarkers and including additional factors such as inflammation (I), synucleinopathy (S), and vascular damage (V) (**FIGURE 8-1**). Further, the new staging system seeks to classify biomarkers into core criteria measures (amyloid and tau), which define the disease, and changes that are nonspecific to AD or resulting from copathologies (N, I, V, and S). Notably, this system classifies anyone who is amyloid positive as having AD, while the other factors, such as tau PET (T₂) and neurodegeneration on MRI (N), are generally used as staging tools to define the severity of disease and expected trajectory of clinical and cognitive decline. Although this classification scheme was originally designed primarily for research, the updated version highlights the importance of translating the proposed biomarkers and definitions to the clinical space, particularly in the context of disease-modifying treatments.

MRI and PET Findings in Clinical, Prodromal, and Preclinical Alzheimer Disease

Patients with AD show marked changes on most biomarker measures used for clinical care and research, including widespread atrophy on structural MRI in both subcortical (ie, hippocampus, amygdala, basal ganglia, and basal forebrain) and cortical regions, most especially the mesial and lateral temporal lobes (**FIGURE 8-2**¹⁴ and **FIGURE 8-3**¹⁵).^{16,17} Longitudinally, patients with AD show rapidly progressive rates of atrophy in both the hippocampus (approximately 4.7%/y) and cortex (approximately 2%/y).¹⁸ Patients with AD also show more white matter hyperintensities than cognitively normal older adults, which may reflect greater comorbid cerebrovascular disease or a direct pathologic impact of AD pathophysiology.¹⁹ Further, parietal white matter hyperintensity progression was associated with the incidence of AD onset.²⁰ Cerebral microhemorrhages on SWI or similar imaging techniques are also common in AD, particularly in patients with AD who have extensive cerebral amyloid angiopathy (CAA).

PET studies of patients with AD have also shown significant alterations in glucose metabolism and the widespread deposition of amyloid and tau throughout the brain (**FIGURE 8-3** and **FIGURE 8-4**²¹).²² In patients with AD, hypometabolism occurs in primarily the lateral parietal and temporal cortices, although in later stages, hypometabolism can be observed throughout the brain. Longitudinally, patients with AD show faster rates of decline in brain metabolism than cognitively normal older adults. The pattern of hypometabolism in patients with AD is distinct from that seen in other dementias with overlapping symptomatology, such as PDD, DLB, or FTLD. The Centers for Medicare & Medicaid Services (CMS) has approved reimbursement for FDG-PET in patients with uncertainty of diagnosis to assist with differential diagnosis because the test improves diagnostic certainty by approximately 50% to 60%.²³

Biomarker category		CSF or plasma analytes	Imaging
Core biomarkers			
Core 1			
A	Amyloid-β (Aβ) proteinopathy	Aβ42	Amyloid positron emission tomography (PET)
T ₁	Phosphorylated and secreted Alzheimer disease (AD) tau	Phosphorylated tau (pTau) 217, pTau 181, pTau 231	
Core 2			
T ₂	AD tau proteinopathy	pTau 205, MTBR-tau 243, non-pTau fragments	Tau PET
Biomarkers of nonspecific processes involved in AD pathophysiology			
N	Injury, dysfunction, or degeneration of neuropil	Neurofilament light chain	Anatomic MRI or CT, fludeoxyglucose (FDG)-PET
I	Inflammation, astrocytic activation	Glial fibrillary acidic protein (GFAP)	
Biomarkers of non-AD copathology			
V	Vascular brain injury		Anatomic infarction, white matter hyperintensity
S	α-Synuclein	α-Synuclein seed amplification assay ^a	

FIGURE 8-1

Revised criteria for diagnosis and staging of Alzheimer disease using biomarkers.

A = amyloid; I = inflammation; MTBR = microtubule-binding region; N = neurodegeneration; S = synucleinopathy; T₁ = core 1 tau biomarker; T₂ = core 2 tau biomarker; V = vascular damage.

^a A fluid analyte that is presently informative only when measured in CSF.

Imaging with amyloid-specific PET tracers demonstrates widespread amyloid deposition throughout the cortex in patients with AD (FIGURE 8-3).²⁴ As discussed later in this article, amyloid positivity on PET is an eligibility requirement for treatment with a monoclonal antibody for patients with cognitive impairment. However, it is notable that amyloid deposition can be found in the setting of other dementias and even in cognitively normal patients, suggesting it is not a definitive correlate of cognitive impairment when present.

Longitudinal accumulation of amyloid on PET is slow in most individuals, including those with AD. According to the hypothesis by Jack and colleagues,¹³ accumulation of amyloid reaches an asymptotic state in the presence of high or

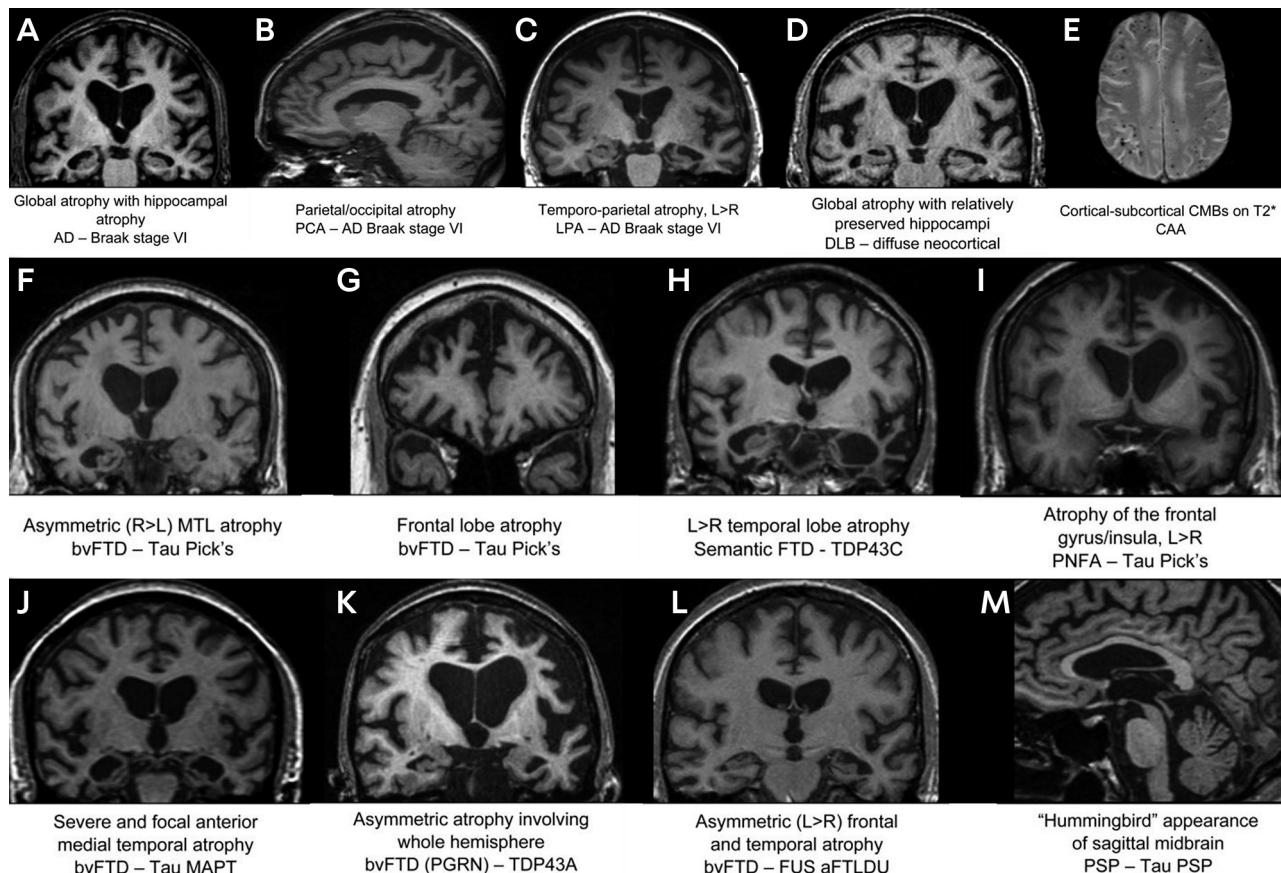


FIGURE 8-2

Structural MRI atrophy in neurodegenerative diseases. Representative sections are shown for multiple patients with confirmed pathology at autopsy, including Alzheimer disease (AD) (A), posterior cortical atrophy (PCA) (B), logopenic aphasia (LPA) (C), dementia with Lewy bodies (DLB) (D), cerebral amyloid angiopathy (CAA) (E), mesial temporal (F) and frontal lobe (G) atrophy in behavioral variant frontotemporal dementia (bvFTD), semantic FTD (H), progressive nonfluent aphasia (PNFA) (I), bvFTD due to an MAPT mutation (J), bvFTD due to a PGRN mutation (K), bvFTD due to a fused in sarcoma (FUS) mutation (L), and progressive supranuclear palsy (PSP) (M). All views are coronal except panels B and M, which are sagittal, and panel E, which is axial.

aFTLDU = atypical frontotemporal lobar dementia with ubiquitin inclusions; CMB = cerebral microbleed; L = left; MTL = mesial temporal lobe; R = right; TDP-43A = transactive response DNA-binding protein 43 type A; TDP-43C = transactive response DNA-binding protein 43 type C.

Modified from Harper L, et al, J Neurol Neurosurg Psychiatry.¹⁴ © 2014 The Authors.

low deposition, thus suggesting reduced rates of amyloid accumulation in those with clinical AD and high amyloid deposition. However, studies suggest that rates of amyloid accumulation are generally faster in people with cognitive impairment than those who are cognitively normal.²⁵

Only one PET tracer targeting tau is currently approved for clinical use (flortaucipir).²⁶ However, tau PET has been widely used in research settings and clinical trials to date. Patients with AD show significant tau deposition on PET in the mesial and lateral temporal and parietal lobes, as well as in the frontal lobe in more advanced cases (FIGURE 8-3).²⁷ The location and intensity of signal in tau PET images provide important information for staging disease severity and can recreate the topographic staging patterns of tau deposition *in vivo* described by Braak and colleagues.²⁸ Staging of tau deposition using PET may be important for targeting treatment in clinical settings in the future.^{28,29} The TRAILBLAZER-ALZ 2 (Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease) trial of donanemab selected individuals for treatment based on levels of tau PET deposition and found the greatest treatment efficacy in amyloid-positive individuals with low to medium tau deposition.³⁰ Longitudinal change in tau deposition is slow compared with that of amyloid, suggesting pathologic protein accumulation occurs in a longer time scale, but is greater in individuals with AD than in patients with MCI or in cognitively normal adults.³¹

MILD COGNITIVE IMPAIRMENT. Amnestic MCI is considered a prodromal stage of AD, with approximately 50% of patients with MCI progressing to a diagnosis of AD dementia within 5 years.³² Neuroimaging studies of patients with MCI have

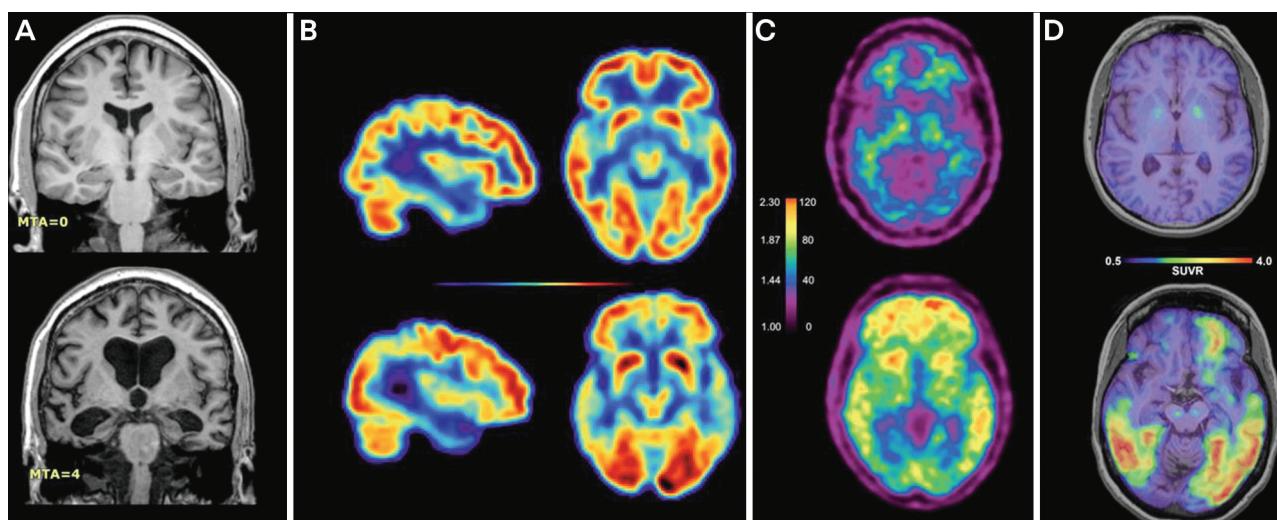


FIGURE 8-3

Neuroimaging from a cognitively normal control (top row) compared with a patient with Alzheimer disease (AD) (bottom row). Neuroimaging shows widespread atrophy on a coronal structural MRI (A, bottom image), glucose hypometabolism on a fludeoxyglucose positron emission tomography (FDG-PET) scan (B, bottom image), significantly elevated Pittsburgh Compound B amyloid PET (C, bottom image), and elevated flortaucipir tau PET (D, bottom image).

MTA = mesial temporal lobe atrophy; SUVR = standardized uptake value ratio.

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provided additional evidence that MCI is a transition stage between normal cognition and dementia, showing AD-like patterns of brain atrophy, glucose hypometabolism, and amyloid and tau deposition that are often less severe or extensive than in clinical AD dementia but markedly abnormal relative to cognitively normal adults. Patients with MCI show significant atrophy in the mesial and lateral temporal lobes, most especially in the entorhinal cortex and hippocampus, which is intermediate in severity between patients with AD and cognitively normal adults.³³ More severe entorhinal or hippocampal atrophy is

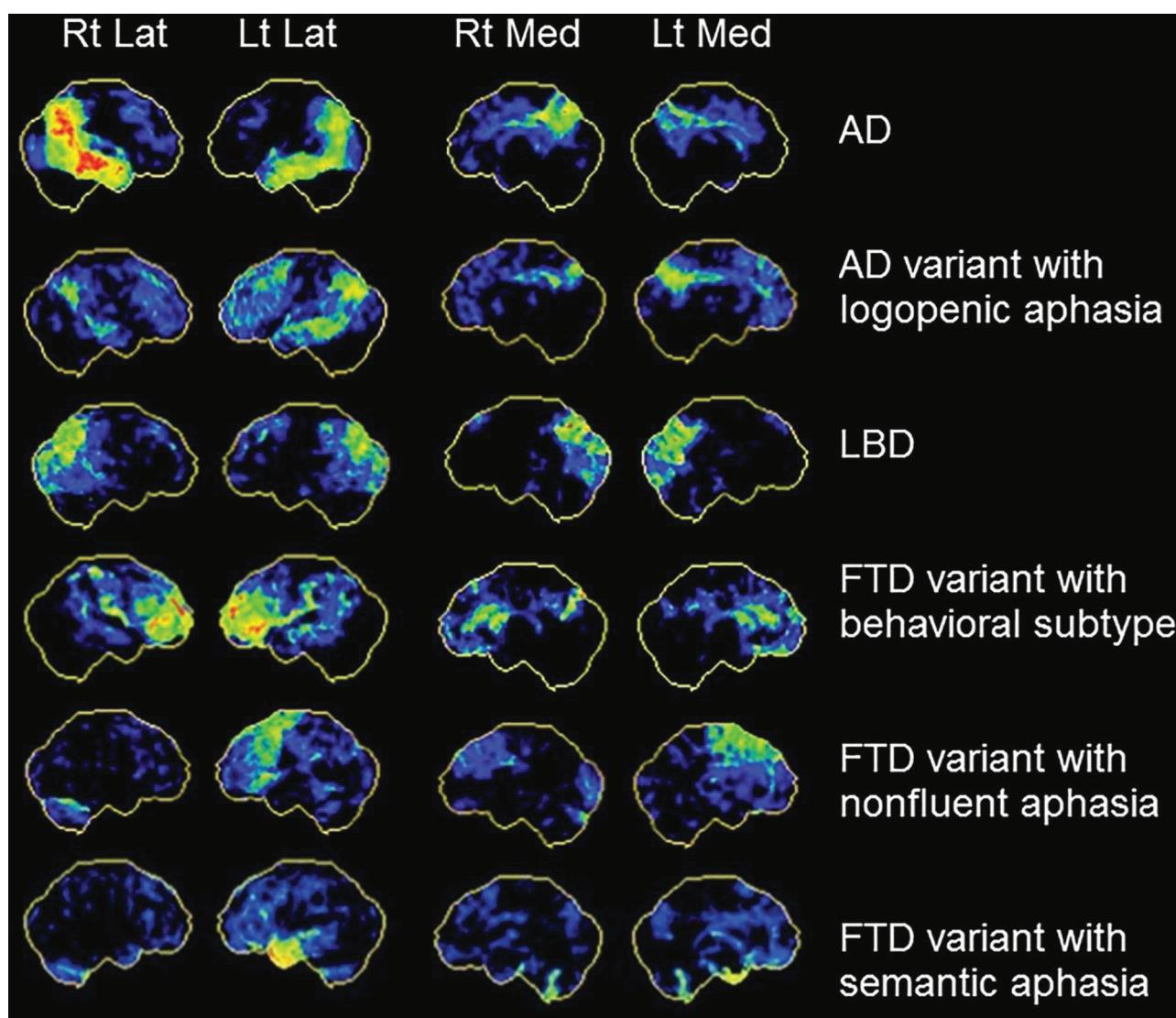


FIGURE 8-4

Hypometabolic patterns in neurodegenerative diseases. Examples of fludeoxyglucose positron emission tomography (FDG-PET) patterns displayed as cortical surface projections. Areas of increased signal represent those with the greatest hypometabolism relative to a reference sample for multiple neurodegenerative diseases, including Alzheimer disease (AD), logopenic aphasia, Lewy body dementia (LBD), behavioral variant frontotemporal dementia (FTD), progressive nonfluent aphasia FTD, and semantic variant FTD.

Lat = lateral; LBD = Lewy body dementia; Lt = left; Med = medial; Rt = right.

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linked to a higher risk of future conversion from MCI to AD within a few years.¹⁷ Longitudinally, patients with MCI show rapid volume loss in the hippocampus and cortex relative to cognitively normal adults but slower rates than those seen in patients with AD.¹⁸ Advanced MRI metrics of brain structure and function also show intermediate impairments in patients with MCI that are often reflective of disease severity and symptomatology.

FDG-PET in patients with MCI demonstrates glucose hypometabolism in temporoparietal, posterior cingulate, and parietal regions, which can predict future dementia conversion.³⁴ Most patients with MCI show widespread amyloid deposition, which is most significant in the mesial parietal and frontal lobes.³⁵ Amyloid-positive patients with MCI show poorer cognition and a faster rate of cognitive decline and progression to dementia than those who are amyloid negative.³⁶ Notably, A β -positive patients with MCI who meet all eligibility criteria are approved for treatment with monoclonal antibodies (ie, aducanumab, lecanemab, donanemab), which is described in more detail later in this article.

Patients with MCI also have significant tau deposition, most prominently in the mesial and lateral temporal lobes.²⁷ Patients with more advanced MCI may also have tau deposition in the parietal and secondary visual association areas (similar to Braak stages V and VI). Tau deposition in the setting of MCI is more common in patients who are also A β positive, although high tau deposition can be found in A β -negative individuals in rare cases; these patients may represent false-negative amyloid PET determinations.³⁷ Longitudinally, patients with MCI show faster rates of tau accumulation than cognitively normal adults, particularly in mesial and lateral temporal and parietal lobes, which is associated with faster rates of cognitive decline.

PRECLINICAL ALZHEIMER DISEASE. According to the diagnostic staging system described earlier, any individual who is A β positive is considered to have AD.⁴ Because approximately 25% to 30% of older adults who are cognitively normal are A β positive, many people can be classified as being in preclinical stages of AD. Amyloid positivity in cognitively normal adults is strongly linked to *APOE** ϵ 4 genotype with ϵ 4 carriers showing a higher rate of amyloid positivity than ϵ 4 noncarriers.³⁸ Some abnormalities in brain structure and function, as well as tau deposition, have been seen in patients with preclinical AD, although the considerable heterogeneity of this group regarding stage and proximity to a cognitively impaired diagnosis (ie, MCI or AD dementia), as well as the presence or absence of additional risk factors, is likely to affect the consistency of the findings. Structural MRI of individuals with preclinical AD has shown mixed findings; some studies suggest mild atrophy in the subiculum and presubiculum subregions of the hippocampus, whereas others have found minimal atrophic changes.³⁹ Longitudinally, people with preclinical AD show an accelerated rate of brain atrophy relative to A β -negative or *APOE** ϵ 4-negative cognitively normal adults, especially those who subsequently convert to a diagnosis of MCI or AD dementia.⁴⁰ Patients with preclinical AD also have mixed findings on FDG-PET, with some having hypometabolism in an AD-like distribution (ie, mesial temporal lobe, temporoparietal, cingulate) and others having hypermetabolism in frontal and temporal regions. Finally, A β -positive cognitively normal adults show greater tau deposition and faster rates of accumulation than A β -negative cognitively normal adults. Tau PET deposition in patients with preclinical AD

can also be staged by using Braak staging, similar to patients with MCI and AD, although cognitively normal individuals rarely show a Braak stage greater than IV.

Use of Neuroimaging in Disease-Modifying Treatment Regimens

Early in 2023, a second monoclonal antibody targeting A β , lecanemab, was approved by the FDA.⁴¹ Importantly, the clinical trials (CLARITY, CLARITY-AD) on which that approval was based consistently showed a statistically significant slowing of disease progression (as measured by the Clinical Dementia Rating scale sum of boxes) compared with placebo in patients in mild clinical stages of AD.⁴² Lecanemab was subsequently approved by the FDA on a fast-track designation for use in amyloid biomarker-positive patients with MCI or mild AD dementia meeting all inclusion criteria. A β -positive cognitively normal individuals are not eligible for monoclonal antibody treatments at this time, although ongoing clinical trials are evaluating the efficacy of these treatments in this population. Appropriate use criteria for this medication have been recommended by Cummings and colleagues.⁴³ After FDA approval, CMS granted coverage for the cost of the treatment and some associated diagnostics (ie, biomarker studies) for eligible individuals. Numerous hospitals and medical facilities across the United States are now providing lecanemab infusion treatments to eligible and interested patients following the prescription indications.⁴⁴ More recently, donanemab was also approved by the FDA, subsequent to a clinical trial showing significant slowing of disease progression relative to placebo, especially in individuals with low to medium levels of tau deposition.^{11,30} Prescribing information for donanemab follows similar appropriate use criteria and is targeted to the same population (amyloid biomarker-positive patients with MCI and mild AD) as lecanemab.

Neuroimaging tools play a major role in the new clinical protocol for lecanemab and donanemab treatments. Amyloid PET is one of two primary methods by which amyloid biomarker positivity is determined; the other is currently an assay of CSF. With amyloid PET now covered by CMS for the purpose of defining eligibility of patients for lecanemab treatment, amyloid PET scans are becoming widely used in a clinical setting. Most commonly, amyloid PET scans are read by a trained neuroradiologist to classify individuals as amyloid positive or negative, although quantitative studies particularly in the context of clinical research are also being pursued. In addition to amyloid PET, MRI has an important role in the lecanemab indications for use. One common side effect of monoclonal antibody treatments is ARIA, which are most common in patients with comorbid cerebrovascular disease or CAA and who are homozygous for the *APOE** ϵ 4 allele.^{45,46} Two types of ARIA have been observed secondary to monoclonal antibody treatments, including ARIA due to edema (ARIA-E) and ARIA due to hemorrhage (ARIA-H).^{45,46} ARIA-E is characterized by the leaking of fluid in the brain that results in interstitial vasogenic edema or sulcal effusion, which presents as hyperintense parenchymal or sulcal abnormalities on T2-weighted and FLAIR images (**FIGURE 8-5** and **CASE 8-1**). ARIA-H is characterized by one or more microhemorrhages or macrohemorrhages, which can be observed as hypointense hemosiderin deposits on T2* gradient echo (GRE) or SWI (**FIGURE 8-5**). Most ARIA cases are asymptomatic or feature mild symptoms such as headache, confusion, vomiting, and gait disturbance, although moderate to severe symptoms can occur. Most

KEY POINTS

- Neuroimaging studies have provided additional evidence that mild cognitive impairment is a transition stage between normal cognition and dementia, showing AD-like patterns of brain atrophy, glucose hypometabolism, and amyloid and tau deposition that are often less severe or extensive than in clinical AD dementia but markedly abnormal relative to cognitively normal adults.
- According to the AD and related disorders biomarker diagnostic staging system, any individual who is A β positive is considered to have AD.
- The clinical trials on which approval for lecanemab was based consistently showed a statistically significant slowing of disease progression (as measured by the Clinical Dementia Rating scale sum of boxes) compared with placebo in patients in mild clinical stages of AD.
- Amyloid-related imaging abnormalities are a common side effect of monoclonal antibody treatments and are most common in patients with comorbid cerebrovascular disease or cerebral amyloid angiopathy and who are homozygous for the *APOE** ϵ 4 allele.

ARIA cases resolve within 4 months after suspension or discontinuation of treatment. Information about ARIA severity metrics and recommendations for treatment alterations or discontinuation after an ARIA diagnosis can be found in the lecanemab appropriate use recommendations.⁴³ For more information, refer to the article "Treatment of Alzheimer Disease" by David S. Geldmacher, MD, FACP, FANA,⁴⁷ in this issue of *Continuum*.

Before monoclonal antibody treatment, patients must undergo MRI within 12 months of treatment initiation for eligibility. Specifically, to be eligible for lecanemab, for example, patients must not have on MRI (1) more than four microhemorrhages (defined as 10 mm or less at the greatest diameter); (2) one or more macrohemorrhages (defined as greater than 10 mm at the greatest diameter); (3) an area of superficial siderosis; (4) evidence of vasogenic edema; (5) two or more lacunar infarcts or stroke involving a major vascular territory; (6) severe subcortical hyperintensities (Fazekas scale grade 3 or greater); (7) evidence of A β angiitis; (8) CAA-related inflammation; or (9) other major intracranial pathology that may cause cognitive impairment. In addition, patients must be tracked with MRI to screen for the development of ARIA after treatment initiation, requiring multiple repeat MRIs. The lecanemab prescribing information and appropriate use criteria indicate that repeat MRI is required before the 5th infusion (approximately 9 to 10 weeks after initiation), the 7th infusion (approximately 13 to 14 weeks after initiation), the 14th infusion

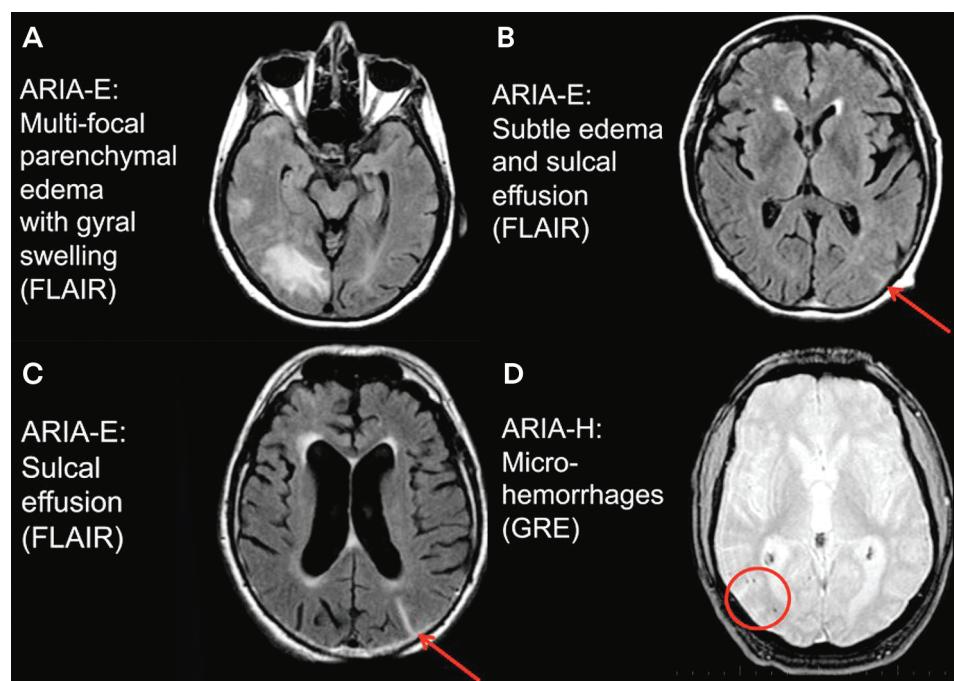


FIGURE 8-5

Amyloid-related imaging abnormalities (ARIA). ARIA are a major side effect of anti-amyloid monoclonal immunotherapies, and they are generally observed by MRI with either fluid-attenuated inversion recovery (FLAIR) or T2* gradient echo (GRE) or susceptibility-weighted imaging (SWI). ARIA can present as ARIA due to edema (ARIA-E), which features parenchymal edema (A, B), sulcal effusion (B, C, arrows), and potentially gyral swelling (A), and ARIA due to hemorrhage (ARIA-H), which features microhemorrhages (D, circle).

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(approximately 27 to 28 weeks after initiation), and the 26th infusion (approximately 1 year after initiation). Safety MRI is also suggested if any symptoms of potential ARIA emerge, such as dizziness, loss of consciousness, and others. Overall, the newly approved monoclonal antibody treatments, and likely most treatments to come, require extensive neuroimaging for both eligibility determination and safety monitoring, suggesting long-term clinical utility for neuroimaging biomarkers in the diagnosis and treatment of dementia.

Atypical Alzheimer Disease

Although most patients with AD present with a characteristic amnestic phenotype, uncommon presentations of AD are invariably encountered in neurologic practice. Neuroimaging is an essential tool in characterizing these presentations. For more information about these presentations, refer to the article “Atypical Presentations of Alzheimer Disease” by David Jones, MD, Victoria Pelak, MD, and Emily Rogalski, PhD,⁴⁸ in this issue of *Continuum*.

EARLY-ONSET ALZHEIMER DISEASE. Most patients with AD are diagnosed after the age of 65 and, thus, are considered to have late-onset AD. However, approximately 5% of all patients with AD have an onset before age 65 and, therefore, have early-onset AD. Generally, neuroimaging findings in early-onset AD are similar to the patterns seen in late-onset AD described earlier, with amyloid and tau deposition, glucose hypometabolism, and brain atrophy. However, some studies have suggested that patients with early-onset AD have more severe pathology on neuroimaging measures than patients with late-onset AD, including more severe global atrophy and greater amyloid and tau deposition at the same general level of cognitive performance. LEADS (the Longitudinal Early-onset Alzheimer’s Disease Study) is a large multisite longitudinal neuroimaging study to investigate the clinical and biomarker course of patients with early-onset AD.⁴⁹ Initial findings from LEADS suggest that these

A 72-year-old man who was APOE*ε4 positive was diagnosed with mild Alzheimer disease and started on anti-amyloid monoclonal antibody treatment. After the fourth infusion, he reported headache, nausea, and vomiting, which were partially improved by using over-the-counter pain medication and did not interfere with daily functioning. Fluid-attenuated inversion recovery (FLAIR) MRI revealed areas of parenchymal edema measuring 6 cm at the widest point in the right occipital lobe (FIGURE 8-5A).

CASE 8-1

This patient likely experienced an amyloid-related imaging abnormality due to effusion (ARIA-E) secondary to the monoclonal antibody treatment. The ARIA-E would be considered symptomatic with moderate severity based on the size of the lesion (6 cm) and the presence of clinical symptoms. According to the appropriate use recommendations, treatment suspension was suggested due to the moderate and symptomatic ARIA-E, with a potential reinitiation of treatment after resolution of the ARIA-E.

COMMENT

patients have a signature cortical atrophy pattern that includes significant atrophy in areas of the lateral temporal, inferior parietal, and mesial parietal lobes with relative sparing of the mesial temporal lobe.⁴⁹ Patients with early-onset AD also have a greater volume of white matter hyperintensities than age-matched cognitively normal adults and patients with non-AD early-onset dementia (defined as A β -negative early-onset dementia cases).⁵⁰ Finally, significantly greater amyloid and tau deposition on PET was observed in patients with early-onset AD than in age-matched cognitively normal adults and patients with non-AD dementia (defined as A β -negative young-onset cases)⁵¹; the amyloid and tau deposition is also more severe in women and *APOE** ϵ 4-positive individuals.⁵²

AUTOSOMAL DOMINANT EARLY-ONSET ALZHEIMER DISEASE. In addition to sporadic forms of early-onset AD, nearly 5% of AD cases are caused by dominantly inherited genetic variations in *PSEN1*, *PSEN2*, or *APP*. One notable characteristic of these autosomal dominant AD forms is the consistency of age of onset within a family. Thus, researchers can generally predict the approximate age of onset expected for an individual who carries the genetic variation decades before, thereby allowing for analyses of the preclinical time course of biomarker changes. A 2018 study evaluating longitudinal trajectories in the Dominantly Inherited Alzheimer's Network, a large consortium study including more than 350 symptomatic and asymptomatic genetic variation carriers, as well as noncarriers, demonstrated that amyloid measures became abnormal approximately 20 years before the expected symptom onset, followed by altered glucose metabolism approximately 15 years before expected onset, and finally cortical thinning approximately 5 to 10 years before expected onset.⁵³ Further, the precuneus was identified as the earliest region to show changes in all three measures. Although conducted in patients with autosomal dominant early-onset AD, this study provides strong support for the hypothetical biomarker cascade proposed by Jack and colleagues¹³ for late-onset AD, suggesting temporal ordering of biomarker changes. These findings are also supported by previous studies in smaller samples suggesting that asymptomatic carriers of the genetic variation show accelerating atrophy as they near their estimated age of onset, hypometabolism on FDG-PET, more white matter hyperintensities, and significant amyloid and tau deposition that is associated with future cognitive decline. Symptomatic carriers of these genetic variants show more severe pathology than asymptomatic carriers and noncarriers, including widespread subcortical and cortical atrophy, more white matter hyperintensities, greater glucose hypometabolism, and more extensive and significant deposition of amyloid and tau. Although the patterns of atrophy, hypometabolism, and amyloid and tau deposition in patients with autosomal dominant early-onset AD are similar to those seen in patients with late-onset AD, some notable differences have been observed including more frontotemporal atrophy,⁵⁴ greater amyloid deposition in the striatum,⁵⁵ and more frontal tau deposition in patients with familial early-onset AD than those with sporadic late-onset AD.⁵⁶

POSTERIOR CORTICAL ATROPHY. Patients with posterior cortical atrophy (PCA) have marked atrophy in the posterior regions of the brain, including in the occipital lobe, visual association areas, posterior parietal and temporal lobes, and mesial parietal lobe (**FIGURE 8-2B** and **FIGURE 8-6**).⁵⁷ Longitudinally, patients

with PCA show faster occipital atrophy rates than patients with logopenic aphasia.⁵⁸ FDG-PET studies in patients with PCA show some overlap with traditional AD patterns, including hypometabolism in temporal and parietal lobes, but with considerably more occipital hypometabolism than in patients with typical AD (FIGURE 8-6).⁵⁹ Patients with PCA show widespread amyloid deposition that is similar to that seen in patients with typical AD, except for greater occipital lobe amyloid (FIGURE 8-6).⁵⁹ Finally, tau deposition in patients with PCA is greatest in posterior cortical regions, including the parietal lobe, occipital lobe, and posterior regions of the temporal lobe,⁵⁹ which is associated with alterations in functional connectivity (FIGURE 8-6).⁶⁰

LOGOPENIC APHASIA. Patients with logopenic aphasia show atrophy of the temporoparietal region of the language-dominant hemisphere (usually the left hemisphere), with less atrophy in the contralateral hemisphere.^{59,61} In a recent meta-analysis, atrophy in the setting of logopenic aphasia is greatest in the left more than the right middle and superior temporal gyri, inferior parietal lobule,

KEY POINTS

- Some studies have suggested that patients with early-onset AD have more severe pathology on neuroimaging measures than patients with late-onset AD, including more severe global atrophy and greater amyloid and tau deposition at the same general level of cognitive performance.

- Amyloid measures become abnormal approximately 20 years before expected AD symptom onset, followed by altered glucose metabolism approximately 15 years before expected onset, and finally cortical thinning approximately 5 to 10 years before expected onset.

- Patients with posterior cortical atrophy demonstrate marked atrophy in the occipital lobes, visual association areas, posterior parietal and temporal lobes, and mesial parietal lobes.

- In more severely impaired patients with logopenic aphasia, atrophy is observed in the left perisylvian regions of the left anterior temporal lobe and inferior frontal lobe.

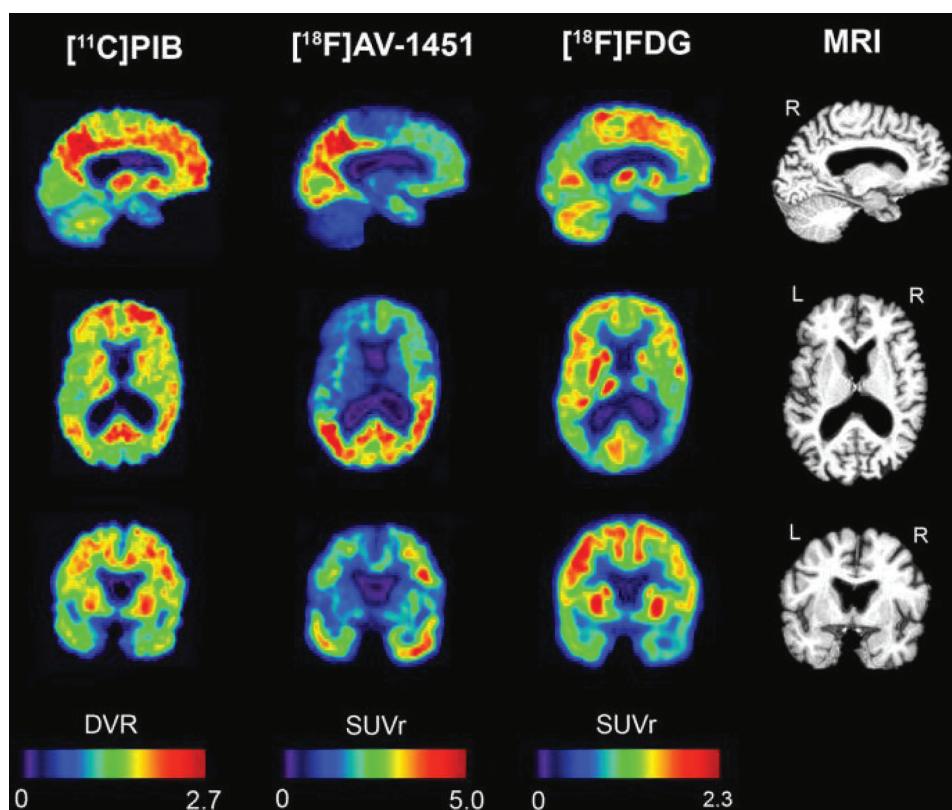


FIGURE 8-6

Neuroimaging from a patient with posterior cortical atrophy including Pittsburgh Compound B (PiB) amyloid positron emission tomography (PET) (first column), flortaucipir tau PET (second column), fludeoxyglucose (FDG)-PET (third column), and structural MRI (fourth column). Areas of high signal are shown in red and low signal in blue. Scans show high levels of amyloid and tau deposition on PiB and AV1451 PET, respectively; posterior glucose hypometabolism on FDG-PET; and posterior atrophy on structural MRI.

DVR = distribution volume ratio; L = left; R = right; SUVr = standardized uptake value ratio.

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and fusiform gyrus (**FIGURE 8-2C**).⁶² In more severely impaired patients, atrophy is also observed in the left perisylvian regions of the left anterior temporal lobe and inferior frontal lobe.⁶¹ Longitudinally, patients with logopenic aphasia have accelerated atrophy rates in the lateral and posterior temporal lobes.⁵⁸ Glucose metabolism in FDG-PET studies in patients with logopenic aphasia is reduced in the temporoparietal region of the language-dominant hemisphere (usually the left hemisphere), particularly the inferior parietal lobe (**FIGURE 8-4**).⁶² Most patients with logopenic aphasia have significant amyloid deposition in AD-like regions, although some patients are amyloid negative. Finally, tau deposition on PET is observed in patients with logopenic aphasia in the left hemisphere in mesial and lateral parietal, temporal, and occipital lobes. Longitudinally, patients with logopenic aphasia, compared with patients with PCA, have faster rates of tau accumulation in the right parietal and temporal lobes, as well as the bilateral occipital lobes.⁵⁸

VASCULAR COGNITIVE IMPAIRMENT

Vascular cognitive impairment comprises cognitive disorders caused by changes in the cerebrovascular system, including subcortical ischemic vascular dementia, multi-infarct dementia, hemorrhagic dementia, and genetic forms of vascular cognitive impairment such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).^{63,64} The most common form of sporadic vascular cognitive impairment is subcortical ischemic vascular dementia, which is often secondary to cardiovascular risk factors (ie, hypertension, hyperlipidemia, diabetes, and obesity). The diagnosis of vascular cognitive impairment is reliant on MRI findings of cerebral small vessel disease or other cerebrovascular damage. In 2023, updated Standards for Reporting Vascular Changes on Neuroimaging criteria were published to modernize the neuroimaging features of small vessel disease.⁷ These criteria identified multiple pathologies that can be viewed by using MRI as characteristic for small vessel disease including (1) recent small subcortical infarcts, (2) lacunes (of presumed vascular origin), (3) white matter hyperintensities (of presumed vascular origin), (4) enlarged perivascular spaces, (5) cerebral microbleeds, (6) cortical superficial siderosis, and (7) cortical cerebral microinfarcts (**FIGURE 8-7**).⁶⁵ Although most of these findings can be seen in both normal aging and other dementias, the small vessel disease pathology in patients with vascular cognitive impairments is much more severe and widespread than in cognitively normal adults. Patients with vascular cognitive impairment also show both gray and white matter atrophy, which is associated with the extent of white matter hyperintensity burden,⁶⁶ as well as reduced white matter integrity on DWI.⁶⁷

Task-based functional MRI (fMRI) studies have shown reduced activation during tasks in patients with vascular cognitive impairment. Images in these patients also show alterations in resting-state fMRI studies, including reduced connectivity in the parietal and frontal lobes, as well as the cingulate gyrus. Patients with vascular cognitive impairment have focal hypometabolism on FDG-PET studies that often presents as an asymmetric or scattered pattern but near cortical or subcortical arteries or watershed regions. Patients with vascular cognitive impairment are generally amyloid and tau negative on PET, which can allow a distinction from patients with CAA, who generally are amyloid positive; for more information, refer to the article “Vascular Cognitive Impairment” by Lisa C. Silbert, MD, MCR, FAAN,⁶⁸ in this issue of *Continuum*.

Cerebral Amyloid Angiopathy

In patients with CAA, amyloid is deposited primarily in the vessel walls of small cerebral arteries and capillaries. Although some CAA is seen in patients with typical AD, patients with primary CAA have markedly different symptoms than patients with typical AD secondary to symptomatic, spontaneous local hemorrhages that can cause cognitive and neurologic symptoms, as well as headache and altered consciousness. The most notable findings in patients with primary CAA are cerebrovascular damage markers on MRI, including white matter hyperintensities on T2-weighted scans and microhemorrhages and cortical superficial siderosis on T2* or SWI sequences (FIGURE 8-2E).⁶⁹ The revised Boston Criteria (version 2.0), which are used to diagnose CAA, include changes in the in vivo MRI markers as necessary for diagnosis, including brain hemorrhages and cortical superficial siderosis.⁷⁰ Cortical or subcortical infarcts and enlarged perivascular spaces are also seen in patients with CAA; however, given that these findings are also commonly observed in patients with vascular dementia, they are not definitive for a diagnosis. Amyloid PET studies in patients with CAA demonstrate widespread amyloid deposition, particularly in the occipital lobe, which is similar to scans seen in patients with typical AD.⁷¹ Finally, tau PET may show increased tau deposition in patients with CAA in regions that also show microbleeds and cortical superficial siderosis.⁷²

KEY POINT

- MRI can illustrate multiple features characteristic of small vessel disease including (1) recent small subcortical infarcts, (2) lacunes (of presumed vascular origin), (3) white matter hyperintensities (of presumed vascular origin), (4) enlarged perivascular spaces, (5) cerebral microbleed(s), (6) cortical superficial siderosis, and (7) cortical cerebral microinfarcts.

Comorbidity of Cerebrovascular Disease With Other Dementia Pathologies

Most patients with dementia who subsequently undergo autopsy ultimately are diagnosed as having had mixed dementia, which is a condition with more than

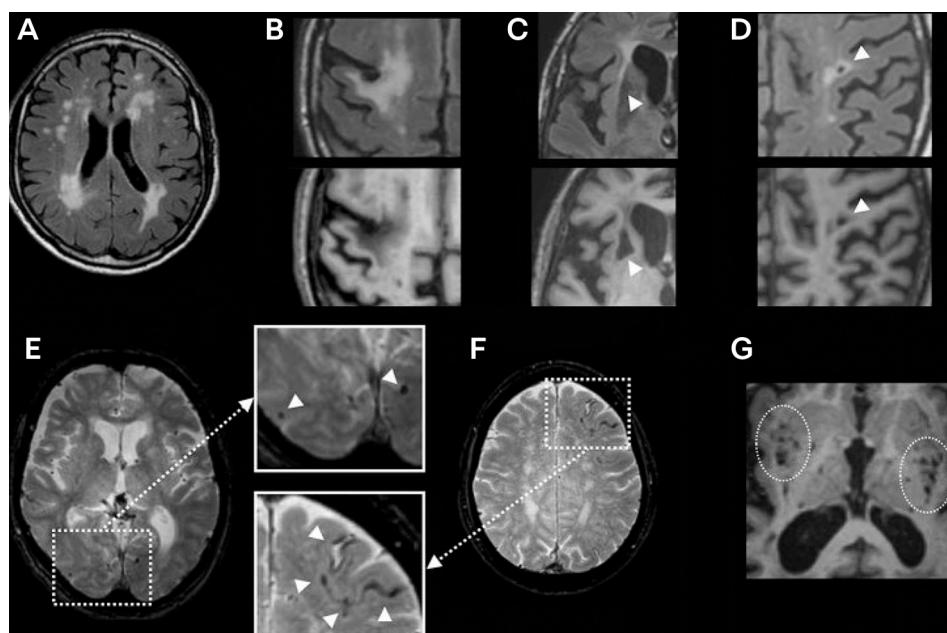


FIGURE 8-7

Vascular lesions on brain MRI. Patients with vascular cognitive impairment or mixed dementias may present with several different vascular lesions on structural MRI, including white matter hyperintensities (A), cortical (B) and large subcortical infarcts (C, arrowheads), lacunar infarcts (D, arrowheads), microbleeds (E, arrowheads in the inset), cortical superficial siderosis (F, arrowheads in the inset), and enlarged perivascular spaces (G, ovals). Note that panels include a mixture of axial T1-weighted and T2-weighted sequences.

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one pathology identified on neuropathologic analysis. Cerebrovascular disease is the most common comorbid pathology seen with other dementia syndromes, including AD. However, given that neuroimaging techniques are currently optimized for AD (ie, PET tracers for tau and amyloid) and vascular (ie, MRI) pathologies, the co-occurrence of other types of pathology, including α -synuclein, transactive response DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS), and others, may be underestimated because these are difficult to assess *in vivo*. A CSF-based assay called *real-time quaking-induced conversion* has shown promise as a novel biomarker to detect α -synuclein in patients⁷³; however, to date, this technique is currently used mostly in research studies rather than clinical settings. Currently, determining whether the ischemic burden is causing clinical symptoms or is a secondary factor is difficult because of the high frequency of cerebrovascular disease comorbidity with other disease-causing pathologies. Patients with both AD and vascular pathology on neuroimaging have white matter hyperintensities and more advanced white matter degeneration on structural MRI and DWI compared with patients with a single pathology.⁷⁴ Overall, the frequency of mixed-dementia cases should be considered during the development of novel therapeutic interventions and pharmaceuticals for dementia.

PARKINSON DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

Parkinson disease (with or without dementia), DLB, and multiple system atrophy (MSA) are characterized by pathologic protein aggregations of α -synuclein, called *Lewy bodies*.⁷⁵ Clinically, PDD and DLB differ primarily by the order of onset of symptoms, with PDD characterized by the onset of motor symptoms before cognitive symptoms whereas patients with DLB have an onset of cognitive symptoms before or concurrent with motor symptoms. However, pathologically and in imaging biomarkers, PDD and DLB are highly similar. Therefore, these diseases are discussed simultaneously here, noting that patients with PDD often have less severe cerebral pathology and imaging findings than patients with DLB.⁷⁶ Alternatively, MSA is a rare Lewy body-related disease characterized by parkinsonian symptoms of varying severity, cerebellar ataxia, and in some cases prominent autonomic dysfunction, which are generally divided into parkinsonian type MSA and cerebellar ataxia type MSA, based on the predominant symptoms.⁷⁷

Structural MRI studies in patients with DLB and PDD show cortical atrophy relative to controls in the insula, middle and posterior cingulate, superior temporal-occipital areas, lateral orbitofrontal lobe, other regions of the frontal lobe, inferior parietal lobe, temporal lobe, and occipital lobe (**FIGURE 8-2D**).⁷⁶ Notably, the atrophy tends to be more severe in patients with DLB than PDD, particularly in cortical regions. Patients with PDD or DLB have relative sparing of atrophy in the mesial temporal lobe, especially when compared with patients with AD. When patients with PDD or DLB have mixed pathology, such as amyloid deposition on PET or cerebrovascular disease on MRI, they have more severe global atrophy than those without apparent mixed pathology.⁷⁸ Longitudinally, patients with PDD or DLB have faster atrophy rates in the temporal lobe and temporal-occipital areas, which again is generally more severe in the setting of DLB than PDD.⁷⁹ SWI provides imaging of iron deposition in nigrosomes, which are small bundles of dopaminergic cells in the substantia nigra pars compacta that, when intact, show a hyperintense signal

that resembles the tail of a swallow, called the *swallow tail sign* (FIGURE 8-8⁸⁰).⁸¹ Patients with DLB and Parkinson disease show a loss of the swallow tail sign on SWI.⁸²

Hypometabolism in the striatum, cerebellum, and frontal, parietal, and occipital lobes is observed in FDG-PET studies, with relative sparing of the mesial temporal lobe (FIGURE 8-4).⁸³ Patients with PDD or DLB also have a characteristic feature on FDG-PET referred to as the *cingulate island sign*, which is a relative sparing of hypometabolism in the posterior cingulate compared with the surrounding areas (FIGURE 8-9⁸⁴). More than half of patients with DLB have amyloid deposition on PET, whereas patients with PDD are less frequently positive for amyloid.⁷⁸ Compared with patients with AD, amyloid-positive patients with PDD or DLB have less overall tracer uptake but more uptake in the primary visual cortex, which is associated with a faster decline in visuospatial function. Tau PET studies in patients with PDD or DLB have increased tau in the inferior temporal gyrus and precuneus, but this generally occurs only in patients who are amyloid positive.⁸⁵ Patients with Parkinson disease, as well as those with PDD or DLB, also have marked deficits in dopaminergic neurotransmission relative to controls and patients with other dementias. Thus, PET and SPECT measures of dopaminergic neurotransmission represent excellent biomarkers for refining the differential diagnosis. Both presynaptic (eg, dopamine transporter and vesicular monoamine transporter 2) and postsynaptic dopaminergic targets (ie, dopamine receptors) show reduced tracer binding on PET and SPECT studies in patients with PDD or DLB, which provides good differentiation from patients with AD⁸⁶; for more information, refer to the article “Dementia With Lewy Bodies and Parkinson Disease Dementia” by James E. Galvin, MD, MPH,⁸⁷ in this issue of *Continuum*.

KEY POINTS

- The most notable findings in patients with primary CAA are cerebrovascular damage markers on MRI, including white matter hyperintensities on T2-weighted scans and microhemorrhages and cortical superficial siderosis on T2* or SWI sequences.

- SWI provides imaging of iron deposition in nigrosomes, which are small bundles of dopaminergic cells in the substantia nigra pars compacta that when intact show a hyperintense signal that resembles the tail of a swallow, called the *swallow tail sign*.

- A notable (but nonspecific) sign of multiple system atrophy, called the *hot cross bun sign*, is a cruciform hyperintensity in the pons on T2-weighted imaging.

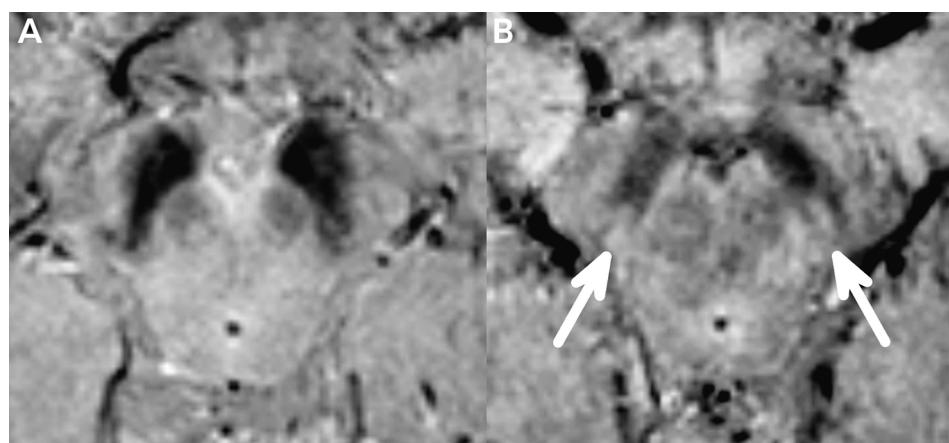


FIGURE 8-8

Swallow tail sign in a patient with Parkinson disease compared with a control image. Susceptibility-weighted imaging (SWI) shows the absence of a swallow tail sign in a patient with Parkinson disease (A) compared with a control (B) that shows the swallow tail sign. Note that a loss of swallow tail sign also is observed in patients with dementia with Lewy bodies. The swallow tail sign on axial high-resolution SWI (B, arrows) represents the presence of nigrosome-1 in the substantia nigra, which shows high signal, surrounded by low signal from the pars compacta (anteriorly and laterally) and the mesial lemniscus (mesially) resulting in a pattern similar to the tail of a swallow bird.

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Multiple System Atrophy

Patients with MSA have atrophy of the cerebellum, pons, thalamus, substantia nigra, and parietal and occipital lobes relative to controls.⁸⁸ A particularly notable but nonspecific sign of MSA, called the *hot cross bun sign*, is a cruciform hyperintensity in the pons on T2-weighted imaging (FIGURE 8-10).⁸⁹

Longitudinally, increased atrophy rates in the same regions, including the cerebellum, pons, and midbrain, are observed in patients with MSA. This atrophy is associated with cognitive decline and progressive impairment in extrapyramidal and cerebellar motor function, as well as autonomic dysfunction.⁹¹ Decreased glucose metabolism on FDG-PET has been observed in patients with MSA,⁹² whereas minimal amyloid positivity is observed. Tau deposition is rare in the setting of MSA and is likely secondary to comorbid amyloid pathology rather than α -synuclein pathology.⁹³ Similar to the findings in the setting of PDD or DLB, dopaminergic SPECT studies show reduced binding in the striatum that is associated with disease severity and duration in parkinsonian type MSA but not in cerebellar ataxia type MSA.⁹² However, distinction between parkinsonian syndromes with dopaminergic SPECT or PET is not currently possible. Finally, a 2023 study demonstrated significant uptake of an α -synuclein-specific PET tracer, ACI-12589, in the cerebellar white matter and middle cerebellar peduncles in patients with MSA that sensitively distinguished these patients from controls and patients with other neurodegenerative disorders including Parkinson disease, PDD, and DLB, as well as AD, progressive supranuclear palsy (PSP), and hereditary ataxias.⁹⁴

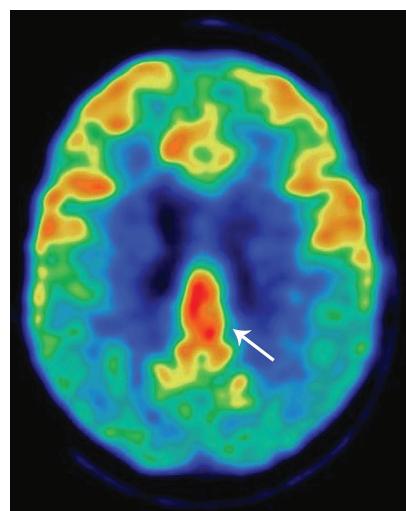


FIGURE 8-9

Cingulate island sign on fludeoxyglucose positron emission tomography (FDG-PET) in a patient with dementia with Lewy bodies. The cingulate island sign (arrow) is defined as relative preservation in glucose metabolism in the posterior cingulate relative to significant hypometabolism in the precuneus and cuneus on FDG-PET. The cingulate island sign supports the diagnosis of dementia with Lewy bodies.

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FRONTOTEMPORAL LOBAR DEGENERATION

FTLD diseases are defined by their pathologic characteristics and feature degeneration of primarily the frontal or temporal lobes or both. Several subtypes of clinical disorders are classified as FTLD, which can be generally divided into two classes based on symptoms, specifically those with primarily behavioral symptoms (behavioral variant FTD) and those with primarily language impairments (primary progressive aphasia). In addition, FTLD syndromes can feature extrapyramidal and parkinsonian motor symptoms with behavioral and cognitive impairments. Current diagnostic criteria for FTLD of all types can be found in previous reports.^{95,96} Behavioral variant FTD is characterized by behavioral disturbances, including disinhibition, obsessive-compulsive behaviors, and others, as well as cognitive impairment, particularly in executive

function. Semantic dementia is characterized by impaired semantic memory and single-word comprehension, whereas progressive nonfluent aphasia, features speech production difficulties with agrammatism, phonemic errors, and anomia. Two FTLD-related disorders that feature cognitive impairment and motor symptoms are discussed here, including (1) corticobasal degeneration (CBD), which features markedly asymmetric apraxia, akinesia, limb rigidity, focal myoclonus, dystonia, and alien limb syndrome in addition to cognitive impairment⁹⁰ and (2) PSP, which is characterized by symmetric bradykinesia, truncal rigidity, postural instability, pseudobulbar syndrome with dysarthria and dysphagia, and supranuclear palsy of vertical gaze.⁹⁰

Pathology associated with FTLD is generally caused by pathologic deposition of either tau or TDP-43, a TAR DNA-binding protein. Most FTLD cases are sporadic, but many are linked to genetic variants primarily in one of four genes: microtubule-associated protein tau (*MAPT*), granulin precursor (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), or *FUS*; for more information about this, refer to the article “Genetics and Neuropathology of Neurodegenerative Dementias” by Sonja W. Scholz, MD, PhD, FAAN, and Inma Cobos, MD, PhD,⁹⁷ in this issue of *Continuum*. The onset of FTLD most commonly occurs before the age of 60, although it can happen later in rare cases. Multiple longitudinal multisite observational clinical and biomarker studies of FTLD are ongoing (ie, the ALLFTD study⁹⁸) and will provide new data about important biomarker and pathologic findings in this group of diseases soon⁹⁹; for more information, refer to the article “Frontotemporal Dementia” by David Glenn Clark, MD,¹⁰⁰ in this issue of *Continuum*.

Behavioral Variant Frontotemporal Dementia

Patients with behavioral variant FTD have atrophy in the frontal and temporal lobes, insula, anterior cingulate cortex, and orbitofrontal cortex, as well as in subcortical regions, including the amygdala, striatum, globus pallidus, thalamus, and hippocampus (FIGURE 8-2F and 8-2G).¹⁰¹ Differences in atrophy patterns in patients with behavioral variant FTD by underlying pathology (ie, tau or TDP-43) are observed,¹⁰² with patients with FTD due to tauopathy demonstrating atrophy in the prefrontal cortex, temporal lobe, anterior cingulate, and insula, which is

KEY POINTS

- Patients with behavioral variant frontotemporal dementia have atrophy in the frontal and temporal lobes, insula, anterior cingulate cortex, and orbitofrontal cortex, as well as in subcortical regions, including the amygdala, striatum, globus pallidus, thalamus, and hippocampus.

- Patients with semantic dementia have significant focal atrophy in the ventrolateral anterior temporal lobe, most especially in the temporal pole, that presents bilaterally but is more severe in the language-dominant hemisphere (most commonly the left hemisphere).

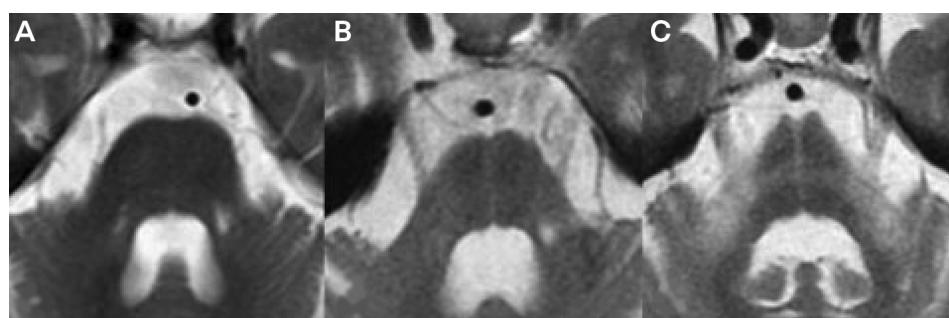


FIGURE 8-10

Hot cross bun sign on MRI of patients with multiple system atrophy. Multiple grades of the hot cross bun sign, which is a hyperintense signal of the cruciform on T2-weighted imaging, are shown in patients with multiple system atrophy, including no hot cross bun sign (grade 0: negative) (A), intermediate (grade 1: clear vertical line only) (B), and severe (grade 2: clear vertical and horizontal lines) (C).

Modified from Sugiyama A, et al, BMC Neurol.⁸⁹ © 2020 The Authors.

mostly bilateral but may be slightly greater on the left in some cases. Alternatively, patients with behavioral variant FTD with TDP-43 pathology have frontal, temporal, and parietal atrophy, which tends to be markedly asymmetric (either side can be predominant). Further, there is an anterior-posterior difference in patients with behavioral variant FTD depending on underlying pathology where PCA is greater in patients with TDP-43 pathology, whereas frontal atrophy is greater in patients with behavioral variant FTD secondary to tau.

Longitudinally, patients with behavioral variant FTD have faster atrophy rates in the frontal and temporal lobes than controls, regardless of underlying pathology.¹⁰³ One of the most useful tools for differential diagnosis in patients with behavioral variant FTD is FDG-PET, which can distinguish AD and FTLD based on a profile of temporoparietal versus frontal hypometabolism, respectively (**FIGURE 8-4**). Specifically, patients with behavioral variant FTD have frontal lobe hypometabolism on FDG-PET, which later spreads to include the anterior cingulate, parietal lobe, and temporal lobe. Subcortical regions, including the basal ganglia, insula, and thalamus, have also shown hypometabolism in patients with behavioral variant FTD.¹⁰⁴ Amyloid deposition is uncommon in patients with behavioral variant FTD and is generally exclusionary for FTLD.

Tau PET studies in patients with sporadic behavioral variant FTLD show significant deposition in the basal ganglia, anterior cingulate cortex, and insula in about half of cases, perhaps reflecting the known variability in the underlying pathology of behavioral variant FTD (ie, tau versus TDP-43).¹⁰⁵ However, the strength of the tracer signal on tau PET (using currently available ligands) in these patients was significantly lower than that seen in patients with AD, and in a groupwise comparison, patients with behavioral variant FTD did not show significantly elevated uptake compared with controls.¹⁰⁵ The absence of significant tracer retention likely reflects a lack of sensitivity of the current tau tracers to non-AD tau deposition.

Semantic Dementia

Patients with semantic dementia have significant focal atrophy in the ventrolateral anterior temporal lobe, most especially in the temporal pole, that presents bilaterally but is significantly more severe in the language-dominant hemisphere (most commonly the left hemisphere) (**FIGURE 8-2H**).¹⁰⁶ However, some individuals present with bilateral or right hemisphere-dominant atrophy, which is linked to a higher likelihood of prosopagnosia. Other regions showing atrophy in the setting of semantic dementia include the left subcallosal area, amygdala, hippocampus, caudate, parahippocampal gyrus, middle temporal gyrus, entorhinal cortex, and perirhinal cortex. Longitudinally, patients with semantic dementia show a high rate of progressive gray matter atrophy in the left more than the right temporal lobe, as well as atrophy in the temporal, periventricular, and callosal white matter.¹⁰³

FDG-PET studies in patients with semantic dementia demonstrate significant asymmetric hypometabolism in the anterior temporal lobe (usually left more than right), most especially in the temporal pole (**FIGURE 8-4**).¹⁰⁷ Amyloid PET studies in patients with semantic dementia are usually negative. Although semantic dementia is primarily thought to be caused by TDP-43 pathology, studies in some patients with semantic dementia have shown significant tau PET tracer (ie, flortaucipir, THK-5351, PI-2620) uptake in the anterior temporal lobe,

fusiform gyrus, and insula.¹⁰⁵ These findings may represent off-target binding to TDP-43, monoamine oxidase, or comorbid tau fibrils in the region. Even a familial patient carrying a *C9orf72* variation, which generally results in TDP-43 pathology, also showed tau PET tracer binding, suggesting potential nonspecific binding of the tracer.¹⁰⁸ Future studies are needed to better understand these observations.

Progressive Nonfluent Aphasia

Patients with progressive nonfluent aphasia have focal asymmetric atrophy in the language-dominant hemisphere (usually the left hemisphere) in the inferior frontal lobe and frontal operculum, including the Broca area (BA 44 and BA 45), as well as the insula, lentiform nucleus, inferior and middle frontal gyri, premotor cortex, dorsolateral prefrontal cortex, and supplementary motor area (**FIGURE 8-2I**).¹⁰⁶ The atrophy observed in patients with progressive nonfluent aphasia often results in a widening of the left sylvian fissure. The severity of atrophy may be dependent on the underlying pathology; patients with progressive nonfluent aphasia with underlying tauopathy have been reported to have severe temporal atrophy compared with those with other proteinopathies (ie, TDP-43).¹⁰⁹ Longitudinally, patients with progressive nonfluent aphasia have rapid atrophy of the frontal lobe, insula, striatum, and inferior parietal regions.¹⁰³ The atrophy in these patients progresses along the frontal aslant tract from the frontal operculum to the supplementary motor cortex, which may result in distortion errors in spontaneous speech and verbal fluency.

FDG-PET studies in patients with progressive nonfluent aphasia show asymmetric inferior frontal hypometabolism, including in the Broca area, and peri-insular hypometabolism in the language-dominant hemisphere (usually the left hemisphere for right-handed individuals) (**FIGURE 8-4**).¹¹⁰ The reverse pattern (right more than left hypometabolism) has been observed in some left-handed individuals because their right hemisphere may be the language-dominant hemisphere.¹¹¹ Other regions showing hypometabolism in the setting of progressive nonfluent aphasia include the premotor and supplementary motor areas. Amyloid PET studies in patients with progressive nonfluent aphasia are largely negative, with incidental comorbid amyloid deposition occurring in rare instances in older individuals. A study found that approximately 90% of patients with progressive nonfluent aphasia were amyloid negative.¹¹² Tau PET studies in patients with progressive nonfluent aphasia demonstrated increased tracer uptake in the left more than right frontal operculum, inferior frontal gyri, and middle frontal gyri.¹⁰⁵

Genetic Forms of Frontotemporal Dementia

Patients with hereditary FTLD show similar but not identical patterns of frontal and temporal lobe atrophy as seen in patients with sporadic FTLD. The most prominent atrophic changes are seen in clinically impaired individuals, although genetic variation carriers in preclinical stages of disease may also have atrophic changes, especially those with *C9orf72* variations. Specifically, patients with the *C9orf72* variation have symmetric atrophy in the frontal lobe, anterior temporal lobe, thalamus, parietal lobe, and occipital lobe, as well as cerebellar atrophy.¹¹³ Longitudinally, *C9orf72* variation carriers have heterogeneous rates of atrophy across individuals. Hypometabolism in the temporal lobe, orbitofrontal cortex, frontal lobe, parietal lobe, posterior cingulate, insula, caudate, and thalamus on

KEY POINTS

- Patients with progressive nonfluent aphasia have focal asymmetric atrophy in the language-dominant hemisphere (usually the left hemisphere) in the inferior frontal lobe and frontal operculum, as well as the insula, lentiform nucleus, inferior and middle frontal gyri, premotor cortex, dorsolateral prefrontal cortex, and supplementary motor area.

- Patients with *C9orf72* genetic variations have symmetric atrophy in the frontal lobe, anterior temporal lobe, thalamus, parietal lobe, and occipital lobe, as well as cerebellar atrophy.

FDG-PET was observed in *C9orf72* variation carriers, which occurs up to 10 years before the onset of clinical symptoms.¹¹⁴ Finally, mixed results have been observed in *C9orf72* variation carriers in tau PET studies, with some studies showing increased flortaucipir signal in the frontal and temporal lobes¹⁰⁵ and others showing minimal binding of tau PET tracers.¹¹⁵ Given that *C9orf72* genetic variants cause abnormal TDP-43 deposition, the tau PET signal in *C9orf72* variation carriers may be off-target binding similar to that seen in patients with semantic dementia.

MAPT variation carriers typically have more significant atrophy in the temporal lobe, including the mesial temporal lobe, than patients with other types of genetic variations or sporadic behavioral variant FTD, as well as atrophy in the parietal lobe, basal ganglia, insula, orbitofrontal cortex, and brainstem (**FIGURE 8-2J**).^{116,117} *MAPT* variation carriers also have faster atrophy rates in the temporal, frontal, and parietal lobes than noncarriers.¹¹⁸ FDG-PET studies in *MAPT* variation carriers showed hypometabolism in the anterior cingulate, frontal lobe, parietal lobe, and anteromesial temporal lobes, even in asymptomatic individuals.^{116,119} Finally, tau PET studies in *MAPT* variation carriers have shown mixed findings based on the type of *MAPT* variation.¹²⁰ Individuals with *MAPT* variations resulting in 4-repeat-only tau fibrils have low levels of tau PET tracer binding, whereas those with mixed 3-repeat and 4-repeat tau have high levels of tau PET signal.

Patients with a variation in *GRN* show highly asymmetric temporoparietal, inferior frontal, and parietal atrophy (**FIGURE 8-2K**).¹¹³ *GRN* variation carriers also show prominent white matter hyperintensity that is more extensive than patients with sporadic behavioral variant FTLD or behavioral variant FTLD secondary to another gene variant.¹²¹ Generally, fast longitudinal atrophy rates have been reported in *GRN* variation carriers compared with noncarriers. *GRN* variation carriers show hypometabolism on FDG-PET in the temporal, frontal, and parietal lobes, as well as the anterior cingulate and insula.¹²² Finally, one study demonstrated no increased uptake of flortaucipir in a *GRN* variation carrier,¹²³ whereas another showed some mild tracer retention that may reflect off-target binding.¹⁰⁵

Corticobasal Degeneration

Patients with CBD have asymmetric frontal and parietal lobe atrophy that includes the primary motor and sensory cortices, as well as atrophy in the corpus callosum, midbrain, basal ganglia, thalamus, and substantia nigra contralateral to the most affected side of the body.^{124,125} Temporal lobe atrophy was observed in patients with CBD with progressive cognitive impairment. In addition, a summary measure called the *magnetic resonance parkinsonism index*, which is calculated as the ratio of the pons to midbrain areas times the ratio of the middle cerebellar peduncles width by the superior cerebellar peduncles width, provides good differentiation of patients with autopsy-confirmed CBD from those with PSP but could not differentiate patients with CBD from those with other dementias.^{125,126} Longitudinally, patients with CBD have accelerated atrophy in the premotor and primary-motor cortices, somatosensory cortex, parietal lobe, and corticospinal tract.¹²⁷ Hypometabolism in the posterior frontal lobes, paracentral lobule, sensorimotor cortex, thalamus, basal ganglia, middle cingulate, parietal lobe, and substantia nigra has been reported in patients with CBD.¹²⁸ Amyloid PET is largely negative in patients with CBD unless comorbid

AD pathology is present. Finally, studies have evaluated tau PET with multiple tracers in patients with CBD or corticobasal syndrome and found increased tracer retention, suggesting tau deposition, in the premotor cortex, globus pallidus, subthalamic nucleus, dorsolateral prefrontal cortex, subcortical white matter, and basal ganglia, especially contralateral to the side of the body more affected with motor symptoms.¹²⁹ Longitudinal tau PET studies suggest deposition of tau increases over time, which was associated with disease progression.

Progressive Supranuclear Palsy

Patients with PSP show marked atrophy in the midbrain that is greater than that seen in the pons.¹³⁰ This pattern of atrophy is characteristic of PSP and is described as the hummingbird sign on a sagittal view and the Mickey Mouse sign or morning glory sign on an axial view (**FIGURE 8-2M** and **FIGURE 8-11**).¹³¹¹³² In addition, the magnetic resonance parkinsonism index provides good

KEY POINTS

- *MAPT* gene variation carriers typically have more significant atrophy in the temporal lobe, including the mesial temporal lobe, than patients with other types of genetic variations or sporadic behavioral variant frontotemporal lobar degeneration, as well as atrophy in the parietal lobe, basal ganglia, insula, orbitofrontal cortex, and brainstem.

- Patients with gene variations in GRN show highly asymmetric temporoparietal, inferior frontal, and parietal atrophy.

- A summary measure called the *magnetic resonance parkinsonism index* provides good differentiation of patients with autopsy-confirmed CBD from those with PSP but could not differentiate patients with CBD from those with other dementias.

- A pattern of atrophy that is greater in the midbrain than the pons is characteristic of PSP and is described as the hummingbird sign on sagittal MRI and the Mickey Mouse sign or morning glory sign on axial MRI.

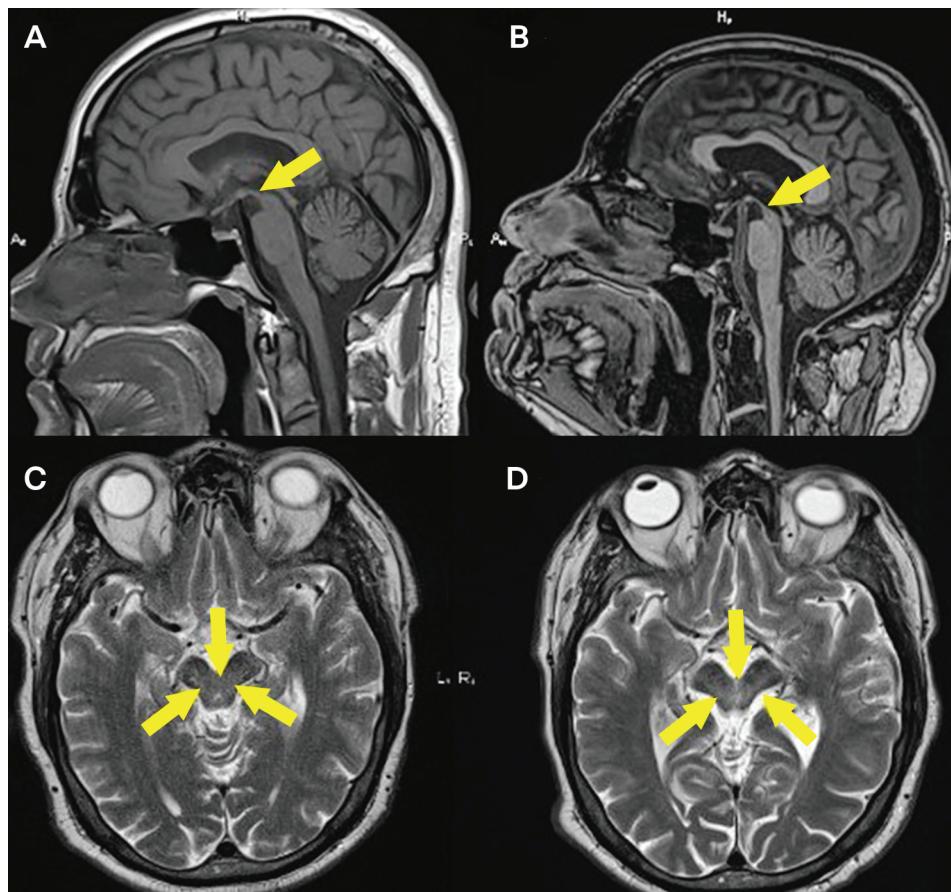


FIGURE 8-11

Structural MRI of a patient with progressive supranuclear palsy. Longitudinal sagittal structural MRI of a patient with progressive supranuclear palsy shows a thinning of the midbrain relative to the pons at baseline (A) and follow-up (B), known as the hummingbird sign (A and B, arrows), with considerable progression, including a concave appearance of the midbrain, at follow-up. Similarly on the axial view, at baseline some degeneration of the midbrain is observed (C, arrows), but significant progression of the midbrain atrophy (D, arrows) is observed at a follow-up visit, reflecting the morning glory sign (concave lateral margins) and Mickey Mouse sign (reduced anteroposterior diameter).

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differentiation of patients with PSP from patients with CBD and those with other dementias.¹²⁵ Patients with PSP have additional atrophy in the cortical and subcortical regions, including in the posterior frontal lobe, premotor cortex, supplementary motor area, and caudate nucleus, as well as the brainstem, and cerebellum. Longitudinally, patients with PSP have faster pons, cerebellar, and whole-brain atrophy rates than controls, as well as accelerated atrophy rates of the midbrain relative to both controls and patients with Parkinson disease.¹³³ FDG-PET studies in patients with PSP show glucose hypometabolism in the prefrontal cortex, caudate, pallidum, mesencephalon, and subthalamic nucleus, as well as the thalamus, which is associated with increased postural instability and falls.¹²⁸ Amyloid PET studies are negative in patients with PSP in the absence of co-occurring AD pathology. Finally, studies with multiple tau tracers have suggested increased tracer retention in the basal ganglia, midbrain, subthalamic nucleus, substantia nigra, cerebellar dentate, and other subcortical regions of patients with PSP, which was shown to correlate with the amount of clinical impairment in some cases and not in others.¹³⁴

CONCLUSION

Neuroimaging techniques provide important information about atrophy patterns, brain functional changes, metabolic dysfunction, and pathologic proteins in multiple neurodegenerative diseases, including early- and late-onset AD and related dementias, vascular cognitive impairment, DLB, PDD, and FTLD. Novel tracers for important pathologic proteins such as TDP-43, α -synuclein, and others will improve the understanding of early detection, diagnosis, and clinical course of patients with these diseases.

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Fluid Biomarkers in Dementia Diagnosis

By Joseph F. Quinn, MD, FAAN; Nora E. Gray, PhD

ABSTRACT

OBJECTIVE: This article familiarizes neurologists with the currently available CSF and plasma biomarkers for the diagnosis of dementia and diagnosis-dependent treatment decisions.

LATEST DEVELOPMENTS: For Alzheimer disease, the recent US Food and Drug Administration (FDA) approval of monoclonal antibody therapy has increased the urgency of confirming the pathologic diagnosis with biomarkers before initiating therapy. The new availability of disease-modifying therapies also highlights the need for biomarkers to monitor efficacy over time. Both of these needs have been partially addressed by the emergence of improved blood-based biomarkers for Alzheimer disease. Regarding other forms of dementia, the latest development is a CSF assay for aggregated α -synuclein, which permits the biomarker confirmation of synuclein pathology in Lewy body dementia.

ESSENTIAL POINTS: CSF biomarkers for the diagnosis of Alzheimer disease, Lewy body dementia, and Creutzfeldt-Jakob disease are well established. Blood-based biomarkers for dementia diagnosis are emerging and rapidly evolving. Sensitivity and specificity for diagnosis continue to improve, and they are being incorporated into diagnostic decisions. Fluid biomarkers for monitoring the efficacy of therapy are not yet established. Because serial CSF examinations are impractical, the validation of blood-based biomarkers of disease activity will be critical for addressing this unmet need.

INTRODUCTION

The diagnosis of mild cognitive impairment and dementia should begin with a careful history and examination, including mental status examination, and should proceed to structural brain imaging and blood work to exclude treatable causes of dementia according to American Academy of Neurology (AAN) practice parameters.¹ After these basics are complete, it may be appropriate to clarify the diagnosis with CSF and blood-based biomarkers in select cases. As with any diagnostic test, fluid biomarkers should be used when the results will impact management decisions, including patient and family counseling, symptomatic therapies, and disease-modifying therapies.

The advent of US Food and Drug Administration (FDA)-approved anti-amyloid therapies for the treatment of Alzheimer disease (AD) has

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heightened the practical clinical importance of methods to ascertain specific dementia diagnoses. Although amyloid imaging methods are now well validated, they are expensive and unavailable in some areas. The use of CSF and blood-based biomarkers of brain pathology may address both cost and access issues for either outright diagnosis or stratifying risk so that amyloid positron emission tomography (PET) imaging is not unnecessarily performed on individuals who can be shown to be at very low risk of AD pathology. This role in risk stratification will become increasingly important if anti-amyloid therapies are approved for use in asymptomatic individuals, as large-scale population screening with amyloid PET is simply not possible because of costs and resource availability.

CSF BIOMARKERS CURRENTLY USED IN THE DIAGNOSIS OF DEMENTIA

Early efforts to develop CSF biomarkers of AD were based on the assumption that the proteins comprising the classical lesions of AD would be ideal candidates as biomarkers in CSF. In the case of tau, the chief component of the neurofibrillary tangle, the finding was intuitive: Patients with AD, who have brains full of tau-containing neurofibrillary tangles, also have increased levels of tau in CSF.² The findings with amyloid- β (A β) were less intuitive but no less informative: Patients with AD, who have brains full of A β plaques, have lower CSF levels of A β 1-A β 42 compared with age-matched controls,³ presumably due to sequestration within the plaques. It is important to note that CSF levels of A β are influenced by the collection tube, as A β adheres to polystyrene (hard plastic), making levels in the fluid artificially lower when collected in polystyrene, and therefore to obtain reliable CSF A β measurements it is necessary to collect the sample in a polypropylene (soft plastic) tube. A test combining CSF tau and CSF A β 1-A β 42 was commercially offered for many years, with high tau and low A β 42 interpreted as evidence for AD pathology, whereas low CSF tau and high A β 42 was interpreted as consistent with healthy control status. However, it became apparent that elevated CSF tau is nonspecific because increases in CSF tau are seen in any brain injury in which the normally intracellular tau was spilled into the CSF due to neuronal damage, including not only AD but stroke, traumatic brain injury, encephalitis, and non-AD neurodegenerative disease (with especially high CSF levels in Creutzfeldt-Jakob disease [CJD]).

Starting more than a decade ago, the most widely used AD CSF biomarker panel was modified to include a phosphorylated form of tau that is relatively specific to AD (pTau181).⁴ The result is now reported as the ratio of A β 42 to tau (ie, the amyloid-tau index [ATI]) and the absolute level of pTau181. If the ATI is low and the level of pTau181 is high, that is interpreted as strong evidence for AD pathology. If the ATI is high and the level of pTau is low, that is interpreted as a healthy control. There are other combinations possible, and those are reported as indeterminate. Several high-performance platforms are now available for measuring these CSF biomarkers in clinical laboratories,^{5,6} but only one commercial laboratory is currently offering a CSF test for AD including A β 1-A β 42, tau, and pTau181.

Efforts to develop CSF biomarkers of other types of dementia by measuring levels of other lesion-associated proteins have also been successful. For example, CJD is a rapidly progressive form of dementia that is important to distinguish from treatable causes of encephalopathy. CSF 14-3-3 protein was identified

KEY POINTS

- The advent of US Food and Drug Administration (FDA)-approved anti-amyloid therapies for the treatment of Alzheimer disease has heightened the practical clinical importance of methods to ascertain specific dementia diagnoses.
- CSF levels of amyloid- β (A β) are influenced by the collection tube, as A β adheres to polystyrene (hard plastic) making levels in the fluid artificially lower when collected in polystyrene. To obtain reliable CSF A β measurements, it is necessary to collect the sample in a polypropylene (soft plastic) tube.
- The amyloid-tau index and the absolute level of phosphorylated tau 181 (pTau181) is a much stronger indicator of Alzheimer disease pathology than either A β or total tau alone.
- Prion real-time quaking-induced conversion methods have shown excellent sensitivity and specificity for aggregated prion protein and have become a mainstay in the diagnosis of Creutzfeldt-Jakob disease.

empirically as a marker of CJD, but it is important to note that the 14-3-3 protein is a normal intraneuronal protein, which, like tau, spills into CSF in the context of any significant neuronal injury,⁷ so elevated levels must be interpreted with caution in the differential diagnosis of rapidly progressive dementia. Another approach to the biomarker diagnosis of CJD is based on the knowledge that CJD is characterized neuropathologically by aggregates of the prion protein. Although the measurement of absolute CSF levels of prion protein is not useful diagnostically, pathologically aggregated prion is expected to be specific to CJD. Because CSF levels of the aggregated form of prion are too low to measure, methods to amplify levels of the aggregated protein have been developed. These amplification measures are all similar but go by varied names including real-time quaking-induced conversion (RT-QuIC), seeded amplification assay, and protein misfolding cyclic amplification.⁸ Prion RT-QuIC methods have shown excellent sensitivity and specificity⁹ for aggregated prion protein and have become a mainstay in the diagnosis of CJD (**TABLE 9-1**).

The amplification principles behind the prion RT-QuIC assay are theoretically applicable to any aggregated protein and have recently been applied to α -synuclein, the protein that aggregates in Lewy bodies in Parkinson disease and related disorders, including Lewy body dementia and multiple system atrophy.¹⁰ Although absolute levels of α -synuclein in CSF do not reliably distinguish patients from controls, the seeded amplification assay for aggregated α -synuclein has shown excellent sensitivity and specificity for Parkinson disease,¹¹ Lewy body dementia,¹² and multiple system atrophy. Sensitivity and specificity have also been established for autopsy-confirmed cases with and without Lewy body pathology.¹³ The assay also appears to have a role in diagnosing prodromal cases of synucleinopathy, including rapid eye movement (REM) sleep behavior disorder¹⁴ and asymptomatic Parkinson disease gene carriers.¹¹ A commercial α -synuclein seed amplification assay has been available since 2022. It is reported in a dichotomous fashion as positive or negative, without reference to quantitative aspects. Although several studies have demonstrated that particular elements of seed amplification assays may distinguish synuclein strains in Parkinson disease compared with Lewy body dementia or multiple system

TABLE 9-1

Clinically Useful CSF Biomarkers for the Differential Diagnosis of Dementia

	Amyloid- β (A β)1-A β 42	Tau	Phosphorylated tau 181	14-3-3 protein	Prion real-time quaking-induced conversion	Synuclein real- time quaking- induced conversion
Alzheimer disease	Low	High	High	Within normal limits	Negative	Negative
Creutzfeldt- Jakob disease	Within normal limits	High	Within normal limits	High	Positive	Negative
Parkinson disease dementia	Variable	Variable	Variable	Within normal limits	Negative	Positive
Lewy body dementia	Variable	Variable	Variable	Within normal limits	Negative	Positive

atrophy,¹⁵ the currently available assay does not provide that distinction. In total, the currently available CSF tests for AD, synucleinopathy, and CJD are valuable in differential diagnoses of dementia and can play significant roles in management decisions (**CASE 9-1**).

CSF BIOMARKERS WITH A POTENTIAL ROLE IN DEMENTIA MANAGEMENT

With the advent of disease-modifying therapies for AD, it is tempting to speculate about biomarkers that might serve as outcome measures in clinical

A 65-year-old man presented to the neurology clinic with a report of “rapidly progressive dementia.” He was working as a teacher until 1.5 years before presentation when he retired in the absence of any obvious cognitive decline. After retirement, he was noted to repeat himself and forget appointments. His walking slowed, and based on his flat facial expression, family speculated that he might be depressed, but his symptoms progressed slowly until the past 6 months, when his condition began to fluctuate, with episodes of near delirium, some days with visual hallucinations, and spontaneous improvements in between. On examination, he was alert and cooperative and scored 19/30 on the Montreal Cognitive Assessment (MoCA), with 0/5 visuospatial, 1/3 serial sevens, 0/1 verbal fluency, and 2/5 recall. He had a masked face, mild symmetric slowing, and rigidity but no tremor or myoclonus. He ambulated slowly without aids but with a depressed arm swing. Complete blood cell count, chemistry panel, thyroid-stimulating hormone (TSH), and vitamin B₁₂ levels were within normal limits. Brain MRI, including diffusion-weighted imaging (DWI), showed mild generalized atrophy but no other abnormalities.

The patient proceeded to CSF collection and had normal blood cell count, glucose, and protein. Real-time quaking-induced conversion for the prion protein was negative, further diminishing concern for Creutzfeldt-Jakob disease (CJD). His amyloid-β 42 to tau ratio was low, and his pTau 181 level was elevated, consistent with Alzheimer disease (AD) pathology. The seeded amplification assay was positive, indicative of concomitant α-synuclein pathology.

A diagnosis of Lewy body dementia with concomitant AD pathology was made, and the patient began symptomatic therapy with cholinesterase inhibitors with a good response.

CASE 9-1

This case illustrates the utility of CSF biomarkers in the differential diagnosis of dementia. The question of rapid progression frequently raises concerns about CJD, and in this case, the clinical presentation and MRI did not yield any evidence of CJD but also could not rule out the possibility. Some other features suggested Lewy body dementia, which often coexists with AD pathology. Although several diagnostic tests are available, a single CSF collection has the potential to clarify multiple diagnostic possibilities.

COMMENT

practice to evaluate the efficacy of these expensive, burdensome, long-term therapies. A good comparison for practicing neurologists would be the use of serial MRI in patients with multiple sclerosis to evaluate the efficacy of disease-modifying therapy. The appearance of new or enhancing white matter lesions is interpreted as evidence of persistent disease activity and drives decisions about continuing or changing treatments. Similar examples of biomarkers that inform treatment decisions are evident in other areas of medicine (eg, human immunodeficiency virus [HIV] viral load in the management of HIV, liver function tests in the management of chronic hepatitis, glycosylated hemoglobin A_{1C} in the management of diabetes, creatine phosphokinase in the management of chronic muscle disease).

A CSF biomarker that reflects ongoing neuronal or synaptic damage may be a consideration for this role, and some have been identified. CSF neurofilament light chain, a normal intraneuronal protein that spills into the spinal fluid during neuronal injury, has been correlated with the rate of progression of cognitive decline in AD,^{16,17} mild cognitive impairment,¹ and even asymptomatic aging.^{18,19} Markers of synaptic injury are also of great interest, because synaptic damage is the best correlate of dementia severity in clinicopathologic studies, and CSF neurogranin^{20,21} and other synaptic markers^{22,23} have been correlated with the rate of progression of AD. Glial markers of neurodegeneration may also be useful for this purpose, and CSF glial fibrillary acidic protein (GFAP)^{19,24} has shown promise in this area.

Some of these CSF biomarkers have been incorporated into trials of clinically effective antibody therapies (TABLE 9-2²⁵⁻²⁸). However, serial CSF examination is more invasive and less acceptable to patients compared with serial imaging or other types of monitoring. Blood-based biomarkers are much more likely to be acceptable to patients, and the past decade has seen considerable advancement in the definition and validation of blood-based biomarkers for dementia, which is the topic of the next section.

CURRENTLY AVAILABLE BLOOD-BASED BIOMARKERS FOR THE DIAGNOSIS OF DEMENTIA

It has long been known that A_β is measurable in plasma, but until the past decade, plasma A_β measurements were not thought to provide diagnostically useful information. Two elements helped move plasma measurements into the realm of diagnostic utility: (1) the reliance on the ratio of A_β42/A_β40 rather than

TABLE 9-2

CSF Biomarker Changes in Patients Treated With Anti-amyloid Antibody Compared With Placebo in Clinical Trials

	Amyloid- β (A β)	Tau	Phosphorylated tau (pTau)	Neurofilament light chain	Glial fibrillary acidic protein (GFAP)
Aducanumab ²⁵	Increased A β 42	Decreased tau	Decreased pTau181	Not reported	Not reported
Lecanemab ²⁶	Increased A β 42	Decreased tau	Decreased pTau181	No change	Not reported
Donanemab ^{27,28}	Not reported	Not reported	Not reported	Not reported	Not reported

absolute levels, and (2) measurement by mass spectrometry, which improved the precision and reproducibility of measurements compared to enzyme-linked immunosorbent assays (ELISAs). The ratio of A β 42/A β 40 has excellent diagnostic value in CSF, where there is a 50% difference between patients with AD and healthy control subjects but only a 20% difference in plasma,²⁹ amplifying the need for precise measurements. More than 20 studies from 2014 to 2022 evaluated the sensitivity and specificity of both ELISA and mass spectrometry-derived plasma A β 42/A β 40 ratios by comparing them with CSF and PET A β results, and a review confirmed that mass spectrometry measurements achieved greater diagnostic accuracy than ELISA.²⁹ This ratio, measured by mass spectrometry, has been offered commercially for several years by two laboratories, but limitations in sensitivity and specificity have restricted its widespread use by clinicians because of appropriate concerns over limited precision in the context of such a life-changing diagnosis. Efforts to improve the precision of the test have led predictably to phosphorylated forms of tau that in the brain are relatively specific for AD.

As in CSF, plasma levels of pTau are elevated in patients with AD relative to control subjects, but the diagnostic value of these measurements varies depending on the particular isoform being measured. Although pTau181 continues to be the isoform used in commercially available CSF assays, other forms of pTau have shown greater diagnostic specificity in both CSF and plasma. For example, one study of two independent cohorts of participants with symptoms of AD found that elevations in CSF pTau217 and pTau205 were better correlated with tau PET compared with CSF pTau181.³⁰ These species are also measurable in plasma and increased in patients with AD relative to healthy controls, but the confounding effect of comorbidities is important to consider. For example, both pTau181 and pTau217 were measured in plasma samples from a large number of participants in the Mayo Clinic Study of Aging, and although each demonstrated good to excellent discriminatory value in distinguishing individuals with positive versus negative amyloid PET scans, artificially high levels were also seen in individuals with renal insufficiency.³¹ Head-to-head comparison of pTau assays in patients with mild cognitive impairment, including various assays of pTau181, pTau217, and pTau231, concluded that, although several assays showed relatively high accuracy in predicting brain amyloid status and progression to AD, mass spectrometry-based plasma measures of pTau217 performed best.³² In fact, increased plasma pTau 217 can be shown to be equivalent to FDA-approved CSF biomarkers in predicting amyloid PET status.³³

Plasma biomarkers have consequently been incorporated into strategies for stratifying the risk of AD pathology on PET so that patients with low risk are spared further screening, whereas patients with high risk go on to amyloid or tau PET scans to determine if they meet criteria for therapy. Protocols and cutoffs for this type of stratification have been published,^{34,35} and recommendations for incorporating this approach into the workflow for evaluating candidates for anti-amyloid immunotherapy have been described (**CASE 9-2**).^{36,37}

Plasma biomarkers of AD have consequently been the subject of several excellent reviews^{38,39} and may eventually be validated as stand-alone diagnostic tests rather than a means to stratify indications for PET scanning. As of this writing, at least two mass spectrometry-based plasma AD biomarker tests are being marketed. Both report the plasma A β 42/A β 40 ratio and pTau217. One

KEY POINTS

- Clinically useful CSF biomarkers for Alzheimer disease, Creutzfeldt-Jakob disease, and α -synuclein pathology are currently available. The Creutzfeldt-Jakob disease and α -synuclein biomarkers require CSF collection. The Alzheimer disease biomarkers are being rapidly refined for use in blood samples.

- CSF indicators of neuronal injury and degeneration, such as neurofilament light chain and glial fibrillary acidic protein (GFAP), are emerging as potentially useful biomarkers of disease.

- The ratio of A β 42/A β 40 and measurements done by mass spectrometry have improved the precision and reproducibility of blood measurements.

- The diagnostic utility of plasma pTau measurements is confounded by comorbidities. The most effective pTau biomarker species for progression to Alzheimer disease is pTau217.

- There are significant differences in the abundance and predictive value of fluid biomarkers across racial and ethnic groups. This needs to be considered when weighing treatment decisions for underrepresented groups.

test reports the absolute value of pTau 217, and another reports pTau₂₁₇ as a fraction of total tau, having published evidence of validation of the latter approach.⁴⁰

BLOOD-BASED BIOMARKERS WITH A POTENTIAL ROLE IN DEMENTIA MANAGEMENT

As mentioned earlier, it is tempting to speculate about biomarkers that might serve as outcome measures in clinical practice to evaluate the efficacy of emerging disease-modifying therapies for AD. There are CSF biomarkers that may serve this purpose, but if plasma biomarkers were sensitive to the degenerative process in the brain, serial blood sampling would be far more preferable than serial CSF sampling. It remains to be seen whether plasma biomarkers will serve this purpose, but there are some encouraging data. In addition to plasma levels of various species of A_β and tau, additional plasma biomarkers have been evaluated and, in some cases, incorporated into clinical trials.⁴¹ For example, plasma neurofilament light chain is a sensitive marker of neurodegeneration, although it is not specific to a particular diagnosis.^{38,42,43} Plasma GFAP, a marker of astrocytic activation (also described earlier in CSF), has also been shown to distinguish between healthy people and those with AD pathology.⁴⁴⁻⁴⁶ Although, in principle, any of these plasma biomarkers might have a role in monitoring treatment efficacy, clinical trials of clinically effective

CASE 9-2

A 70-year-old man with amnestic mild cognitive impairment presented for evaluation for anti-amyloid immunotherapy. He had slowly progressive memory impairment over the past 2 years, and neuropsychological evaluation documented memory impairment in the mild cognitive impairment range but intact attention, language, and visuospatial function. The balance of his neurologic examination was normal. Complete blood cell count, chemical panel, thyroid-stimulating hormone (TSH), and vitamin B₁₂ levels were within normal limits. Brain MRI showed mild generalized atrophy but no other abnormalities, including no evidence of microhemorrhages or amyloid angiopathy. A blood sample was tested for Alzheimer disease (AD) plasma biomarkers. His plasma amyloid- β 42/40 ratio was depressed, and his pTau to total tau ratio was elevated, suggestive of AD. With this relative evidence of brain amyloidosis, the patient went on to CSF testing, which revealed a low amyloid-tau index and elevated pTau₁₈₁, confirming the presence of amyloid pathology. He then proceeded to anti-amyloid immunotherapy. The presumptive clinical diagnosis was AD, and the patient then proceeded to anti-amyloid antibody therapy.

COMMENT

This case illustrates the utility of plasma and CSF biomarkers for confirming brain amyloid pathology, which is a prerequisite for anti-amyloid therapy. Amyloid positron emission tomography (PET) is expensive and not universally available, so CSF testing continues to have a role for this purpose.

anti-amyloid antibodies have shed some light on which ones may ultimately serve this role in clinical practice (**TABLE 9-3**).

DIFFERENCES IN FLUID BIOMARKERS ACROSS RACIAL AND ETHNIC GROUPS

Rates of age-related dementias have been reported to differ among racial and ethnic groups, with Hispanic/Latino and African American people generally being more affected than non-Hispanic White people and Asian American people generally being less affected than non-Hispanic White people. Evidence also suggests that significant differences exist across these groups in the abundance of fluid biomarkers and their predictive value for dementia. For instance, in one study of 1862 participants, cognitively unimpaired Mexican American people were found to have higher plasma total tau than either African American or non-Hispanic White people, whereas cognitively unimpaired African American people had a higher A β 42/A β 40 ratio than non-Hispanic White people.⁴⁷ In the same study, differences were also observed in plasma biomarkers among participants with mild cognitive impairment, with African American people showing lower levels of plasma total tau and neurofilament light chain than non-Hispanic White people.⁴⁷ Plasma pTau markers have been found to be less predictive of brain amyloid positivity among African American people compared with non-Hispanic White people.⁴⁸ Similar differences have been observed in CSF biomarkers, as well. CSF total tau, pTau181, and neurofilament light chain have been found to be lower in African American participants than in non-Hispanic White people, although, interestingly, differences were not seen in CSF levels of either A β 42 or A β 40 or the ratio.^{49,50}

Recent evidence suggests that longitudinal tracking of these biomarkers may not show the same discrepancies. For instance, in one study, although the baseline A β 42/A β 40 ratio was lower in African American people, the longitudinal change in plasma A β 42/A β 40 ratio was similar in African American people and non-Hispanic White people and that longitudinal change was equally predictive of brain amyloid positivity.⁵¹

These differences in fluid biomarker levels and their association with disease states are important to bear in mind as they have meaningful impacts on diagnosis and treatment decisions for Mexican American and African American people.

Plasma Biomarker Changes in Patients Treated With Antibody Compared With Placebo in Clinical Trials

TABLE 9-3

	Amyloid- β (A β)	Tau	Phosphorylated tau (pTau)	Neurofilament light chain	Plasma glial fibrillary acidic protein (GFAP)
Aducanumab ²⁵	Not reported	Not reported	Decreased pTau181	Not reported	Not reported
Lecanemab ²⁶	Increased A β 42/A β 40 ratio	Not reported	Decreased pTau181	No treatment effect	Decreased GFAP
Donanemab ^{27,28}	No treatment effect on A β 42/A β 40 ratio	Not reported	Decreased pTau217	No treatment effect	Decreased GFAP

DIRECT-TO-CONSUMER TESTING

In July 2023, one manufacturer began offering blood-based biomarker testing directly to consumers.⁵² Consumers can order the test online and are then scheduled for a blood draw at a local facility, with results provided through a patient portal. As of this writing, the test is confined to the A β 42/A β 40 ratio. This development may have significant effects on neurology practice, although it has not been widely embraced by the public. If home testing is used more frequently, it will be essential to provide education on how to interpret the results, especially among diverse communities, to avoid a potential delay in seeking medical attention or undue worry.

CONCLUSION

CSF biomarkers are currently available for the differential diagnosis of dementia in clinical practice and for determining amyloid status to consider anti-amyloid antibody treatment. Blood-based biomarkers of AD pathology have also advanced in the past decade and are being used for risk stratification to select patients for CSF or PET determination of amyloid status, in both clinical trials and clinical practice. Blood-based biomarkers may soon serve as stand-alone diagnostic tests for AD pathology in clinical practice.

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Genetics and Neuropathology of Neurodegenerative Dementias

REVIEW ARTICLE



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By Sonja W. Scholz, MD, PhD, FAAN; Inma Cobos, MD, PhD

ABSTRACT

OBJECTIVE: This article provides an overview of the current understanding of the genetic and pathologic features of neurodegenerative dementias, with an emphasis on Alzheimer disease and related dementias.

LATEST DEVELOPMENTS: In recent years, there has been substantial progress in genetic research, contributing significant knowledge to our understanding of the molecular risk factors involved in neurodegenerative dementia syndromes. Several genes have been linked to monogenic forms of dementia (eg, APP, PSEN1, PSEN2, SNCA, GRN, C9orf72, MAPT) and an even larger number of genetic variants are known to influence susceptibility for developing dementia. As anti-amyloid therapies for patients with early-stage Alzheimer disease have entered the clinical arena, screening for the apolipoprotein E ε4 high-risk allele has come into focus, emphasizing the importance of genetic counseling. Similarly, advances in the pathologic classifications of neurodegenerative dementia syndromes and molecular pathology highlight their heterogeneity and overlapping features and provide insights into the pathogenesis of these conditions.

ESSENTIAL POINTS: Recent progress in neurogenetics and molecular pathology has improved our understanding of the complex pathogenetic changes associated with neurodegenerative dementias, facilitating improved disease modeling, enhanced diagnostics, and individualized counseling. The hope is that this knowledge will ultimately pave the way for the development of novel therapeutics.

INTRODUCTION

There have been considerable recent advances in the molecular understanding of neurodegenerative dementia syndromes. In particular, advances in genomic technologies have dramatically accelerated molecular discoveries and expanded awareness of disease-associated pathways. This article discusses major milestones in the molecular characterization of neurodegenerative dementias with a focus on the pertinent genetic and pathologic features of age-related neurodegenerative

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Continued on page 1822

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dementia syndromes, including Alzheimer disease (AD), Lewy body dementia, frontotemporal dementia, and the recently described novel dementia entity limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) (FIGURE 10-1 and FIGURE 10-2). This article also provides an update on the latest concepts relating genetic findings to pathophysiologic understanding and concludes with remarks on potential translational applications, such as genetic testing in the clinical setting, biomarker-supported diagnostics, and the development of novel treatment strategies.

ALZHEIMER DISEASE

AD is the most extensively studied and most common neurodegenerative dementia, affecting approximately 5% of the population older than 60 years. AD is clinically characterized by progressive memory loss and multidomain cognitive decline, involving language, visuospatial orientation, and executive function. Although the histological hallmarks were described more than a century ago,¹ the first disease-modifying therapies have only recently been approved and many questions remain unanswered.

Neuropathology

The pathologic hallmarks of AD include extracellular aggregates of amyloid- β (A β), which is derived from the cleavage of the amyloid precursor protein in plaques, and intracellular aggregates of hyperphosphorylated tau in neurofibrillary tangles, dystrophic neurites, and neuropil threads (FIGURE 10-1). Affected brain regions exhibit progressive synapse loss, dendritic spine loss, and, ultimately, neuronal loss. In parallel, there is an increase in reactive astrocytes and activated microglia, accompanied by microvasculature

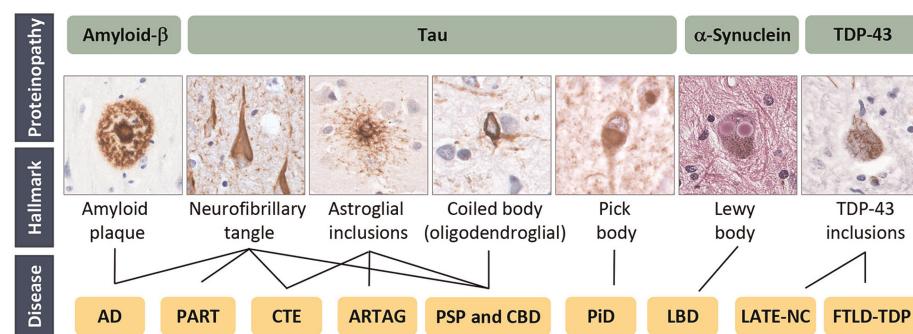


FIGURE 10-1

Pathologic hallmarks of neurodegenerative dementias, showing correspondences between proteinopathies and histopathologic hallmarks in the main neurodegenerative dementias. Representative photographs depict amyloid- β (extracellular), tau, α -synuclein, and transactive response DNA-binding protein 43 (TDP-43) (intracellular) aggregates found in neurons (ie, tangles, Pick bodies, Lewy bodies, TDP-43 inclusions) or glial cells (coiled bodies and astroglial inclusions).

AD = Alzheimer disease; ARTAG = age-related tau astrogliopathy; CBD = corticobasal degeneration; CTE = chronic traumatic encephalopathy; FTLD = frontotemporal lobar degeneration; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes; LBD = Lewy body disease; PART = primary age-related tauopathy; PiD = Pick disease; PSP = progressive supranuclear palsy.

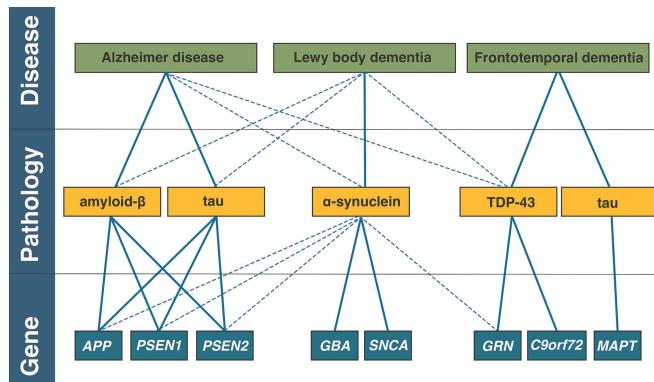


FIGURE 10-2

Gene-pathology-disease relationships in common familial dementias. This figure illustrates the pathologic and clinical syndromes associated with mendelian forms of dementia. APP = amyloid precursor protein; C9orf72 = chromosome 9 open reading frame 72; GBA = β -glucocerebrosidase; GRN = progranulin; MAPT = microtubule-associated protein tau; PSEN1 = presenilin 1; PSEN2 = presenilin 2; SNCA = α -synuclein; TDP-43 = transactive response DNA-binding protein 43.

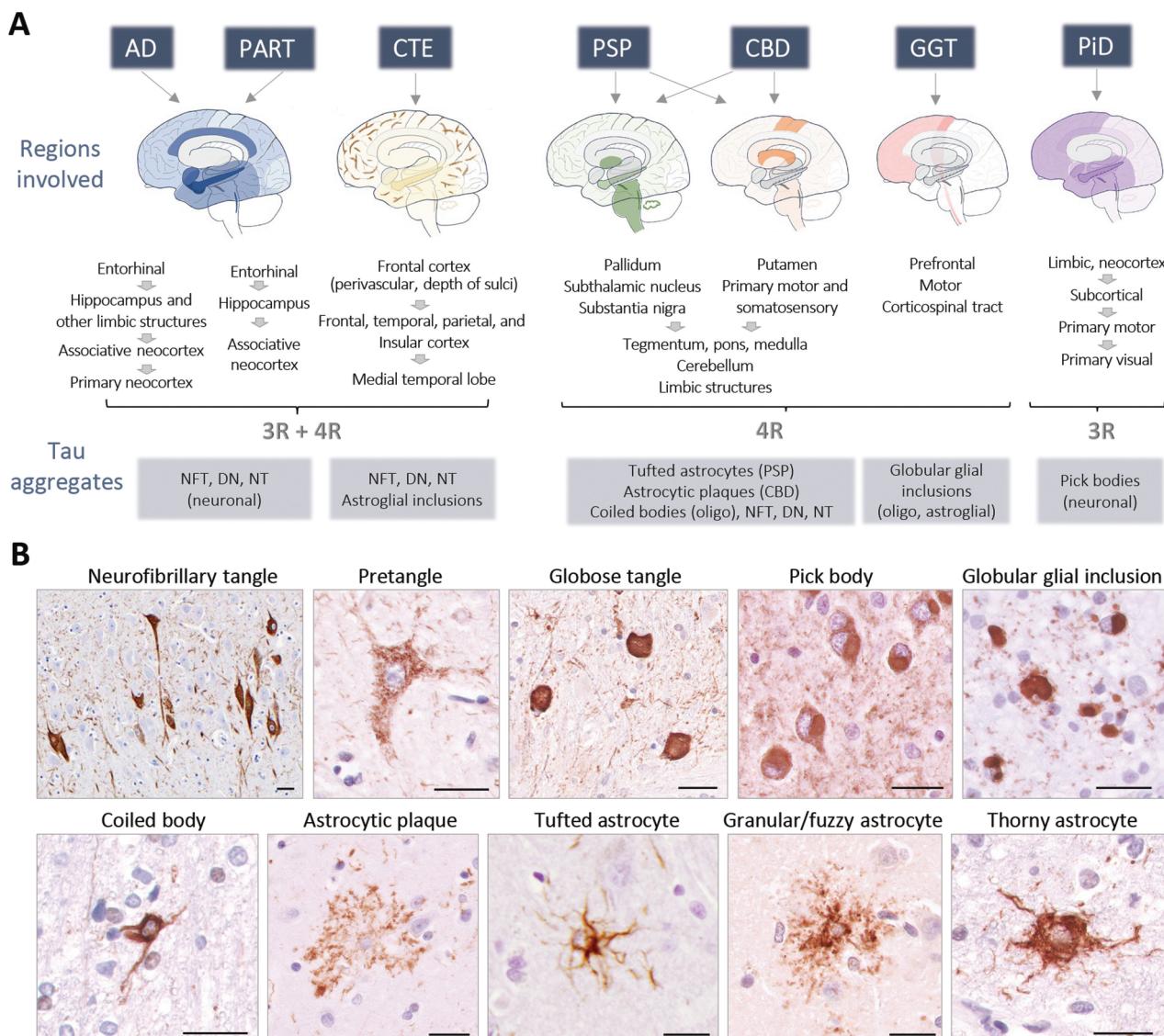
cerebral amyloid angiopathy. Histopathologically, this manifests as lymphocytic perivascular infiltrate (known as *cerebral amyloid angiopathy-related inflammation*), which can be angiolytic (known as *A β -related angiitis*) and cause rapidly progressive dementia. Cerebral amyloid angiopathy can be hereditary or sporadic and may occur in isolation or in association with AD.

The stereotypical progression of A β plaques and tau pathology in the forebrain provides the grounds for AD diagnosis and grading. A β pathology precedes tau pathology. Amyloid plaque accumulation starts in the neocortex and spreads to the hippocampus and other limbic regions, subsequently affecting the basal ganglia and thalamus, brainstem, and cerebellum.² Tau pathology correlates with neurodegeneration at the tissue level, atrophy at the brain region level, and with the progression of memory and cognitive deficits in patients. Neurofibrillary tangles first appear in pyramidal neurons within the transentorhinal cortex and then progress to the entorhinal cortex, the hippocampal cornu ammonis region, and neocortical neurons. Initially, associative cortices are impacted, whereas primary sensory, somatosensory, and motor cortices become involved in advanced disease stages.³ Within the brainstem, the noradrenergic locus ceruleus neurons accumulate hyperphosphorylated tau at a young age,⁴ although they do not appear to die until intermediate to late stages of AD.⁵ According to the current consensus diagnostic criteria, both amyloid and tau pathology are necessary for diagnosing AD neuropathologic changes.^{6,7} Cases with amyloid-only pathology represent an early or preclinical stage, which may progress to AD if the disease continues to advance, or reflect resistance if individuals maintain a low burden of AD pathology over time. This distinction is likely influenced by factors such as the patient's age, genetic background (including the *APOE* genotype status), cognitive reserve, and other environmental factors. People without dementia with a high burden of AD pathology are considered resilient.⁸ Cases with tau-only pathology are classified as primary age-related tauopathy.⁹

disturbances, including blood-brain barrier dysfunction and microvascular damage. Amyloid deposits frequently accumulate in the walls of small blood vessels and capillaries in the cerebral cortex, a condition known as cerebral amyloid angiopathy. In some patients, amyloid buildup in blood vessel walls can trigger an autoimmune response, leading to inflammatory

KEY POINTS

- Alzheimer disease (AD) is clinically characterized by progressive memory loss and multidomain cognitive decline, involving language, visuospatial orientation, and executive function.
- The pathologic hallmarks of AD include extracellular amyloid- β (A β) plaques and intracellular aggregates of hyperphosphorylated tau in neurofibrillary tangles, dystrophic neurites, and neuropil threads.
- Resistance is the ability to avoid significant AD pathology during aging, whereas resilience is the ability to remain cognitively normal despite having significant AD pathology.

**FIGURE 10-3**

Neuropathology of tauopathies. A, Schematic representation of brain region involvement and type of tau aggregates in secondary tauopathies (Alzheimer disease [AD], primary age-related tauopathy [PART], and chronic traumatic encephalopathy [CTE]) with three-repeat (3R) + four-repeat (4R) tau isoforms, primary tauopathies with 4R tau isoforms (progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], glial globular tauopathy [GGT]), and primary tauopathies with 3R tau isoforms (Pick disease [PiD]). For each disorder, the regions involved are colored, with darker colors representing the most affected areas. The predominant types of neuronal or glial tau inclusions for each disorder are listed. B, Representative microphotographs of tau aggregates by immunohistochemistry (tau-binding AT8 antibodies), including pretangles, neurofibrillary tangles, and globose tangles (3R + 4R; neuronal; AD), Pick bodies (3R; neuronal; PiD), globular glial inclusions (4R; predominantly oligodendroglial; GGT), coiled bodies (4R; oligodendroglial; PSP/CBD), as well as various 4R astrocytic aggregates (astrocytic plaques from CBD, tufted astrocytes from PSP, and granular or fuzzy and thorn-shaped astrocytes from age-related tau astrogliopathy). Scale bars: 25 μ m.

DN = dystrophic neurite; NFT = neurofibrillary tangle; NT = neuropil thread.

$\text{A}\beta$ is generated through sequential enzymatic processing of the amyloid precursor protein, resulting in the production and extracellular release of $\text{A}\beta$ fragments and an amyloid precursor protein intracellular domain with functions in gene transcription regulation. $\text{A}\beta$ plaques primarily consist of fibrillar $\text{A}\beta$ with high $\text{A}\beta_{42}/\text{A}\beta_{40}$ ratios and are categorized into diffuse plaques and neuritic plaques. Diffuse plaques represent an early stage of $\text{A}\beta$ deposition, whereas the later neuritic plaques are characterized by a core of highly aggregated $\text{A}\beta$, surrounded by dystrophic neurites containing phosphorylated tau-positive aggregates, activated microglia (ie, disease-associated microglia), and reactive astrocytes. In advanced stages, amyloid burden reaches a plateau where both diffuse plaques and neuritic plaques coexist in the neocortical parenchyma. The plaque microenvironment represents dynamic interactions among different cell types, between fibrillar and oligomeric amyloid species, and between amyloid and other proteins like endolysosomal proteins. Thus, the plaque microenvironment is a highly dynamic niche that likely influences $\text{A}\beta$ aggregation and clearance and the integrity of the surrounding neuropil.

Tau pathology arises from hyperphosphorylation and other posttranslational modifications of the microtubule-associated protein tau that is encoded by the *MAPT* gene. In humans, alternative splicing of *MAPT* produces six isoforms, including three-repeat (3R) and four-repeat (4R) isoforms, determined by the exclusion or inclusion of a repeat region in exon 10. Tau pathology in AD involves both 3R and 4R isoforms and is predominantly intraneuronal. The early stages of tau pathology involve an increase in oligomeric tau,¹⁰ which subsequently aggregates in pretangles and mature neurofibrillary tangles (FIGURE 10-3). After neuronal death, “ghost” tangles may persist for some time. Although normal tau protein primarily resides in axons where it forms the axonal scaffolds, pathologic tau in AD mislocalizes to dendrites (and, to a lesser extent, axons) as threads and to the somatodendritic compartment as neurofibrillary tangles. Oligomeric tau is also present in synapses where it may contribute to glial-mediated synapse elimination during the early stages of AD progression.¹¹ Tau intracellular mislocalization may result from and contribute to disruptions in various cellular pathways, including synaptic function, axonal transport, the ubiquitin-proteasome system, and the autophagy-lysosomal system.

AD is a heterogeneous disorder in its clinical manifestations and pathology. Typical and atypical variants of AD, such as posterior cortical atrophy (CASE 10-1), limbic-sparing AD, and limbic-predominant AD, reflect distinct patterns of atrophy and varying degrees of neurofibrillary tangle densities in the affected regions.¹²

In 2021, distinct molecular subtypes of AD were proposed based on the predominant pathophysiologic mechanisms identified through transcriptomics, including tau, $\text{A}\beta$, neuroinflammation, synaptic function, mitochondrial activity, and myelination,¹³ which may be associated with different genetic risk factors. Efforts to understand the mechanisms underlying this AD heterogeneity are needed to evaluate clinical trials and potential therapeutics.

Genetics

After aging, a positive family history is the strongest biological risk factor for AD. Having a first-degree relative with AD increases the risk of developing the disease by approximately 70%; compared to the general population without a

KEY POINTS

- After aging, a positive family history is the strongest biological risk factor for AD, and the total genetic contribution based on twin studies is estimated to be about 70%.
- Variations in the genes encoding presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) are well-recognized causes of familial, autosomal dominantly inherited AD.
- The “amyloid cascade” hypothesis posits that the initial, molecular cause of AD is the abnormal deposition of extracellular $\text{A}\beta$ peptide.
- The apolipoprotein E $\epsilon 4$ (*APOE*^{* $\epsilon 4$}) allele is the strongest and most common high-risk gene for AD.
- Individuals with one copy of *APOE*^{* $\epsilon 4$} have an approximately threefold risk of developing AD compared with the general population, whereas homozygote carriers have a nearly 15-fold risk.
- *APOE*^{* $\epsilon 4$} carriers are a high-risk population for developing amyloid-related imaging abnormalities on brain MRI that relate to the presence of cerebral amyloid angiopathy.

CASE 10-1

A 51-year-old woman presented with a 1-year history of visuospatial difficulty. She reported trouble navigating stairs, reaching for objects, and processing information from text and tables. She did not experience word-finding problems, short-term memory issues, hallucinations, or symptoms of rapid eye movement (REM) sleep behavior disorder. She showed no signs of weakness, numbness, rigidity, or tremor. Her language skills were fluent with normal comprehension, and her visual fields and fundoscopy results were unremarkable. She had no family history of neurodegenerative disease, neuropsychiatric conditions, or seizures. Brain MRI revealed mild focal atrophy of the superior parietal lobes bilaterally, without evidence of small vessel ischemic disease. Her presentation was most consistent with posterior cortical atrophy. Genetic testing revealed that she was homozygous for the apolipoprotein E $\epsilon 4$ (*APOE* $^*\epsilon 4$) allele. In the following years, her visuospatial difficulties continued to deteriorate, and she started to experience word-finding difficulties, although other language domains and memory were unaffected.

An amyloid positron emission tomography (PET) scan at age 54 years showed marked, diffusely symmetric uptake involving the frontal, temporal, parietal, and occipital lobes bilaterally, indicating the presence of frequent amyloid neuritic plaques. She progressed to develop severe visuospatial dysfunction, dysnomia, rigidity in her arms and legs, and myoclonus. Her memory and judgment remained intact until advanced stages of the disease. Her language became effortful and vague, but comprehension was preserved. She engaged in regular exercise and received around-the-clock caregiving, which helped prevent falls. She died at age 64 years, and a brain autopsy was performed.

Her brain weighed 1070 g (2.36 lbs). It exhibited moderate to severe diffuse cortical atrophy involving the frontal, parietal, temporal, and occipital lobes, as well as mild atrophy of the hippocampus, entorhinal cortex, and amygdala. Neuropathologic examination confirmed Alzheimer disease neuropathologic change. There were no Lewy bodies or transactive response DNA-binding protein 43 (TDP-43) copathology and no vascular brain lesions. Cerebral amyloid angiopathy was severe. Notably, the occipital lobe displayed severe neuronal loss, gliosis, and vacuolization. The tau burden was remarkably high, including threads in the white matter. Although the tau burden in the hippocampus was similarly high, the degree of neurodegeneration in this region was relatively low (FIGURE 10-4).

COMMENT

This case illustrates the clinical and pathologic heterogeneity observed in a patient with Alzheimer disease who is homozygous for the high-risk *APOE* $^*\epsilon 4$ allele.

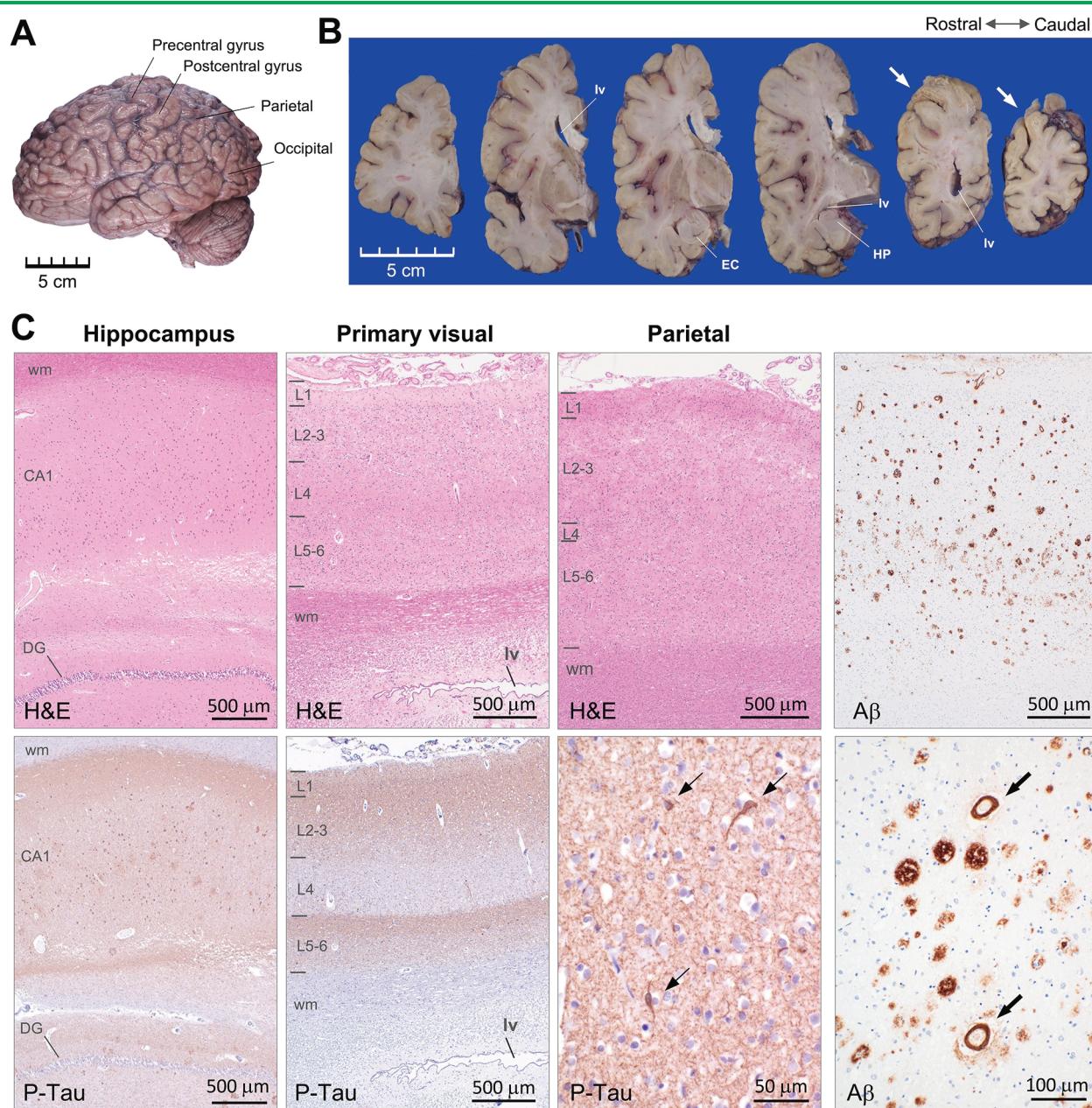


FIGURE 10-4

Pathology results exhibiting posterior cortical atrophy in the patient in **CASE 10-1** who was homozygous for the apolipoprotein E ε4 allele. **A**, Lateral view of the brain (1070 g [2.36 lb]) displaying diffuse cortical atrophy, primarily affecting the occipital, parietal, and frontal lobes, and to a lesser extent the temporal lobes, with sparing of the precentral and postcentral gyri. **B**, Coronal sections of the left hemisphere highlighting atrophy of the posterior parietal and occipital cortex (arrows). The medial temporal lobe including the hippocampus and entorhinal cortex are relatively preserved and the temporal horn of the lateral ventricle is not significantly dilated. **C**, Hematoxylin and eosin (H&E), and phosphorylated tau (P-Tau) (AT8 antibody) in formalin-fixed paraffin-embedded coronal sections through the hippocampus, primary visual cortex (BA17), and posterior parietal cortex. The hippocampal cornu ammonis shows a high burden of tau pathology, including tangles and neuropil threads, and neuritic plaques, with relatively preserved neuronal density. The BA17 cortex is very thin and exhibits a high burden of tau pathology with the characteristic pattern of Alzheimer disease (ie, highest in layers [L] 2–3 and 5). Arrows indicate neurofibrillary tangles. Immunohistochemistry for amyloid-β (Aβ) (6E10 antibody) in sections through the occipital cortex (**C**, top right) and temporal cortex (**C**, bottom right) highlights diffuse plaques, frequent neuritic plaques, and cerebral amyloid angiopathy.

DG = dentate gyrus; EC = entorhinal cortex; HP = hippocampus; Iv = lateral ventricle; wm = white matter.

family history, the risk for people with two first-degree relatives is 4 times greater, and it is nearly 15 times greater for people with four first-degree relatives.¹⁴ Having second-degree and third-degree relatives also increases the risk of developing the disease, with higher risk in people who have multiple affected relatives. In total, the genetic contribution toward the risk of developing AD is estimated to be approximately 70% based on twin studies.¹⁵ It is not surprising that the earliest advances in understanding the molecular pathogenesis of AD were driven by genetic discoveries. Most notably, variants in the genes encoding presenilin 1 (*PSEN1*),¹⁶ presenilin 2 (*PSEN2*),^{17,18} and amyloid precursor protein (*APP*)¹⁹ are well-recognized causes of familial, autosomal dominantly inherited AD (TABLE 10-1). A comprehensive database of variants in these genes can be found at alzforum.org/mutations. The pathobiological consequences of variants in *APP*, *PSEN1*, and *PSEN2* are increased production or decreased solubility of A β , resulting in the formation of amyloid plaques. Based on transgenic murine models, A β deposition also results in increased tangle formation,²⁰ though the exact molecular link between the two protein deposits is still debated. These insights are at the core of the “amyloid cascade” hypothesis, which posits that the initiating, molecular cause of AD is the abnormal deposition of extracellular A β peptide leading to downstream events, including synaptic loss, plaque and tangle formation, and, ultimately, neuronal death.²¹ Over the past 3 decades, this hypothesis has been the main driver behind treatment development efforts, culminating in the accelerated US Food and Drug Administration (FDA) approval of the three anti-amyloid immunotherapies: aducanumab in 2021, lecanemab-irmb in 2023, and donanemab-azbt in 2024, the first disease-modifying therapies for AD. Aside from insights into the relatively rare familial forms of AD, accounting for about 5% of patients, there has also been remarkable progress in understanding the genetic contributions to the sporadic form of the disease that accounts for the remaining 95% of cases.

An ever-increasing number of risk genes have been implicated using genome-wide association study (GWAS) approaches.^{22,23} Among these, the apolipoprotein E $\epsilon 4$ (*APOE*^{* $\epsilon 4$}) allele is the strongest and most common high-risk gene, found in 15% to 25% of the general population and almost one-half of patients with AD. Individuals with one copy of *APOE*^{* $\epsilon 4$} have an approximately threefold risk of developing AD compared with the general population, whereas homozygous carriers have a nearly 15-fold risk. However, ethnic and racial background appears to modulate the *APOE*^{* $\epsilon 4$} association with AD, as people of African or Hispanic ancestry with an *APOE*^{* $\epsilon 4$} allele have a lower risk than White people.²⁴ *APOE*^{* $\epsilon 4$} has multiple functions that are not completely understood, but one of the pathogenic mechanisms seems to be impaired A β transport and clearance across the blood-brain barrier, resulting in the formation of amyloid plaques.²⁵ The same mechanism also plays a role in the pathogenesis of cerebral amyloid angiopathy, a frequent copathology in AD, whereby *APOE*^{* $\epsilon 4$} drives A β deposition in the tunica media of small and medium-sized arteries, leading to smooth muscle cell death and rendering them susceptible to intracerebral hemorrhages. Cerebral amyloid angiopathy copathology has been intensely debated in the recent literature as anti-amyloid therapies have entered the clinical arena.

APOE^{* $\epsilon 4$} carriers are a high-risk population for developing amyloid-related imaging abnormalities on brain MRI that relate to the presence of cerebral amyloid angiopathy.²⁶ Specifically, vasogenic edema and intracerebral hemorrhage are well-recognized adverse events of anti-amyloid therapies,

emphasizing the need for careful monitoring and pretreatment genetic counseling. For more information, refer to the article “Treatment of Alzheimer Disease” by David S. Geldmacher, MD, FACP, FANA,²⁷ in this issue of *Continuum*.

To date, GWAS approaches have implicated about 90 common variants across 75 loci that contribute to susceptibility to AD.^{22,23} Although several risk genes have been discovered within these loci (eg, *APOE*, *TREM2*, *ABCA7*, *BIN1*, *CLU*, *CR1*, *PICALM*), for many loci the identification of the exact functional variant or gene contributing to disease risk remains unclear. A notable limitation of these

Genetic and Pathologic Features of the Most Common Monogenic Forms of Alzheimer Disease and Related Dementias

TABLE 1

Gene	Chromosome	Protein	Variations	Diseases	Mode of inheritance	Pathologic hallmarks
APP	21	Amyloid precursor protein	Missense, duplication, deletions	Alzheimer disease (with or without Lewy body dementia [LBD])	Autosomal dominant Autosomal recessive (rare)	Amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs) (with or without Lewy bodies, Lewy neurites)
<i>PSEN1</i>	14	Presenilin 1	Missense	Alzheimer disease (with or without LBD)	Autosomal dominant	Aβ plaques, NFTs (with or without Lewy bodies, Lewy neurites)
<i>PSEN2</i>	1	Presenilin 2	Missense	Alzheimer disease (with or without LBD)	Autosomal dominant	Aβ plaques, NFTs (with or without Lewy bodies, Lewy neurites)
GRN	17	Progranulin	Missense, splice site, deletion, loss of function (LOF)	Frontotemporal dementia (FTD) (with or without LBD)	Autosomal dominant	Transactive response DNA-binding protein 43 (TDP-43) inclusions (with or without Lewy bodies, Lewy neurites)
C9orf72	9	Chromosome 9 open reading frame 72	Repeat expansion	FTD (with or without amyotrophic lateral sclerosis)	Autosomal dominant	TDP-43 inclusions
MAPT	17	Microtubule associated protein tau	Missense, splice site	FTD	Autosomal dominant	Tau-positive aggregates
SNCA	4	α-synuclein	Missense, duplication, triplication	LBD	Autosomal dominant	Lewy bodies, Lewy neurites
GBA	1	β-glucocerebrosidase	Missense, LOF	LBD	Autosomal dominant ^a /high-risk allele	Lewy bodies, Lewy neurites

^a GBA variations have reduced penetrance.

genetic advances is that they mostly come from studies in individuals of European ancestry,²⁸ making it difficult to interpret their role in non-European populations. Limited research shows that the genetic architecture of AD varies based on ethnic and racial background.^{24,29} For example, the *ABCA7* risk allele is associated with a stronger risk for AD in individuals of African ancestry, highlighting the need to increase efforts for studying the disease in ancestrally diverse populations. Although each GWAS risk locus in isolation is not sufficient to cause disease, their combined contributions, as estimated using polygenic risk scores, explain approximately 11% of the genetic liability to disease risk.¹⁵ The remaining unexplained or “missing” heritability is a topic of ongoing research efforts and may be attributed to rare variants, gene-environment interactions, structural variants, or variants in complex regions of the genome that are not sufficiently captured using current methods. Based on these fundamental insights, AD is recognized as a genetically complex disease with both common and rare variants contributing to its pathogenesis.³⁰ The number of identified risk genes associated with AD is expected to grow over the coming years because of an increase in population-scale studies, the use of advanced genomic and computational tools, and multiancestry study designs.³⁰

Pathway enrichment analyses using polygenic risk scores derived from GWAS approaches have implicated crucial roles of the innate immune system, lipid metabolism, and endocytotic processes as key components of disease risk.^{30,31} These pivotal observations improve disease modeling and provide new opportunities for treatment developments that extend beyond the current amyloid-focused approaches. For example, neuroinflammation plays an important role in worsening the severity of AD by exacerbating A β and tau pathologies,³² highlighting anti-inflammatory strategies as possible therapeutic avenues. In fact, in recognizing the complex pathogenesis of AD, future treatment developments may have to shift to multitarget therapies that are tailored to the patient’s individual risk profiles and disease stage (eg, preclinical, prodromal, early versus advanced dementia). Another important lesson learned from GWAS approaches is that the genetic architecture of AD partially intersects with the architecture of other neurodegenerative dementias. For example, the *APOE*ε4* and *BIN1* risk alleles have been reproducibly associated with both AD and Lewy body dementia,³³ and genetic variations in *GRN*, which encodes progranulin, have been associated with AD, Parkinson disease, Lewy body dementia, and frontotemporal dementia.^{23,33-35} These examples highlight the concept of genetic pleiotropy as an important driver for multiproteinopathic pathologies in age-related neurodegenerative diseases and implicate shared biological pathways that could be targeted for therapy developments.

LEWY BODY DEMENTIA

Lewy body dementia is the second most common neurodegenerative dementia after AD in the population older than 65 years, affecting about 1.4 million people in the United States. Lewy body dementia presents clinically with fluctuating attention, visual hallucinations, parkinsonism, and rapid eye movement (REM) sleep behavior disorder.³⁶ On histopathology, it is characterized by eosinophilic, neuronal inclusions known as Lewy bodies that are also hallmarks of Parkinson disease (**FIGURE 10-1**). Lewy bodies mostly consist of misfolded α -synuclein protein fibrils. However, AD copathology, in the form of amyloid plaques and neurofibrillary tangles, is also found in most patients.³⁷ As such, Lewy body dementia

is considered to sit along a spectrum between AD and Parkinson disease, with possibly shared biological processes. Based on the timeline of developing motor symptoms versus dementia, Lewy body dementia patients are divided into two clinical subtypes by the arbitrary “1-year-rule”: (1) Parkinson disease dementia presenting with early motor symptoms, and (2) dementia with Lewy bodies presenting with dementia before or within 1 year of motor symptom onset.³⁶

Neuropathology

The spectrum of Lewy body disease pathology comprises clinical cases of Parkinson disease and Lewy body dementia. The pathologic hallmark of these disorders is Lewy bodies within neuronal somas and Lewy neurites in the neuronal processes (FIGURE 10-1). Another α -synucleinopathy is multiple system atrophy, which features α -synuclein aggregates, predominantly in glial cells. Indeed, the hallmark of multiple system atrophy is the presence of α -synuclein-positive glial cytoplasmic inclusions in oligodendrocytes, with intraneuronal inclusions, both cytoplasmic and nuclear, also present but typically in sparse quantities. Together, Lewy body dementia, multiple system atrophy, and Parkinson disease make up the triad of synucleinopathies.

The current consensus diagnostic criteria for Lewy body disease pathology³⁸ are based on a dichotomous approach to scoring Lewy body pathology as either absent or present, progressively involving various brain regions, including the olfactory bulb, dorsal motor nucleus of vagus, substantia nigra, amygdala, cingulate cortex, medial temporal cortex, frontal cortex, and parietal cortex. Accordingly, it is classified as olfactory-only and amygdala-predominant (typically asymptomatic), brainstem-predominant (consistent with a clinical diagnosis of Parkinson disease), limbic, or neocortical (usually corresponding to a clinical diagnosis of Lewy body dementia). Lewy bodies are frequently found in older individuals, particularly in the brainstem and limbic system. Whether they represent incidental Lewy body disease or are part of normal aging remains unclear. Clinical symptoms are accompanied by frank neurodegeneration in the regions involved. For instance, in Parkinson disease, the substantia nigra shows loss of dopaminergic neurons, extracellular neuromelanin deposits, reactive gliosis, and the presence of Lewy bodies and Lewy neurites. In advanced stages of Parkinson disease, substantia nigra Lewy bodies can become very rare.

The distinction between Parkinson disease dementia and dementia with Lewy bodies relies entirely on clinical criteria. In both, the postmortem pathology is similar and classified as neocortical or diffuse Lewy body disease. Notably, the vast majority of people with diffuse Lewy body disease also present with AD neuropathologic changes in the brain, which are diagnosed and graded as in AD. Although synergistic interactions between α -synuclein, A β , and tau have been demonstrated,^{39,40} why and how AD pathology develops almost inexorably in the brains of those with diffuse Lewy body disease is unknown. The neuropathologic basis for the characteristic cognitive fluctuations, hallucinations, sleep disturbances, and other neuropsychiatric symptoms in Lewy body dementia also remains unclear.

Genetics

Lewy body dementia is an etiologically complex disorder that is thought to be influenced by aging, genetic, environmental, and lifestyle factors. The disease usually manifests as a sporadic condition of late adulthood. However, rare

KEY POINTS

- Genome-wide association studies have implicated about 90 common variants across 75 loci that contribute to susceptibility to AD.

- Genome-wide association study approaches have implicated crucial roles of the innate immune system, lipid metabolism, and endocytic processes as key components of AD risk.

- Lewy body dementia is characterized by eosinophilic neuronal inclusions consisting of misfolded α -synuclein protein fibrils known as Lewy bodies and Lewy neurites in neuronal processes.

familial occurrences have been described, suggesting that genetic risk factors play a role.^{41–45} Although the genetic architecture of Lewy body dementia is only partially understood, important lessons about its pathogenesis have been learned by expanding research insights from AD and Parkinson disease to the Lewy body dementia field and the application of modern genomic approaches. Variations in the gene *SNCA*, which encodes α-synuclein, are a rare cause of familial, autosomal dominant Parkinson disease (**TABLE 10-1**).³⁰ However, the clinical presentation of *SNCA* variation carriers typically includes prominent nonmotor symptoms, including dementia, which is more consistent with Lewy body dementia.⁴⁶ Aside from rare, highly penetrant *SNCA* variants, common genetic variants at the *SNCA* locus have also been associated with susceptibility for Lewy body dementia,^{30,33} with milder risk variants identified in the sporadic form of the disease. Interestingly, the association signal at the *SNCA* locus is different in Lewy body dementia compared with Parkinson disease, whereby the functional variant is located at the 5' end of the gene, overlapping the noncoding transcript *SNCA-AS1* that regulates the expression of *SNCA*.³³ The same signal has also been found in a 2022 GWAS of REM sleep behavior disorder,⁴⁷ a common prodromal presentation of Lewy body dementia. Functional genomic evaluations have shown that the associated allele is protective by lowering the transcription of *SNCA*.⁴⁷ As such, small molecules or gene therapies that lower *SNCA* transcription may have disease-modifying potential in Lewy body dementia and are currently being studied.

Variations in the genes *APP*, *PSEN1*, and *PSEN2* are known causes of AD,^{16–19} and variations in *GRN*, which encodes progranulin, can cause frontotemporal dementia.³⁵ Notably, the neuropathologic evaluation of patients with these familial dementia syndromes commonly demonstrates extensive Lewy body copathology,^{48–50} suggesting possible shared biological mechanisms. It is not surprising that large-scale genomic screening efforts identified pathogenic variations in these genes in patients with Lewy body dementia,^{34,51} with mixed clinical and pathologic features. These observations illustrate overlaps in the molecular biology of age-related dementia syndromes that may be important for the development of future treatments. An important milestone in the study of the genetics of Lewy body dementia was the observation that variations in *GBA*, which encodes the lysosomal enzyme β-glucocerebrosidase, are significantly associated with increased risk for Lewy body disease (**TABLE 10-1**).^{52–53} In the general population, heterozygous variations in this high-risk gene are present in 10% of patients with Parkinson disease and 13% of patients with Lewy body dementia,⁵⁴ and in 30% of patients with Lewy body dementia who are of Ashkenazi Jewish ancestry.⁵⁵ As a pleomorphic risk gene, harboring common and rare disease-associated changes of varying effect size, *GBA* risk variants can be categorized into mild or severe changes, following a classification scheme developed for patients with Gaucher disease, which is caused by homozygous variations in *GBA*. Although understanding of the exact genotype-phenotype correlations is limited, severe variation carriers with Parkinson disease have been noted to manifest with disease about 5 years earlier compared with mild variation carriers (53 versus 58 years).⁵⁶ Nonetheless, more work is needed to understand the variable penetrance and severity of *GBA* variations in the broader Lewy body diseases spectrum.

GWAS studies have provided crucial insights into the pathogenesis of Lewy body dementia. To date, five risk loci have been reproducibly associated with

Lewy body dementia, including *GBA*, *BIN1*, *TMEM175*, *SNCA*, and *APOE*.³³ Of these, *GBA*, *SNCA*, and *TMEM175* are known risk loci for Parkinson disease, whereas *BIN1* and *APOE* are known AD risk loci. These findings illustrate the partially overlapping genetic architectures between AD, Parkinson disease, and Lewy body dementia. Along the same lines, pathway enrichment analysis based on GWAS approaches has implicated shared pathways, including endolysosomal function, regulation of endocytosis, A β formation, tau-protein binding, and others,³³ highlighting targets for possible cross-disease treatment opportunities. A 2021 GWAS of structural variants in Lewy body dementia identified a common deletion within the gene *TPCN1*, which encodes the endolysosomal two-pore segment channel 1, as a common risk locus.⁵⁷ This locus has also been suggested as being associated with AD,²² illustrating pleiotropic effects and emphasizing a role of the endolysosomal pathway in the pathogenesis of Lewy body dementia. Despite important advances in the genetic characterization of Lewy body dementia, most of the estimated heritability remains unexplained.³³ Increasing cohort sizes for gene discoveries, recruiting patients of diverse ancestries, and applying modern genomic tools such as multiomic data integration are at the core of ongoing efforts to map the genetic architecture of this disease and pave the way for improved molecular understanding and targeted therapies.

LATE AND OTHER AGE-RELATED PATHOLOGIES

Through comprehensive neuropathologic characterization of brains from older individuals, both with and without dementia, the high prevalence of aging-associated pathology and mixed pathologies has become clear.⁵⁸ These include TDP-43, α -synuclein, and tau pathologies. They most frequently occur in association with AD and other neurodegenerative diseases but can also occur in isolation, constituting distinct entities classified as LATE,⁵⁹ primary age-related tauopathy,⁹ and age-related tau astroglialopathy (**FIGURE 10-1**).⁶⁰ When isolated, they typically progress slowly; however, when they reach sufficient severity, they become associated with cognitive and memory impairment. Consequently, reporting these pathologies in brain autopsies has become relevant for investigating their potential contributions and synergistic effects on aging and disease progression. The defining neuropathologic features and consensus diagnostic criteria for these disorders and the genetic risk factors for LATE are summarized here.

LATE

LATE is estimated to affect more than 20% of individuals older than 80 years. LATE neuropathologic changes progressively involve the amygdala (stage 1), hippocampus (stage 2), and middle frontal gyrus (stage 3). The neuropathologic hallmark, known as TDP-43 proteinopathy, includes the loss of normal nuclear TDP-43 immunoreactivity and the presence of inclusions of phosphorylated TDP-43 in the neuronal cytoplasm, nucleus, or both. The TDP-43 staining pattern resembles type A frontotemporal lobar degeneration (FTLD)-TDP but it does not fit precisely into the established FTLD-TDP subtypes. LATE neuropathologic changes can be associated with hippocampal sclerosis. Pathologically, hippocampal sclerosis is defined as nearly total neuronal loss and gliosis in the hippocampal cornu ammonis 1 and the adjacent subiculum and presents as the end stage of various conditions, including medial temporal lobe epilepsy, ischemic vascular injury, and neurodegenerative disorders such as LATE, FTLD-TDP, and AD. Hippocampal sclerosis occurs in more than 70% of

KEY POINTS

- Missense or copy-number variations in the *SNCA* gene can cause familial Lewy body dementia on rare occasions, and common genetic variations within *SNCA* have been associated with susceptibility to sporadic Lewy body dementia.
- Variations in *GBA*, which encodes the lysosomal enzyme β -glucocerebrosidase, are associated with increased risk for Lewy body disease.
- TDP-43 proteinopathy in limbic-predominant age-related TDP-43 encephalopathy (LATE) resembles type A frontotemporal lobar degeneration (FTLD)-TDP and is associated with hippocampal sclerosis in approximately 70% of cases.

FTLD-TDP and LATE cases. A common polymorphism (rs5848) in *GRN* is a risk factor for hippocampal sclerosis in older patients, independently of TDP43 proteinopathy.^{61,62} Although current genetic insights into LATE are limited, risk alleles in *GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE*ε4* have been shown to be important for developing LATE.⁵⁹ These observations illustrate the importance of genetic pleiotropy in age-related proteinopathies and indicate that LATE shares pathobiological mechanisms with AD and frontotemporal dementia. However, more research is required to understand the pathogenesis of this neurodegenerative entity.

Primary Age-related Tauopathy

Primary age-related tauopathy neuropathology is characterized by AD-type tau pathology without or with only a few A_β plaques.⁹ Tau pathology in primary age-related tauopathy exhibits a regional distribution pattern similar to AD, with a comparable tau isoform composition (3R and 4R), phosphorylation states, and ultrastructure. It primarily occurs in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas, with very rare spread to neocortical regions. The question of whether primary age-related tauopathy represents a distinct neurodegenerative disease or is part of the spectrum of AD-related pathologic changes constitutes two complementary perspectives. Limited genetic research has shown that the *APOE*ε4* allele is less commonly found in patients with primary age-related tauopathy compared with AD,⁶³ which suggests that the genetic architecture of primary age-related tauopathy may differ from that of AD. However, more research into the genetic underpinnings of this condition is required.

Age-related Tau Astroglialopathy

Although there is no consensus on diagnostic criteria for age-related tau astroglialopathy, reported neuropathology describes a spectrum of tau pathology in astrocytes, featuring 4R tau-immunopositive inclusions.⁶⁰ These inclusions include thorn-shaped astrocytes and granular or fuzzy astrocytes, and are primarily located in subpial, subependymal, and perivascular areas, with lower density in white and gray matter. These astroglial inclusions display distinct morphology compared with the tufted astrocytes, astrocytic plaques, and globular astroglial inclusions observed in FTLD. Genetic risk factors for age-related tau astroglialopathy are unknown.

FRONTOTEMPORAL DEMENTIAS

Frontotemporal dementia is the second most common early-onset dementia after AD. The clinical presentations are heterogeneous, including progressive changes in behavior and personality (behavioral variant frontotemporal dementia) and language (progressive nonfluent aphasia and semantic dementia).⁶⁴ Research has shown that the clinical features of frontotemporal dementia can overlap with motor neuron disease and the atypical parkinsonism syndromes progressive supranuclear palsy and corticobasal syndrome.⁶⁴

Neuropathology

FTLD is an umbrella term for the neuropathologic diseases found in patients with a clinical frontotemporal dementia syndrome and that encompass a range of neuropathologic entities that are primarily classified based on the genetics

and the type of proteinopathy present. These subtypes include FTLD-tau (tau inclusions), FTLD-TDP (TDP-43 inclusions), FTLD-FUS (FUS protein inclusions, including cases with *FUS* variations), FTLD-UPS (ubiquitin inclusions, including cases with *CHMP2B* variations), and the rare FTLD—not-otherwise-specified group, which lacks distinctive FTLD histology and does not exhibit tau, TDP-43, FUS, or ubiquitin inclusions. Although the term *FTLD* originated from the classic “knife-edge” atrophy of the frontal and temporal lobes in Pick disease, it now encompasses a range of disorders that affect various cognitive and motor systems in the forebrain, brainstem, and spinal cord.

FTLD-tau is further subclassified based on the tau isoforms forming inclusions (**FIGURE 10-3**): 3R (Pick disease), 4R (progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], globular glial tauopathy), and 3R + 4R.⁶⁵ Most variations in *MAPT*, located on chromosome 17, are associated with FTLD (3R, 4R, or mixed) and are grouped under the diagnosis of frontotemporal dementia with parkinsonism linked to chromosome 17. Pick bodies, the hallmark of Pick disease, are round, perinuclear 3R tau inclusions primarily found in pyramidal and granular neurons, including dentate gyrus granular cells. PSP and CBD have overlapping clinical and pathologic features, including glial 4R-tau inclusions. Tufted astrocytes are most abundant in PSP, whereas astrocytic plaques are the hallmark of CBD. Oligodendroglial coiled bodies are abundant in both. Neuronal globose tangles are seen particularly in the brainstem in both PSP and CBD. Regionally, tau pathology and neurodegeneration are most prominent in the substantia nigra and other brainstem nuclei, cerebellar dentate, subthalamic nucleus, pallidum, and hippocampus in PSP, and in primary motor and somatosensory cortices and putamen in CBD. The white matter is heavily affected in CBD, with abundant threadlike processes. The rare globular glial tauopathy can be genetic or sporadic and features widespread, distinctive globular glial (oligodendroglial and astrocytic) inclusions predominantly in frontotemporal distribution.

The most frequent FTLD-TDP subtype features an expansion of $[GGGGCC]_n$ hexanucleotides in the gene *C9orf72*. This repeat expansion is indeed the most common genetic cause of both familial and sporadic frontotemporal dementia and amyotrophic lateral sclerosis.⁶⁶ Other FTLD-TDP subtypes involve variations in *GRN*, *VCP*, or *TARDBP* (the gene that encodes TDP-43). FTLD-TDP is characterized by the presence of TDP-43/ubiquitin-positive inclusions, along with the loss of normal nuclear expression of TDP-43. These inclusions can manifest as neuronal cytoplasmic inclusions, neuronal intranuclear inclusions, dystrophic neurites, or glial cytoplasmic inclusions. A harmonized classification system for FTLD-TDP pathology categorizes it into types A, B, C, and D, based on the predominant inclusions, clinical features, and genetic associations.⁶⁷

Genetics

Genetic factors play an important role in the pathogenesis of frontotemporal dementia, with about 40% of patients reporting a family history. Variants in *C9orf72*, *GRN*, and *MAPT* are particularly prominent in this patient population (**TABLE 10-1**). Of these, the most common cause of familial frontotemporal dementia is a pathogenic $[GGGGCC]_n$ -hexanucleotide repeat expansion in *C9orf72*, accounting for 25% of familial frontotemporal dementia and 6% of apparently sporadic cases.⁶⁶ An increasing number of less common familial forms of FTLD have been reported in recent years, including dominantly

KEY POINTS

- Primary age-related tauopathy and age-related tau astrogliopathy are primary age-related tauopathies that exhibit tau aggregates predominantly in neurons and glia, respectively, without significant amyloid deposition.
- Primary age-related tauopathy exhibits a regional distribution pattern of tau similar to AD, including tau isoforms, tau phosphorylation, and ultrastructure, but it rarely spreads beyond the medial temporal lobe.
- FTLD is an umbrella term for the neuropathologic diseases found in patients with clinical frontotemporal dementia syndromes, encompassing a range of neuropathologic entities that are primarily classified based on the genetics and proteinopathy present.
- Gene variations in *C9orf72*, *GRN*, and *MAPT* are common causes of FTLD.

inherited variations in the genes *CCNF*, *CHCHD10*, *CHMP2B*, *DCTN1*, *FUS*, *KIF5A*, *OPTN*, *SQSTM1*, *TARDBP*, *TBK1*, *TIA1*, *TUBA4A*, *UBQLN2*, and *VCP*. Although these genetic syndromes are rare, the increasing availability of gene panel testing and whole-exome sequencing offers opportunities to screen for these variations and establish a molecular diagnosis. Importantly, these rare variations are providing crucial insights into disease-associated pathways, such as impairment in RNA transcription, protein homeostasis, cytoskeletal transport, and mitochondrial function.

Sporadic cases of FTLD account for about 60% of cases and have been associated with high-risk variants in loci including *MAPT* in the tauopathies PSP and CBD⁶⁸ and *TMEM106B* in FTLD-TDP.⁶⁹ In addition, genome-wide association studies have implicated common variants at the human leukocyte antigen locus, supporting the notion of a role of the immune system in the pathogenesis of FTLD.^{70,71} Two loci within the *DPP6* and *UNC13A* genes have been shown to be significantly associated with FTLD-TDP.⁷¹ An additional locus encompassing the genes *RAB38* and *CTSC* has been suggested as associated with behavioral variant frontotemporal dementia. *RAB38* and *CTSC* play an important role in lysosomal biology and, together with *GRN* and *TMEM106B*, highlight the role of lysosomal dysfunction. Taken together, genetic advances have provided crucial molecular insights into the pathogenesis of FTLD and hopefully, a better understanding of the pathophysiology of FTLD will ultimately improve therapy developments.

OTHER NEURODEGENERATIVE DEMENTIAS

Other neurodegenerative dementia syndromes with a genetic etiology include Huntington disease, prion diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and adult-onset Niemann-Pick disease type C. This section briefly summarizes these dementia syndromes.

Huntington Disease

Huntington disease is an autosomal dominant disorder caused by the expansion of CAG (polyglutamine) trinucleotide repeats within the *HTT* gene, encoding huntingtin, a ubiquitous scaffolding protein with roles in regulating intracellular transport, autophagy, and transcription.⁷² The size of the expansion is associated with the age of onset and clinical manifestations. Huntington disease pathology is characterized by prominent atrophy of the caudate and putamen, which is graded on a scale from 0 to 4 using the Vonsattel grading system and is marked by the loss of medium spiny neurons. At later stages, the cerebral cortex also exhibits neuronal loss. Abnormal ubiquitinated huntingtin protein aggregates are observed within neurons, both in the cytoplasm and intranuclearly. They are present in the striatum, neocortex, entorhinal cortex, and hippocampal formation, but not in the pallidum or the substantia nigra.^{73,74} It remains uncertain whether huntingtin aggregates themselves are pathogenic.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

CADASIL is caused by variations in *NOTCH3*, many of which are cysteine-altering changes that lead to the misfolding and aggregation of the Notch3 protein. The abnormal protein appears as granular, osmophilic material within

the media of small arteries, thickening their walls and replacing smooth muscle cells. These changes result in lacunar and cystic infarcts, predominantly in the white matter.

Adult-onset Niemann-Pick Disease Type C

The spectrum of Niemann-Pick disease includes Niemann-Pick disease type C, a sphingolipid storage disorder caused by homozygous or compound heterozygous variations in either *NPC1* or *NPC2*. It is characterized by intracellular accumulations of glycosphingolipids and unesterified cholesterol in the endolysosomal system. Niemann-Pick disease type C is characterized by progressive cerebral atrophy, white matter sclerosis, and widespread balloon neurons containing abnormal storage lipid-containing granules and Alzheimer-type neurofibrillary tangles.

Genetic Prion Diseases

Genetic prion diseases are less common than sporadic Creutzfeldt-Jakob disease⁷⁵ and include Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and familial Creutzfeldt-Jakob disease. They have overlapping features and manifest as a rapidly progressive syndrome with dementia, extrapyramidal or pyramidal involvement, ataxia, and myoclonus. Familial fatal insomnia presents with early progressive insomnia and dysautonomia. Genetic prion diseases are caused by variations in the *PRNP* gene, which encodes the PrP protein. Certain *PRNP* pathogenic variants are associated with specific neuropathologic phenotypes. The pathology is characterized by spongiform change, which is microvacuolization, resulting from neuropil damage in the gray matter.

Creutzfeldt-Jakob disease predominantly affects the neocortex, Gerstmann-Sträussler-Scheinker syndrome the cerebellum, and fatal familial insomnia the thalamus. The distribution of atrophy is variable and discontinuous. The abnormal PrP protein is the hallmark of prion diseases and unique for its self-propagating and transmissible nature. In some prion diseases, abnormal PrP protein also aggregates as amyloid plaques, which differ from AD A β plaques. For example, multicentric plaques containing abnormal PrP protein are frequently observed in the cerebellar cortex of patients with Gerstmann-Sträussler-Scheinker syndrome.

GENETIC TESTING IN CLINICAL PRACTICE

In recent years, genetic testing for familial forms of dementia has become more widely accessible. Genetic testing may be considered as an ancillary diagnostic tool to uncover a molecular diagnosis, particularly in cases with a family history, and shorten the diagnostic odysseys in people struggling with a complex neurodegenerative syndrome. Further, a genetic diagnosis allows for refined counseling of patients and at-risk family members and may open opportunities for participation in targeted clinical trials. However, genetic testing should only be done after appropriate counseling about the advantages and disadvantages of testing. Genetic testing for high-risk alleles is generally not recommended in routine clinical practice and is currently limited to research studies. One notable exception is testing for *APOE** ϵ 4 in patients with mild cognitive impairment or mild dementia due to AD who are considering anti-amyloid therapies (ie, aducanumab, lecanemab-irmab, and donanemab-azbt). *APOE** ϵ 4 carriers are a high-risk group for amyloid-related imaging abnormalities in a dose-dependent

manner, with homozygous cases being at a higher risk than heterozygotes. Screening for this common risk allele will allow for improved risk stratification, adjustment in the frequency of safety monitoring and dosing, and minimization of exposing high-risk individuals to potentially harmful therapies.

ROLE OF BIOMARKERS

As new treatments targeting AD pathology receive FDA regulatory approval and enter clinical practice, the use of biomarkers to diagnose and stage AD in living patients has become of crucial importance. The revised criteria are based on fluid and imaging biomarkers that reflect AD pathogenesis.⁷⁶ They use the AT(N) classification scheme (amyloid and tau proteinopathies, and neurodegeneration) and incorporate biomarkers for copathologies frequently associated with AD, such as α -synuclein and vascular pathology (TABLE 10-2). For instance, it has been estimated that more than 10% of individuals with preclinical AD also have α -synuclein pathology.⁷⁷ Thus, comprehensive postmortem examination describing the primary underlying pathology and copathologies are essential for correlating biomarkers and the underlying neuropathology. Additionally, brain bank methods ensuring adequate tissue preservation for high-content imaging

TABLE 10-2

Amyloid and Tau Proteinopathies and Neurodegeneration Biomarkers and Neuropathology^{a,b}

Biomarkers				
Pathogenic process	CSF	Plasma	Imaging	Postmortem neuropathology
A Amyloid- β (A β) proteinopathy	A β 42, A β 42/A β 40 ^c	A β 42	Amyloid positron emission tomography (PET)	Diffuse plaques, neuritic plaques, cerebral amyloid angiopathy
T Tau proteinopathy	Phosphorylated tau181 (pTau181), pTau205, pTau231, nonphosphorylated tau fragments, microtubule-binding region Tau243	pTau217	Tau PET	Neurofibrillary tangles, dystrophic neurites, neuropil threads
N Neurodegeneration (neuropil injury)	Neurofilament light chain (NfL)	NfL	Structural MRI, fludeoxyglucose (FDG)-PET	Synapse and dendritic spine loss, neuronal loss, spongiosis
I Inflammation	Glial fibrillary acidic protein (GFAP)	GFAP	Not applicable	Reactive astrocytes, activated microglia
S α -Synuclein proteinopathy	α -Synuclein seeding amplification assay	Not applicable	Not applicable	Lewy bodies, Lewy neurites
V Vascular injury	Not applicable	Not applicable	MRI infarcts, white matter hyperintensities, enlarged perivascular spaces	Infarcts, microinfarcts, arteriolosclerosis, cerebral amyloid angiopathy

^a Modified from Jack CR Jr, et al, Alzheimers Dement.⁷⁶ © 2024 The Alzheimer's Association.

^b Correspondence between fluid (CSF and plasma) and imaging biomarkers and postmortem neuropathology.

^c A β 42/A β 40 refers to the ratio of two forms of A β peptides created by the cleavage of amyloid precursor protein.

and multiomics technologies are vital for facilitating research to better understand AD progression and evaluate the effects of new therapies.

CONCLUSION

In recent years, we have seen notable advances in the pathologic classifications of neurodegenerative dementia syndromes and our understanding of the molecular pathology underlying these diseases. These advances have provided important insights into the pathogenesis of age-related neurodegenerative diseases that can then act as springboards to future drug development. In particular, the genetic characterization of neurodegenerative dementias has improved our understanding of familial forms of dementia, which can aid in more rapidly establishing a molecular diagnosis for our patients in the clinic. The growing number of genetic variants influencing susceptibility for developing dementia also identify critical disease-associated pathways and illustrate overlaps in the genetic architectures of neurodegenerative dementias. This knowledge will hopefully improve molecular studies and pave the way for targeted interventions.

USEFUL WEBSITES

ALZFORUM FOUNDATION

This website provides a comprehensive database of disease-associated variations in genes implicated in AD.

alzforum.org/mutations

ALZHEIMER'S ASSOCIATION

The Alzheimer's Association provides revised criteria for the diagnosis and staging of AD.

aaic.alz.org/diagnostic-criteria.asp

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DISCLOSURE

Continued from page 1801

Neurology (AAN) interests or activities. An immediate family member of Dr Scholz has received personal compensation for serving as an employee of NIH. An immediate family member of Dr Scholz has received intellectual property interests from a discovery or technology relating to health care. Dr Scholz has received research support from NIH. An immediate family member of Dr Scholz has received research support from NIH. Dr Cobos reports no disclosure.

Treatment of Alzheimer Disease

REVIEW ARTICLE



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By David S. Geldmacher, MD, FACP, FANA

ABSTRACT

OBJECTIVE: Symptom-oriented treatment has been the mainstay of Alzheimer disease (AD) pharmacotherapy for decades. This article reviews the evidence basis for symptomatic treatments for AD and the emerging data on amyloid-lowering therapies with possible disease-slowing effects.

LATEST DEVELOPMENT: Amyloid-lowering monoclonal antibody therapies entered clinical use in 2021. In July 2023, lecanemab became the first of these to gain full US Food and Drug Administration (FDA) approval and limited Medicare payment coverage. Donanemab gained similar approval status in July 2024. The approved agents remove amyloid plaque from the brain and appear to slow clinical disease progression but can produce significant adverse events known as amyloid-related imaging abnormalities with cerebral edema or effusion and with cerebral hemorrhages. Extensive safety monitoring is therefore required, including scheduled MRI scans. Also in 2023, brexpiprazole became the first agent specifically approved by the FDA for agitation associated with AD. Suvorexant, an orexin receptor antagonist, previously was approved for the treatment of insomnia in people with mild and moderate AD.

ESSENTIAL POINTS: There is robust evidence for the use of acetylcholinesterase inhibitors for patients with mild, moderate, and severe dementia due to AD, including outcomes beyond changes in cognitive screening test scores. More limited studies support the use of memantine in moderate and severe stages. These agents have a primary effect of delaying decline in cognition and function and postponing the emergence of adverse behaviors. Pharmacotherapy for behavioral and psychological symptoms is less predictable, and most clinical trials have had negative results. Anti-amyloid therapies provide the first FDA-approved option to alter AD pathology, but an understanding of overall utility and value to patients remains in its infancy.

INTRODUCTION

Alzheimer disease (AD) was first recognized more than a century ago with a clinicopathologic correlation tying together early-onset (then considered “presenile”) dementia and the pathologic features of neuritic plaques and neurofibrillary tangles. In the intervening years, AD has been conceptualized in many ways, ranging from a purely biological state to a naturally emerging social issue in an aging society.

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Dr Geldmacher has received personal compensation in the range of \$500 to \$4999 for serving as a consultant for Penn Partners, on a scientific advisory or data safety monitoring board for Oligomerix, Inc, and as a CME presenter with WebMed LLC; in the range of \$5000 to \$9999 for serving as a consultant for Eisai Co, Ltd, Genentech, Inc, and Lilly, as a CME presenter/committee member with HMP Global, and as a CME program developer/presenter with Physicians Postgraduate Press, Inc; in the range of \$10,000 to \$49,999 for *Continued on page 1844*

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Geldmacher discusses the unlabeled/investigational use of acetylcholinesterase inhibitors in patients with mild cognitive impairment, citalopram and sertraline for the treatment of agitation in patients with dementia, donanemab for the treatment of early Alzheimer disease, and trazodone for sleep disturbance in patients with dementia.

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This has led to a variety of models for what constitutes treatment for AD. Treatments can be considered in the context of relieving symptoms, treating causes of cellular dysfunction, or removing pathology. They could be described in pharmacologic, nonpharmacologic, and societal constructs. Treatments might also be directed toward primary or secondary prevention, risk factor reduction, and general brain health promotion. The requirements for regulatory drug approvals from placebo-controlled clinical trials typically lead to publications that report results from standardized assessment instruments such as the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog)¹ or the Severe Impairment Battery.² These assessments are often not available or feasible in clinical settings, so the neurologist's determinations of treatment success or failure must be based on other outcomes. There is also extensive literature on behavioral and psychosocial interventions for people with dementia and their care partners, but most neurologists lack the special training and extensive time commitments required to implement those approaches. Discussions of treatment are further complicated by the recognition that AD pathology is likely present for years, if not decades, before symptoms emerge, and that there is a range of clinical severity from asymptomatic, through mild cognitive impairment (MCI), to dementia at mild, moderate, and severe stages. Given the breadth of the field, including dozens of agents and mechanisms of action under active investigation, it is important to note that this article focuses on pharmacologic treatments approved by the US Food and Drug Administration (FDA) and directed at altering the clinical expression of AD and its pathology.

SYMPTOMATIC THERAPIES

Although anti-amyloid therapies targeting neuritic plaques entered clinical use in 2021, people with AD can still be expected to express symptoms over the course of the illness. This will continue to be the case until true prevention of AD emerges, a prospect that remains years, possibly decades, in the future. The symptoms associated with AD are often characterized as changes in cognition, function, and behavior. These phenomena are clearly interrelated, but clinical trials typically report the results of assessments focused on specific domains. At a pragmatic level, impaired daily function most closely correlates with the cognitive deficits in AD, whereas the behavioral profile varies more among individuals and stages of severity. A summary of the available drugs and dosing forms is presented in TABLE 11-1.³

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors were the first drugs approved by the FDA for the treatment of mild and moderate dementia due to AD. Interest in this mechanism of action arose from discoveries that activity of the neurotransmitter acetylcholine was reduced in the brains of people with AD; this finding was further correlated with autopsy findings of neuronal loss in the ventral forebrain nucleus basalis of Meynert. Inhibition of the catabolic enzyme acetylcholinesterase was hypothesized as a method for increasing synaptic acetylcholine concentrations in the cortex, thereby improving cognition. The first large-scale acetylcholinesterase inhibitor clinical trial reporting significant treatment effects was published in 1992, and many others followed.⁴ Subsequently, four acetylcholinesterase inhibitor medications (tacrine,

donepezil, rivastigmine, and galantamine) were approved for use in the United States to treat AD at mild and moderate stages of dementia. Later studies expanded the approved treatment range to include severe-stage dementia. Given its poor safety profile compared with the other agents, tacrine was subsequently withdrawn from use in the United States. Although the overall effectiveness of the acetylcholinesterase inhibitor class is often summarized with the

TABLE 11-1

Symptom-directed Drugs, Doses, and Formulations for the Treatment of Alzheimer Disease

Drug and formulation	Indicated Alzheimer disease severity	Initial dose	Target dose	Comment
Donepezil				
Immediate-release tablet ^a	Mild, moderate, severe	5 mg/d for 4 weeks	5-10 mg/d	Oral dissolving tablet available with identical dosing
Transdermal system	Mild, moderate, severe	5 mg/d	5-10 mg/d	Patch is changed every 7 days
Galantamine				
Immediate-release tablet	Mild, moderate	4 mg 2 times a day	8-12 mg 2 times a day	Oral solution (4 mg/mL) available with identical dosing
Extended-release capsule	Mild, moderate	8 mg daily	16-24 mg/d	
Rivastigmine				
Immediate-release capsule	Mild, moderate	1.5 mg 2 times a day	3-6 mg 2 times a day	Oral solution (2 mg/mL) with same dosing schedule
Transdermal	Mild, moderate, severe	4.6 mg/d	9.4-13.3 mg/d	Dose may be increased every 4 weeks; patch is changed every day; 13.3 mg/d is the only dosage form of rivastigmine approved for severe-stage Alzheimer disease
Memantine				
Immediate-release tablets	Moderate, severe	5 mg/d	10 mg 2 times a day	Dose can be increased by 5 mg/d weekly; oral solution (2 mg/mL) available with identical dosing
Extended-release tablets	Moderate, severe	7 mg/d	28 mg/d	Dose can be increased by 7 mg/d weekly
Donepezil/memantine combination				
Capsule (donepezil plus extended-release memantine)	Moderate, severe	Match existing dosages	Donepezil 10 mg/memantine 28 mg	Not recommended for initial dosing of either component drug

^a Donepezil 23-mg tablets use an alternative formulation with a slower time to peak and higher maximum concentration than the 5-mg and 10-mg dose formulations.³ This formulation can be considered after a patient has received 3 months of stable dosing at 10 mg/d.

undefined term *modest*, clinically meaningful benefits of treatment have been consistently observed,⁵ and members of the class are frequently prescribed. Given the long interval since the publication of the primary studies that identified the efficacy and safety profiles of acetylcholinesterase inhibitor treatment, a detailed review of the effectiveness is warranted.

COGNITIVE OUTCOMES. Among patients with mild to moderate AD, randomized, double-blind, placebo-controlled trials of acetylcholinesterase inhibitors demonstrated consistent benefits on cognitive outcomes in studies of up to 24 months. The approved agents have no discernable differences in efficacy.⁶ The drug-placebo difference was generally 3 to 5 points on the 70-point ADAS-Cog¹ over a 6-month treatment course.⁷ The baseline ADAS-Cog score for these trial participants was about 25 points (low scores represent less

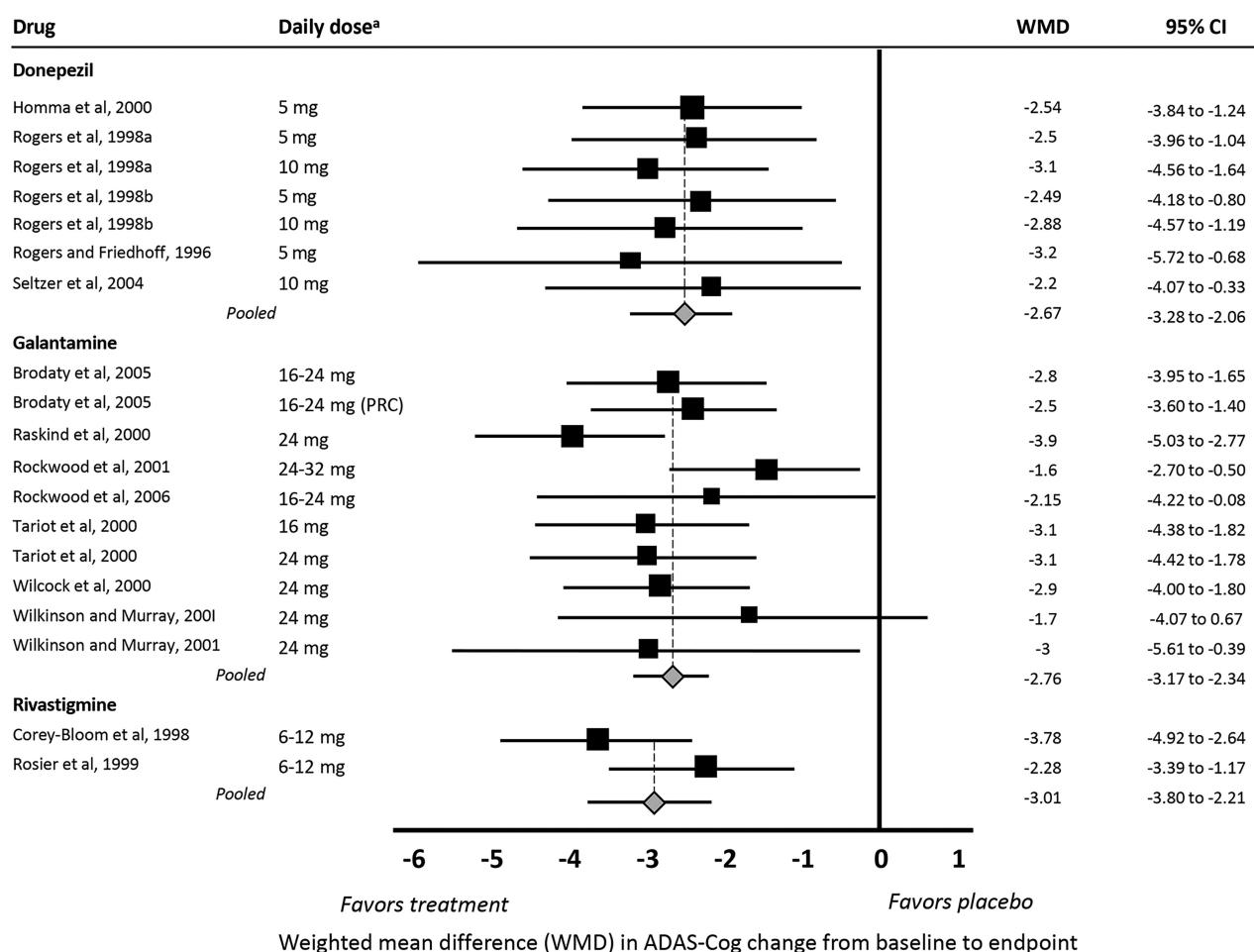


FIGURE 11-1

FIGURE II. Meta-analysis of cognitive outcomes as measured by Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) for acetylcholinesterase inhibitor treatment compared with placebo. All references are as cited by Hansen and colleagues.⁵

CI = confidence interval; PRG = prolonged-release capsule.

^a Limited to doses recommended by product labeling.

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impairment). This suggests that the acetylcholinesterase inhibitors are associated with a magnitude of benefit of about 10% to 20% compared with placebo. Importantly, the average observed benefit was a delay in decline, rather than improvement from baseline scores, on cognitive and global functional ratings at the conclusion of the treatment period. A summary of ADAS-Cog outcomes in acetylcholinesterase inhibitor trials is presented in **FIGURE 11-1**. Studies comparing cognition in acetylcholinesterase inhibitor-treated patients with models of projected changes in scores over time suggest that beneficial effects of continued treatment may be sustained through 3 to 5 years.⁷ Less is understood about the clinical meaningfulness of cognitive benefits of acetylcholinesterase inhibitor treatment in severe stages of AD, but both donepezil and rivastigmine have formulations approved for use in that population.

In contrast to the ADAS-Cog, brief cognitive screening tests such as the Mini-Mental State Examination (MMSE)⁸ are familiar to most neurologists. One study showed no decline in the MMSE scores of patients with mild- and moderate-stage AD dementia on donepezil for more than 1 year, whereas placebo-treated patients' scores declined by 2.5 points.⁹ Similarly, a study conducted in more typical practice settings demonstrated a benefit of donepezil of about 0.8 MMSE points versus placebo after 2 years of treatment, even with a 6-week interruption of therapy during the treatment period.¹⁰ Acetylcholinesterase inhibitors have not shown consistent benefits for cognition or function among patients with MCI.¹¹ Some of this apparent lack of efficacy may be because the neuropsychological tests used are insensitive to the patterns of cognitive impairment seen in MCI. For example, a 48-week trial of donepezil among patients with MCI showed no beneficial effect versus placebo on the MMSE.¹² However, the MMSE is known to be less sensitive than the Montreal Cognitive Assessment (MoCA) to the cognitive deficits typically expressed in MCI,¹³ and no definitive clinical trials with MoCA as an outcome have been reported. Furthermore, patients with clinically defined MCI show significant heterogeneity in the biomarker expression of AD pathology, such as fludeoxyglucose positron emission tomography (FDG-PET) and amyloid PET status. This variability in the pathologic basis of MCI, including dementia with Lewy bodies and varying severity of subcortical cerebrovascular damage influences the likelihood of identifying benefits, as well as balancing risk-benefit determinations. There have been no acetylcholinesterase inhibitor trials limited to participants with biomarker-confirmed AD. A systematic review of clinical trial results indicated that acetylcholinesterase inhibitors do not demonstrate efficacy in reducing symptoms in patients with mild cognitive impairment.¹⁴

FUNCTIONAL OUTCOMES. Acetylcholinesterase inhibitor therapy is associated with statistically significant, but small, absolute advantages over placebo on measures of daily function. Improvement from baseline ability is unlikely, especially as dementia severity increases.¹⁵ As an alternative to assessing declines in mean scores on a daily function rating scale, analysis of a 1-year placebo-controlled trial of donepezil examined the likelihood that losses in functional ability would occur, as well as the timing of decline.¹⁶ About half of the treated participants, 51%, showed "no clinically evident functional loss" over 48 weeks compared with 35% for participants taking placebo. This time-to-endpoint interpretation suggested acetylcholinesterase inhibitor treatment was associated with a 5-month delay of decline in daily function when compared with placebo.¹⁶

KEY POINTS

- Cognitive and functional outcomes of symptomatic treatment of Alzheimer disease (AD) track together; behavioral outcomes are less predictable.
- There will be continued roles for symptomatic therapies used concurrently with anti-amyloid therapies in people with dementia due to AD.
- There are no clinically relevant differences in cognitive or functional outcomes between the available acetylcholinesterase inhibitor drugs for the treatment of patients with AD.
- Acetylcholinesterase inhibitors have not shown consistent benefits on cognitive or functional outcomes among patients with mild cognitive impairment.
- Improvement in daily function is generally not observed with acetylcholinesterase inhibitor treatment in patients with AD, but delayed decline was observed in clinical trials.

BEHAVIORAL OUTCOMES. Neuropsychiatric disturbances in AD, also known as *behavioral and psychological symptoms of dementia*, range from apathy and depression to restless motor activity and agitation. Many AD clinical trials have used the Neuropsychiatric Inventory as a secondary outcome for measuring behavioral symptoms.¹⁷ All of the available acetylcholinesterase inhibitors have demonstrated stabilization or improvement of behavioral and psychological symptoms of dementia in studies of 6 to 12 months that included patients with mild through severe stages of AD dementia. Overall, there appears to be a small, but significant, benefit in favor of acetylcholinesterase inhibitor treatment for behavioral and psychological symptoms of dementia,^{5,15} but the greatest effects seem to be in delayed emergence of the difficult behaviors rather than resolution of existing problems. Notably, donepezil was no more effective than placebo in reducing agitation that was already present at the time of trial entry.¹⁸ However, donepezil has demonstrated benefits for delusions and mood disturbances, as well as for overall Neuropsychiatric Inventory scores.^{19,20}

CARE PARTNER–RELATED OUTCOMES, NURSING HOME PLACEMENT, AND MORTALITY.

Care partners are an important source of information about treatment success and failure among patients with AD. Physicians acknowledge that the assessments used in clinical trials do not capture important aspects of response to treatment in AD.²¹ Consistent with this, care partners reported greater treatment effects of acetylcholinesterase inhibitors than study evaluators in one open-label study,²² but this was not observed in a double-blind study, perhaps because care partners of placebo-treated patients reported similar benefits.²³ Double-blind, placebo-controlled trials showed that care partners of patients treated with an acetylcholinesterase inhibitor spent 45 to 60 minutes less per day in caregiving activities compared with care partners of placebo-treated patients.^{24,25}

Care partners of patients with AD have identified delayed nursing home placement as an extremely important outcome. Both observational studies of patients who completed double-blind, placebo-controlled trials and population-based studies suggest that acetylcholinesterase inhibitor treatment is associated with delayed time to, or reduced risk for, nursing home placement.^{26–29} Treatment earlier in the course of illness and more clearly evident beneficial responses to treatment appear to be predictors of delayed nursing home placement.^{26,29,30} It is important to note that strong psychosocial support for care partners is also associated with delayed nursing home placement and that there do not appear to be additive effects for pharmacologic and nonpharmacologic treatment approaches for delaying nursing home placement.^{31,32} In addition to the likely benefit of delaying nursing home placement, long-term acetylcholinesterase inhibitor therapy is associated with reduced all-cause mortality among patients with dementia.³³

ADVERSE TREATMENT EFFECTS AND THEIR MANAGEMENT. Gastrointestinal disturbances such as nausea, vomiting, anorexia, and weight loss are the most common adverse effects of oral formulations of the acetylcholinesterase inhibitors.⁵ These are dose related, with higher doses causing higher frequency and greater severity of symptoms. The frequency of adverse effects identified in clinical trials, which is included in the required prescribing information for each agent, appears to be higher than is observed in typical practice settings.^{34,35} There are likely many contributors to those differences, including the timing of dose

escalation. Studies with longer intervals or smaller increments between dose increases reported lower frequencies of adverse events.³⁶ Of the oral acetylcholinesterase inhibitors, donepezil is the best tolerated, rivastigmine has the highest rate of adverse effects and treatment withdrawals,^{34,36,37} but these are remarkably lower with the use of the transdermal formulation.³⁸ Dizziness was also frequently reported among patients treated with acetylcholinesterase inhibitors in trials. Notably, bradycardia is more frequent among patients using acetylcholinesterase inhibitors and is associated with increased risks for syncope, falls, and pacemaker placement.^{39,40} Co-administration of acetylcholinesterase inhibitors and beta-blockers may exacerbate the cardiac risks.⁴¹ Patients taking donepezil report an increased incidence of vivid dreams and associated sleep disturbances; these can be reduced by taking the medication in the morning and, if the symptoms persist, by lowering the dose.³⁶

SWITCHING AND DISCONTINUING ACETYLCHOLINESTERASE INHIBITORS. Studies have not demonstrated that one acetylcholinesterase inhibitor provides superior efficacy to the others for patients with mild or moderate AD,^{5,6} so there is little or no indication to change agents based on lack of, or loss of, perceived efficacy. There are also no systematic data nor strong theoretic rationale to suggest that adding a second acetylcholinesterase inhibitor would provide greater benefit. Instead, doses should be optimized, with an understanding of potential risks and benefits. The 23-mg formulation of donepezil was associated with higher cognitive test scores than the 10-mg daily dose but had no added benefit on global functional assessments; adverse effects were also more frequent on the higher dose.⁴² Use of the rivastigmine 13.3-mg transdermal patch demonstrated some improvements in cognitive test scores and daily function compared with lower doses, but those effects were generally not sustained beyond 6 months of treatment.⁴³ If a patient has an intolerance to the initially selected acetylcholinesterase inhibitor, transition to a different agent or formulation is warranted after resolution of the adverse effects.

Few studies have systematically examined the effects of acetylcholinesterase inhibitor discontinuation. After 12 or 24 weeks of donepezil treatment, prior cognitive benefits were no longer discernable 6 weeks after active treatment was discontinued and failed to rebound to treated levels when therapy was resumed.⁴⁴ Another trial with more pragmatic enrollment criteria found no persistent loss of function when donepezil was discontinued for 6 weeks after 48 weeks of therapy.¹⁰ Worsening of neuropsychiatric symptoms has also been reported after blinded withdrawal of donepezil treatment after 12 weeks of treatment.²⁰ In 2021, a more recent systematic review of available discontinuation studies concluded that “discontinuing cholinesterase inhibitors may result in worse cognitive, neuropsychiatric, and functional status.”⁴⁵ For patients who experience problems swallowing tablets or capsules, orally dissolving tablets, oral solutions, and transdermal formulations may be good alternatives. Among patients with severe-stage dementia who resist oral medication administration, and for whom acetylcholinesterase inhibitor therapy remains warranted, transdermal rivastigmine or donepezil may be appropriate. For many patients, a trial off medication can help determine whether the acetylcholinesterase inhibitor was providing benefit. If cognitive abilities decline within 2 to 3 weeks of discontinuation, treatment should be resumed, but if no acute worsening is noted, the medication was likely no longer providing benefit.

KEY POINTS

- Acetylcholinesterase inhibitor treatment is associated with delayed emergence of behavioral and psychological symptoms of dementia.
- Reduced time spent in caregiving for patients with AD is associated with acetylcholinesterase inhibitor treatment.
- Most studies show persistent acetylcholinesterase inhibitor treatment for AD is associated with delayed (or reduced risk for) nursing home placement, but the effects are not additive with intensive care partner support.
- Gastrointestinal symptoms are the most common side effects of acetylcholinesterase inhibitor treatment and can be reduced by slower dose escalation.
- Transdermal rivastigmine was associated with no more frequent gastrointestinal symptoms than placebo.
- Donepezil is generally the best-tolerated oral acetylcholinesterase inhibitor.
- If a patient has an intolerance to the initially selected acetylcholinesterase inhibitor, transition to a different agent or formulation is warranted after resolution of the adverse effects.

N-methyl-D-aspartate Receptor Modulation

Memantine is the only FDA-approved agent in the class of *N*-methyl-D-aspartate (NMDA) glutamate receptor modulators. It was approved in the United States in 2004 for use in patients with AD at moderate to severe stages of dementia. The exact mechanism by which it exerts its symptomatic benefit is unclear. However, there is no systematic evidence that memantine provides neuroprotective effects among people with AD, and the FDA-approved prescribing information specifically states that there is “no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer’s disease.”⁴⁶ Clinical trial support for memantine is much more limited than for the acetylcholinesterase inhibitors, particularly for monotherapy.

MEMANTINE MONOTHERAPY EFFICACY AND SAFETY. Treatment with memantine 20 mg daily resulted in less decline in cognition (as measured by the Severe Impairment Battery²) over a 28-week double-blind placebo-controlled trial that enrolled people with moderate and severe stages of AD dementia.⁴⁷ Both the memantine and placebo groups exhibited a decline in cognition compared with baseline. Similarly, both activities of daily living and global function scores were better for treated patients than those on placebo at the study’s conclusion, but the scores were lower than at the study’s start. A second trial in a similar population did not demonstrate benefits of memantine relative to placebo on either cognitive or global measures at the end of 24 weeks of treatment, but some benefits were seen at earlier time points.⁴⁸ Neither study demonstrated benefits of memantine on the Neuropsychiatric Inventory Questionnaire, but agitation was reported less frequently among patients on active treatment in both studies. Patients enrolled in these trials had generally much more severe impairment than those in acetylcholinesterase inhibitor trials; all had MMSE scores of 14 or less.

In another trial among nursing home patients with severe AD dementia and MMSE scores less than 10, lower dosing (10 mg daily) of memantine was associated with benefits on global scales similar to the effects of 20 mg daily, but this trial did not specifically assess cognitive outcomes.⁴⁹ Consistent with the lessening benefit of memantine over the study period reported by Van Dyck and colleagues,⁴⁸ open-label follow-up of the cohort reported by Reisberg and colleagues⁴⁷ revealed diminishing benefits over 12 months of memantine monotherapy. Cognitive scores among patients who had been on placebo for the double-blind portion of the study and then started memantine treatment were not significantly different from those who had been on active therapy for the full 48 weeks.⁵⁰ Memantine was well tolerated in both studies, with no adverse effects occurring more often in the treated groups than placebo. Studies of memantine in milder stages of AD identified less robust and more variable benefits. Meta-analysis of memantine’s results among 411 patients with mild-stage AD dementia in three clinical trials identified no evidence for benefit in that group.⁵¹ No clinical trials identifying beneficial response to memantine in patients with MCI have been reported.

COMBINATION THERAPY WITH MEMANTINE AND ACETYLCHOLINESTERASE INHIBITORS.

Memantine is most frequently prescribed in conjunction with acetylcholinesterase inhibitors. When memantine was added to chronic donepezil therapy for patients with moderate and severe AD dementia (MMSE

scores of 5 to 14), cognitive test scores stabilized, and the patients experienced less decline than those maintained on donepezil therapy plus placebo.⁵² Fixed-dose combinations of donepezil 10 mg and extended-release memantine 7 mg, 14 mg, 21 mg, or 28 mg are available in the United States. There are no published efficacy data for the fixed-dose formulation; FDA approval was based on bioequivalence to the component drugs. This formulation may be helpful to enhance adherence to the pharmacologic treatment plan when patients resist taking a larger number of pills or for those who have limited supervision for drug administration. A 2022 systematic review found “ambiguous” evidence regarding the use of acetylcholinesterase inhibitors and memantine as combination therapy, suggesting that there may be slight benefits for patients with moderate and severe AD dementia.⁵³ Another review identified “small clinical benefit” for memantine in moderate and severe AD dementia, whether used alone or in combination.⁵⁴

LONG-TERM OUTCOMES. There are very limited data on the long-term efficacy of memantine monotherapy on outcomes such as nursing home placement and mortality. Most long-term outcome studies include patients on memantine in combination with an acetylcholinesterase inhibitor. There may be small benefits to combination therapy on mortality and placement, but these are not consistently observed.^{53,55,56}

SYMPTOMATIC THERAPIES FOR BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS

Behavioral symptoms are often far more distressing to care partners of patients with AD than cognitive losses. However, there is no systematic evidence that pharmacotherapy for behavioral and psychological symptoms of dementia reduces care partner burden.⁵⁷ Because they can arise in response to many factors in addition to degenerative brain pathology, including general medical, social, and environmental factors, behavioral and psychological symptoms of dementia can be extremely challenging to treat.⁵⁸ There is consensus that nonpharmacologic approaches are a necessary component of successful treatment, but experts often disagree about the most appropriate choice of medications and course of therapy. Clinical trials of individual agents have offered little additional guidance, and before May 2023, no drugs had been approved specifically for the treatment of behavioral and psychological symptoms of dementia in patients with AD.

When recognizable psychiatric diagnoses are identified as part of the expression of behavioral and psychological symptoms of dementia, it is reasonable to treat those symptoms with approved agents, such as treating depression with selective serotonin reuptake inhibitors (SSRIs). It is important to note that behavioral and psychological symptoms of dementia arise from a far more heterogeneous combination of contributing factors than is typical for primary psychiatric illnesses. Treatment outcomes, even for depression, are highly variable, and the risk for harm associated with pharmacotherapy is therefore increased without clearly predicted benefits.⁵⁹ Similarly, there is little systematic evidence to support the efficacy of antipsychotic drugs to treat most behavioral and psychological symptoms of dementia, although there is a clear risk for potential harm.⁶⁰ Prescribers should be aware of and communicate the risks associated with antipsychotic drug use in patients with dementia, including a greater than 1.5-fold increased risk for all causes of death observed among

KEY POINTS

- Patients with dementia who discontinue acetylcholinesterase inhibitor drugs may demonstrate noticeable worsening of cognitive, neuropsychiatric, or functional status in the first weeks after stopping treatment; resumption of therapy can be considered.
- Memantine is a symptomatic therapy for patients with AD; clinical evidence does not indicate it alters neurodegeneration.
- Cognitive and functional benefits of memantine monotherapy fade by 12 months of treatment in patients with AD.
- Memantine showed no benefit in patients with mild-stage AD.
- There is no systematic evidence that pharmacotherapy for behavioral symptoms in patients with AD reduces care partner burden.
- Treatment outcomes for selective serotonin reuptake inhibitor (SSRI) agents in patients with AD and depression are less predictable than in patients with primary depression.

treated patients in placebo-controlled trials.⁶¹ Those observations resulted in a boxed warning in the US prescribing information for members of this class. More recent evidence suggests that mortality risks tend to be expressed early in the course of treatment and increase with higher doses.^{62,63} Among the atypical antipsychotics studied through 2015, excess mortality appears to be highest for haloperidol and lowest for quetiapine.⁶³

Sleep Cycle Disturbances

Disruptions of the physiologic melatonin cycle, which serves as a circadian pacemaker, are typical with AD pathology and may contribute to the sleep disturbances frequently seen in people with the illness. The nature of sleep abnormalities varies widely among patients and may include reduced sleep at night, frequent awakening, and excessive daytime somnolence, as well as late-day agitated behaviors (ie, sundowning). Overall, there is little systematic evidence to support any specific drug treatment to improve sleep for people with AD.⁶⁴ As with other behavioral and psychological symptoms of dementia, nonpharmacologic approaches are the foundations of successful treatment. These should include recommendations for increased daytime activity and good sleep hygiene. Therapeutic melatonin at up to 10 mg daily may attenuate the breakdown of the circadian cycle. It produces no serious side effects, but consistent patterns of sleep improvement have not been demonstrated.^{65,66} One very small trial ($N = 30$) demonstrated beneficial effects of trazodone 50 mg on sleep parameters without adverse effects on daytime wakefulness or cognition.⁶⁷ Definitive larger-scale trials confirming these findings have not been published. A 2022 study using zolpidem demonstrated small benefits on some sleep parameters in people with AD; there were mild but measurable adverse effects on cognition, suggesting an unfavorable overall risk-to-benefit profile.⁶⁸ Suvorexant, an orexin antagonist, improved total sleep time in patients with mild and moderate AD treatment and resulted in relatively low rates of daytime somnolence; it is FDA approved for use in this population. Despite the objective benefits evident on polysomnography, there was limited evidence for subjective improvement in sleep quality. No overt adverse effects on cognition were reported with suvorexant treatment.⁶⁹

Agitation

Agitation is a frequent adverse behavior in people with AD. It is associated with emotional distress and can be broken into three broad categories: (1) restless behaviors, (2) verbal aggression, and (3) physical aggression. The SSRI agents citalopram and sertraline have demonstrated efficacy for nonpsychotic agitation in placebo-controlled trials and are generally better tolerated than antipsychotics.⁷⁰ In May 2023, brexpiprazole became the first agent specifically approved for the treatment of agitation related to AD. The approval was based on two clinical trials suggesting that doses of 2 mg/d reduced the severity of agitation reported by care partners.⁷¹

DISEASE-MODIFYING THERAPIES

From its recognition in 1906 through the end of the 20th century, a diagnosis of AD was inferred from clinical patterns but could only be confirmed by direct examination of brain tissue, usually by autopsy. Rapid advances in understanding the molecular biology of AD in the 1980s and 1990s allowed for

the characterization of the amyloid- β ($A\beta$) peptide that accumulated in plaques, as well as the development of transgenic animals that could replicate elements of the plaque and tangle pathology. Subsequently, Shenk and colleagues⁷² discovered that immunizing transgenic mice that express AD pathology resulted in clearance of the pathology. This opened a new path forward for immunotherapies with the potential for both the treatment and prevention of AD.⁷² A second critical step in the progress toward effective disease-modifying therapies was the development of an imaging technique to visualize $A\beta$ plaques in patients using PET. This technology, along with PET tracers more readily available in clinical settings, allows accurate *in vivo* identification of AD pathology⁷³ and provides biomarker evidence that the pathology is altered by treatment.⁷⁴

Despite these breakthroughs, most early trials of anti-amyloid immunotherapies were unsuccessful and identified a high risk for adverse effects. The most significant complication was the treatment-related emergence of amyloid-related imaging abnormalities (ARIA). First reported as a complication of amyloid-lowering therapies in 2010, ARIA can be expressed as edema or effusion (ARIA-E) or as hemorrhagic change, including microhemorrhages and superficial siderosis (ARIA-H). ARIA are most often asymptomatic and detected by routinely scheduled surveillance MRI. They typically arise early in the course of therapy or after increasing the dosage of the immunotherapy, but they can be severe and influence decisions about continuing treatment. An association with apolipoprotein E (ApoE) genotype has also been identified, with *APOE4* heterozygotes, compared with noncarriers, expressing an increased risk for ARIA, and homozygotes experiencing the highest rate of ARIA events. Despite these concerns, several monoclonal antibodies directed at amyloid achieved varying levels of success in clinical trials and have moved forward into clinical use. Although broadly similar in that they bind to aggregated or fibrillar forms of $A\beta$ and demonstrate plaque clearance on PET, there are differences in their specific epitope targets, dosing patterns, clinical effectiveness, and adverse event profiles that warrant individual consideration.

Aducanumab

Aducanumab was granted accelerated approval by the FDA in June 2021 based on results of Phase 3 clinical trials that showed significant reductions in cerebral amyloid levels among participants with early AD (defined as MCI due to AD and AD dementia at a mild stage).⁷⁵ Interpretation of these studies was complicated by their early cessation after a futility analysis that suggested the drug was not providing clinical effectiveness. Although they followed identical designs, subsequent analysis determined that one of the two trials, called EMERGE, showed efficacy on the specified clinical outcome measures, but the second trial, called ENGAGE, did not.⁷⁵ Additional post hoc analyses suggested that participants receiving high-dose aducanumab therapy (10 mg/kg monthly for 18 months) achieved the most clinical benefit, reflected as slowing of decline on clinical measures of severity. Subgroups of participants in both studies underwent amyloid PET scans, which demonstrated significant clearance of amyloid signal in the cerebral cortex. The magnitude of the amyloid clearance increased with both drug dose and time on treatment. For those undergoing sequential PET scans, 31% of treated patients in ENGAGE and 48% of those in EMERGE had sufficient amyloid removal over 78 weeks to be considered

KEY POINTS

- SSRI antidepressants citalopram and sertraline can reduce nonpsychotic agitation in people with AD.
- Brexpiprazole is the only drug specifically approved for agitation associated with AD; it is classed as an antipsychotic and has a boxed warning.
- Amyloid-related imaging abnormalities including effusion or edema and hemorrhage can be serious adverse effects of amyloid-lowering treatments.
- Approved amyloid-lowering monoclonal antibodies reduce plaque burden and are FDA approved for use in patients with early AD.

amyloid negative.⁷⁵ In a controversial decision, the FDA determined that the biomarker findings were sufficient for aducanumab to receive the accelerated approval status, allowing for prescriptive therapy outside of clinical trials. Appropriate use recommendations for aducanumab treatment have been published, but uptake was very limited, largely because Medicare and most other insurers declined to cover the costs of the medication. Aducanumab has been discontinued by its manufacturer and will not be available after 2024.

Lecanemab

Lecanemab received accelerated approval from the FDA in January 2023 followed by traditional full approval in July 2023 after publication of Phase 2 and Phase 3 clinical trials that identified optimal dosing and clinical effectiveness over 18 months of therapy among patients with early AD, encompassing MCI and mild AD dementia.^{76,77} IV administration at 10 mg/kg every 2 weeks was associated with slowing of decline compared with placebo across multiple clinical endpoints, generally of 25% to 35% magnitude. Analysis of 698 participants in an amyloid PET scan substudy showed more than 70% reduction in cortical amyloid over 18 months of therapy, bringing the average amyloid burden below the threshold for treatment.⁷⁷ There was a 26% rate of acute infusion reactions, most frequently after the first dose. Infusion reaction symptoms included fever, flushing, chills, and blood pressure fluctuations. These were generally abated by pretreatment with nonsteroidal anti-inflammatory drugs, antihistamines, or glucocorticoids.⁷⁷ Both ARIA-E (12.6%) and ARIA-H (17.3%) were identified as complications of treatment with greater frequency associated with *APOE4* gene dose. Appropriate use recommendations suggest *APOE* genotyping before initiating treatment to inform individual risk for ARIA events.⁷⁸ Following the FDA's approval decision, the US Centers for Medicare & Medicaid Services (CMS) announced that it would pay for the cost of lecanemab treatment under a "coverage with evidence determination" program for eligible beneficiaries who are enrolled in a CMS-approved registry that will track treatment outcomes such as cognitive test scores and functional status. As with aducanumab, appropriate use recommendations have been published and provide practical guidance for prescribers.⁷⁸

Donanemab

In July 2024, a third anti-amyloid antibody, donanemab, was approved by the FDA for patients with MCI caused by AD pathology and patients with mild AD dementia. The approval was based on both Phase 2 and Phase 3 data with generally similar results.^{79,80} Across various clinical outcomes in the 18-month Phase 3 trial, a 22% to 36% slowing in progression of symptoms versus placebo was observed.⁸⁰ The effectiveness of donanemab in slowing decline was affected by tau burden, which was measured at study entry with tau PET. Patients with high tau burden showed less alteration of the clinical course than those with low or medium tau burden. There was significant clearing of plaque in the treated group, with 76% of the sample falling below the threshold for treatment by the end of the 76-week study. ARIA were reported in 36.8% of the treated group; ARIA-E occurred in 24%, and ARIA-H in 19.7% with some patients experiencing both. With the FDA approval, CMS acknowledged that donanemab would be included in the "coverage with evidence determination" process along with lecanemab.

Future Directions

There are many approaches to disease modification in AD under investigation in human clinical trials. As of July 2024, there were 187 active trials involving 141 agents; about 80% of these agents are intended as disease modifiers.⁸¹ The largest proportion of the trials target amyloid, tau, and neuroinflammation. No additional disease-modifying therapies for AD are anticipated to achieve FDA approval before 2026.

KEY POINT

- Phase 3 trial results for lecanemab and donanemab show similar magnitudes of effects, about 25% to 35% slowed rates of clinical progression in treated patients with early AD.

PRACTICAL ADVICE

Given the broad impact of AD on patients and families, and the many targets for pharmacotherapy—including cognition, daily function, behavior, and pathology—there are few sources of practical advice for neurologists on optimal treatment approaches.

Symptomatic Therapies for Cognition and Function

Many clinicians prescribe acetylcholinesterase inhibitors off-label for patients with MCI, particularly those with more severe deficits. Memantine has not demonstrated efficacy in MCI. Based on the available evidence, acetylcholinesterase inhibitor therapy should usually be recommended for a patient presenting with mild AD dementia, weighing the potential for individual risks such as bradycardia and existing gastrointestinal symptoms. Counseling for realistic expectations is important. Only a minority of patients, perhaps 20%, show clear-cut improvement on cognitive scales after beginning an acetylcholinesterase inhibitor; a more typical response is a stabilization of the course with a delay in decline of 9 to 12 months.⁷ There are no overall differences in efficacy among the acetylcholinesterase inhibitors, and most studies suggest donepezil is the best tolerated of the oral agents. It can be started at 5 mg daily and increased to 10 mg after 1 month; more rapid titration is associated with a higher risk for nausea or diarrhea. Administration of the once-daily dose in the morning may reduce the risk for adverse effects on sleep.⁸² If alternative administration pathways are appropriate, transdermal rivastigmine beginning at 4.6 mg/d is generally well tolerated. There are no systematic data to guide the timing of discontinuation of acetylcholinesterase inhibitors, but presumptive effects may be present for 3 or more years from treatment initiation. Memantine has not demonstrated benefits in patients with mild AD.

Guidance for acetylcholinesterase inhibitor use is generally similar for a patient presenting with moderate-stage AD dementia. Clinical trials demonstrating acetylcholinesterase inhibitor efficacy enrolled patients with MMSE scores as low as 10, but there is little added benefit of the 23-mg formulation over the usual 10-mg daily dosage.^{43,83} Memantine appears to offer maximum benefits when added to existing donepezil therapy rather than being initiated as monotherapy.⁵² Effective memantine doses range from 10 mg daily through 28 mg (extended release) daily. For patients presenting with severe-stage AD dementia (such as those requiring assistance with self-care activities), careful consideration of the potential risks of treatment and high likelihood of minimally detectable benefits is warranted. Counseling families on realistic expectations for these patients is very important because a clinical trial of donepezil in this group did not demonstrate positive effects on either daily function or neuropsychiatric symptoms.⁸⁴ There is growing consensus that acetylcholinesterase inhibitors and memantine should be “deprescribed” for patients with advanced AD.⁸⁵

Symptomatic Therapies for Behavioral and Psychological Symptoms of Dementia

When present, regardless of dementia stage, initial or concomitant treatment of behavioral and psychological symptoms of dementia with nonpharmacologic approaches is always warranted. A consensus algorithm for the prevention and treatment of agitation associated with neurocognitive disorders including AD was published in 2023.⁸⁶ It calls for a systematic evaluation of the symptoms through the steps of “investigate, plan, and act” and a stepwise progression through nonpharmacologic approaches and pharmacotherapies directed by the circumstances and severity of the behavioral disturbances (**FIGURE 11-2** and **FIGURE 11-3**).

Disease-modifying Therapies

For patients presenting with MCI due to AD or mild AD dementia, consideration of disease-modifying therapies in conjunction with symptomatic therapies is appropriate. The presence of AD pathology should be determined by CSF testing or amyloid PET scans. Blood-based biomarkers for AD diagnosis are rapidly

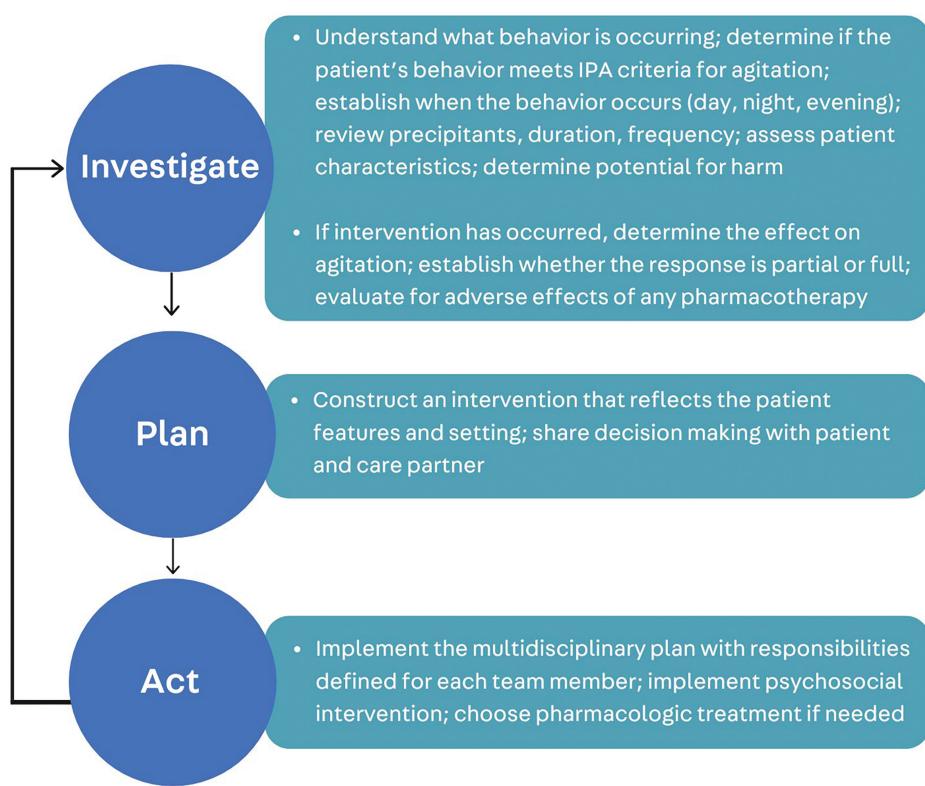


FIGURE 11-2

The Investigate, Plan, Act (IPA) approach to agitation evaluation, management, and prevention proposed by the International Psychogeriatric Association's Agitation Work Group. The IPA steps should be repeated until the agitation reaches acceptable levels. Successful implementation should reduce or prevent recurrent episodes. M de la Flor, PhD, Illustrator.

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improving and may soon supplant CSF or PET measures to identify treatment candidates. Both *APOE* genotype and brain MRI to assess for microhemorrhages and superficial siderosis should be obtained to characterize and inform patients of their risks of ARIA during anti-amyloid treatments. No direct comparison studies of the efficacy of lecanemab and donanemab have been reported, but 18-month clinical efficacy outcomes are broadly similar. Considerations in treatment choice might include higher rates of acute infusion reaction and the inconvenience of dosing every 2 weeks with lecanemab in comparison with higher rates of ARIA (especially in *APOE4* carriers) but once-monthly treatments with donanemab (TABLE 11-2). Although tau PET scans were performed to classify patients in the donanemab Phase 3 trial, the prescribing information does not include a requirement for tau PET, and it is not typically covered by Medicare or other payers. For patients enrolled in Medicare or Medicaid, prescribers will need to establish credentials to enter patient data on

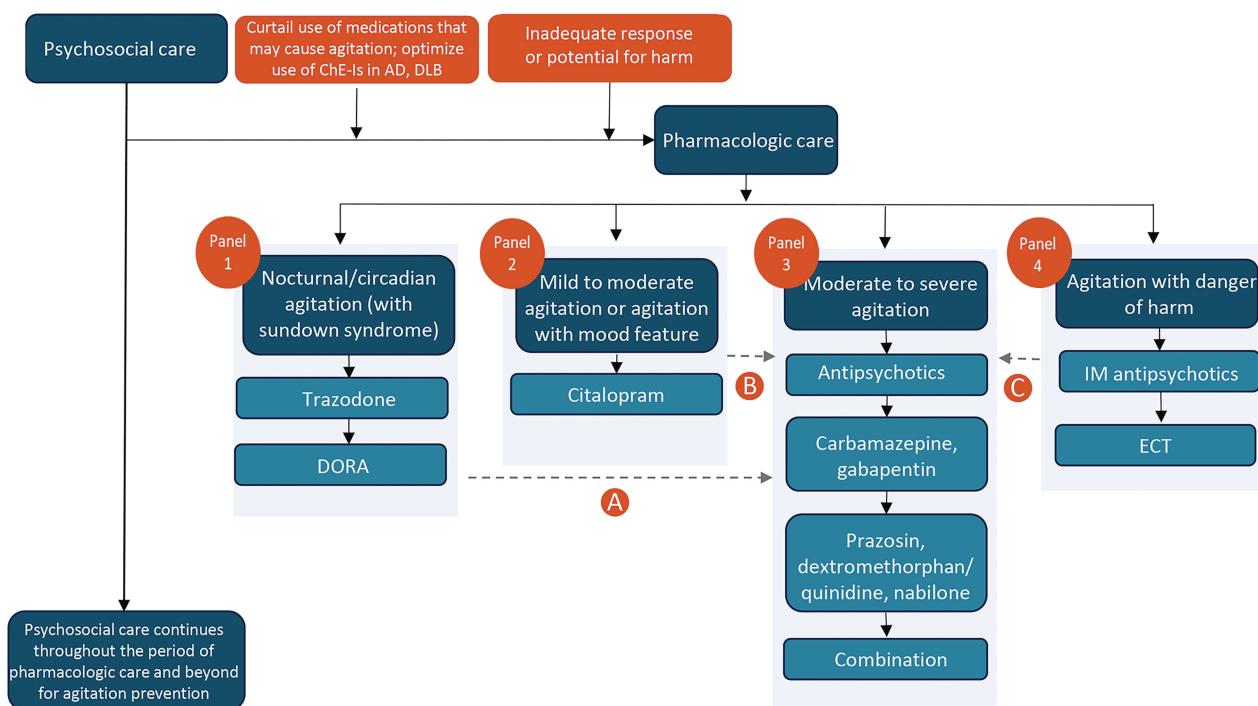


FIGURE 11-3

The Investigate, Plan, Act (IPA) agitation treatment algorithm proposed by the International Psychogeriatric Association's Agitation Work Group. Psychosocial care is considered first and continued throughout the agitation episode with plans to curtail future agitation. Pharmacologic care is personalized and guided by the major features of the agitation including whether it has a circadian pattern or occurs mostly at night (Panel 1), is mild to moderate or has mood changes (Panel 2), is of moderate or severe severity but does not present a danger to self or others (Panel 3), or is severe and represents a treat of harm (Panel 4). Pharmacologic strategies progress from Panel 1 to Panel 3 if the first treatments fail (arrow A). Pharmacologic strategies advance from Panel 2 to Panel 3 if the first treatments fail (arrow B). Pharmacologic strategies are adjusted to Panel 3 once the very severe agitation addressed in Panel 4 is controlled (arrow C). M de la Flor, PhD, Illustrator.

AD = Alzheimer disease; ChE-Is = cholinesterase inhibitors; DLB = dementia with Lewy bodies; DORA = dual orexin receptor antagonist; ECT = electroconvulsive therapy.

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cognitive and functional scales in a CMS-approved registry every 6 months. The schedule for safety monitoring for ARIA with brain MRI and the specific dosing plans vary by agent and should be maintained in adherence with the prescribing information and published appropriate use recommendations.^{78,87}

Health Equity and Disparities

The costs associated with the clinical diagnosis and biomarker confirmation of eligibility for amyloid-lowering therapies are high. This has raised concerns about representation in clinical trials and access to treatment among underserved populations.⁸⁸ Most amyloid-lowering therapies are currently managed through expert centers, such as memory clinics, but evidence suggests underserved populations, especially Black Americans, do not have representative access to such clinics and specialized diagnostics such as PET scans.⁸⁹ These issues affect nearly all aspects of dementia care, but the complicated management of monoclonal antibody therapies will likely magnify disparities. Cultural and social factors contribute to the diagnosis of dementia being made more frequently at

TABLE 11-2

Comparison of Key Efficacy and Safety Outcomes for Lecanemab and Donanemab

	Lecanemab ⁷⁷	Donanemab ⁸⁰
Efficacy measure		
Clinical Rating Scale-Sum of Boxes (CDR-SB) % slowing	27%	29%
CDR-SB points difference	0.45	0.67
Mean baseline amyloid (centiloids)	78	104
Mean amyloid clearance (centiloids)	52	86
Centiloid reduction	66%	83%
Patients amyloid negative at 18 months	68%	76%
Safety measures		
Net amyloid-related imaging abnormalities due to hemorrhage (ARIA-H) (treated-placebo)	8%	12%
Net amyloid-related imaging abnormalities due to cerebral edema or effusion (ARIA-E) (treated-placebo)	11%	22%
ARIA-E by genotype (raw)		
ε3/ε3	5%	15%
ε3/ε4	11%	21%
ε4/ε4	33%	36%
ARIA-H by genotype (raw)		
ε3/ε3	12%	19%
ε3/ε4	14%	32%
ε4/ε4	40%	50%

more advanced stages in Black and Hispanic patients⁹⁰; earlier diagnosis is critical for access to potentially effective treatments because of the data suggesting greater efficacy of amyloid-reducing therapies at milder pathologic stages.

CASE 11-1 illustrates a typical presentation and course of treatment for a patient presenting with amnestic MCI and AD pathology. For more information on a practical approach for the implementation of disease-modifying agents, refer to the article “Implementing New Dementia Care Models in Practice” by Vijay K. Ramanan, MD, PhD,⁹¹ in this issue of *Continuum*.

A 65-year-old woman presented to the clinic for evaluation of memory concerns. She reported an increase in misplacing objects that began when she moved to a new home. She denied other cognitive changes and any losses in daily function. Her husband reported that she demonstrated increasing repetitiveness and difficulty finding words in conversation. These deficits were frustrating to her. She was occasionally irritable as a result. No other symptoms or signs of depression were reported. Her medical history included medically well-controlled hypothyroidism and dyslipidemia. Her family history included Alzheimer disease (AD) in her father.

On examination, she had word-finding difficulty and repetitiveness in conversation but followed commands without difficulty. She scored 20/30 on the Montreal Cognitive Assessment (MoCA), with 0/5 word recall and errors in trail-making, cube-copying, and clock-drawing. MRI of her brain revealed mild diffuse cerebral cortical atrophy with prominence in her medial temporal lobes. Amnestic multidomain mild cognitive impairment, presumably due to AD pathology, was diagnosed. Donepezil 5 mg daily was initiated. She developed uncomfortable, loose stools. Transdermal rivastigmine 4.6 mg/d was substituted for the donepezil. The loose stools resolved over 2 to 3 days, and she tolerated rivastigmine escalation to 9.5 mg/d without difficulty. After 3 months of treatment, her MoCA score was stable at 20/30, and she remained independent in all daily functions. She voiced interest in undergoing treatment with anti-amyloid therapy. A florbetapir PET scan revealed a loss of gray-white differentiation in the cerebral cortex, indicating moderate to frequent amyloid neuritic plaques suggestive of AD pathology. Lecanemab treatment was begun. Sequential MRIs identified no amyloid-related imaging abnormalities through 6 months of treatment. Her MoCA score declined by 3 points with a loss of serial 7 calculations. Both her husband and she reported continued independence with all activities of daily living.

CASE 11-1

This case illustrates a typical presentation of AD-related mild cognitive impairment, the most common adverse effect of acetylcholinesterase inhibitor treatment, and overall maintenance of independence over time on combined symptomatic and disease-modifying therapies.

COMMENT

CONCLUSION

There are multiple opportunities for pharmacologic treatment of people experiencing the symptoms of AD. Although this review focused on pharmacotherapies, lifestyle recommendations and nonpharmacologic approaches to optimize the quality of life for affected people and their care partners are important at all stages of the illness. Drug treatment plans can and should begin early in the course of symptoms and can be directed by tests to identify that AD pathology is present in the brain. The clinical trial results for lecanemab and donanemab suggest optimal efficacy for those agents in patients with less pathologic burden, which may disadvantage members of underserved communities. They are appropriate for people with MCI due to AD, and data continue to emerge to guide decisions about assessing their plaque-lowering effects as a determinant of long-term treatment. The efficacy of treatment with acetylcholinesterase inhibitor drugs in people with mild- and moderate-stage dementia due to AD is well established and is associated with long-term benefits. Higher acetylcholinesterase inhibitor dosing and the addition of memantine may provide some added benefit as patients progress through the moderate stage. Deprescribing cognitive enhancers in advanced disease is often justified. Symptomatic treatments to address mood and other behavioral concerns are often a high priority for care partners, but efficacy is less predictable and risks for harm are high. The progressive nature of AD requires neurologists to maintain an evolving and data-informed treatment plan over the course of the illness.

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Care Partner Burden and Support Services in Dementia

By Angelina J. Polzinelli, PhD, ABPP-CN

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ABSTRACT

OBJECTIVE: Informal care partners are essential to the care of people living with dementia, but they often experience significant burden and receive minimal training, support, and resources. This article provides an overview of care partner experiences, factors contributing to burden, and methods for reducing burden of caregiving in dementia.

LATEST DEVELOPMENTS: The US Department of Health and Human Services National Plan to Address Alzheimer's Disease and the World Health Organization Global Action Plan for dementia have identified support for dementia care partners as a top priority for research and policy in recognition of care partners' instrumental but underresourced role in dementia care. The psychological, financial, social, and physical costs of caregiving, particularly without necessary knowledge, skills, and resources, can lead to care partner burden. Reassuringly, multicomponent interventions can mitigate burden and other negative consequences of caregiving, especially when they are theoretically grounded, inclusive, and culturally relevant.

ESSENTIAL POINTS: Health care providers play a vital role in the early identification of care partner burden through brief, regular assessments. With earlier identification and subsequent intervention (eg, education, skills-based training, local and national resources), the experience of burden and negative health outcomes can be mitigated and quality of life for people living with dementia and their care partners can be improved.

INTRODUCTION

Dementia results in disability and dependence on others for meeting everyday needs. When dementia is progressive, there is an eventual complete dependence on others for basic activities of living, including eating and toileting. Despite increasing complex care needs, most caregiving in dementia is done by informal (ie, unpaid) care partners (also called *caregivers* or *support persons*) who are typically family members and sometimes friends or community members.^{1,2} These vital informal care partners usually do not receive training in how to assist the person living with dementia with the many changing complex tasks and responsibilities that come with this life-altering diagnosis. Further, access to important caregiving

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resources and interventions can be hindered by a lack of awareness, experiences of discrimination in health care settings, scarcity of culturally informed care, and low financial and other resources.³⁻⁵ In this context, care partners often report a high degree of stress and burden, although these outcomes are not an inevitable part of dementia caregiving⁶ and can vary significantly across racial, ethnic, social, and cultural dimensions.⁷ Understanding the factors that contribute to burden, monitoring burden, and connecting care partners with education, resources, and skills-based training can positively affect the quality of life for people living with dementia and their care partners.

WHO ARE THE INFORMAL CARERS?

Care partners spend 133 billion hours caring for people living with dementia annually around the world. In 2030, informal caring estimates are expected to reach 1.4 trillion hours. In low- and middle-income countries, 90% of the care for people living with dementia is done by informal care partners, and two-thirds of them are women.⁸

In the United States, there are 11 million informal care partners of people living with dementia, translating into approximately 18 billion hours of unpaid work, valued at approximately US \$340 billion. Two-thirds of dementia care partners are White non-Latina women who live with the person with dementia.⁸ Approximately 25% are “sandwich generation” carers who are caring for children and for a parent with dementia. Approximately 60% of the carers do not have a college degree, and 40% have a household income of \$50,000 or less. There has been an increase in people aged 18 to 49 who care for a person living with dementia, from 16% in 2015 to 23% in 2023, suggesting changes in the constellation of caregiving kinships.⁸ Care partners tend to be spouses, adult children (daughters), or spouses-in-law (daughters-in-law) of people living with dementia.

Compared with care partners of people without dementia, care partners of people living with dementia spend significantly more hours per week caring and assisting with a greater number of daily activities because of gradual declines in functioning.⁸ This is particularly true of Hispanic, African American, and Asian American care partners, who spend more time caring than White care partners because of lower utilization of formal services.⁷ The amount of time required for caregiving can be equivalent to more than a full-time job. Caregiving time also increases when dementia progresses, with one study showing 151 h/mo (ie, 38 h/wk) at the time of diagnosis and increasing to 283 h/mo (ie, 71 h/wk) 8 years later.⁹

DEFINING CARE PARTNER BURDEN

Many informal care partners experience burden at some point during the caregiving experience. The construct of *burden* has been defined as “the multidimensional response to physical, psychological, emotional, social, and financial stressors associated with the caregiving experience.”¹⁰ This definition recognizes the importance of both objective and subjective components of burden. Although burden is triggered by objective tasks and responsibilities of caring (eg, low financial resources, low family support, behavioral problems), it is the care partner’s appraisal of the situation that determines the experience of burden. Ultimately, it is this subjective experience of burden that dictates health and quality-of-life outcomes.^{10,11}

EFFECTS OF CARE PARTNER BURDEN

Dementia affects not only the individual living with the condition but the larger familial system (for parsimony, *family* is used throughout this article, although it is recognized that people living with dementia receive care from others in their social networks). The family system undergoes significant change, disruption, and reorganization because of dementia that can come with significant personal costs. Role reversals occur between children and parents, disrupting relationships. Retirement plans that were decades in the making may be erased. Careers and education may be put on hold for years to care for an ill grandparent. Families focus large amounts of time, energy, and finances to care for their loved ones who live alone. These significant life disruptions are particularly prominent for the primary care partner, the person who manages most of the day-to-day care responsibilities, planning, and management. These primary care partners are often referred to as *invisible patients* because caregiving in dementia can come with significant but under- or unrecognized cost (ie, burden) to the person providing care.

Caring for a person living with dementia is often motivated by love, spiritual purpose, sense of reciprocity, sense of duty, guilt, or social pressures.¹² Family members may not be aware that they have assumed a care partner role because of the often insidious nature of dementia and cultural expectations. Despite the disproportionate amount of emotional, physical, and financial resources they devote to the person living with dementia, they often do not receive formal training, education, or resources. With time and increasing need, this responsibility can be met with reduced enthusiasm, anger and frustration, and resentment about the toll caregiving has taken on their lives. This is especially true if the motivation for caring was a sense of duty, guilt, or social pressure.¹³ These feelings can lead care partners to feel guilty or ashamed, creating a vicious cycle of feeling trapped, hopeless, and resentful.¹¹

Burden, stress, and strain put care partners at increased risk of physical and mental health issues. High reported stress and burden are associated with cardiovascular problems, impaired immunity, chronic health conditions (eg, diabetes, anemia), insomnia, and increased substance use.^{2,14-16} Depression and anxiety are high, and the sense of well-being is low among care partners of people living with dementia, even compared with other types of care partners.¹⁷ The presence of high psychological distress predicts even worse physical health, including a higher risk of mortality.¹⁸

High burden can lead to care partner burnout, which is the progression of care partner burden to the point where the experience is no longer healthy for the care partner or the person receiving care.¹⁰ Significant burden and burnout also create unsafe conditions for the person living with dementia. Abuse, neglect, mortality, and premature institutionalization are more likely to occur in the context of elevated distress and burden.¹⁹ Burden, therefore, has a significant impact on the health and quality of life for care recipients and partners.

FACTORS CONTRIBUTING TO CARE PARTNER BURDEN

Factors contributing to the experience of burden include characteristics of the person living with dementia, characteristics of the care partner, and the relational context. However, there is a growing appreciation of the interdependence of these factors, contributions of structural and social determinants of health, and recognition that historically low inclusivity and diverse representation prevents a

KEY POINTS

- Despite increasing complex care needs, most of the caregiving for patients with dementia is done by informal (ie, unpaid) care partners who have no training and minimal resources.
- Understanding the factors that contribute to burden, monitoring care partner burden, and connecting care partners with education, resources, and skills-based training can positively affect the quality of life for patients living with dementia and their care partners.
- In the United States, there are 11 million informal care partners of people living with dementia, translating into approximately 18 billion hours of unpaid work, valued at approximately US \$340 billion.
- Burden is “the multidimensional response to physical, psychological, emotional, social, and financial stressors associated with the caregiving experience.”
- Primary care partners are often referred to as *invisible patients* because caregiving can come with significant but under- or unrecognized costs (ie, burden).
- Burden, stress, and strain put dementia care partners at increased risk of physical and mental health issues.
- Abuse, neglect, mortality, and premature institutionalization are more likely to occur in the context of elevated dementia care partner distress and burden.

complete understanding of factors that lead to burden. These concerns highlight the need for inclusive theoretical and conceptual frameworks for a richer understanding of care partner burden across racial-ethnic, social, and cultural groups.^{3,20}

Characteristics of the Person Living With Dementia

Several disease-related factors are highly predictive of care partner burden. One of the most consistently identified contributors to burden is the presence of behavioral and psychological symptoms of dementia (also called *neuropsychiatric symptoms*).^{21,22} For an in-depth review of behavioral and psychological symptoms of dementia, refer to the article “Neuropsychiatric Symptoms in Dementia” by Gad A. Marshall, MD,²³ in this issue of *Continuum*. Almost all individuals with dementia experience at least one behavioral or psychological symptom of dementia over the course of illness.⁸ With increasing behavioral and psychological symptoms of dementia, care partners report greater burden.²⁴⁻²⁶ Irritability, agitation, sleep disturbances, anxiety, apathy, and delusions are particularly difficult for care partners.²⁷ Relatedly, dementia syndromes with more behavioral and psychological symptoms of dementia (eg, behavioral variant frontotemporal dementia, dementia with Lewy bodies) predict higher burden in care partners^{28,29}; for more in-depth discussion of these disorders, refer to the articles “Frontotemporal Dementia” by David Glenn Clark, MD,³⁰ and “Lewy Body Dementia” by James E. Galvin, MD, MPH,³¹ in this issue of *Continuum*. Increasing functional dependence, requiring more instrumental support from care partners, also predicts higher perceived burden.³²⁻³⁴ For example, incontinence is a risk factor for burden and subsequent premature institutionalization.³⁵ As the disease progresses, overall symptom load becomes more severe, care needs increase, and the amount of time spent caregiving increases, leading to more burden, especially in the absence of supportive services.³⁶

Some sociodemographic factors of the person living with dementia are also associated with higher burden. People living with dementia with less education have care partners who experience higher burden.³² Individuals with young-onset dementia are at a stage of life where they have many family and societal responsibilities and contribute to family income. When the person living with dementia is no longer able to fulfill these roles, these responsibilities often fall on the care partner, which can create additional stress. Comparing care partner experience between young-onset dementia and late-onset dementia suggests more burden in young-onset dementia³⁷ but no differences between groups in depression and other negative health indicators.³⁸

Characteristics of the Care Partner

Multiple sociodemographic factors of the care partner are associated with the experience of burden. Female care partners experience higher levels of burden than male care partners, possibly because they take on more responsibilities and spend more time caring, especially for more impaired people living with dementia.^{39,40} Lower socioeconomic background (eg, income, education) predicts a higher burden.²¹ Latino, Black, and Asian American care partners spend more time caring, have higher care demands, and report less access to outside help than non-Latino White care partners, resulting in higher burden.⁴¹⁻⁴⁴ Finally, cross-cultural differences (discussed in more detail later in this article)

around how care partners do or do not seek support from others can affect the sense of burden. For example, some cultures are more likely to emphasize keeping care and support within the family, whereas others may be more likely to reach out to professional caregivers. Regardless, all care partners can benefit from referrals to community and health services but may need to be addressed in appropriate cultural terms.

Psychological factors are one of the lenses through which individuals perceive, appraise, and make sense of their experiences, including their roles and responsibilities in providing care. As a result, these factors are integral components of the experience of burden in caring. Overall psychological health and sense of well-being are inversely predictive of care partner burden.⁴⁵ When anxiety, depression, and stress are present, they contribute to a higher perception of burden from caring responsibilities.^{26,34} Certain personality traits (eg, neuroticism) can influence experience of burden.¹¹ Protective factors include positive coping strategies (eg, problem-focused strategies, religious beliefs), a sense of care partner mastery (ie, having the knowledge, skills, and tools to feel confident caring for their loved one), and finding positive aspects of caring (eg, joy, purpose, gratitude).^{6,21,22,46-48}

Relational Context

Relational context includes the patient-carer dyad and the larger family or immediate social support system. The relationship between the care partner and the person living with dementia is perhaps the most important relational context variable. This refers to both the quality of the relationship and the type of kinship (eg, siblings). Better dyadic adjustment and a perceived positive relationship are associated with less burden.^{43,49} Kinship type shows mixed results with some studies suggesting higher burden in spousal dyads versus adult child-parent dyads and some showing the opposite.²¹ These mixed results may be caused by a multitude of mediating factors for different subgroups of care partners.⁵⁰ For example, cohabitation is associated with higher burden and is more typical of spousal dyads versus parent-child dyads.^{51,52} Some work also suggests that spousal care partners can show resiliency in the face of significant objective burden, whereas parent-child kinships do not.⁴⁷ Outside of the patient-carer dyad, the social support system (eg, other family members, friends, faith community members) can aid with caring responsibilities (ie, instrumental support), offer emotional support, and protect against isolation, which can reduce burden.^{53,54} Alternatively, the presence of family conflict can lead to greater burden.⁵⁵ Sociodemographic and cultural factors also play a role in the perceived helpfulness of social support on the sense of burden.⁴³

Capturing the Complexity of Care Partner Experience

There is growing recognition of the need for broader theoretical frameworks that go beyond standard stress and coping models to understand the complexity of care partner experiences, including burden.^{3,56,57} For example, Bonds Johnson and colleagues⁵⁷ proposed a research framework for understanding and promoting care partner mastery in Black Americans through the lens of the Black Family Socioecological Context Model. This model incorporates the multitude of factors and systems, including individual, family, and sociopolitical, that intersect and interact to influence the lived experience of Black dementia care partners. Dilworth-Anderson and colleagues³ encourage the use of inclusive

KEY POINTS

- One of the most consistently identified contributors to care partner burden is the presence of neuropsychiatric and behavioral disturbances in the person living with dementia.
- Female care partners experience higher levels of burden than male care partners, possibly because they take on more caring responsibilities and spend more time caregiving.
- Factors protecting against burden for care partners include positive coping strategies, a sense of care partner mastery, and finding positive aspects of caring.
- Better relationships between care partners and people living with dementia are associated with less perceived burden.
- More inclusive theoretical frameworks for understanding the complexity of dementia care partner experiences are needed.
- An intersectionality framework supports the evaluation of key factors influencing dementia care partner experience including culture, history, place, and social determinants of health.
- The Zarit Burden Interview is a self-report inventory and is the most widely used measure to assess care partner burden.

conceptual and theoretical models for understanding the complexity of caregiving experiences across sociodemographic factors. Specifically, they suggest the intersectionality framework, which aims to understand how identities, conditions, and statuses interact to affect people's lives.⁵⁸ From within this framework, a multitude of key factors that can influence care partner experience can be assessed, including, culture (norms, values, beliefs), history (generational knowledge and experiences), place (social infrastructure), and social determinants of health.³ For example, in many Asian cultures, the caregiving experience is grounded in cultural values of filial piety and duty, creating an expectation of family caregiving for a spouse, child, or sibling.⁵⁹ In this context, motivations for caring include not only love but also honoring tradition, and care partners may be discouraged from reaching out for assistance with care. However, generational differences, immigration, and acculturation all influence how these cultural norms and values are expressed, changing the experience of caregiving and sense of burden (**CASE 12-1A**).⁵⁶

MEASURING CARE PARTNER BURDEN

Addressing care partner burden in the clinic can be accomplished through validated and freely available self-report measures. Measuring care partner burden helps identify patient care needs, risk of negative health outcomes for people living with dementia and their care partners, and potential education and intervention opportunities (eg, community resources and services). Further, given the reciprocal interaction between dementia symptoms and care partner distress,²⁴ identification of burden can prevent further deterioration of the patient-carer relationship, therefore decreasing the risk of morbidity, mortality, and premature institutionalization of the person living with dementia.⁶⁰

A 2022 systematic review identified four self-report inventories for care partner burden that showed moderate-high to high psychometric properties.⁶¹ The Zarit Burden Interview⁶² is a 22-item self-report inventory and is the most widely used measure of burden. Validated shorter versions are also available^{63,64} (**FIGURE 12-1**), and it has been translated into multiple languages.^{65,66} The Screen for Caregiver Burden is a multidimensional measure assessing care partner experiences (ie, objective) and the appraisal of distress associated with experiences (ie, subjective); longer (25-item)⁶⁷ and shorter (7-item)⁶⁸ versions are available. The Caregiver Burden Inventory^{69,70} is a 24-item measure of five subdomains of burden: (1) time dependence, (2) developmental, (3) physical, (4) social, and (5) emotional. Compared with other measures, this inventory may better target specific domains of care partner needs that would benefit from intervention. Finally, The Burden Scale for Family Caregivers is a single-factor structure, 28- or 10-item inventory of burden.^{71,72} Two benefits of this measure are that it captures aspects of burden that are not a result of direct contact with the person living with dementia and it is available in 20 languages (see the Useful Websites section at the end of this article).

Despite measures of care partner burden being available in multiple languages, there is growing concern that these measures may not sufficiently capture how burden is expressed across different groups and cultures.^{73,74} The ability to properly assess care partner burden is critical to early identification and intervention to reduce negative physical and psychological health outcomes for both the care partner and the person living with dementia.

REDUCING BURDEN AND IMPROVING QUALITY OF LIFE IN DEMENTIA CAREGIVING

Reducing burden and improving quality of life in the setting of dementia care can be supported by building care partner mastery, obtaining community resources and respite care, maintaining peer and social support, and seeking mental health support. There is a robust field of research into the creation of interventions to address these needs of care partners. Encouragingly, multicomponent and comprehensive interventions show promise in relieving perceived burden, although more work is needed to ensure these interventions are culturally relevant.

Promoting Care Partner Knowledge and Mastery

Care partner mastery (ie, self-acknowledged sense of confidence and competence about caregiving) reduces burden and can be built through access to dementia education and skills-based training. Many care partners report a lack of

CASE 12-1A

A 61-year-old woman presented to clinic for an evaluation of gradual decline in memory and increasing anxiety and depression. The patient immigrated to the United States from Honduras as an adult. She was accompanied to the appointment by her 39-year-old daughter and primary care partner. Her daughter provided more than 30 h/wk of care in addition to working a full-time job and caring for her son. The patient was diagnosed with mild to moderate dementia due to suspected Alzheimer disease. After managing the patient's needs, the neurologist inquired about the daughter's feelings about caregiving. The daughter expressed feeling fatigued and unprepared for future changes that dementia would cause but that it was the family's expectation that she, as the oldest daughter, would assume this responsibility. Despite these concerns, she was glad to be able to help and valued the time spent with her mother, especially time spent cooking together, which she felt brought them closer. The daughter's Zarit Burden Interview score suggested minimal to mild perceived burden. Listening to the daughter's concerns, the neurologist offered educational materials about the course of Alzheimer disease, symptoms to watch for, and future care plans. The neurologist also offered information about support groups and encouraged self-care. However, the daughter stated that her focus should be on her mother not herself right now. The neurologist planned to see them for follow-up in 6 months.

This case shows mismatches can occur between objective burden (ie, more than 30 h/wk of caring) and the subjective experience of burden. It also demonstrates how positive experiences in caring and good patient-carer relationships can protect against burden and how cultural values can influence caregiving expectations and feelings about self-care. The Zarit Burden Interview score can be used to compare with future evaluations and assess change over time.

COMMENT

	Never	Rarely	Sometimes	Quite frequently	Nearly always
Do you feel...					
1 that because of the time you spend with your relative that you don't have enough time for yourself?	0	1	2	3	4
2 stressed between caring for your relative and trying to meet other responsibilities (work and family)?	0	1	2	3	4
3 angry when you are around your relative?	0	1	2	3	4
4 that your relative currently affects your relationship with family members or friends in a negative way?	0	1	2	3	4
5 strained when you are around your relative?	0	1	2	3	4
6 your health has suffered because of your involvement with your relative?	0	1	2	3	4
7 you don't have as much privacy as you would like because of your relative?	0	1	2	3	4
8 your social life has suffered because you are caring for your relative?	0	1	2	3	4
9 you have lost control of your life since your relative's illness?	0	1	2	3	4
10 uncertain about what to do about your relative?	0	1	2	3	4
11 you should be doing more for your relative?	0	1	2	3	4
12 you could do a better job in caring for your relative?	0	1	2	3	4

Add items 1-12 (maximum score = 48) _____

0-10: no to mild burden

11-20: mild to moderate burden

21+: high burden

FIGURE 12-1

The 12-item Zarit Burden Interview used to assess care partner burden.

Data from Bédard M, et al, Gerontologist.⁶³

knowledge about dementia and the diseases that cause it.⁸ Basic education about the expected trajectory of dementia in various diseases, needs at different stages, and symptoms to watch for can help care partners create a plan and prepare for the future.¹ Adding skills-based training in behavioral management to this education further increases sense of mastery and reduces burden.⁷⁵ However, structural and social determinants of health, social environments, and physical environments influence the development of mastery. Grounding care partner mastery programs in theoretical frameworks that recognize intersectionality and unique socioecological contexts of caring are better poised to address the challenges and capitalize on the strengths of caring in different cultural groups.⁵⁷

Community Resources and Respite Care

Formal community services include respite care (eg, adult day programs, in-home respite care), meal delivery, transportation assistance, specialized legal counsel, and financial assistance. Respite care reduces perceived burden and increases quality of life.⁷⁶ However, it is typically underutilized and can be difficult for care partners to access.^{77,78} The financial cost of these services can hinder use, but there can also be feelings of guilt or shame associated with “needing a break” or appearing to “evade responsibility.”⁷⁸ There can also be social or cultural pressure not to reach out for support.⁵⁹ Care partners with historically marginalized identities can often face stigma and discrimination from formal care services, further entrenching health disparities in dementia care. Black care partners report feeling like they are “falling through the cracks” because of the lack of culturally informed care.⁷⁹ Similarly, individuals identifying as lesbian, gay, bisexual, transgender, queer or questioning, intersex, and more (LGBTQI+) report a lack of cultural competency among professional staff, making care partners reluctant to seek aid.^{80,81} Those from socially disadvantaged areas report fragmented services, complex medical systems, and inadequate resources as barriers to accessing formal care.⁴ A potential novel way to mitigate some of the typical barriers to service access is through peer-to-peer support, including mentorship⁸² and exchange of services (eg, respite care).⁷⁷ This can be especially helpful to care partners who may be more likely to engage in a reciprocal exchange of assistance or knowledge with someone who has a shared lived experience rather than rely on outside help.

Engaging Social Networks

Social networks can be sources of instrumental and emotional support, and maintaining these networks prevents care partners and people living with dementia from becoming isolated. Social support minimizes distress in care partners,⁸³ and having a larger social network buffers against higher levels of burden when caregiving hours increase.⁸⁴ Social networks appear particularly important for promoting positive aspects of caring in spousal care partners.⁵⁴ However, social and cultural norms and expectations, personal beliefs about caregiving, and relationship quality with individuals in the social network influence decisions to reach out, whether for instrumental or emotional support, and perception of benefit.

Mental Health Support

Outside of social support, evidence-based psychotherapy has shown some promise in helping care partners manage distress.⁸⁵ Most of this work has focused

KEY POINTS

- Dementia education combined with skills-based training in behavioral management increases sense of mastery and reduces care partner burden.
- Respite care can significantly reduce burden, but many dementia care partners may feel guilt or shame about asking for help.
- Lack of culturally informed and culturally competent care can create barriers for dementia care partners in accessing needed services.
- Maintaining social networks is important for promoting positive aspects of dementia caregiving.
- Acceptance and commitment therapy helps dementia care partners face the challenges of caring by accepting difficult feelings and promoting behavior that aligns with values and goals.
- Multicomponent interventions are effective at reducing dementia care partner burden, especially when they are tailored to address unique sociocultural needs.
- Health care providers can regularly assess dementia care partner burden informally through conversation and formally through structured questionnaires.

on cognitive-behavioral therapy, which emphasizes the modification of dysfunctional thoughts and increasing positive activity to change feelings. However, because of the objectively challenging nature of caring, it can be argued that care partners do not have “dysfunctional thoughts” about caring. Accordingly, findings for cognitive-behavioral therapy for care partners are mixed.⁸⁵ Acceptance and commitment therapy, however, promotes psychological flexibility in the face of objectively challenging life situations (eg, caregiving, terminal illness) through the acceptance of thoughts and feelings and aligning actions with personal values, goals, and beliefs.⁸⁶ In a 2021 pilot study, Fowler and colleagues⁸⁶ showed that a 6-week telephone-delivered acceptance and commitment therapy program significantly improved care partner distress and burden up to 6 months after intervention.

Evidence-based Caregiving Interventions

More than 200 interventions have been developed for care partners of people living with dementia.⁸⁴ Structured multicomponent interventions show the most promise^{14,75,87} whereas technology-based, single-component interventions (eg, psychoeducation) have mixed results.^{88,89} These multicomponent interventions often include support groups, respite care, education, and skills-based training, which may serve diverse needs and preferences more effectively than single-component interventions. Despite the proliferation of interventions, few leave the research arena and are implemented in real-world settings,⁹⁰ although there are some exceptions. The Savvy Caregiver program (savvycaregiver.com) is a 6-week skills and education program and has been adapted for different sociocultural contexts (ie, The Great Village⁹¹ for African American care partners and Savvy Caregiver for the LGBTQ community⁹²). The Resources for Enhancing Alzheimer’s Caregiver Health (REACH)-II and REACH-TX are skills-based training and support programs for care partners delivered in a primary care setting (REACH-II) or the community (REACH-TX).⁹² REACH-TX is also available in Spanish. The Savvy Caregiver, REACH-II, and REACH-TX programs have standardized training protocols for health care providers wanting to offer this service to their patients and families (to learn more, visit ncoa.org/evidence-based-programs).

Beyond the need for further translation and implementation of evidence-based interventions, a focus on creating interventions that serve diverse groups is needed.⁹⁰ There is limited knowledge about how current interventions benefit demographic subgroups of individuals, partly because of underreporting of certain sociodemographic factors.^{7,90} Further, intervention development does not actively involve stakeholder voices (ie, care partners and people living with dementia) from diverse sociocultural backgrounds. This can inadvertently reduce efficacy, if, for example, there is a misunderstanding of needs or a mismatch in values and belief systems. However, there are opportunities to use more inclusive theoretical and conceptual frameworks to move care partner intervention science forward and ensure that it is applicable and equitable for individuals of diverse sociocultural backgrounds.^{3,57,74}

HOW CAN NEUROLOGISTS HELP MITIGATE CARE PARTNER BURDEN?

Early identification of the signs of burden is important to prevent burnout and mental and physical deterioration in care partners. Health care providers can assess care partner burden informally through conversation and formally

through structured questionnaires. Ensuring a nonjudgmental tone, providers can ask about feeling overwhelmed, lonely, or fatigued and about the availability of appropriate support to open a dialogue about the experience of burden. Whenever possible, this discussion should take place away from the person living with dementia to encourage frank responses. Observing signs of burden, burnout, and depression during these conversations is also critical. These signs include somatic symptoms (eg, increase in headaches), cognitive concerns (eg, problems concentrating), reporting isolation, weight loss or gain, feeling helpless or hopeless, feeling trapped, insomnia, and increased substance use. Health care providers can also administer a brief screener for care partner burden and quality of life, such as the Zarit Burden Interview (**FIGURE 12-1**) to supplement these conversations. A screener can be administered remotely before a visit or on a tablet during the visit and can track changes in burden longitudinally to identify concerning trends or assess the effects of an intervention (**CASE 12-1B**).

Intervening When Burden Is Identified

Different interventions may be more acceptable to individual care partners depending on personal, economic, sociocultural, or other reasons. Health care providers can support different preferences by ensuring multiple options and alternatives are available. **Supplemental Digital Content Table 1** (<links.lww.com/CONT/A413>) contains multiple resources and can be distributed to patients and families.

STRONGLY ENCOURAGE SELF-CARE. Care partners often neglect their own needs in service of the person they are caring for. Self-care is one of the hardest (but most important) components of caring, especially for female care partners who have been socialized across many cultures to put the needs of others before their own. For some care partners, simply “giving them permission” to put their needs first is an effective strategy. For others, cultural and social values about caring responsibilities can deter people from pursuing self-care needs. For example, when caring is an expected moral and cultural norm for adult daughters and daughters-in-law, a “put yourself first” approach may not work. However, messaging focused on taking care of the self to ensure the best possible care for the person living with dementia might be more acceptable. The analogy of the airplane oxygen mask (ie, putting on your own mask first before you can help others) can be helpful here in explaining why self-care is vital to caring for the person living with dementia. Self-care is not one type of activity, but the components that are often helpful are ones that encourage social engagement, joy, a sense of achievement, creativity, maintaining self-identity outside of caring, sense of meaning or purpose, and relaxation. Social engagement is especially important to maintaining the social network and reducing the risk of isolation. Care partners also need to monitor themselves between medical appointments for signs of burden and burnout.

OFFER ASSISTANCE FOR SEEKING PSYCHOTHERAPY OR COUNSELING. Many care partners can benefit from psychotherapy or counseling to address their mental health needs and learn strategies for managing stress, anxiety, and depression, but they may not know where to start. Providing a list of recommended therapists can relieve a substantial burden on care partners for finding care. Care partners can also be directed to state or provincial psychology licensing associations or psychologytoday.com (or psychologytoday.ca) to find support.

KEY POINTS

- Signs of dementia care partner burden include somatic symptoms, cognitive concerns, isolation, weight changes, feeling helpless or hopeless, feeling trapped, insomnia, and increased substance use.
- Self-care is an important component of caregiving but can be difficult to do, especially for female care partners, because of cultural, personal, and societal expectations about caring.
- Beneficial self-care activities foster social engagement, joy, a sense of achievement, creativity, maintaining self-identity outside of caring, sense of meaning or purpose, and relaxation.
- Providing a list of recommended therapists can relieve a substantial burden on dementia care partners for finding mental health care.
- Educational resources for dementia care partners are freely available on multiple government and nonprofit-supported websites.

Providers with doctorate degrees (eg, PhD, PsyD) in counseling or clinical psychology or licensed clinical social workers (LCSW) have appropriate training to provide services, and some therapists may specialize in issues related to aging and caring. Therapy can help normalize the often stressful experience of caregiving and provide reassurance that care partners are doing the best they can. Therapy offers a safe space to work through problems or difficult feelings and learn strategies for managing stress, depression, sleeping difficulties, and asking for help.

PROVIDE EDUCATION, INFORMATION, AND RESOURCES. Care partners often assume their roles without any knowledge or training about dementia or caring, and it can be difficult to know where to start finding resources. Education about the

CASE 12-1B

The patient in CASE 12-1A and her daughter returned to the clinic 6 months later. The patient was experiencing new-onset irritability and agitation, and her cognition had declined. Her daughter had been promoted, which required a switch from working from home to working in the office. This substantially reduced the flexibility and availability she had to provide care. She wondered whether her absence was the cause of the irritability and agitation. She felt like a “bad daughter” for “putting her career before her family.” She reported feeling overwhelmed and fatigued and was having more headaches and abdominal pain. The Zarit Burden Interview score suggested moderate burden. The neurologist reassured her that she was doing the best she could and that it was clear that she loved and cared about her mother. The neurologist provided resources for skills-based training in managing irritability, agitation, and other behavioral disturbances and recommended exploring day programs, cultural social groups, and faith community groups to keep the patient engaged and active. Given the abdominal pain and headaches, the neurologist reminded the daughter that it was important to take care of herself by taking caring breaks and visiting her doctor so that she could continue providing the best possible care for her mother. The neurologist also provided a list of therapists familiar with the challenges of caregiving.

COMMENT

Changing life circumstances outside of caregiving responsibilities can add additional stress and increase the risk of burden. Clashes between cultural values (eg, familismo [a Latin American value of family above self]) and personal values and goals (eg, career success) can cause further pressure and distress, especially for female carers. Recognizing the somatic symptoms of burden in combination with an increase in the Zarit Burden Interview score, the neurologist offered suggestions for therapy and again encouraged self-care. However, given the previous appointment, the neurologist understood that “giving permission” to engage in self-care would not be a helpful approach. Instead, the neurologist aligned with the care partner’s values and framed self-care as a way to optimize caring for her loved one.

illness that is causing the dementia, long-term trajectory and changing needs and abilities, warning signs that require immediate attention (eg, symptoms of urinary tract infections, which are common in dementia), and proper techniques for managing symptoms enhances care and increases care partner mastery, confidence, and satisfaction. Educational resources for care partners are freely available on multiple government and nonprofit-supported websites (eg, National Institute on Aging, Alzheimer's Association; see **Supplemental Digital Content Table 1**, links.lww.com/CONT/A413). These materials are available in electronic files or as printed materials and can be provided to care partners during clinical visits. These materials can help care partners prepare strategies in advance for dealing with challenges that might occur in the future. Preplanning reduces stress and increases confidence, stability, and a sense of control, helping care partners deal with situations that might otherwise seem unmanageable.¹⁰ Having conversations early on about long-term care preferences and advance directives allows patients living with dementia to have autonomy over these important choices and relieves stress associated with these decisions for the care partner. In the United States, these care coordination and

CASE 12-1C

At the next appointment 6 months later, the patient in **CASE 12-1B** continued to cognitively decline, but behavioral issues were better. The daughter reported feeling more confident and competent in managing the irritability, agitation, and new sleep disturbances with the skills she had learned. The daughter had also started seeing a therapist, who was helping her learn relaxation strategies and manage the complex feelings accompanying caregiving. The patient had started attending a church group for 2 hours/week so that she could socialize and the daughter could run errands. The daughter felt that the socialization was contributing to her mother's improved mood and she was considering part-time day programs but was worried about the cost. Compared with the last appointment, she felt that caregiving tasks had increased because of her mother's functional decline and resistance to bathing. Despite increasing functional impairment, she reported feeling less overwhelmed than previously and was not experiencing the same frequency of headaches. Her Zarit Burden Interview score was at the borderline of mild to moderate burden. The neurologist suggested some local and national agencies to help identify day programs and connected the daughter to a social worker to assist with seeking financial assistance.

COMMENT

Learning skills for managing behavioral disturbances increased the daughter's sense of caregiving mastery, which in turn helped reduce burden. With the perspective of "taking care of the self to take care of the patient," the daughter started informal respite care (ie, church group). Given the positive effects for her and her mother, she was considering more formal services (ie, a day program). Overall burden declined over the 6 months, suggesting the neurologist's interventions had improved the quality of life for both the patient and her daughter.

KEY POINTS

- Health care professionals and staff can obtain training in evidence-based dementia care partner interventions to offer to patients and their families in clinic.
- Care partners should be encouraged to ask for help or ask if another family member might be willing to help coordinate care.
- National organizations and local aging agencies are critical for helping dementia care partners and people living with dementia connect with appropriate resources and services.

planning conversations can be reimbursed under the Medicare “Cognitive Impairment Care Planning” Current Procedural Terminology billing codes: 99483 for cognitive assessment and planning or 99497 and 99498 for advance care planning.⁹³ Finally, offering a caregiving intervention at the clinic can provide an invaluable service to care partners. Health care professionals, staff, and students can receive training in structured, manualized, evidence-based protocols (eg, REACH-II, Savvy Caregiver) that relieve burden and improve quality of life. Clinical social workers may be particularly well suited for this role and could also be instrumental in connecting families with much-needed local resources.

HELP CARE PARTNERS ASK FOR HELP. Whether formal or informal, obtaining help with caring reduces burden and the negative health consequences associated with burden for many care partners. Encouraging care partners to ask for help can be the permission they need to do so. If care partners feel uncomfortable asking for help, there might be another individual in their social network who would be willing to take on the role of asking for and coordinating care. For example, an older female spousal care partner may not feel comfortable asking family for assistance, but her adult son may be willing to reach out on her behalf to coordinate help. Setting up a regular schedule of coordinated care activities prevents care partners from having to continuously ask for help. These activities can include respite care, transportation to medical appointments for the person living with dementia, and medication management. Lotsahelpinghands.com can be a useful website for this type of care coordination.

In addition to informal social support, formal services are also available and can provide substantial assistance and relief (**Supplemental Digital Content Table 1**, links.lww.com/CONT/A413). Providing information about national organizations, such as the Alzheimer’s Association, can connect the care partner to support groups, respite services, care navigators, and legal services. Many of these organizations have hotlines that people can call 24 hours a day, 7 days a week for assistance. Provincial, state, and county agencies on aging and disability are also typically helpful, especially for connecting people who have limited resources with services that they may not otherwise be able to afford. If available, social workers or care navigators can often be the most important connection for care partners. It can be invaluable to have a social worker or care navigator who provides individualized assistance with planning “next steps” and connecting with appropriate local services (**CASE 12-1C**).

CONCLUSION

Informal care partners are an integral part of caring for people with dementia. There can be many positive aspects of caregiving, including joy, gratitude, and a sense of meaning and purpose. But this role can also lead to significant mental, physical, social, and financial costs that often go under- or unrecognized, putting the health of the care partner and the person living with dementia in jeopardy. Health care providers are vital to preventing care partner burden and burnout by identifying early warning signs and providing appropriate intervention through resources, education, and information. Continued efforts in our health care systems are needed to ensure care partners are appropriately supported while they manage most of the complex care needs of a life-altering and ultimately terminal diagnosis in addition to other responsibilities and roles. Evidence-based

multicomponent interventions are a potential key opportunity for providing this support. These types of interventions may be particularly successful when they are grounded in inclusive theoretical frameworks, incorporate key sociocultural belief and value systems, and include the voices of stakeholders (eg, care partners, people living with dementia) in their development. Greater research focus is needed on translating and implementing these interventions in clinical practice where they can be used to improve the lives of care partners and people living with dementia.

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Implementing New Dementia Care Models in Practice

SELECTED TOPICS IN
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By Vijay K. Ramanan, MD, PhD

ABSTRACT

Care for patients with Alzheimer disease and related neurodegenerative causes of dementia is in the midst of a transformation. Recent advancements in diagnostics and therapeutics reflect a rapidly evolving knowledge base and represent positive steps for patients and clinicians facing these progressive diseases; however, the complexities of emerging biomarkers and treatment options present challenges that will require systematic adaptations to routine care to facilitate effective incorporation of these options. This article reviews ongoing updates in the assessment and management of neurodegenerative causes of dementia, focusing on practical models for innovation that practices and health care systems can use to implement these new tools. In particular, sustainable adaptation in the field will benefit from a comprehensive approach implemented at local levels, including (1) education of clinicians and communities to refine perceptions about dementia care, (2) multifaceted stakeholder engagement to optimize infrastructure and workflows to the new era, and (3) investments in personnel to address existing and exacerbated gaps.

INTRODUCTION

Neurodegenerative dementias are extremely common and a leading cause of death worldwide.¹ Although these disorders are far from solved mysteries, advancements in basic and translational science and clinical diagnostics and therapeutics provide reason for optimism about the future. Nevertheless, the pace and character of innovations in the field present a unique challenge for clinicians who must simultaneously navigate a rapidly evolving knowledge base alongside complex health care systems and regulatory structures that may not be set up for swift or transformative change. Developments with lecanemab and other anti-amyloid monoclonal antibody therapies for Alzheimer disease (AD) are some of the many anticipated reasons for the need to modify existing workflows and infrastructure to adapt to the new landscape.² This article discusses opportunities and potential approaches to modernize fundamental aspects of clinical care for patients with neurodegenerative dementias in the present while remaining nimble enough to evolve with future developments.

UPDATING PERCEPTIONS OF DEMENTIA CARE

The general public and even some clinicians are often confused about cognitive and behavioral neurology terminology such as *mild cognitive impairment* (MCI),

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which denotes objectively present cognitive impairment not affecting functioning in instrumental activities of daily living. *Dementia* implies cognitive impairment at a greater severity than seen in MCI and sufficient to impact functioning in instrumental activities of daily living. Specific neurodegenerative diseases such as AD can cause MCI or dementia in an individual.³ The spectrum of phenotypic presentations of AD and related disorders continues to widen, underscoring the observation that memory difficulties do not equal an AD diagnosis and vice versa.⁴ Imprecision with this terminology can have heightened clinical consequences in the era of disease-specific management options. For example, patients with subjective cognitive symptoms in the absence of objective cognitive impairment would not be appropriate candidates for anti-amyloid monoclonal antibody therapies⁵ at this time, with the caveat that the results of the AHEAD 3-45 Study (anticipated in 2027) could alter this framework for some amyloid-positive older adults.⁶ In addition, patients can have MCI or dementia due to a variety of conditions, many of which may be modifiable, reversible, or even preventable.⁷ This reality argues for broadening awareness about AD and non-AD disorders as causes for neurologic syndromes, improving recognition of existing avenues of accurate and timely diagnosis, and increasing comfort with pharmacologic and nonpharmacologic options for management.

Advances in biomarker testing offer another opportunity to educate on neurodegenerative dementias. Postmortem neuropathologic examination remains the gold standard for identifying characteristic brain tissue changes associated with AD and related disorders; however, the availability of high-quality imaging and fluid biomarkers (refer to the articles “Neuroimaging in Dementia” by Shannon L. Risacher, PhD,⁸ and “Fluid Biomarkers in Dementia Diagnosis” by Joseph F. Quinn, MD, FAAN, and Nora E. Gray, PhD,⁹ in this issue of *Continuum*) means that a confident etiologic diagnosis during life should be the desired goal for all patients with cognitive impairment. Nevertheless, biomarker evidence of pathology requires the appropriate clinical context to avoid misdiagnosis and inappropriate referrals. For example, the prevalence of amyloid positivity without cognitive impairment increases with aging to up to 40% by the ninth decade of life.¹⁰ This means that, depending on the specific setting, individuals with neurodegenerative pathology can have (1) a cognitive syndrome caused by that neurodegenerative disease, (2) a cognitive syndrome caused by an alternative etiology, or (3) normal neurologic functioning.

Refining these knowledge gaps among clinicians and the general public has implications for clinical care and professional well-being. Missed or delayed diagnosis of neurodegenerative dementia is more common in patients from Asian, Hispanic, and non-Hispanic Black populations,^{11,12} in those with low neighborhood socioeconomic status,¹³ and in those with atypical clinical syndromes (which are more frequent at younger ages).⁴ Fears and stigmas about dementia can also contribute to a pervasive sense of futility, centering on a “worst-case” or “end-stage” vision or expectation that nothing can be done. These perceptions contribute to delays in seeking help, barriers to the use of available treatment options, and avoidance of support structures.¹⁴ Expanding clinician and health system education, training, and access to diagnostic and therapeutic services for people with neurodegenerative dementias may positively influence disease progression, symptom management, care partner burdens, and

personal and public health expenditures. Improvements in these areas would also promote professional fulfillment and meaningful work for clinicians involved in dementia care, which are factors known to be strong drivers of career satisfaction in the field.¹⁵

INCORPORATING EMERGING TREATMENT OPTIONS

The recent availability of anti-amyloid monoclonal antibody therapies for early symptomatic AD warrants the adaptation of clinical structures to a new treatment environment. In cognitive and behavioral neurology, the use of infused medications that require scheduled safety monitoring represents a marked change from prior management options. Clinical trials, as well as the experiences and workflows from other neurologic subspecialties (eg, multiple sclerosis, neuro-oncology, neuromuscular neurology) with similarly structured treatment approaches can provide a framework for practices. Clinicians and practices should recognize that investment in change now will make future adjustments iterative (akin to incorporating ocrelizumab into a practice already using rituximab) rather than transformative. In addition, clinical care for patients with dementia occurs in a variety of settings, and it is unrealistic to expect that a single approach will be uniformly applicable. Nevertheless, neurologists and related clinicians must be aware of key considerations around emerging treatment options, including templates for addressing challenges that are raised by, but likely not unique to, anti-amyloid monoclonal antibody therapies (FIGURE 1).

Practice Models

Most existing dementia clinics are provider-centric, meaning that a patient sees a clinician who then coordinates evaluation and management. Emerging test and treatment options for dementia can fit within this framework, where the primary clinician establishes a diagnosis and treatment plan, prescribes appropriate therapies, and completes indicated follow-up. Advantages of this approach include its emphasis on clinician autonomy and retention of longer-term clinician-patient relationships. A limitation of this approach involves the potential for wide variation in practice (related to differential expertise, viewpoints amid a rapidly evolving knowledge base, or both) across clinicians, which can contribute to disparities in care. In addition, because amyloid-related imaging abnormalities (ARIA) and other side effects of new therapies are relatively common and may require brisk action, practices need to ensure robust cross-coverage when individual clinicians are attending to other duties or out of office.

Group practice models, where clinicians rotate in staffing a clinic (analogous to inpatient service structures), offer benefits and drawbacks. Developing research suggests that group practice models in medicine can improve patient access and satisfaction, clinic efficiency and resource use, and clinician job satisfaction and quality of life.^{16,17} In the new era of dementia care, the structure of a group practice can also systematize clinical decision making and counseling on treatment risks and benefits. Following the recent availability of anti-amyloid monoclonal antibody therapies in clinical practice, several centers assembled multidisciplinary committees to review cases for treatment candidacy modeled on the approach taken in other settings (eg, tumor boards, epilepsy surgery boards) where there are high stakes, high levels of complexity, and unknowns.¹⁸

KEY POINTS

- Alzheimer disease and related neurodegenerative disorders represent the most common causes of mild cognitive impairment and dementia syndromes in older adults.
- High-quality neuroimaging and fluid (cerebrospinal or blood-based) biomarkers are now widely available to assist in diagnosis and management of neurodegenerative dementias.
- Investing now in adaptations to implement emerging dementia therapies will position practices for resource-efficient iterative adjustments in the future.
- With new therapies for dementia, solitary practitioner models may enhance clinician autonomy and continuity of care, although absence coverage and practice variation across individuals could be limitations.
- In the right setting, group practice models for dementia clinics can offer some advantages in patient access and clinician work-life balance.

Therapy delivery

Patient selection

Clinical decision-making

Practice implications

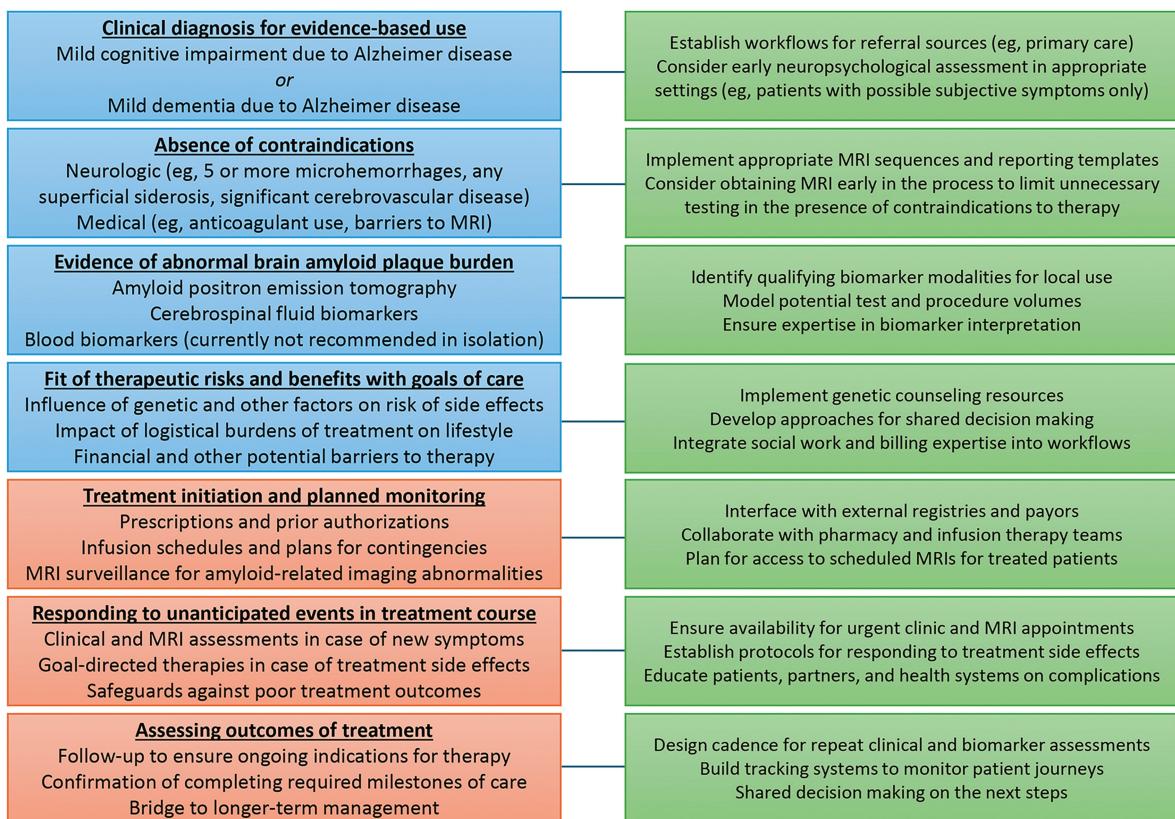


FIGURE 1

Considerations for implementation of anti-amyloid monoclonal therapy in practice. As practices evolve to implement new dementia care models, lessons can be drawn from the early experience with anti-amyloid monoclonal antibody therapies for the treatment of mild symptomatic Alzheimer disease. Clinicians should be aware of the knowledge base and multidisciplinary implications for each step along a patient's journey from initial evaluation through longer-term management.

A downside of the group practice approach for dementia care involves the up-front investment required to change existing clinic structures. In addition, cases in which colleagues disagree on next steps could be challenging to resolve without processes in place, strong interpersonal relationships, and shared objectives and values.

Stakeholder Engagement

Implementing new therapies for the treatment of dementia requires more than simply obtaining access to medications. Early and repeated engagement across health system stakeholders can differentiate practices aiming for optimal patient care and clinic efficiency and sustainability.

RADIOLOGY. Collaboration with radiologists will be integral for emerging dementia therapies. A common potential side effect of anti-amyloid monoclonal antibody therapies is ARIA, which can present with cerebral edema,

microhemorrhages, or superficial siderosis.¹⁹ Certain baseline MRI findings are associated with an increased risk of ARIA and may be contraindications to anti-amyloid monoclonal antibody therapy.²⁵ More broadly, because exclusionary MRI findings may be among the most common reasons for ineligibility for anti-amyloid monoclonal antibody therapies in the general population,²⁰ obtaining imaging early can help prioritize additional testing for patients most likely to be candidates for these treatments. Consensus recommendations exist regarding the MRI sequences and protocols necessary for adequate assessment of ARIA.²¹ In addition, as ARIA findings can be subtle (with implications for clinical decision making), growth of expertise and development of image analysis tools to assist in ARIA detection²² are anticipated to positively impact patient care. Practices planning to implement new therapies can optimize plans through a proactive partnership with radiology departments to ensure access, expertise, and bidirectional support.

The availability and usage of positron emission tomography (PET) imaging may also shift with additional treatment options. Brain fludeoxyglucose PET (FDG-PET) is used in many practices in diagnostic evaluations, owing to its efficacy in differentiating patterns of hypometabolism associated with distinct neurodegenerative diseases and their syndromes.²³ Additional research may guide the potential roles of FDG-PET to gauge response (related to neurodegeneration, synaptic dysfunction, and cognition) to therapies. Since lecanemab became clinically available, insurance coverage of amyloid PET for use in the diagnosis of symptomatic AD has continued to expand, and some insurers are covering serial amyloid PET for treatment monitoring with anti-amyloid monoclonal antibody therapies. At present, tau PET is mostly used in research studies at larger tertiary care centers, although updated guidelines for clinical amyloid and tau PET are in progress²⁴ and may continue to evolve based on early experience with additional anti-amyloid monoclonal antibody therapies²⁵ and results from tau-directed therapeutic trials.²⁶ PET tracers for non-AD neurodegenerative pathologies such as α -synuclein (associated with Lewy body disease)^{27,28} and 4-repeat tau (associated with frontotemporal degenerative disorders)²⁹ are also in development. Practices that use PET imaging modalities should liaise with their local radiology department to ensure rational, impactful, and sustainable use.

NEUROPSYCHOLOGY. In dementia evaluations, neuropsychological testing has historically been used to clarify the etiology of a cognitive syndrome based on the pattern of observed impairments.³⁰ Ongoing roles of neuropsychological testing are being refined with a growing understanding of the imperfect relationship between clinical syndrome and disease etiology, as well as improvements in imaging and fluid biomarkers with high specificity for degenerative etiologies. For example, with the emergence of anti-amyloid monoclonal antibody therapies, high-value indications for neuropsychological testing include differentiating subjective cognitive concerns from MCI and gauging the severity of impairment to discuss use or discontinuation of therapy. For most practices, obtaining standard neuropsychological testing on all patients as routine clinical care will not be practical. Development of abbreviated test batteries and innovative approaches such as self-administered digital assessments may facilitate more efficient paths for baseline evaluation and serial monitoring.³¹

KEY POINTS

- Neurology and radiology collaboration is important for optimizing the delivery of emerging dementia treatments given specific requirements for therapy initiation and safety monitoring.
- Refining indications and delivery methods for neuropsychological assessment will help maximize rational use amid complementary test modalities and new therapeutic options for dementia.

Sustainability of Orders and Scheduling

Emerging treatment options for neurodegenerative dementia are complex, so anticipatory modeling of patient volumes, testing needs, and treatment and complication rates can help practices safeguard against being overwhelmed and anticipate when additional resources may be necessary. New therapies and test modalities often increase demand for prior authorizations and appeals of coverage denials. Addressing these issues, particularly when occurring frequently, can occupy resources and contribute to burnout.³² Several approaches can help mitigate these challenges to best advocate for patients, including training administrative staff to handle prior authorizations and arrange peer-to-peer interactions, developing letter templates for appeals, and leveraging artificial intelligence to predict the likelihood of coverage approvals based on historical trends to set expectations and consider alternatives where needed.³³

For therapies with specific requirements for follow-up, having treatment-focused clinics or dedicated slots (with “turnback” policies to prioritize certain visit types while allowing other visit types to fill remaining openings after a certain time interval) for appointments and testing can ensure that important milestones are completed without monopolizing availability for patients with other conditions managed at that location. Where feasible, flexible clinic templates will also be advantageous. For example, a visit during which concerns of safety, supervision, and living environment are priorities of management may be more involved than an uncomplicated anti-amyloid monoclonal antibody treatment-monitoring visit, and a patient treated with an anti-amyloid monoclonal antibody with new symptoms concerning for ARIA will need an evaluation more urgently to prioritize next steps (eg, obtaining an MRI, pausing infusions) and limit further complications. These challenges provide opportunities for greater integration of advanced practice providers in dementia care through models that support team members practicing to the full extent of their training and abilities.³⁴

Care teams and health systems need to maintain awareness of future updates in the field. AD and related diseases are pathophysiologically complex, and, similar to models applied for other complex disorders (eg, human immunodeficiency virus [HIV], hypertension), neurodegenerative dementia may ultimately require individualized combination therapy approaches targeting multiple mechanisms (eg, amyloid, tau, α -synuclein, inflammation, synaptic dysfunction, or others), potentially administered in a variety of ways (eg, oral, IV, subcutaneous, intrathecal).³⁵ Clinical practices that are too rigid or built solely to support a single therapy modality will likely be at a disadvantage in incorporating new options for treatment.

Clinician Resources

As dementia care becomes more complex, strengthening hub-and-spoke connections between neurology and other relevant specialties will be necessary.³⁶ The number of people with cognitive impairment in the general population far outpaces the capacity for evaluation by dementia specialists alone.³⁷ This reality highlights the need for general neurologists, geriatric psychiatrists, internists, and other clinicians to have the training and tools to evaluate and manage common cognitive disorders and understand when to refer to subspecialist neurologists.³⁸ Particularly with the growing availability of blood-based biomarkers for neurodegenerative disease, education on appropriate use and

interpretation will be critical to limit unnecessary patient angst and therapeutic mistargeting.³⁹ Neurologists with this expertise have a valuable opportunity to shape and share practically focused domain knowledge with a wider audience.

Integration of outpatient practice with inpatient and ancillary teams will also be vital with the emergence of new therapies. Thrombolysis is currently considered to be contraindicated in the presence of anti-amyloid monoclonal antibody therapies because of an elevated risk of intracerebral hemorrhage, including the potential for fatality.^{2,40} This risk emphasizes the importance of awareness among neurology and emergency medicine clinicians who may evaluate patients with acute neurologic symptoms while they receive these therapies. Implementing alerts or best practice advisories in the electronic health record can provide additional safeguards to prompt further investigation. For example, an electronic flag could alert the provider when anticoagulation is being considered for a patient receiving an anti-amyloid monoclonal antibody who has been diagnosed with a new pulmonary embolism. In addition, with many hospitals at near capacity, the development of outpatient or abridged inpatient regimens for the management of ARIA with cerebral edema (eg, 3 days of IV methylprednisolone followed by a 1-month oral prednisone taper) can preserve resources for patients in greatest need of inpatient care. Predetermining protocols for rounding of weight-based drug doses and pretreatment or contingency treatments for infusion reactions can also positively impact patient care and comfort and minimize downstream messages and calls with pharmacies and infusion centers.

Patient Education

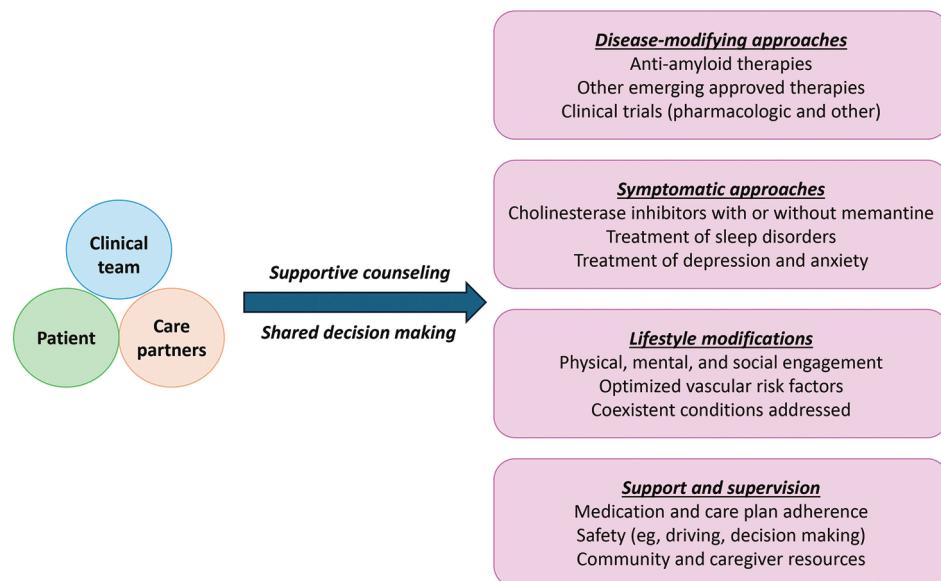
When aducanumab, lecanemab, and donanemab were first approved for potential clinical use, many practices were flooded with patient inquiries. Tempered responses can help to address influxes by empowering nursing and other clinical support staff to answer common patient questions. As research advancements continue and additional therapies are approved, creating frequently asked questions documents should further help clinics educate patients.

For patients being evaluated for anti-amyloid monoclonal antibody therapies, apolipoprotein E (*APOE*) genetic testing is recommended because of the relationship of various *APOE* allele profiles with differential risk of ARIA.^{2,5} Genetic counseling can review potential implications of testing for the patient, current family members, and future generations.⁴¹ Given the widespread shortage of genetic counselors, collaboration with domain experts can yield scalable patient-facing information and materials for pretest and posttest counseling.

With emerging anti-amyloid monoclonal antibody therapies, some practices have employed nurse education visits to review practical aspects of treatment, such as providing contact information for routine questions (whether nursing, administrative staff, or dedicated patient navigators) and assembling medication and testing orders for clinicians to sign. Medical alert cards are another precaution in case patients treated with anti-amyloid monoclonal antibodies are taken to emergency departments in other health systems that may be unaware of ongoing therapy and its implications. In addition, although new disease-modifying therapies for dementia will continue to proliferate, clinicians should reinforce that care of patients is not purely pharmacologic (FIGURE 2). Symptomatic medications, lifestyle modifications, supportive therapies (eg,

KEY POINTS

- With new test and treatment modalities for dementia, having sustainable processes to handle prior authorizations and coverage appeals can minimize burdens on clinicians and practices.
- Disease- or treatment-specific clinic slots, templates, and order sets can streamline patient journeys and balance access across a variety of conditions.
- Future treatment regimens for Alzheimer disease and related disorders are likely to involve combination therapy targeting multiple mechanisms on a personalized basis.
- Clinical practices that retain flexibility in design and operations will have advantages with integrating new dementia treatment options.
- Neurologists have an opportunity to develop and disseminate updates on diagnosis and management of dementia to help support clinicians along a hub-and-spoke model of dementia care.
- Nurse education visits and development of patient-facing brochures and media can help translate complex dementia management concepts for a wide audience to optimize outcomes.

**FIGURE 2**

Comprehensive care for patients with neurodegenerative dementia is ideally multipronged. Management options include both pharmacologic and nonpharmacologic therapies and approaches, considering the specific needs of the patient and care partners. Disease-modifying and symptomatic drug treatments may have roles in management depending on goals of care, coexistent health conditions, and risk-benefit assessments. Improving lifestyle habits, using supportive therapies (eg, speech therapy), and implementing structural or social modifications for safety and supervision provide additional benefits.

physical, occupational, and speech therapy), social work, and community-based resources that alleviate care partner burden will remain crucial in holistic treatment approaches.⁴²

ADDRESSING DISPARITIES IN DEMENTIA CARE

To promote health equity, emerging diagnostic and treatment options for neurodegenerative causes of dementia need to be broadly available and applicable across communities. Recruitment and retention of clinical personnel, improvements in clinical counseling, and promotion of an inclusive culture and robust healthcare structure will all play important roles in meeting this aspiration. In the United States, demographic representation in the neurology workforce is not reflective of the demographic distributions of race and ethnicity in the general population.⁴³ Similar to other common neurologic conditions such as stroke,⁴⁴ multifactorial issues contribute to disparities in care for AD and related causes of dementia.⁴⁵ These disparities are not solely limited to access to tests and drug therapies. For example, data from a nationally representative longitudinal survey-based study in the United States showed that Black and Hispanic older adults with dementia were less likely to have completed an advance care plan compared with non-Hispanic White counterparts.⁴⁶ With the complexities of emerging therapies, enhancements to care planning and other broader aspects of dementia care will be critical for optimizing safety and efficacy. Developments in blood-based biomarkers, which are widely anticipated to be more cost-effective, resource-efficient, and scalable in comparison to PET imaging or CSF analysis, are also part of a broader framework to expand access to

care. Initial research suggests that these biomarkers perform well in diverse populations,⁴⁷ but additional work is needed.

Access to and enrollment in treatment trials for neurodegenerative diseases need to broaden to ensure that findings apply to patients seen in real-world clinical neurology. Limited clinical trial inclusion of diverse populations across race, ethnicity, sex, gender, sexuality, neighborhood, and socioeconomic status is not unique to dementia; however, given that these and other factors are associated with disparities in dementia care,⁴⁸⁻⁵¹ there is an urgent need for interventions to promote positive change. Multipronged strategies will likely be needed, including innovations in trial design, sustained community engagement with identification of champions for long-term support, education around issues related to aging and cognitive decline, structural modifications to ameliorate financial and nonfinancial barriers to care, rebuilding of trust on a backdrop of inappropriate practices with marginalized populations, and engagement in efforts to diversify the workforce.^{52,53} Expertise and comfort with culturally sensitive shared decision making will also be necessary to match clinical steps to personal values, preferences, and goals of care.²

KEY POINTS

- Dementia care is best accomplished holistically, considering medication and nonmedication approaches in combination to address underlying disease, symptoms, and impacts on care partners.

- Disparities in dementia care are complex and motivate interventions to advance health equity throughout our communities.

- Complex new options for dementia diagnosis and management benefit from shared decision making to match the clinical plan values, preferences, and goals of care.

CONCLUSION

Treatment of neurodegenerative causes of dementia remains complex. Emerging diagnostics and therapeutics provide optimism about the future, alongside challenges for clinicians to incorporate new practices into their existing workflows. There will be no single “one size fits all” approach to best practices in this setting, and adaptation will be critical to ensure continued advancements for patients and the field. A systematic framework for approaching potential innovations will allow clinicians to operate with greater confidence in the new era.

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DEMENTIA

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Postreading Self-Assessment and CME Test

SELF-ASSESSMENT
AND CME

By Adam Kelly, MD, FAAN; D. Joanne Lynn, MD, FAAN

DEMENTIA

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ARTICLE 1: ALZHEIMER DISEASE

1 Which brain region is typically affected first by the accumulation of neurofibrillary tangles in Alzheimer disease?

- A amygdala
 - B anterior hippocampus
 - C cingulate gyrus
 - D temporal cortex
 - E transentorhinal cortices
-

2 Presentation with subjective memory concerns without demonstrable loss of function or decline in performance on cognitive tests describes what stage of Alzheimer disease?

- A final phase
 - B mild behavioral impairment
 - C preclinical
 - D symptomatic phase
 - E transitional
-

3 Trisomy 21 is associated with an extremely high risk of development of Alzheimer disease because of the triplication of which gene?

- A APOE
 - B APP
 - C NOTCH3
 - D PSEN1
 - E PSEN2
-

4 Fludeoxyglucose positron emission tomography (FDG-PET) showing hypometabolism in which of the following regions is suggestive of dementia with Lewy bodies?

- A bilateral temporal and parietal lobes
- B frontal and anterior temporal lobes
- C left anterior insula and frontal opercular region
- D occipital cortex with sparing of the posterior cingulate cortex
- E scattered focal cortical and subcortical areas

ARTICLE 2: ATYPICAL PRESENTATIONS OF ALZHEIMER DISEASE

- 5 A 54-year-old man is seen in clinic for evaluation of cognitive symptoms. His wife and other family members report that he has difficulty learning new tasks or following a series of directions. They give a specific example of him having trouble following directions to put together a new piece of furniture, which is an activity he would have done easily in the past. Driving and other tasks he has done on a longer-term basis are still done without difficulty. This pattern would be most consistent with which of the following subtypes of Alzheimer disease (AD)?**
- A AD associated with APP gene variation
B behavioral variant AD
C dysexecutive AD
D logopenic variant of primary progressive aphasia
E posterior cortical atrophy
- 6 The presence of which of the following features can help differentiate between behavioral variant Alzheimer disease and behavioral variant frontotemporal dementia?**
- A age of onset younger than 50 years
B clinical symptoms of impulsivity, inappropriateness, and apathy
C CSF biomarker data supporting Alzheimer disease pathology
D family history following an autosomal dominant inheritance pattern
E high responsiveness to acetylcholinesterase inhibitor therapy
- 7 Which of the following represents one of the early findings that can be used as a core cognitive feature in the diagnosis of posterior cortical atrophy?**
- A alexia
B anomia
C cortical blindness
D extinction to double tactile stimulation
E hemineglect

- 8** A 66-year-old woman is seen in clinic for progressive difficulties with language. Based on her history and examination, she has a decrease in language fluency notable for trouble retrieving words during conversation and on naming tasks, with relative preservation of comprehension and other tasks. Logopenic variant primary progressive aphasia is suspected. Peak atrophy on imaging studies in which of the following regions would support this diagnosis in this patient?
- A anterior temporal lobe
 - B inferior frontal gyrus
 - C parahippocampal gyrus
 - D posterior cingulate gyrus
 - E superior temporal gyrus

ARTICLE 3: FRONTOTEMPORAL DEMENTIA

- 9** Which of the following is a characteristic of nonfluent or agrammatic variant primary progressive aphasia?
- A impaired confrontation naming
 - B impaired single-word comprehension
 - C spared object knowledge
 - D spared repetition
 - E surface dyslexia
- 10** In patients with frontotemporal dementia, atrophy in which of these areas is associated with changes in eating behavior?
- A amygdala
 - B anterior cingulate cortex
 - C dorsolateral frontal cortex
 - D orbitofrontal cortex
 - E thalamus
- 11** Which of the following medications has been demonstrated to be useful in the management of behavioral symptoms associated with frontotemporal dementia?
- A donepezil
 - B galantamine
 - C memantine
 - D rivastigmine
 - E sertraline

ARTICLE 4: LEWY BODY DEMENTIA

12 A 74-year-old man is seen in clinic for evaluation of cognitive dysfunction. His family reports a several-year history of having difficulty carrying out the usual tasks he would perform at home, and he has stopped volunteering at his local community center because it has become too challenging. A neurodegenerative dementia syndrome is suspected. The presence of which of the following features would support a diagnosis of Lewy body dementia as opposed to Alzheimer disease in this patient's case?

- A decreased language fluency
 - B history of depression earlier in life
 - C marked memory dysfunction on neuropsychological evaluation
 - D poor clinical response to acetylcholinesterase inhibitor therapy
 - E presence of visual hallucinations
-

13 A 69-year-old woman with Parkinson disease (PD) is seen in clinic for follow-up. Her motor symptoms have been well controlled on her current dose of levodopa, although she does have considerable impairment of her gait. She does not have any cognitive symptoms at present, but her son has concerns about the future risk of dementia because his grandfather had PD and developed severe dementia approximately 10 years into the course of his disease. Which of the following is a potential risk factor for PD dementia in this case?

- A age older than 70 years
 - B female sex
 - C history of PD dementia
 - D presence of gait and postural instability
 - E use of levodopa as opposed to dopamine agonist therapy
-

14 Decreased metabolism on fludeoxyglucose positron emission tomography (FDG-PET) in the occipital lobes would be most supportive of which of the following diagnoses?

- A Alzheimer disease
- B dementia with Lewy bodies
- C logopenic primary progressive aphasia
- D progressive supranuclear palsy
- E vascular dementia

ARTICLE 5: VASCULAR COGNITIVE IMPAIRMENT

15 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) results from a variant of which gene?

- A COL4A1
- B KRIT1
- C NOTCH3
- D P2RY1
- E SCN1A

16 According to community autopsy studies, what is the most frequent pathologic disease finding related to dementia in older individuals?

- A Alzheimer disease
- B cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- C concurrent Alzheimer disease and vascular disease
- D concurrent vascular disease and traumatic brain injury
- E vascular disease

17 Which of the following was most recently added to the American Heart Association's recommendations of modifiable health behaviors and health factors to reduce the incidence of cognitive impairment?

- A 200 minutes of moderate-intensity activity per week
- B exposure to sunlight
- C ketogenic diet
- D normal liver transaminase levels
- E sleep health

18 Which cognitive domain has the greatest association with MRI white matter hyperintensities?

- A attention
- B executive function
- C language
- D memory
- E perceptual-motor control

ARTICLE 6: LATE, HIPPOCAMPAL SCLEROSIS, AND PRIMARY AGE-RELATED TAUOPATHY

19 Which of the following best describes the observed patterns of hippocampal sclerosis among older adults with cognitive dysfunction?

- A hippocampal sclerosis among older adults occurs only as a result of prior trauma
- B hippocampal sclerosis is always a pathologic finding when seen in older adults
- C hippocampal sclerosis is an uncommon finding, seen in less than 5% of patients aged 85 or older
- D the prevalence of hippocampal sclerosis increases after age 85
- E when hippocampal sclerosis is present in older adults, it is always with typical Alzheimer disease pathology

20 An 87-year-old woman is seen in clinic follow-up for her cognitive impairment. After a thorough evaluation for causes, including MRI that showed bilateral hippocampal atrophy out of proportion to her degree of cortical atrophy, a presumptive diagnosis of limbic-associated age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) with hippocampal sclerosis is made. Her son is a physician and is concerned about the association between hippocampal sclerosis and seizures and asks if the patient should be placed on an antiseizure medication. Which of the following is the best next step in management?

- A no additional seizure-directed management is needed
- B perform 24-hour EEG
- C perform serial EEGs to look for discharges
- D start lamotrigine
- E start levetiracetam

21 Which of the following best describes the observed clinical phenotype in instances in which patients have coexistent pathologies of Alzheimer disease (AD) and limbic-associated age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE)?

- A clinical phenotype resembling behavioral variant frontotemporal dementia is most commonly seen
- B coexistent AD and LATE pathologies have not been observed
- C compared with patients with isolated LATE, more global cognitive impairment with more rapid decline is expected
- D most patients will have clinical features of logopenic primary progressive aphasia
- E paradoxically mild phenotype is most commonly seen

22 A 97-year-old man is seen in neurology clinic for evaluation of memory dysfunction. He has had a very slow decline in his memory over the past 5 years, with only minimal involvement of other cognitive domains. He has no motor dysfunction and no neuropsychiatric features in his examination, although his memory dysfunction is notable enough to affect his usual activities. MRI has revealed mild atrophy of the cortex and hippocampus bilaterally. Which of the following is the most likely diagnosis in this case?

- A Alzheimer disease
- B dementia with Lewy bodies
- C frontotemporal dementia
- D limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE)
- E primary age-related tauopathy

ARTICLE 7: NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA

23 Which of the following types of dementia is most likely to present with early neuropsychiatric symptoms of well-formed and colorful visual hallucinations?

- A Alzheimer disease
- B behavioral variant frontotemporal dementia
- C Lewy body disease
- D primary progressive aphasia
- E vascular dementia

24 Across multiple types of dementia, the neuropsychiatric symptom of apathy has been most strongly associated with atrophy in which of the following areas?

- A anterior cingulate
- B dorsolateral prefrontal area
- C hippocampus
- D insula
- E parietal region

25 Which of the following should be the first-line pharmacologic treatment for neuropsychiatric symptoms in Alzheimer disease dementia if nonpharmacologic or behavioral modification approaches are unsuccessful?

- A antidepressants
- B antipsychotics
- C benzodiazepines
- D cholinesterase inhibitors
- E stimulants

ARTICLE 8: NEUROIMAGING IN DEMENTIA

26 Studies of patients in the preclinical stages of Alzheimer disease indicate which of the following is the earliest manifestation?

- A abnormal brain atrophy
- B abnormal measures of tau in CSF
- C bilateral parietal hypometabolism by fludeoxyglucose positron emission tomography (FDG-PET)
- D cognitive impairment
- E deposition of amyloid detected by brain PET

27 Positron emission tomography (PET) studies of patients with early Alzheimer disease typically demonstrate hypometabolism of glucose in which of the following areas?

- A anterior cingulate
- B cerebellum
- C lateral parietal
- D occipital
- E orbital frontal

28 Which of the following neuroimaging techniques is best for assessment of the presence and severity of cerebral microbleeds?

- A diffusion-weighted imaging (DWI)
- B single-photon emission CT (SPECT)
- C susceptibility-weighted imaging (SWI)
- D T1-weighted MRI
- E T2-weighted/fluid-attenuated inverted recovery (FLAIR) MRI

ARTICLE 9: FLUID BIOMARKERS IN DEMENTIA DIAGNOSIS

29 A 68-year-old man with concerns about memory dysfunction purchases a direct-to-consumer product to assess his risk of dementia. His results include an elevated level of plasma phosphorylated tau 217 (pTau₂₁₇). Which of the following factors may result in a falsely elevated pTau₂₁₇ result in this patient?

- A age older than 65
- B chronic kidney disease
- C diabetes
- D family history of Alzheimer disease
- E history of concussions as a teenager

30 A 76-year-old woman is undergoing evaluation for presumed Alzheimer disease (AD) based on a 2-year history of slowly worsening memory and cognitive function. She undergoes CSF analysis, including measurement of amyloid-tau index (ATI) and phosphorylated tau 181 (pTau181) level. Which of the following profiles would be most supportive of a diagnosis of AD in this patient?

- A high ATI, high pTau181
- B high ATI, low pTau181
- C high pTau181, regardless of ATI
- D low ATI, high pTau181
- E low ATI, low pTau181

31 Which of the following best describes the performance of plasma-based amyloid- β 42 (A β 42)/A β 40 testing in the diagnosis of patients with suspected dementia?

- A A β 42/A β 40 can effectively identify asymptomatic patients at risk for Alzheimer disease (AD)
- B increased A β 42/A β 40 ratio is highly predictive of AD
- C low A β 42/A β 40 is most predictive of vascular causes of cognitive dysfunction
- D plasma A β 42/A β 40 ratio is more predictive than CSF A β 42/A β 40
- E predictive ability of plasma A β 42/A β 40 is limited by a low precision of testing

ARTICLE 10: GENETICS AND NEUROPATHOLOGY OF NEURODEGENERATIVE DEMENTIAS

32 Mutation in which of the following genes is the strongest and most common high-risk gene for Alzheimer disease?

- A apolipoprotein E
- B complement receptor 1
- C contactin-associated protein 1
- D double C2 domain α
- E NOTCH3

33 What is thought to be the initiating pathologic process of Alzheimer disease?

- A arteriolosclerosis
- B deposition of extracellular amyloid- β (A β) peptide
- C development of dystrophic neurites
- D neurofibrillary tangle formation
- E neuropil thread accumulation

34 Which of the following is the strongest biological risk factor for Alzheimer disease after aging?

- A alcohol use disorder
 - B atherosclerosis
 - C head trauma
 - D heavy smoking history
 - E positive family history
-

ARTICLE 11: TREATMENT OF ALZHEIMER DISEASE

35 An 81-year-old woman is seen in clinic for follow-up of her dementia. Her Montreal Cognitive Assessment (MoCA) score is 23/30, down from 25/30 when checked 1 year ago, and her family reports some greater impairment in her usual activities. Treatment with donepezil is considered. Which of the following best summarizes the potential benefit of donepezil in this case?

- A delayed decline in global functional ratings
 - B improved gait speed, as measured by Timed Up and Go test
 - C improved responsiveness to antipsychotic treatment
 - D improvement in MoCA score by an average of 3 points
 - E stable cognitive performance for the next 3 to 5 years
-

36 A 74-year-old man is seen in clinic for ongoing management of his dementia. Based on some newly recognized functional limitations compared with his last visit, such as difficulty making his bill payments on time, treatment with donepezil is considered. The patient and his family should be counseled on which of the following adverse effects of treatment that is most commonly observed in this setting?

- A behavioral disturbances
 - B brain hemorrhage
 - C nausea and vomiting
 - D seizure
 - E supraventricular tachycardia
-

37 Which of the following best describes the observed frequency of amyloid-related imaging abnormalities (ARIA) related to lecanemab treatment in patients with mild cognitive impairment and mild Alzheimer disease?

- A <5%
- B 8% to 11%
- C 12% to 17%
- D 20% to 24%
- E 25% to 29%

ARTICLE 12: CARE PARTNER BURDEN AND SUPPORT SERVICES IN DEMENTIA

38 Which of the following psychotherapeutic approaches helps care partners face the challenges of giving care to a person with dementia?

- A acceptance and commitment therapy
 - B biodynamic psychotherapy
 - C dialectical behavioral therapy
 - D exposure therapy
 - E psychoanalysis
-

39 Care partner burden is primarily determined by which of the following?

- A amount of family support
 - B care partner's appraisal of the situation
 - C family financial stressors
 - D patient's behavioral symptoms
 - E time requirement for caregiving
-

40 Which of the following is associated with increased care partner burden?

- A culturally informed care
- B dementia education
- C neuropsychiatric symptoms
- D respite care
- E skills-based training in behavioral management

Postreading Self-Assessment and CME Test—Preferred Responses

SELF-ASSESSMENT
AND CME

By Adam Kelly, MD, FAAN; D. Joanne Lynn, MD, FAAN

DEMENTIA

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at continpub.com/CME, participants may earn up to 20 AMA PRA Category 1 Credits™ toward SA-CME. US participants have up to 3 years from the date of publication online to earn SA-CME credits.

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ARTICLE 1: ALZHEIMER DISEASE

- 1** The preferred response is **E (transentorhinal cortices)**. In the earliest stages of Alzheimer disease, tau undergoes hyperphosphorylation and abnormal aggregation in the presence of accumulating amyloid- β (A β) with resultant neurofibrillary tangle formation. This starts in the transentorhinal cortices in the medial temporal lobe and then spreads in a predictable pattern to the anterior hippocampus and limbic and temporal cortices, followed by association cortices and then unimodal cortices. For more information, refer to **page 1588** of the *Continuum* article “Alzheimer Disease.”

- 2** The preferred response is **E (transitional)**. New cognitive symptoms in individuals 50 years of age or older such as subjective memory concerns without a demonstrable decline in performance on objective tests are recognized as potential early manifestations of Alzheimer disease, as are some new neuropsychiatric symptoms. The emergence of behavioral and cognitive symptoms not sufficient to cause significant impairment is considered to constitute the transitional period of Alzheimer disease. For more information, refer to **pages 1588 to 1589** of the *Continuum* article “Alzheimer Disease.”

- 3** The preferred response is **B (APP)**. People with trisomy 21 have three copies of chromosome 21, the chromosome that carries the amyloid precursor protein gene. Excessive production of APP leads to an accumulation of amyloid- β (A β) and triggers the amyloid cascade. For more information, refer to **page 1589** of the *Continuum* article “Alzheimer Disease.”

- 4** The preferred response is **D (occipital cortex with sparing of the posterior cingulate cortex)**. Fludeoxyglucose positron emission tomography (FDG-PET) typically shows bitemporal and biparietal hypometabolism. FDG-PET findings in dementia with Lewy bodies may be distinguished from Alzheimer disease by involvement of the occipital region sometimes with relative sparing of the posterior cingulate cortex. Frontotemporal dementia is characterized by hypometabolism of the frontal and anterior temporal lobes. Progressive nonfluent aphasia may be associated with left anterior insular and frontal opercular region hypometabolism. Scattered focal cortical and subcortical areas of hypometabolism may be seen in vascular dementia. For more information, refer to **page 1604** of the *Continuum* article “Alzheimer Disease.”

ARTICLE 2: ATYPICAL PRESENTATIONS OF ALZHEIMER DISEASE

- 5 The preferred response is **C (dysexecutive Alzheimer disease [AD]).** Several less common presentations of AD do not involve the usual memory symptoms seen with typical AD. Of these, dysexecutive AD would be most likely to cause trouble with multitasking or learning new tasks, with relative preservation of well-engrained tasks that have been done on a longer-term basis. For more information, refer to **pages 1616 to 1617** of the *Continuum* article "Atypical Presentations of Alzheimer Disease."
- 6 The preferred response is **C (CSF biomarker data supporting Alzheimer disease pathology).** There is significant overlap in the clinical phenotypes of behavioral variant Alzheimer disease (AD) and behavioral variant frontotemporal dementia, including common symptoms such as impulsivity and social inappropriateness. Both may also include imaging studies showing atrophy or dysfunction of the frontal and temporal regions. A key part of the diagnostic process is obtaining biomarkers that are consistent with AD pathology, such as CSF studies or amyloid positron emission tomography (PET). For more information, refer to **pages 1620 to 1621** of the *Continuum* article "Atypical Presentations of Alzheimer Disease."
- 7 The preferred response is **A (alexia).** Several visual, visuospatial, and related clinical features can be used in the diagnostic process for posterior cortical atrophy, with the specific criterion that three different features must be present in the early or presenting stage of the disorder. Of the options listed, alexia would qualify as a core cognitive feature. Cortical blindness can be seen as a late manifestation of posterior cortical atrophy but would not be expected in the early stages. For more information, refer to **page 1623** of the *Continuum* article "Atypical Presentations of Alzheimer Disease."
- 8 The preferred response is **E (superior temporal gyrus).** Logopenic variant primary progressive aphasia can be seen with the clinical findings described here, namely decreased language fluency from word-retrieval dysfunction. It is most closely associated with Alzheimer disease neuropathologic changes, with predominant involvement in the dominant superior temporal gyrus and temporoparietal junction. For more information, refer to **page 1635** of the *Continuum* article "Atypical Presentations of Alzheimer Disease."

ARTICLE 3: FRONTOTEMPORAL DEMENTIA

- 9** The preferred response is **C (spared object knowledge)**. In addition to core features of agrammatism and effortful, halting speech, spared object knowledge is a feature of nonfluent or agrammatic variant primary progressive aphasia. Other potential features include impaired comprehension of complex syntactically complex sentences and spared single-word comprehension. The incorrect distractors are features of semantic variant primary progressive aphasia. For more information, refer to **pages 1646 to 1647** of the *Continuum* article "Frontotemporal Dementia."
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- 10** The preferred response is **D (orbitofrontal cortex)**. Atrophy of the frontal or temporal lobes may occur early in the disease course of frontotemporal dementia. Locations of atrophy correspond to some clinical syndromes. Changes in eating behavior are associated with atrophy of the right insula and orbitofrontal cortex. For more information, refer to **page 1652** of the *Continuum* article "Frontotemporal Dementia."
-
- 11** The preferred response is **E (sertraline)**. Serotonergic medications such as the selective serotonin reuptake inhibitors (SSRIs) sertraline, paroxetine, citalopram, and fluoxetine have beneficial effects on behavioral symptoms. One trial found a beneficial effect of olanzapine for psychosis, anxiety, and agitation in frontotemporal dementia. Cholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia because they may cause cognitive and behavioral worsening. Memantine has not been found to be beneficial. For more information, refer to **pages 1666 to 1667** of the *Continuum* article "Frontotemporal Dementia."

ARTICLE 4: LEWY BODY DEMENTIA

- 12** The preferred is **E (presence of visual hallucinations)**. There can be a fair amount of overlap between the clinical phenotype of Lewy body dementia and Alzheimer disease, although some important aspects of the history and examination can help distinguish these possibilities. Among the options listed here, a history of hallucinations, particularly visual but also in other sensory modalities, would be more suggestive of Lewy body dementia as opposed to Alzheimer disease. For more information, refer to **page 1674** of the *Continuum* article "Lewy Body Dementia."

- 13** The preferred response is **D (presence of gait and postural instability)**. Dementia is a fairly common manifestation of Parkinson disease (PD), especially late in the course of the disease, with an estimated 75% of patients with PD for more than 10 years showing cognitive symptoms in some form. Other risk factors for PD dementia include advanced age, cognitive symptoms at the time of PD diagnosis, and more severe motor dysfunction including gait and postural instability. For more information, refer to **page 1674** of the *Continuum* article "Lewy Body Dementia."

- 14** The preferred response is **B (dementia with Lewy bodies)**. Brain imaging, including fludeoxyglucose positron emission tomography (FDG-PET) to evaluate for changes in regional brain metabolism, can be useful in helping differentiate neurodegenerative conditions with significant clinical overlap. In particular, when trying to differentiate Alzheimer disease from dementia with Lewy bodies, atrophy of the hippocampus and medial temporal lobe would be more suggestive of Alzheimer disease, whereas occipital hypometabolism would be more suggestive of dementia with Lewy bodies. For more information, refer to **page 1679** of the *Continuum* article "Lewy Body Dementia."

ARTICLE 5: VASCULAR COGNITIVE IMPAIRMENT

- 15** The preferred response is **C (NOTCH3)**. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) results from variations of the epidermal growth factor-like repeat domain of the *NOTCH3* gene. These variations affect the endothelial smooth muscle cells and cause them to degenerate with resultant vessel injury and stenosis. For more information, refer to **page 1708** of the *Continuum* article "Vascular Cognitive Impairment."
- 16** The preferred response is **C (concurrent Alzheimer disease and vascular disease)**. Community-based autopsy studies have shown that mixed pathologies related to dementia are more common than any single pathology alone. The combination of Alzheimer disease and vascular disease is the most common pathologic finding. For more information, refer to **page 1700** of the *Continuum* article "Vascular Cognitive Impairment."

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- 17** The preferred response is **E (sleep health)**. The American Heart Association updated its recommendations for cardiovascular health in 2022 by adding sleep health to previous guidance, which included recommendations for diet, physical activity, body mass index, abstinence from nicotine, and maintenance of healthy blood pressure, blood glucose, and lipid levels. These make up the “Life’s Essential 8” for the prevention of vascular cognitive impairment. For more information, refer to **page 1718** of the *Continuum* article “Vascular Cognitive Impairment.”
-
- 18** The preferred response is **B (executive function)**. In small vessel ischemic brain disease, executive function is the cognitive domain most impacted by MR-visible white matter hyperintensities. Memory and global cognition measures may also be affected. For more information, refer to **page 1703** of the *Continuum* article “Vascular Cognitive Impairment.”

ARTICLE 6: LATE, HIPPOCAMPAL SCLEROSIS, AND PRIMARY AGE-RELATED TAUOPATHY

- 19** The preferred response is **D (the prevalence of hippocampal sclerosis increases after age 85)**. Hippocampal sclerosis is a relatively common finding in older adults, with an estimated prevalence of 10% to 20% in adults older than 85. This prevalence is also thought to increase over time, whereas the prevalence of severe Alzheimer disease pathology tends to level off in this age group. This is part of the justification for a diagnosis of limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) with or without hippocampal sclerosis as a distinct clinical entity resulting in cognitive impairment in older adults. For more information, refer to **page 1728** of the *Continuum* article “LATE, Hippocampal Sclerosis, and Primary Age-related Tauopathy.”
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- 20** The preferred response is **A (no additional seizure-directed management is needed)**. Although hippocampal sclerosis can be seen in conjunction with temporal lobe epilepsy, the finding of hippocampal sclerosis during the diagnostic work-up for cognitive dysfunction in an older adult is related to an independent clinical-pathologic phenotype. Specifically, the finding of hippocampal sclerosis in this context does not seem to confer a risk for seizures, and unless there are clinical reasons to proceed with EEG testing and empiric antiseizure medication, these can be deferred. For more information, refer to **page 1732** of the *Continuum* article “LATE, Hippocampal Sclerosis, and Primary Age-related Tauopathy.”

- 21** The preferred response is **C (compared with patients with isolated limbic-associated age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy [LATE], more global cognitive impairment with more rapid decline is expected).** A more severe phenotype manifesting as global cognitive dysfunction and more rapid clinical decline is observed in patients who are found to have pathologic changes consistent with both Alzheimer disease and LATE than in patients with LATE in the absence of AD. This observed pattern may have important implications for the diagnostic and treatment approach in these patients. For more information, refer to **page 1733** of the *Continuum* article "LATE, Hippocampal Sclerosis, and Primary Age-related Tauopathy."
- 22** The preferred response is **E (primary age-related tauopathy).** This clinical presentation of a patient older than 90 years developing a very slowly progressive, memory-predominant cognitive disorder would be most consistent with primary age-related tauopathy. The late age at onset, the slow progression, and the lack of significant involvement of other cognitive domains or neuropsychiatric features would be more common with primary age-related tauopathy than with Alzheimer disease. The lack of significant hippocampal changes argues against limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), although this would also be a consideration. For more information, refer to **page 1739** of the *Continuum* article "LATE, Hippocampal Sclerosis, and Primary Age-related Tauopathy."

ARTICLE 7: NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA

- 23** The preferred response is **C (Lewy body disease).** Each type of dementia is associated with different neuropsychiatric symptom presentations. In Lewy body disease, patients often present early on with well-formed and colorful visual hallucinations as well as apathy, depression, anxiety, and various sleep disturbances. For more information, refer to **page 1746** of the *Continuum* article "Neuropsychiatric Symptoms in Dementia."
- 24** The preferred response is **A (anterior cingulate).** Apathy has been associated with anterior cingulate atrophy across multiple types of dementia, including Alzheimer disease, frontotemporal dementia, and vascular dementia. For more information, refer to **page 1749** of the *Continuum* article "Neuropsychiatric Symptoms in Dementia."

- 25** The preferred response is **D (cholinesterase inhibitors)**. It is recommended to first give a trial of cholinesterase inhibitors, memantine, or a combination of both for the treatment of neuropsychiatric symptoms in Alzheimer disease dementia before using psychotropic medications. For more information, refer to **page 1752** of the *Continuum* article “Neuropsychiatric Symptoms in Dementia.”

ARTICLE 8: NEUROIMAGING IN DEMENTIA

- 26** The preferred response is **E (deposition of amyloid detected by brain positron emission tomography [PET])**. Studies of patients in the preclinical stages of Alzheimer disease indicate that the earliest abnormality is abnormal deposition of amyloid in the brain as detected by CSF studies or PET, followed by tau accumulation, parietal hypometabolism, brain atrophy, and cognitive impairment. For more information, refer to **page 1763** of the *Continuum* article “Neuroimaging in Dementia.”
- 27** The preferred response is **C (lateral parietal)**. Positron emission tomography (PET) studies of patients with early Alzheimer disease first show hypometabolism in primarily the lateral parietal and temporal cortices. Later in the disease, hypometabolism takes on a more global distribution. For more information, refer to **page 1764** of the *Continuum* article “Neuroimaging in Dementia.”
- 28** The preferred response is **C (susceptibility-weighted imaging [SWI])**. SWI is an MRI technique that sensitively detects compounds that distort the magnetic field, including paramagnetic compounds such as breakdown products of hemoglobin in cerebral microbleeds. For more information, refer to **page 1762** of the *Continuum* article “Neuroimaging in Dementia.”

ARTICLE 9: FLUID BIOMARKERS IN DEMENTIA DIAGNOSIS

- 29** The preferred response is **B (chronic kidney disease)**. Blood-based biomarkers that are sold directly to patients, as opposed to being ordered through a medical professional office, are commercially available, and providers should expect patients to bring these results for interpretation. Although phosphorylated tau (pTau) levels in serum are good predictors of which patients will have positive amyloid positron emission tomography (PET) scans, they can be falsely elevated in certain circumstances, such as kidney insufficiency. Head trauma can also be associated with elevated pTau levels, although this would be seen with acute head injury, not a remote history. For more information, refer to **page 1795** of the *Continuum* article “Fluid Biomarkers in Dementia Diagnosis.”

- 30** The preferred response is **D (low amyloid-tau index [ATI], high phosphorylated tau 181 [pTau181])**. This patient is presenting with a clinical scenario that would be suggestive of an Alzheimer disease (AD) diagnosis, although in some cases, proceeding with CSF analysis or other testing can help further support a diagnosis. Of the options listed, a low ATI and high pTau181 level would provide the strongest evidence of AD because amyloid would remain somewhat sequestered within plaques but tau would continue to spill into CSF due to ongoing cellular injury. For more information, refer to **page 1791** of the *Continuum* article "Fluid Biomarkers in Dementia Diagnosis."

- 31** The preferred response is **E (predictive ability of plasma amyloid- β 42 [A β 42]/A β 40 is limited by a low precision of testing)**. Levels of different forms of amyloid, including A β 42 and A β 40, can be measured in plasma, and evidence has shown that the ratio between these two levels (A β 42/A β 40) as opposed to their absolute measurements can be predictive of Alzheimer disease (AD). However, differences in the levels of A β 42 and A β 40 are less in plasma than in CSF, and as a result, even small amounts of imprecision in measurements can significantly affect whether a patient's results are considered normal or abnormal. This has limited the more widespread use of plasma A β 42/A β 40 in evaluating patients with possible AD. For more information, refer to **pages 1794 to 1795** of the *Continuum* article "Fluid Biomarkers in Dementia Diagnosis."

ARTICLE 10: GENETICS AND NEUROPATHOLOGY OF NEURODEGENERATIVE DEMENTIAS

- 32** The preferred response is **A (apolipoprotein E)**. The apolipoprotein E $\epsilon 4$ (*APOE* $^{\star}\epsilon 4$) allele is the strongest and most common high-risk gene for Alzheimer disease. Individuals who are heterozygous for the *APOE* $^{\star}\epsilon 4$ allele have a threefold risk of developing Alzheimer disease, and those who carry two *APOE* $^{\star}\epsilon 4$ alleles have a nearly 15-fold risk. For more information, refer to **page 1808** of the *Continuum* article "Genetics and Neuropathology of Neurodegenerative Dementias."

- 33** The preferred response is **B (deposition of extracellular amyloid- β [A β] peptide)**. The "amyloid cascade" hypothesis posits that the initiating cause of Alzheimer disease is the abnormal deposition of extracellular A β peptide. Subsequent steps in the cascade include synaptic loss, plaque and neurofibrillary tangle formation, and neuronal death. For more information, refer to **page 1808** of the *Continuum* article "Genetics and Neuropathology of Neurodegenerative Dementias."

- 34** The preferred response is **E (positive family history)**. The strongest biological risk factor for Alzheimer disease is aging, followed by a positive family history. For more information, refer to **pages 1805 and 1808** of the *Continuum* article “Genetics and Neuropathology of Neurodegenerative Dementias.”

ARTICLE 11: TREATMENT OF ALZHEIMER DISEASE

- 35** The preferred response is **A (delayed decline in global functional ratings)**. Donepezil and other acetylcholinesterase inhibitors are treatment options for patients with mild to moderate Alzheimer disease. Patients and families should be counseled that these agents may delay cognitive and global functional decline but would not be anticipated to help recover any memory or other cognitive dysfunction that has already been lost. For more information, refer to **pages 1826 to 1827** of the *Continuum* article “Treatment of Alzheimer Disease.”
- 36** The preferred response is **C (nausea and vomiting)**. Donepezil and other acetylcholinesterase inhibitors can be associated with several adverse effects, although gastrointestinal symptoms such as nausea, vomiting, and diarrhea are most commonly seen. This is usually dose dependent and associated with oral approaches, so these symptoms may be mitigated by the use of transdermal preparations. For more information, refer to **pages 1828 to 1829** of the *Continuum* article “Treatment of Alzheimer Disease.”
- 37** The preferred response is **C (12% to 17%)**. Amyloid-related imaging abnormalities (ARIA) are a major concern as an adverse reaction to anti-amyloid treatments in patients with mild cognitive impairment and mild Alzheimer disease. In Phase 2 and Phase 3 trials of lecanemab, ARIA due to edema (ARIA-E) were seen in 12.6% of patients and ARIA due to hemorrhage (ARIA-H) were seen in 17.3% of patients, with higher rates observed in patients with APOE^{*ε4} alleles. For more information, refer to **page 1834** of the *Continuum* article “Treatment of Alzheimer Disease.”

ARTICLE 12: CARE PARTNER BURDEN AND SUPPORT SERVICES IN DEMENTIA

- 38** The preferred response is **A (acceptance and commitment therapy)**. Acceptance and commitment therapy is one form of psychotherapy that has been shown to help care partners face the challenges of giving care to a person with dementia. This intervention promotes acceptance of thoughts and feelings that arise during caregiving and the alignment of actions with personal values and goals with the development of psychological flexibility. For more information, refer to **pages 1853 to 1854** of the *Continuum* article "Care Partner Burden and Support Services in Dementia."
- 39** The preferred response is **B (care partner's appraisal of the situation)**. The experience of care partner burden is determined by the care partner's personal appraisal of the situation. Various physical, psychological, emotional, social, and financial stressors related to caregiving may serve as potential sources of burden, but it is the care partner's response to these stressors that determines the degree of burden. For more information, refer to **page 1846** of the *Continuum* article "Care Partner Burden and Support Services in Dementia."
- 40** The preferred response is **C (neuropsychiatric symptoms)**. The presence of neuropsychiatric symptoms in dementia is associated with a higher degree of care partner burden. The most difficult symptoms include irritability, agitation, sleep disturbances, anxiety, apathy, and delusions. For more information, refer to **page 1848** of the *Continuum* article "Care Partner Burden and Support Services in Dementia."

ERRATUM

In the October 2024 issue of *Continuum* (Pain Management in Neurology, Vol. 30, No. 5), the following error occurred:

In question 7 of “Postreading Self-Assessment and CME Test–Preferred Responses” by Nuri Jacoby, MD, FAAN, and James W. M. Owens Jr, MD, PhD (*Continuum: Lifelong Learning in Neurology* 2024;30: 1560), the preferred response was incorrectly identified as “B (low back pain with radiation into the buttock)” when it should have been “C (lower lumbar and gluteal pain).”

See the corrected preferred response below.

Jacoby N, Owens Jr JWM. Postreading self-assessment and CME test–preferred responses. *Continuum (Minneapolis Minn)* 2024;30(5, Pain Management in Neurology):1558-1566.

7 The preferred response is **C (lower lumbar and gluteal pain)**. Lower lumbar and gluteal pain would suggest cluneal nerve targets for injection. For more information, refer to **page 1355** of the *Continuum* article “Spine Pain.”

LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Dementia issue, participants will be able to:

- ◆ Apply a practical approach to recognize and stage patients with cognitive impairment due to Alzheimer disease
- ◆ Identify the distinguishing features of atypical Alzheimer disease variants, recognize their unique pathophysiologic pathways and diagnostic indicators, and implement tailored management strategies for each variant
- ◆ Describe the major clinical syndromes, neuropathology, and genetic variations associated with frontotemporal lobar degeneration
- ◆ Recognize the clinical syndrome of Lewy body dementia and discuss the current state of biomarkers, treatments, and emerging controversies
- ◆ Discuss how dysfunction of the vasculature contributes to cognitive impairment and dementia risk in older individuals, updated diagnostic criteria, and treatment recommendations
- ◆ Describe the pathologic and clinical characteristics linked to limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy (LATE), hippocampal sclerosis, and primary age-related tauopathy
- ◆ Discuss the prevalence, pathophysiology, assessment, and management of neuropsychiatric symptoms in patients with dementia
- ◆ Identify and describe neuroimaging findings in the most common age-related dementias
- ◆ Discuss currently available CSF and plasma biomarkers for the diagnosis of dementia and diagnosis-dependent treatment decisions
- ◆ Describe the pertinent genetic and pathologic features of Alzheimer disease and related dementias
- ◆ Implement evidence-based pharmacologic treatment plans for people with mild cognitive impairment or dementia due to Alzheimer disease
- ◆ Describe care partner experiences in dementia, recognize factors that cause and are consequences of burden, and identify resources for care partner education, support, training, and care guidance
- ◆ Discuss the challenges raised by emerging diagnostics and therapeutics for neurodegenerative causes of dementia and facilitate innovations in practice, research, and education for clinicians

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Dementia issue covers the following core competencies:

- ◆ Patient Care and Procedural Skills
- ◆ Medical Knowledge
- ◆ Practice-Based Learning and Improvement
- ◆ Interpersonal and Communication Skills
- ◆ Professionalism
- ◆ Systems-Based Practice

LIST OF ABBREVIATIONS

Dementia

3R	Three-repeat	FDG	Fludeoxyglucose
4R	Four-repeat	FLAIR	Fluid-attenuated inversion recovery
Aβ	Amyloid- β	fMRI	Functional magnetic resonance imaging
AAN	American Academy of Neurology	FTD	Frontotemporal dementia
AD	Alzheimer disease	FTLD	Frontotemporal lobar degeneration
AD8	Ascertain Dementia 8 questionnaire	FUS	Fused in sarcoma
ADAS-Cog	Alzheimer's Disease Assessment Scale cognitive subscale	GFAP	Glial fibrillary acidic protein
ADL	Activities of daily living	GRE	Gradient echo
AHA	American Heart Association	GWAS	Genome-wide association study
ALS	Amyotrophic lateral sclerosis	H&E	Hematoxylin and eosin
ApoE	Apolipoprotein E	HIV	Human immunodeficiency virus
APOEϵ2	Apolipoprotein E ϵ 2	IADL	Instrumental activities of daily living
APOEϵ4	Apolipoprotein E ϵ 4	IV	Intravenous
ARIA	Amyloid-related imaging abnormalities	LATE	Limbic-predominant age-related transactive response
ARIA-E	Amyloid-related imaging abnormalities due to cerebral edema or effusion	LBD	DNA-binding protein 43 encephalopathy
ARIA-H	Amyloid-related imaging abnormalities due to cerebral hemorrhage	LGBTQ	Lewy body dementia
ATI	Amyloid-tau index	MCI	Lesbian, gay, bisexual, transgender, and queer
ASA	American Stroke Association	MIBG	Mild cognitive impairment
A/T/N	Amyloid, tau, neurodegeneration	MMSE	Metaiodobenzylguanidine
CAA	Cerebral amyloid angiopathy	MoCA	Mini-Mental State Examination
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy	MRI	Montreal Cognitive Assessment
CBD	Corticobasal degeneration	MSA	Magnetic resonance imaging
CDR	Clinical Dementia Rating	NIH	Multiple system atrophy
CJD	Creutzfeldt-Jakob disease	NMDA	National Institutes of Health
CMS	Centers for Medicare & Medicaid Services	PCA	N-methyl-D-aspartate
CSF	Cerebrospinal fluid	PDD	Posterior cortical atrophy
CT	Computed tomography	PET	Parkinson disease dementia
DICE	Describe-investigate-create-evaluate	PPA	Positron emission tomography
DLB	Dementia with Lewy bodies	PSP	Primary progressive aphasia
DNA	Deoxyribonucleic acid	pTau	Progressive supranuclear palsy
DWI	Diffusion-weighted imaging	RBD	Phosphorylated tau
ECG	Electrocardiogram	REACH	Rapid eye movement sleep behavioral disorder
EEG	Electroencephalogram	REM	Resources for Enhancing Alzheimer's Caregiver Health
ELISA	Enzyme-linked immunosorbent assay	RNA	Rapid eye movement
FDA	US Food and Drug Administration	RT-QuIC	Ribonucleic acid
		SPECT	Real-time quaking-induced conversion
		SSRI	Single-photon emission computed tomography
		SWI	Selective serotonin reuptake inhibitor
		TDP-43	Susceptibility-weighted imaging
		TIA	Transactive response DNA-binding protein 43
		TSH	Transient ischemic attack
			Thyroid-stimulating hormone

DEMENTIA

ARTICLE 1: DIAGNOSING ALZHEIMER DISEASE

Gregory S. Day, MD, MSc, MSCI, FAAN. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1584–1613.

ABSTRACT

OBJECTIVE:

This article reviews the current understanding of Alzheimer disease (AD), including the natural history, common risk factors, and expected progression of AD neuropathologic change so that neurologists can apply this knowledge to identify patients with symptoms, signs, and findings on common diagnostic tests consistent with AD.

LATEST DEVELOPMENTS:

The advent of potential disease-modifying therapies emphasizes the need to develop and deploy a practical and efficient approach to diagnose patients with cognitive impairment due to AD.

ESSENTIAL POINTS:

The accumulation and spread of cerebral amyloid plaques and tau tangles in patients with AD leads to synaptic dysfunction, neuronal loss, and the eventual emergence and progression of cognitive impairment. A pragmatic and organized approach is needed to recognize patients with symptomatic AD in clinical practice, stage the level of impairment, confirm the clinical diagnosis, and apply this information to advance therapeutic decision making.

KEY POINTS

- Although dementia has many possible causes, Alzheimer disease (AD) is the most common cause in older individuals.
- Advancing age is the greatest driver of AD risk across the population.
- AD is the sixth-leading cause of death in Americans, the fifth-leading cause of death in people 65 years old and older, and the only “top 10” cause of death that cannot be prevented, halted, or cured.
- The total lifetime cost of caring for someone with dementia was estimated in 2022 to exceed US \$390,000. AD is one of the costliest conditions for society.
- AD is a disease state characterized by specific neuropathologic changes, whereas dementia is a clinical syndrome associated with declines in memory and other cognitive domains (eg, executive, visuospatial, language function) that are sufficient to impair daily function.
- AD is a multistage illness that progresses across decades.

- The accumulation of amyloid- β plaques and neurofibrillary tangles in people who are not yet symptomatic marks the preclinical period of AD, a phase during which disease is measurable but clinical consequences are not.
- Disruption of neuronal function within the hippocampus and amygdala may herald the onset of subtle behavioral and cognitive concerns in otherwise high-functioning individuals.
- The symptomatic phase of AD represents the final phase of a process that typically evolves across decades.
- Age is the most common nonmodifiable risk factor for AD.
- One-third (or more) of dementia cases worldwide could be eliminated through adequate management of modifiable risk factors.
- Typically, patients with AD have an age at symptomatic onset within or beyond the seventh decade of life.
- An accurate assessment of cognitive function in the setting of AD requires taking adequate time for the clinical assessment.
- Impaired self-awareness (ie, anosognosia) is a common feature in patients with AD that may limit insight into the scope, severity, and impact of symptoms and compromise the diagnostic assessment.
- The gradual onset and progression of short-term memory loss should increase the pretest probability for AD as the cause of cognitive impairment.
- When possible, cognitive concerns should be illustrated by examples.
- Curiosity is encouraged in history taking, particularly when exploring substantial life changes in the setting of AD.
- Examples and follow-up questions may help codify impairment, clarify the impact on daily activities, and firm up the time of onset and symptomatic progression of AD.
- Cognitive impairment attributed to AD should progress over time with the spread of AD neuropathology.
- Language deficits are common later in the symptomatic course of typical (amnestic) AD.
- Behavioral manifestations may accelerate cognitive decline, threaten patient and care partner safety, and substantially increase the burden of care, the risk of institutionalization, and mortality in patients with AD.
- The neurologic examination should be normal early in the symptomatic course of AD.
- Accurate staging of impairment is essential to guide counseling, care, and access to resources for patients with AD and their care partners.
- Driving safety should be routinely evaluated in patients with symptomatic AD.
- Structural neuroimaging is indicated in patients with suspected AD to exclude occult lesions or other anomalies that may contribute to or explain impairment.
- Indications for fludeoxyglucose positron emission tomography (FDG-PET) (and insurance reimbursement in the United States) include the differentiation between AD and frontotemporal lobar degeneration in patients with a recent diagnosis of dementia and documented cognitive decline ongoing for at least 6 months.
- Documented declines across serial evaluations may increase diagnostic certainty, representing a useful diagnostic test for AD.
- The advent of AD-modifying therapies for patients with early symptomatic disease clearly emphasizes the value of an early and accurate diagnosis of AD.

ARTICLE 2: ATYPICAL PRESENTATIONS OF ALZHEIMER DISEASE

David Jones, MD; Victoria Pelak, MD; Emily Rogalski, PhD. Continuum (Minneapolis Minn). December 2024; 30 (6 Dementia):1614–1641.

ABSTRACT

OBJECTIVE:

This article provides a comprehensive review of the distinct features of four atypical Alzheimer disease (AD) variants: dysexecutive AD, behavioral variant AD, posterior cortical atrophy, and

the logopenic variant of primary progressive aphasia. It also elucidates their clinical presentations, underlying pathophysiologic pathways, diagnostic indicators, and management requirements.

LATEST DEVELOPMENTS:

Recent research has revealed that these atypical AD forms vary not only in clinical manifestations but in their functional neuroanatomy spanning a common pathophysiologic spectrum. Imaging techniques, such as MRI, fludeoxyglucose positron emission tomography (FDG-PET), and tau PET, have identified distinct abnormalities in specific brain regions associated with each variant. This same variability is less tightly coupled to amyloid imaging. Emerging diagnostic and therapeutic strategies should be tailored to each variant's unique features.

ESSENTIAL POINTS:

Atypical forms of AD often present with symptoms that are predominantly nonmemory related, distinguishing them from the more common memory-centric presentation of the disease. Two distinct clinical and pathologic entities, dysexecutive AD and behavioral variant AD, have replaced the outdated term *frontal AD*. Posterior cortical atrophy is another variant that mainly affects higher-order visual functions, which can lead to misdiagnoses because of its atypical symptom profile. Logopenic primary progressive aphasia is marked by difficulties in word retrieval, a challenge that may not be readily apparent if the person compensates by using circumlocution. Modern diagnostic techniques, such as MRI, PET, and biomarker analysis, have proven crucial for the accurate diagnosis and differentiation of these atypical AD variants. In treating these forms, it is critical to use tailored therapeutic interventions that combine pharmacotherapy with nonpharmacologic strategies to effectively manage the disease.

KEY POINTS

- Atypical forms of Alzheimer disease (AD) are defined by predominant symptoms in nonmemory cognitive domains.
- Atypical presentations of AD have unique pathophysiologic pathways, diagnostic indicators, and management requirements.
- Dysexecutive AD and behavioral variant AD are distinct presentations, and the term *frontal AD* should no longer be used.
- Patients with dysexecutive AD have impaired planning, organization, and decision making.
- Compromised working memory and cognitive flexibility manifest in impairments of cognitively effortful tasks while automatic activities are more preserved in patients with dysexecutive AD.
- In the setting of dysexecutive AD, memory loss can be the focus of the reported clinical symptoms as many are unfamiliar with the role of executive function for daily tasks.
- For patients with dysexecutive AD, changes in behavior are secondary to the impact of impaired executive function and are not themselves the primary driver of dysfunction.
- In behavioral variant AD, changes in behavior are the root cause of impaired daily functioning, similar to behavioral variant frontotemporal dementia (FTD).
- Amyloid and tau biomarkers are positive in dysexecutive AD and behavioral variant AD, but the spatial distribution of tau positron emission tomography (PET), fludeoxyglucose (FDG)-PET, and MRI changes more closely align with the unique functional anatomy of these two syndromes.
- Function of parietal and frontal regions related to working memory is commonly abnormal in patients with dysexecutive AD.
- Function of medial frontal regions related to behavior is commonly abnormal in patients with behavioral variant AD and behavioral variant FTD.
- Failure on performance validity testing commonly leads to misinterpretations of neuropsychological testing in the setting of dysexecutive AD.

- In patients with dysexecutive AD, the hippocampus is commonly spared and appears normal on MRI.
- The management of dysexecutive AD and behavioral variant AD combines pharmacotherapy with tailored nonpharmacotherapeutic approaches.
- AD is the most common underlying pathology accounting for posterior cortical atrophy (PCA) syndrome.
- PCA is characterized by higher-order visual dysfunction with relative sparing of memory and other cognitive domains, judgment, and insight early in the presentation.
- People with PCA often present to an eye care provider with significant visual concerns that can go unaccounted for in the presence of a normal eye examination.
- Difficulty reading is a common presenting concern for patients with PCA.
- Delays in diagnosis of PCA can occur because of the nature of initial symptoms (ie, visual and not memory), the characteristic young onset (65 years or younger), preservation of insight, and adequate performance on measures of global cognition at presentation.
- The 2017 PCA consensus criteria specify that 3 of 16 core features must be met for the diagnosis of PCA. Features belong to occipitoparietal and occipitotemporal visual pathways including all elements of Balint and Gerstman syndromes.
- Neuroimaging characteristics of PCA are supportive of the diagnosis and include posterior findings of cortical atrophy on MRI, hypometabolism on FDG-PET, or hypoperfusion on single-photon emission computed tomography (SPECT), as are posterior and occipital tau PET abnormalities.
- Patients with PCA are classified as having PCA-pure when they have no other associated syndromes or PCA-plus when PCA occurs in association with another clinical syndrome such as corticobasal syndrome.
- It is important to keep PCA features in mind while conducting a focused history and examination and using specific visual assessment tools in the office and during formal neuropsychological evaluation.
- Recently published recommendations for the clinical assessment of PCA provide several options for assessment tools and visual stimuli for detecting the unique core features of PCA.
- AD CSF biomarkers for PCA are indistinguishable from profiles for typical AD, whereas MRI, FDG-PET, and tau PET can reveal patterns of posterior atrophy, hypometabolism, and tau deposition that reflect the PCA clinical phenotype.
- Symptom management for patients with PCA should follow that established for AD and be guided by patient needs. It is unknown whether the risks or benefits of anti-amyloid therapies are different for the PCA phenotype.
- In vivo biomarkers play a key role in the diagnosis of AD because there is no one-to-one relationship between clinical phenotype and underlying neuropathology.
- Logopenic primary progressive aphasia (PPA) is characterized by word retrieval failures, which can occur in spontaneous speech or confrontation naming. These deficits may be obscured if the individual is adept at using simplified words or circumlocution.
- Many neuropsychological instruments developed to assess nonlanguage domains rely on preserved language for successful performance, which can make it challenging for clinicians to ascertain the presence or absence of impairment when aphasia is prominent.
- The ε4 allele of APOE is an important risk factor for amnestic dementia associated with AD neuropathologic change but does not show the same association with PPA.
- Nonpharmacologic interventions, care, counseling, and support programs may address care partner burden, family relationships, communication breakdowns, as well as language impairment to maximize quality of life for people with PPA and their care partners.
- The diagnostic journey for patients with PPA tends to take years rather than months.

ARTICLE 3: FRONTOTEMPORAL DEMENTIA

David Glenn Clark, MD. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1642–1672.

ABSTRACT

OBJECTIVE:

This article discusses frontotemporal dementia (FTD) syndromes using a simplified framework of three core syndromes, including details on their pathology and unique genetic variations.

LATEST DEVELOPMENTS:

FTD includes at least seven major clinical syndromes. The three core syndromes are behavioral variant FTD and two forms of progressive aphasia, commonly referred to as the nonfluent variant and semantic variant of primary progressive aphasia. Clinical features reflect the involvement of major functional brain networks. Derangements of three proteins account for nearly all underlying pathology for FTD syndromes: transactive response DNA-binding protein 43 (TDP-43) (approximately 50% of cases), MAPT (45% of cases), and FUS (5% of cases). The clinical presentation and imaging provide clues to the underlying pathology. FTD is more heritable than Alzheimer disease, with variations in *C9orf72*, *MAPT*, or *GRN* (which encodes progranulin) occurring in more than 10% of FTD cases.

ESSENTIAL POINTS:

The framework described here will provide clinicians with a foundation for understanding the complex and heterogeneous set of FTD syndromes. There are currently no disease-modifying or US Food and Drug Administration (FDA)-approved treatments for FTD, but clinical trials are underway, including some targeting presymptomatic genetic variation carriers. Available FTD treatments address deficits in behavior or language nonpharmacologically or through the off-label use of medications approved for other indications. Improvements in biomarkers will accelerate the discovery of new pharmacologic treatments.

KEY POINTS

- Frontotemporal dementia (FTD) is the second most common form of degenerative dementia among people younger than 65 years.
- The three core syndromes of FTD are behavioral variant FTD, nonfluent variant primary progressive aphasia (PPA), and semantic variant PPA, with behavioral variant FTD being the most common.
- A common report from family members of patients with behavioral variant FTD is that the patient no longer seems like the same person, but personality changes can be more subtle.
- The key features of nonfluent variant PPA are grammatical omissions, effortful and hesitating speech, and difficulty with articulation.
- Typical features of semantic variant PPA are loss of single-word comprehension and deficits of irregular word reading.
- Prosopagnosia is a deficit of face recognition that may occur in the context of a more general object agnosia.
- The most important features for the taxonomy of PPA are agrammatism, word comprehension, and repetition of phrases and sentences.
- About 15% of patients with behavioral variant FTD have amyotrophic lateral sclerosis (ALS) and 30% of patients with ALS have FTD.

- Although not among the core FTD syndromes, corticobasal syndrome and progressive supranuclear palsy syndrome are considered to be part of the FTD spectrum.
- The clinical features of degenerative diseases reflect the spread of disease within functional brain networks.
- The salience network underpins many behaviors and skills that are disrupted in behavioral variant FTD.
- The hubs of the network underlying grammar and fluency are in the left anterior insula and pars opercularis of the inferior frontal lobe.
- Semantic memory relies on an amodal bihemispheric network with hubs in the anterior temporal lobes, especially the perirhinal cortex.
- Atrophy of the right temporal lobe is associated with mixed features of behavioral variant FTD and semantic dementia.
- Nearly all cases of FTD-ALS have underlying transactive response DNA-binding protein 43 (TDP-43) pathology.
- More than 80% of cases of semantic variant PPA or semantic dementia have underlying TDP-43 type C pathology.
- Consider a hereditary form of frontotemporal lobar degeneration in any patient with a family history suggestive of FTD phenotypes in other relatives.
- Striking asymmetry of atrophy should raise the question of a variation in the gene *GRN*. Variations in the gene *MAPT* are associated with greater temporal atrophy than variations in the gene *C9orf72*, which are associated with greater frontal atrophy.
- Levels of neurofilament light chain mark the severity of neuroaxonal loss in neurodegenerative diseases and may be measured in plasma or CSF.
- Behavioral interventions for FTD can be tailored to an individual patient's needs.
- Serotonergic medications are the main pharmacologic agents with utility in FTD.

ARTICLE 4: LEWY BODY DEMENTIA

James E. Galvin, MD, MPH. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1673-1698.

ABSTRACT

OBJECTIVE:

Lewy body dementia (LBD) is an umbrella term describing two closely related conditions: Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB). LBD is the second most common cause of neurodegenerative dementia but is often underrecognized in clinical practice. This review covers the key epidemiologic, clinical, cognitive, behavioral, and biomarker features of LBD and discusses current treatment options.

LATEST DEVELOPMENTS:

Indicative biomarkers of LBD improve the ability to make a diagnosis and include single-photon emission computed tomography (SPECT) of the dopamine system (brain) and the noradrenergic system (cardiac), and polysomnography. α -Synuclein-specific biomarkers in spinal fluid, skin, plasma, and brain imaging are in active development with some available for clinical use. Prodromal stages of PDD and DLB have been contextualized, and diagnostic criteria have been published. An emerging theme is whether an integrated staging system focusing on protein aggregation, rather than clinical symptoms, may advance research efforts.

ESSENTIAL POINTS:

LBD is a common cause of cognitive impairment in older adults but is often subject to significant delays in diagnosis and treatment, increasing the burden on patients and family care partners.

Understanding key features of disease and the use of biomarkers will improve recognition. Earlier detection may also facilitate the development of new therapeutics and enrollment in clinical trials.

KEY POINTS

- Lewy body dementia (LBD) is common but underrecognized and underdiagnosed in routine clinical practice.
- LBD is an umbrella term that encompasses two related clinical diagnoses: Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB).
- Although initial clinical presentations may differ between PDD and DLB, the common underlying pathology of α -synuclein aggregation may present an opportunity to uniformly describe both clinical and pathologic progressions.
- LBD is a male-predominant disorder with a slightly earlier age of onset than Alzheimer disease (AD).
- Criteria for the diagnosis of PDD and DLB exist, with high specificity when applied in clinical and research settings.
- Indicative biomarkers greatly improve the reliability of LBD diagnosis but are largely indirect measures of neuronal injury and neurodegeneration.
- Prodromal stages of PDD and DLB exist, and diagnostic criteria are available to assist in their recognition.
- Patients with LBD tend to perform more poorly on Stroop color-word, card-sorting, and phonemic verbal fluency tasks than patients with comparably staged AD.
- The memory deficit in LBD differs from AD in that it tends to be one of retrieval rather than encoding or consolidation and storage, with significant improvement noted with cueing in LBD relative to AD.
- The cognitive and neuropsychiatric profile of LBD is distinct from AD and can assist in the diagnosis.
- Although they are not specifically diagnostic, autonomic and constitutional symptoms of LBD are less common in patients with AD and can assist in the diagnosis.
- Biomarkers specific for α -synuclein pathology are currently available in CSF and skin and are being developed in plasma and positron emission tomography (PET).
- In patients with LBD, hallucinations that are nonthreatening to the patient and do not disturb function may not require any pharmacologic intervention.
- There are no specific approved treatments for most symptoms of LBD, but clinical experience and case series inform off-label use of medications for individual symptoms.

ARTICLE 5: VASCULAR COGNITIVE IMPAIRMENT

Lisa C. Silbert, MD, MCR, FAAN. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1699–1725.

ABSTRACT

OBJECTIVE:

Vascular cognitive impairment is a major contributor to age-associated cognitive decline, both independently and as a contributor to mixed dementia syndromes. This article reviews the current understanding of how vascular dysfunction contributes to cognitive impairment and dementia risk in older individuals and includes updated diagnostic criteria and treatment recommendations.

LATEST DEVELOPMENTS:

Clinical and research criteria have been evolving to more accurately determine the full prevalence of vascular cognitive impairment. The Boston Criteria version 2.0 for cerebral

amyloid angiopathy now includes multiple punctate MRI T2 white matter hyperintensities and MR-visible perivascular spaces in addition to previously described T2* hemorrhagic signatures. MR-visible perivascular spaces are associated with both vascular cognitive impairment and Alzheimer disease, potentially linking cerebrovascular dysfunction to neurodegenerative disorders through its role in brain waste clearance. The American Heart Association's goal for cardiovascular health promotion, "Life's Essential 8," has been updated to include sleep health and acknowledges psychological well-being and social determinants of health as fundamental components necessary to achieve optimal cardiovascular health for all adults.

ESSENTIAL POINTS:

Vascular cognitive impairment is a common and often underrecognized contributor to cognitive impairment in older individuals, with heterogeneous etiologies requiring individualized treatment strategies. Effective cerebrovascular disease risk factor modification starting in midlife is critical to reducing the risk of Alzheimer disease and related dementias, with the goal of preventing vascular brain injury and maintaining cognitive reserve in the presence of nonvascular age-related brain pathologies.

KEY POINTS

- Community autopsy studies show that mixed pathologies are more common than any one pathology in older individuals. The most common combination is Alzheimer disease (AD) and cerebrovascular pathology.
- Cerebrovascular disease lowers the threshold for manifesting cognitive impairment when other pathologies are present. Treatment goals include the maintenance of cognitive reserve with advancing age when copathologies are likely to be present.
- The term *vascular cognitive impairment* includes a wide range of cerebrovascular-related cognitive decline, including those with mild impairment but preserved function, vascular dementia, and mixed-etiology dementias.
- More than one-half of patients who have a clinical stroke will have poststroke cognitive impairment. Stroke doubles the risk of dementia, with hemorrhagic stroke conveying a higher dementia risk than ischemic stroke.
- MRI features of small vessel ischemic disease associated with vascular cognitive impairment include lacunes, microinfarcts, microhemorrhages, enlarged perivascular spaces, and white matter hyperintensities.
- Subcortical infarcts, or lacunes, are seen on MRI in up to 23% of older individuals. Lacunar infarcts located in the basal ganglia and thalamus have the greatest association with cognitive impairment.
- Pathologically, MRI white matter hyperintensities are associated with myelin pallor, demyelination, axonal loss, inflammation, microinfarcts, and gliosis. Vascular features associated with MRI white matter hyperintensities include cerebral amyloid angiopathy (CAA), arteriolosclerosis, and venous collagenosis.
- Executive dysfunction has the greatest association with MRI white matter hyperintensities, although impairment in other areas, including memory, can be observed. Greater white matter hyperintensity burden is associated with increased risk for stroke, dementia, and overall mortality.
- MRI indicators of small vessel ischemic disease are observed in midlife and are associated with later cognitive decline, highlighting the need to address vascular risk factors early in adulthood, before vascular brain injury.
- Cerebral microinfarcts are common in older populations, particularly in people with vascular dementia. The presence of cerebral microinfarcts increases the risk of dementia independently of AD pathology.
- Cerebral microinfarcts are associated with arteriolosclerosis, atherosclerosis, and CAA. Mechanisms leading to cognitive impairment include both focal and long-range tissue injury occurring via associated white matter tracts.
- CAA is characterized by the deposition of amyloid- β 40 (A β 40) in walls of cortical and leptomeningeal arterioles and small arteries and occurs in the presence or absence of parenchymal AD pathology.
- The Boston Criteria version 2.0 for CAA includes MRI white matter hyperintensity in a multispot pattern and

- MR-visible perivascular spaces within the centrum semiovale, in addition to hemorrhagic features on susceptibility-weighted images (SWI) and T2* sequences.
- CAA can present clinically as acute neurologic decline after hemorrhagic stroke, transient focal neurologic episodes, gradual cognitive decline and dementia, or subacute cognitive decline due to CAA-related inflammation.
 - The most common hereditary form of vascular cognitive impairment is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The NOTCH3 variation location partially explains the difference in disease severity across patients.
 - CADASIL is characterized by migraine, subcortical strokes, and young-onset vascular cognitive impairment. MRI features include subcortical lacunes, SWI and T2* cerebral microbleeds, and fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities involving the anterior temporal poles.
 - Cardiac dysfunction, including atrial fibrillation, congestive heart failure, and coronary heart disease, increases the risk for vascular cognitive impairment. Acute myocardial infarction is associated with cognitive decline years later. Presumed mechanisms include associated microinfarcts, global hypoperfusion, inflammation, and microhemorrhages.
 - A greater increase in cardiovascular risk factors over time raises the risk for both AD and vascular dementia. Whether cognitive effects from cerebrovascular disease are independent of, or synergistic with, AD pathology has not been resolved.
 - Midlife cardiovascular risk factors have been associated with amyloid pathology on positron emission tomography (PET) in later life, as well as cortical neurodegeneration occurring independently of AD pathology.
 - Pathologically, posterior white matter lesions are associated with AD pathology, consistent with in vivo findings demonstrating greater posterior MRI T2 white matter hyperintensities in patients with autosomal dominant AD.
 - The perivascular space plays a role in waste clearance from the brain. MR-visible perivascular space in the basal ganglia has greater associations with cerebrovascular disease and vascular cognitive impairment, whereas centrum semiovale perivascular space is more associated with AD and CAA.
 - Vascular cognitive impairment treatment and prevention should focus on stroke risk factors, including blood pressure control. For patients with a history of stroke or transient ischemic attack, individualized secondary stroke prevention measures are warranted.
 - The American Heart Association's "Life's Essential 8" recommendations for optimal cardiovascular health include a healthy diet and weight; physical activity; nicotine avoidance; glucose, lipid, and blood pressure control; and adequate sleep.
 - Older Black and Hispanic or Latino adults are disproportionately affected by AD and related dementias, largely because of health care disparities in the management of stroke and vascular risk factors.
 - Contributors to health disparities in vascular cognitive impairment include lack of social support, limited health care access, and implicit and explicit bias in disease management. Addressing health care inequities is fundamental in vascular cognitive impairment prevention.

ARTICLE 6: LATE, HIPPOCAMPAL SCLEROSIS, AND PRIMARY AGE-RELATED TAUOPATHY

Vijay K. Ramanan, MD, PhD; Jonathan Graff-Radford, MD. Continuum (Minneapolis Minn). December 2024; 30 (6 Dementia):1726–1743.

ABSTRACT

OBJECTIVE:

Although Alzheimer disease (AD) is the most common neurodegenerative cause of dementia, neurologists must be aware of other etiologies that can mimic the amnestic-predominant syndrome and medial temporal brain involvement typically associated with AD. This article reviews recent updates surrounding limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), hippocampal sclerosis, and primary age-related tauopathy.

LATEST DEVELOPMENTS:

LATE neuropathologic change occurs in approximately 40% of autopsied older adults, including occurrences in isolation in some older individuals with amnestic cognitive impairment. LATE neuropathologic change is often, but not always, associated with hippocampal sclerosis (neuronal loss and gliosis in the hippocampus and associated structures) and frequently coexists with AD and other neurodegenerative pathologies. Although there is no direct clinical biomarker for TDP-43 pathology, recent studies suggest that a clinical diagnosis of LATE can be achieved through the integration of multiple data points. Primary age-related tauopathy refers to the pathologic finding (in some cognitively unimpaired older adults as well as some individuals with cognitive impairment) of medial temporal-predominant neurofibrillary tangles in the absence of amyloid- β (A β) plaques. Recent consensus frameworks have attempted to resolve ambiguities of nomenclature and diagnosis for these entities, and efforts toward in vivo biomarkers are ongoing.

ESSENTIAL POINTS:

LATE, with or without hippocampal sclerosis, and primary age-related tauopathy belong in the differential diagnosis (along with AD, argyrophilic grain disease, and other disorders) for slowly progressive amnestic-predominant cognitive impairment, particularly in individuals older than 75 years. Accurate recognition of clinical and diagnostic test features supportive of these non-AD entities is vital to optimize patient counseling, therapeutic selection, and novel biomarker development.

KEY POINTS

- Alzheimer disease (AD) is the most common neurodegenerative cause of dementia and typically manifests with amnestic-predominant cognitive decline.
- As many as 15% to 20% of individuals diagnosed clinically with probable AD dementia lack biological evidence of the disease, highlighting the importance of awareness of potential AD mimics.
- Limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE) is an increasingly recognized cause of slowly progressive amnestic impairment, particularly among individuals older than 75 years.
- LATE neuropathologic change is marked by aberrantly localized and phosphorylated TDP-43 primarily within the limbic system.
- In older individuals, findings of hippocampal sclerosis (neuronal loss and gliosis in the hippocampus) are typically the result of neurodegenerative disease, with LATE being the most commonly associated entity.
- Compared with people with AD, individuals with LATE typically have a longer clinical course with milder intensity of functional impairment and a lack of prominent neocortical signs.
- Currently, there are no direct antemortem imaging or fluid biomarkers of LATE, although several approaches are in active development.
- Amygdalar and hippocampal atrophy is often striking in LATE, out of proportion to the degree of impairment or extent of neocortical atrophy observed.
- Preferential volume loss (on MRI) and hypometabolism (on FDG-PET) in the medial temporal regions with a

relative absence of parietal or inferior or lateral temporal involvement may serve as supportive biomarkers for LATE in the appropriate clinical context.

- Among individuals with an amnestic dementia and amyloid PET positivity, the ratio of inferior to medial temporal metabolism on FDG-PET may serve as a surrogate to detect tau PET negativity and a resulting high likelihood of LATE and hippocampal sclerosis.
- AD and LATE commonly coexist in older adults with cognitive impairment and, when present concomitantly, are associated with faster rates of clinical decline and brain atrophy.
- LATE neuropathologic change is associated with distinctive clinical presentations and postmortem histologic features of TDP-43 pathology compared with frontotemporal lobar degeneration associated with TDP-43.
- The presence of neurofibrillary tangle pathology involving tau is a nearly ubiquitous finding among the oldest adults (ie, individuals older than 90 to 100 years).
- Primary age-related tauopathy* refers to the finding of medial temporal–predominant AD-type neurofibrillary tangles in the absence of amyloid- β (A β) plaque accumulation.
- Individuals with primary age-related tauopathy may be cognitively unimpaired or may have a mild, amnestic-predominant syndrome.
- The severity and topographic distribution of neurofibrillary tangles in primary age-related tauopathy influence the likelihood of incident cognitive impairment.
- At this time, the presence of definite primary age-related tauopathy can be determined only through postmortem neuropathologic studies.
- Hippocampal atrophy (on MRI) and medial temporal hypometabolism (on FDG-PET) can be seen in patients with primary age-related tauopathy, but these findings are not specific to that diagnosis.
- Tau PET using newer-generation tracers represents an emerging biomarker for identifying primary age-related tauopathy, in the context of a lack of evidence for brain amyloidosis.
- A systematic clinical approach integrating syndromic features and appropriate use and interpretation of biomarkers can help to distinguish among AD and common mimics in older adults.
- With new disease-modifying therapies for AD, high-confidence etiologic diagnoses will be critical to maximize treatment benefits for those eligible and minimize unnecessary treatment-related complications in individuals with non-AD diagnosis or multi-etiology dementia.

ARTICLE 7: NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA

Gad A. Marshall, MD. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1744–1760.

ABSTRACT

OBJECTIVE:

This article discusses the prevalence, pathophysiology, assessment, and management of neuropsychiatric symptoms in patients with dementia.

LATEST DEVELOPMENTS:

There is a growing body of evidence localizing neuropsychiatric symptoms in dementia to frontal circuits in the brain, as well as relating them to pathologic changes seen in different dementias. Although very few medications have been approved by the US Food and Drug Administration (FDA) for the treatment of neuropsychiatric symptoms in dementia, there are more clinical trials showing the benefit of antidepressants, stimulants, and antipsychotics. In line with that trend, in

2023, the FDA approved the use of brexpiprazole, an atypical antipsychotic, for the treatment of agitation in Alzheimer disease dementia.

ESSENTIAL POINTS:

Neuropsychiatric symptoms are a core feature of all dementias and often emerge before cognitive symptoms manifest. They are highly clinically significant symptoms that disrupt the lives of patients and care partners and greatly influence the decision to place patients in long-term care facilities. The first line of treatment for neuropsychiatric symptoms in dementia is nonpharmacologic behavioral modification, but clinicians often must supplement this intervention with medications using an empiric approach.

KEY POINTS

- A core feature of all dementias, and sometimes a leading feature, is the development of neuropsychiatric symptoms.
- The development of late-life neuropsychiatric symptoms that were not previously present during young adulthood is usually an indicator of a developing neurodegenerative disease.
- Over the course of dementia, nearly all patients will experience one or more neuropsychiatric symptoms.
- In patients with Alzheimer disease dementia, the most prevalent neuropsychiatric symptoms are irritability, anxiety, depression, apathy, sleep disturbances, and agitation.
- Mild behavioral impairment is a new clinical construct that represents a prodrome for dementia, similar to mild cognitive impairment, but with a focus on neuropsychiatric symptoms.
- Behavioral variant frontotemporal dementia is often mistaken for a primary psychiatric condition because of the prominent neuropsychiatric symptoms and its earlier age of onset than more common dementias such as Alzheimer disease.
- Neuropsychiatric symptoms are highly clinically relevant symptoms and often have a greater influence on clinical outcomes than cognitive symptoms in dementia.
- The most widely used assessment for determining the presence and progression of neuropsychiatric symptoms in dementia is the Neuropsychiatric Inventory in which the questions are typically addressed to the care partner.
- Although considerable variability has been reported in the localization of neuropsychiatric symptoms, some patterns have emerged, such as the involvement of frontal-subcortical networks, particularly at the stage of dementia.
- The first-line treatment for neuropsychiatric symptoms in dementia is a nonpharmacologic or behavior modification approach.
- Very few medications are indicated by the US Food and Drug Administration (FDA) for the treatment of neuropsychiatric symptoms in dementia, and therefore, an empiric treatment approach is undertaken, warranting further caution.
- The first step in the behavior modification approach for the treatment of neuropsychiatric symptoms in patients with dementia is a careful review and identification of the target symptoms and their potential triggers with the patient and care partner, as well as a review of the patient's environment.
- It is important to make sure that the proposed behavior modification in patients with dementia can be carried out by the care partner and patient and is not beyond their abilities or circumstances to perform.
- When starting a medication for the treatment of neuropsychiatric symptoms in dementia, it is recommended to start low and go slow because the patients are usually older and more susceptible to potential medication side effects.
- The most commonly used psychotropic medications for the treatment of neuropsychiatric symptoms in patients with dementia are selective serotonin reuptake inhibitors (SSRIs), primarily escitalopram, citalopram, and sertraline.
- When using benzodiazepines to treat neuropsychiatric symptoms in dementia, lorazepam and clonazepam

are the preferred choices because they are not as long-acting as diazepam and their effect is not as immediate as diazepam or alprazolam and, thus, are less prone to dependence.

- Patients with Lewy body disease are often sensitive to antipsychotics, which should be avoided in these patients if possible.
- Antipsychotics typically have more significant short-term and long-term side effects than other psychotropic medications and so must be used with caution, at low doses if possible, and potentially discontinued after stabilization of symptoms in patients with dementia.
- It is important to work with the patient and care partner in deciding which course of action to take to treat neuropsychiatric symptoms in patients with dementia, and improve the patient's and care partner's quality of life.

ARTICLE 8: NEUROIMAGING IN DEMENTIA

Shannon L. Risacher, PhD. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1761-1789.

ABSTRACT

OBJECTIVE:

This article captures the current literature regarding the use of neuroimaging measures to study neurodegenerative diseases, including early- and late-onset Alzheimer disease, vascular cognitive impairment, frontotemporal lobar degeneration disorders, dementia with Lewy bodies, and Parkinson disease dementia. In particular, the article highlights significant recent changes in novel therapeutics now available for the treatment of Alzheimer disease and in defining neurodegenerative disease using biological frameworks. Studies summarized include those using structural and functional MRI (fMRI) techniques, as well as metabolic and molecular emission tomography imaging (ie, positron emission tomography [PET] and single-photon emission computerized tomography [SPECT]).

LATEST DEVELOPMENTS:

Neuroimaging measures are considered essential biomarkers for the detection and diagnosis of most neurodegenerative diseases. The recent approval of anti-amyloid antibody therapies has highlighted the importance of MRI and PET techniques in treatment eligibility and monitoring for associated side effects. Given the success of the initial biomarker-based classification system for Alzheimer disease (the amyloid, tau, neurodegeneration [A/T/N] framework), researchers in vascular cognitive impairment have created similar techniques for biomarker-based diagnosis. Further, the A/T/N framework for Alzheimer disease has been updated to include several pathologic targets for biomarker detection.

ESSENTIAL POINTS:

Neurodegenerative diseases have a major health impact on millions of patients around the world. Neuroimaging biomarkers are rapidly becoming major diagnostic tools for the detection, monitoring, and treatment of neurodegenerative diseases. This article educates readers about the current literature surrounding the use of neuroimaging tools in neurodegenerative diseases along with recent important developments in the field.

KEY POINTS

- One of the biggest developments in the treatment of Alzheimer disease (AD) in the past 2 years is the approval of anti-amyloid antibody treatments.
- Biological-based diagnostic criteria, which largely depend on neuroimaging and other biomarker measures,

are being developed for other neurodegenerative conditions beyond AD, including synucleinopathies and cerebral small vessel disease.

- Three monoclonal antibody treatments have been approved by the US Food and Drug Administration (FDA) (ie, aducanumab, lecanemab, and donanemab).
- Imaging with amyloid-specific PET tracers demonstrates widespread amyloid deposition throughout the cortex in patients with AD.
- Neuroimaging studies have provided additional evidence that mild cognitive impairment is a transition stage between normal cognition and dementia, showing AD-like patterns of brain atrophy, glucose hypometabolism, and amyloid and tau deposition that are often less severe or extensive than in clinical AD dementia but markedly abnormal relative to cognitively normal adults.
- According to the AD and related disorders biomarker diagnostic staging system, any individual who is A β positive is considered to have AD.
- The clinical trials on which approval for lecanemab was based consistently showed a statistically significant slowing of disease progression (as measured by the Clinical Dementia Rating scale sum of boxes) compared with placebo in patients in mild clinical stages of AD.
- Amyloid-related imaging abnormalities are a common side effect of monoclonal antibody treatments and are most common in patients with comorbid cerebrovascular disease or cerebral amyloid angiopathy and who are homozygous for the APOE* ϵ 4 allele.
- Some studies have suggested that patients with early-onset AD have more severe pathology on neuroimaging measures than patients with late-onset AD, including more severe global atrophy and greater amyloid and tau deposition at the same general level of cognitive performance.
- Amyloid measures become abnormal approximately 20 years before expected AD symptom onset, followed by altered glucose metabolism approximately 15 years before expected onset, and finally cortical thinning approximately 5 to 10 years before expected onset.
- Patients with posterior cortical atrophy demonstrate marked atrophy in the occipital lobes, visual association areas, posterior parietal and temporal lobes, and mesial parietal lobes.
- In more severely impaired patients with logopenic aphasia, atrophy is observed in the left perisylvian regions of the left anterior temporal lobe and inferior frontal lobe.
- MRI can illustrate multiple features characteristic of small vessel disease including (1) recent small subcortical infarcts, (2) lacunes (of presumed vascular origin), (3) white matter hyperintensities (of presumed vascular origin), (4) enlarged perivascular spaces, (5) cerebral microbleed(s), (6) cortical superficial siderosis, and (7) cortical cerebral microinfarcts.
- The most notable findings in patients with primary CAA are cerebrovascular damage markers on MRI, including white matter hyperintensities on T2-weighted scans and microhemorrhages and cortical superficial siderosis on T2* or SWI sequences.
- SWI provides imaging of iron deposition in nigrosomes, which are small bundles of dopaminergic cells in the substantia nigra pars compacta that when intact show a hyperintense signal that resembles the tail of a swallow, called the *swallow tail sign*.
- A notable (but nonspecific) sign of multiple system atrophy, called the *hot cross bun sign*, is a cruciform hyperintensity in the pons on T2-weighted imaging.
- Patients with behavioral variant frontotemporal dementia have atrophy in the frontal and temporal lobes, insula, anterior cingulate cortex, and orbitofrontal cortex, as well as in subcortical regions, including the amygdala, striatum, globus pallidus, thalamus, and hippocampus.
- Patients with semantic dementia have significant focal atrophy in the ventrolateral anterior temporal lobe, most especially in the temporal pole, that presents bilaterally but is more severe in the language-dominant hemisphere (most commonly the left hemisphere).
- Patients with progressive nonfluent aphasia have focal asymmetric atrophy in the language-dominant hemisphere (usually the left hemisphere) in the inferior frontal lobe and frontal operculum, as well as the insula, lentiform nucleus, inferior and middle frontal gyri, premotor cortex, dorsolateral prefrontal cortex, and supplementary motor area.

- Patients with *C9orf72* genetic variations have symmetric atrophy in the frontal lobe, anterior temporal lobe, thalamus, parietal lobe, and occipital lobe, as well as cerebellar atrophy.
- *MAPT* gene variation carriers typically have more significant atrophy in the temporal lobe, including the mesial temporal lobe, than patients with other types of genetic variations or sporadic behavioral variant frontotemporal lobar degeneration, as well as atrophy in the parietal lobe, basal ganglia, insula, orbitofrontal cortex, and brainstem.
- Patients with gene variations in *GRN* show highly asymmetric temporoparietal, inferior frontal, and parietal atrophy.
- A summary measure called the *magnetic resonance parkinsonism index* provides good differentiation of patients with autopsy-confirmed CBD from those with PSP but could not differentiate patients with CBD from those with other dementias.
- A pattern of atrophy that is greater in the midbrain than the pons is characteristic of PSP and is described as the hummingbird sign on sagittal MRI and the Mickey Mouse sign or morning glory sign on axial MRI.

ARTICLE 9: FLUID BIOMARKERS IN DEMENTIA DIAGNOSIS

Joseph F. Quinn, MD, FAAN; Nora E. Gray, PhD. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1790–1800.

ABSTRACT

OBJECTIVE:

This article familiarizes neurologists with the currently available CSF and plasma biomarkers for the diagnosis of dementia and diagnosis-dependent treatment decisions.

LATEST DEVELOPMENTS:

For Alzheimer disease, the recent US Food and Drug Administration (FDA) approval of monoclonal antibody therapy has increased the urgency of confirming the pathologic diagnosis with biomarkers before initiating therapy. The new availability of disease-modifying therapies also highlights the need for biomarkers to monitor efficacy over time. Both of these needs have been partially addressed by the emergence of improved blood-based biomarkers for Alzheimer disease. Regarding other forms of dementia, the latest development is a CSF assay for aggregated α -synuclein, which permits the biomarker confirmation of synuclein pathology in Lewy body dementia.

ESSENTIAL POINTS:

CSF biomarkers for the diagnosis of Alzheimer disease, Lewy body dementia, and Creutzfeldt-Jakob disease are well established. Blood-based biomarkers for dementia diagnosis are emerging and rapidly evolving. Sensitivity and specificity for diagnosis continue to improve, and they are being incorporated into diagnostic decisions. Fluid biomarkers for monitoring the efficacy of therapy are not yet established. Because serial CSF examinations are impractical, the validation of blood-based biomarkers of disease activity will be critical for addressing this unmet need.

KEY POINTS

- The advent of US Food and Drug Administration (FDA)-approved anti-amyloid therapies for the treatment of Alzheimer disease has heightened the practical clinical importance of methods to ascertain specific dementia diagnoses.

- CSF levels of amyloid- β (A β) are influenced by the collection tube, as A β adheres to polystyrene (hard plastic) making levels in the fluid artificially lower when collected in polystyrene. To obtain reliable CSF A β measurements, it is necessary to collect the sample in a polypropylene (soft plastic) tube.
- The amyloid-tau index and the absolute level of phosphorylated tau 181 (pTau181) is a much stronger indicator of Alzheimer disease pathology than either A β or total tau alone.
- Prion real-time quaking-induced conversion methods have shown excellent sensitivity and specificity for aggregated prion protein and have become a mainstay in the diagnosis of Creutzfeldt-Jakob disease.
- Clinically useful CSF biomarkers for Alzheimer disease, Creutzfeldt-Jakob disease, and α -synuclein pathology are currently available. The Creutzfeldt-Jakob disease and α -synuclein biomarkers require CSF collection. The Alzheimer disease biomarkers are being rapidly refined for use in blood samples.
- CSF indicators of neuronal injury and degeneration, such as neurofilament light chain and glial fibrillary acidic protein (GFAP), are emerging as potentially useful biomarkers of disease.
- The ratio of A β 42/A β 40 and measurements done by mass spectrometry have improved the precision and reproducibility of blood measurements.
- The diagnostic utility of plasma pTau measurements is confounded by comorbidities. The most effective pTau biomarker species for progression to Alzheimer disease is pTau217.
- There are significant differences in the abundance and predictive value of fluid biomarkers across racial and ethnic groups. This needs to be considered when weighing treatment decisions for underrepresented groups.

ARTICLE 10: GENETICS AND NEUROPATHOLOGY OF NEURODEGENERATIVE DEMENTIAS

Sonja W. Scholz, MD, PhD, FAAN; Inma Cobos, MD, PhD. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1801-1822.

ABSTRACT

OBJECTIVE:

This article provides an overview of the current understanding of the genetic and pathologic features of neurodegenerative dementias, with an emphasis on Alzheimer disease and related dementias.

LATEST DEVELOPMENTS:

In recent years, there has been substantial progress in genetic research, contributing significant knowledge to our understanding of the molecular risk factors involved in neurodegenerative dementia syndromes. Several genes have been linked to monogenic forms of dementia (eg, APP, PSEN1, PSEN2, SNCA, GRN, C9orf72, MAPT) and an even larger number of genetic variants are known to influence susceptibility for developing dementia. As anti-amyloid therapies for patients with early-stage Alzheimer disease have entered the clinical arena, screening for the apolipoprotein E ϵ 4 high-risk allele has come into focus, emphasizing the importance of genetic counseling. Similarly, advances in the pathologic classifications of neurodegenerative dementia syndromes and molecular pathology highlight their heterogeneity and overlapping features and provide insights into the pathogenesis of these conditions.

ESSENTIAL POINTS:

Recent progress in neurogenetics and molecular pathology has improved our understanding of the complex pathogenetic changes associated with neurodegenerative dementias, facilitating improved disease modeling, enhanced diagnostics, and individualized counseling. The hope is that this knowledge will ultimately pave the way for the development of novel therapeutics.

KEY POINTS

- Alzheimer disease (AD) is clinically characterized by progressive memory loss and multidomain cognitive decline, involving language, visuospatial orientation, and executive function.
- The pathologic hallmarks of AD include extracellular amyloid- β (A β) plaques and intracellular aggregates of hyperphosphorylated tau in neurofibrillary tangles, dystrophic neurites, and neuropil threads.
- Resistance is the ability to avoid significant AD pathology during aging, whereas resilience is the ability to remain cognitively normal despite having significant AD pathology.
- After aging, a positive family history is the strongest biological risk factor for AD, and the total genetic contribution based on twin studies is estimated to be about 70%.
- Variations in the genes encoding presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (APP) are well-recognized causes of familial, autosomal dominantly inherited AD.
- The “amyloid cascade” hypothesis posits that the initial, molecular cause of AD is the abnormal deposition of extracellular A β peptide.
- The apolipoprotein E ϵ 4 (*APOE** ϵ 4) allele is the strongest and most common high-risk gene for AD.
- Individuals with one copy of *APOE** ϵ 4 have an approximately threefold risk of developing AD compared with the general population, whereas homozygote carriers have a nearly 15-fold risk.
- *APOE** ϵ 4 carriers are a high-risk population for developing amyloid-related imaging abnormalities on brain MRI that relate to the presence of cerebral amyloid angiopathy.
- Genome-wide association studies have implicated about 90 common variants across 75 loci that contribute to susceptibility to AD.
- Genome-wide association study approaches have implicated crucial roles of the innate immune system, lipid metabolism, and endocytic processes as key components of AD risk.
- Lewy body dementia is characterized by eosinophilic neuronal inclusions consisting of misfolded α -synuclein protein fibrils known as Lewy bodies and Lewy neurites in neuronal processes.
- Missense or copy-number variations in the *SNCA* gene can cause familial Lewy body dementia on rare occasions, and common genetic variations within *SNCA* have been associated with susceptibility to sporadic Lewy body dementia.
- Variations in *GBA*, which encodes the lysosomal enzyme β -glucocerebrosidase, are associated with increased risk for Lewy body disease.
- TDP-43 proteinopathy in limbic-predominant age-related TDP-43 encephalopathy (LATE) resembles type A frontotemporal lobar degeneration (FTLD)-TDP and is associated with hippocampal sclerosis in approximately 70% of cases.
- Primary age-related tauopathy and age-related tau astrogliopathy are primary age-related tauopathies that exhibit tau aggregates predominantly in neurons and glia, respectively, without significant amyloid deposition.
- Primary age-related tauopathy exhibits a regional distribution pattern of tau similar to AD, including tau isoforms, tau phosphorylation, and ultrastructure, but it rarely spreads beyond the medial temporal lobe.
- FTLD is an umbrella term for the neuropathologic diseases found in patients with clinical frontotemporal dementia syndromes, encompassing a range of neuropathologic entities that are primarily classified based on the genetics and proteinopathy present.
- Gene variations in *C9orf72*, *GRN*, and *MAPT* are common causes of FTLD.

ARTICLE 11: TREATMENT OF ALZHEIMER DISEASE

David S. Geldmacher, MD, FACP, FANA. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1823-1844.

ABSTRACT

OBJECTIVE:

Symptom-oriented treatment has been the mainstay of Alzheimer disease (AD) pharmacotherapy for decades. This article reviews the evidence basis for symptomatic treatments for AD and the emerging data on amyloid-lowering therapies with possible disease-slowng effects.

LATEST DEVELOPMENT:

Amyloid-lowering monoclonal antibody therapies entered clinical use in 2021. In July 2023, lecanemab became the first of these to gain full US Food and Drug Administration (FDA) approval and limited Medicare payment coverage. Donanemab gained similar approval status in July 2024. The approved agents remove amyloid plaque from the brain and appear to slow clinical disease progression but can produce significant adverse events known as amyloid-related imaging abnormalities with cerebral edema or effusion and with cerebral hemorrhages. Extensive safety monitoring is therefore required, including scheduled MRI scans. Also in 2023, brexpiprazole became the first agent specifically approved by the FDA for agitation associated with AD. Suvorexant, an orexin receptor antagonist, previously was approved for the treatment of insomnia in people with mild and moderate AD.

ESSENTIAL POINTS:

There is robust evidence for the use of acetylcholinesterase inhibitors for patients with mild, moderate, and severe dementia due to AD, including outcomes beyond changes in cognitive screening test scores. More limited studies support the use of memantine in moderate and severe stages. These agents have a primary effect of delaying decline in cognition and function and postponing the emergence of adverse behaviors. Pharmacotherapy for behavioral and psychological symptoms is less predictable, and most clinical trials have had negative results. Anti-amyloid therapies provide the first FDA-approved option to alter AD pathology, but an understanding of overall utility and value to patients remains in its infancy.

KEY POINTS

- Cognitive and functional outcomes of symptomatic treatment of Alzheimer disease (AD) track together; behavioral outcomes are less predictable.
- There will be continued roles for symptomatic therapies used concurrently with anti-amyloid therapies in people with dementia due to AD.
- There are no clinically relevant differences in cognitive or functional outcomes between the available acetylcholinesterase inhibitor drugs for the treatment of patients with AD.
- Acetylcholinesterase inhibitors have not shown consistent benefits on cognitive or functional outcomes among patients with mild cognitive impairment.
- Improvement in daily function is generally not observed with acetylcholinesterase inhibitor treatment in patients with AD, but delayed decline was observed in clinical trials.
- Acetylcholinesterase inhibitor treatment is associated with delayed emergence of behavioral and psychological symptoms of dementia.

- Reduced time spent in caregiving for patients with AD is associated with acetylcholinesterase inhibitor treatment.
- Most studies show persistent acetylcholinesterase inhibitor treatment for AD is associated with delayed (or reduced risk for) nursing home placement, but the effects are not additive with intensive care partner support.
- Gastrointestinal symptoms are the most common side effects of acetylcholinesterase inhibitor treatment and can be reduced by slower dose escalation.
- Transdermal rivastigmine was associated with no more frequent gastrointestinal symptoms than placebo.
- Donepezil is generally the best-tolerated oral acetylcholinesterase inhibitor.
- If a patient has an intolerance to the initially selected acetylcholinesterase inhibitor, transition to a different agent or formulation is warranted after resolution of the adverse effects.
- Patients with dementia who discontinue acetylcholinesterase inhibitor drugs may demonstrate noticeable worsening of cognitive, neuropsychiatric, or functional status in the first weeks after stopping treatment; resumption of therapy can be considered.
- Memantine is a symptomatic therapy for patients with AD; clinical evidence does not indicate it alters neurodegeneration.
- Cognitive and functional benefits of memantine monotherapy fade by 12 months of treatment in patients with AD.
- Memantine showed no benefit in patients with mild-stage AD.
- There is no systematic evidence that pharmacotherapy for behavioral symptoms in patients with AD reduces care partner burden.
- Treatment outcomes for selective serotonin reuptake inhibitor (SSRI) agents in patients with AD and depression are less predictable than in patients with primary depression.
- Suvorexant is the only US Food and Drug Administration (FDA)-approved agent for treatment of sleep disturbance in patients with AD.
- SSRI antidepressants citalopram and sertraline can reduce nonpsychotic agitation in people with AD.
- Brexpiprazole is the only drug specifically approved for agitation associated with AD; it is classed as an antipsychotic and has a boxed warning.
- Amyloid-related imaging abnormalities including effusion or edema and hemorrhage can be serious adverse effects of amyloid-lowering treatments.
- Approved amyloid-lowering monoclonal antibodies reduce plaque burden and are FDA approved for use in patients with early AD.
- The risk of amyloid-related imaging abnormalities increases with APOE4 gene dose; genotyping to predict amyloid-related imaging abnormalities risk is recommended.
- Phase 3 trial results for lecanemab and donanemab show similar magnitudes of effects, about 25% to 35% slowed rates of clinical progression in treated patients with early AD.

ARTICLE 12: CARE PARTNER BURDEN AND SUPPORT SERVICES IN DEMENTIA

Angelina J. Polzinelli, PhD, ABPP-CN. Continuum (Minneapolis). December 2024; 30 (6 Dementia):1845–1862.

ABSTRACT

OBJECTIVE:

Informal care partners are essential to the care of people living with dementia, but they often experience significant burden and receive minimal training, support, and resources. This article

provides an overview of care partner experiences, factors contributing to burden, and methods for reducing burden of caregiving in dementia.

LATEST DEVELOPMENTS:

The US Department of Health and Human Services National Plan to Address Alzheimer's Disease and the World Health Organization Global Action Plan for dementia have identified support for dementia care partners as a top priority for research and policy in recognition of care partners' instrumental but underresourced role in dementia care. The psychological, financial, social, and physical costs of caregiving, particularly without necessary knowledge, skills, and resources, can lead to care partner burden. Reassuringly, multicomponent interventions can mitigate burden and other negative consequences of caregiving, especially when they are theoretically grounded, inclusive, and culturally relevant.

ESSENTIAL POINTS:

Health care providers play a vital role in the early identification of care partner burden through brief, regular assessments. With earlier identification and subsequent intervention (eg, education, skills-based training, local and national resources), the experience of burden and negative health outcomes can be mitigated and quality of life for people living with dementia and their care partners can be improved.

KEY POINTS

- Despite increasing complex care needs, most of the caregiving for patients with dementia is done by informal (ie, unpaid) care partners who have no training and minimal resources.
- Understanding the factors that contribute to burden, monitoring care partner burden, and connecting care partners with education, resources, and skills-based training can positively affect the quality of life for patients living with dementia and their care partners.
- In the United States, there are 11million informal care partners of people living with dementia, translating into approximately 18billion hours of unpaid work, valued at approximately US \$340billion.
- Burden is "the multidimensional response to physical, psychological, emotional, social, and financial stressors associated with the caregiving experience."
- Primary care partners are often referred to as *invisible patients* because caregiving can come with significant but under- or unrecognized costs (ie, burden).
- Burden, stress, and strain put dementia care partners at increased risk of physical and mental health issues.
- Abuse, neglect, mortality, and premature institutionalization are more likely to occur in the context of elevated dementia care partner distress and burden.
- One of the most consistently identified contributors to care partner burden is the presence of neuropsychiatric and behavioral disturbances in the person living with dementia.
- Female care partners experience higher levels of burden than male care partners, possibly because they take on more caring responsibilities and spend more time caregiving.
- Factors protecting against burden for care partners include positive coping strategies, a sense of care partner mastery, and finding positive aspects of caring.
- Better relationships between care partners and people living with dementia are associated with less perceived burden.
- More inclusive theoretical frameworks for understanding the complexity of dementia care partner experiences are needed.
- An intersectionality framework supports the evaluation of key factors influencing dementia care partner experience including culture, history, place, and social determinants of health.
- The Zarit Burden Interview is a self-report inventory and is the most widely used measure to assess care partner burden.
- Dementia education combined with skills-based training in behavioral management increases sense of mastery and reduces care partner burden.

- Respite care can significantly reduce burden, but many dementia care partners may feel guilt or shame about asking for help.
- Lack of culturally informed and culturally competent care can create barriers for dementia care partners in accessing needed services.
- Maintaining social networks is important for promoting positive aspects of dementia caregiving.
- Acceptance and commitment therapy helps dementia care partners face the challenges of caring by accepting difficult feelings and promoting behavior that aligns with values and goals.
- Multicomponent interventions are effective at reducing dementia care partner burden, especially when they are tailored to address unique sociocultural needs.
- Health care providers can regularly assess dementia care partner burden informally through conversation and formally through structured questionnaires.
- Signs of dementia care partner burden include somatic symptoms, cognitive concerns, isolation, weight changes, feeling helpless or hopeless, feeling trapped, insomnia, and increased substance use.
- Self-care is an important component of caregiving but can be difficult to do, especially for female care partners, because of cultural, personal, and societal expectations about caring.
- Beneficial self-care activities foster social engagement, joy, a sense of achievement, creativity, maintaining self-identity outside of caring, sense of meaning or purpose, and relaxation.
- Providing a list of recommended therapists can relieve a substantial burden on dementia care partners for finding mental health care.
- Educational resources for dementia care partners are freely available on multiple government and nonprofit-supported websites.
- Health care professionals and staff can obtain training in evidence-based dementia care partner interventions to offer to patients and their families in clinic.
- Care partners should be encouraged to ask for help or ask if another family member might be willing to help coordinate care.
- National organizations and local aging agencies are critical for helping dementia care partners and people living with dementia connect with appropriate resources and services.

ARTICLE 13: IMPLEMENTING NEW DEMENTIA CARE MODELS IN PRACTICE

Vijay K. Ramanan, MD, PhD. Continuum (Minneapolis Minn). December 2024; 30 (6 Dementia):1863-1873.

ABSTRACT

Care for patients with Alzheimer disease and related neurodegenerative causes of dementia is in the midst of a transformation. Recent advancements in diagnostics and therapeutics reflect a rapidly evolving knowledge base and represent positive steps for patients and clinicians facing these progressive diseases; however, the complexities of emerging biomarkers and treatment options present challenges that will require systematic adaptations to routine care to facilitate effective incorporation of these options. This article reviews ongoing updates in the assessment and management of neurodegenerative causes of dementia, focusing on practical models for innovation that practices and health care systems can use to implement these new tools. In particular, sustainable adaptation in the field will benefit from a comprehensive approach implemented at local levels, including (1) education of clinicians and communities to refine perceptions about dementia care, (2) multifaceted stakeholder engagement to optimize

infrastructure and workflows to the new era, and (3) investments in personnel to address existing and exacerbated gaps.

KEY POINTS

- Alzheimer disease and related neurodegenerative disorders represent the most common causes of mild cognitive impairment and dementia syndromes in older adults.
- High-quality neuroimaging and fluid (cerebrospinal or blood-based) biomarkers are now widely available to assist in diagnosis and management of neurodegenerative dementias.
- Investing now in adaptations to implement emerging dementia therapies will position practices for resource-efficient iterative adjustments in the future.
- With new therapies for dementia, solitary practitioner models may enhance clinician autonomy and continuity of care, although absence coverage and practice variation across individuals could be limitations.
- In the right setting, group practice models for dementia clinics can offer some advantages in patient access and clinician work-life balance.
- Neurology and radiology collaboration is important for optimizing the delivery of emerging dementia treatments given specific requirements for therapy initiation and safety monitoring.
- Refining indications and delivery methods for neuropsychological assessment will help maximize rational use amid complementary test modalities and new therapeutic options for dementia.
- With new test and treatment modalities for dementia, having sustainable processes to handle prior authorizations and coverage appeals can minimize burdens on clinicians and practices.
- Disease- or treatment-specific clinic slots, templates, and order sets can streamline patient journeys and balance access across a variety of conditions.
- Future treatment regimens for Alzheimer disease and related disorders are likely to involve combination therapy targeting multiple mechanisms on a personalized basis.
- Clinical practices that retain flexibility in design and operations will have advantages with integrating new dementia treatment options.
- Neurologists have an opportunity to develop and disseminate updates on diagnosis and management of dementia to help support clinicians along a hub-and-spoke model of dementia care.
- Nurse education visits and development of patient-facing brochures and media can help translate complex dementia management concepts for a wide audience to optimize outcomes.
- Dementia care is best accomplished holistically, considering medication and nonmedication approaches in combination to address underlying disease, symptoms, and impacts on care partners.
- Disparities in dementia care are complex and motivate interventions to advance health equity throughout our communities.
- Complex new options for dementia diagnosis and management benefit from shared decision making to match the clinical plan values, preferences, and goals of care.

Issue Overview

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Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Dementia issue, participants will be able to:

- Apply a practical approach to recognize and stage patients with cognitive impairment due to Alzheimer disease
- Identify the distinguishing features of atypical Alzheimer disease variants, recognize their unique pathophysiologic pathways and diagnostic indicators, and implement tailored management strategies for each variant
- Describe the major clinical syndromes, neuropathology, and genetic variations associated with frontotemporal lobar degeneration
- Recognize the clinical syndrome of Lewy body dementia and discuss the current state of biomarkers, treatments, and emerging controversies
- Discuss how dysfunction of the vasculature contributes to cognitive impairment and dementia risk in older individuals, updated diagnostic criteria, and treatment recommendations
- Describe the pathologic and clinical characteristics linked to limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy (LATE), hippocampal sclerosis, and primary age-related tauopathy
- Discuss the prevalence, pathophysiology, assessment, and management of neuropsychiatric symptoms in patients with dementia
- Identify and describe neuroimaging findings in the most common age-related dementias
- Discuss currently available CSF and plasma biomarkers for the diagnosis of dementia and diagnosis-dependent treatment decisions
- Describe the pertinent genetic and pathologic features of Alzheimer disease and related dementias
- Implement evidence-based pharmacologic treatment plans for people with mild cognitive impairment or dementia due to Alzheimer disease
- Describe care partner experiences in dementia, recognize factors that cause and are consequences of burden, and identify resources for care partner education, support, training, and care guidance
- Discuss the challenges raised by emerging diagnostics and therapeutics for neurodegenerative causes of dementia and facilitate innovations in practice, research, and education for clinicians

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Dementia issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement

- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Apostolova reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Silbert discusses the off-label use of memantine and donepezil for the treatment of vascular dementia.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Clark discusses the unlabeled use of amantadine, amphetamine, aripiprazole, carbamazepine, citalopram, fluoxetine, lamotrigine, olanzapine, paroxetine, quetiapine, risperidone, selegiline, sertraline, and trazodone for the treatment of frontotemporal dementia.

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