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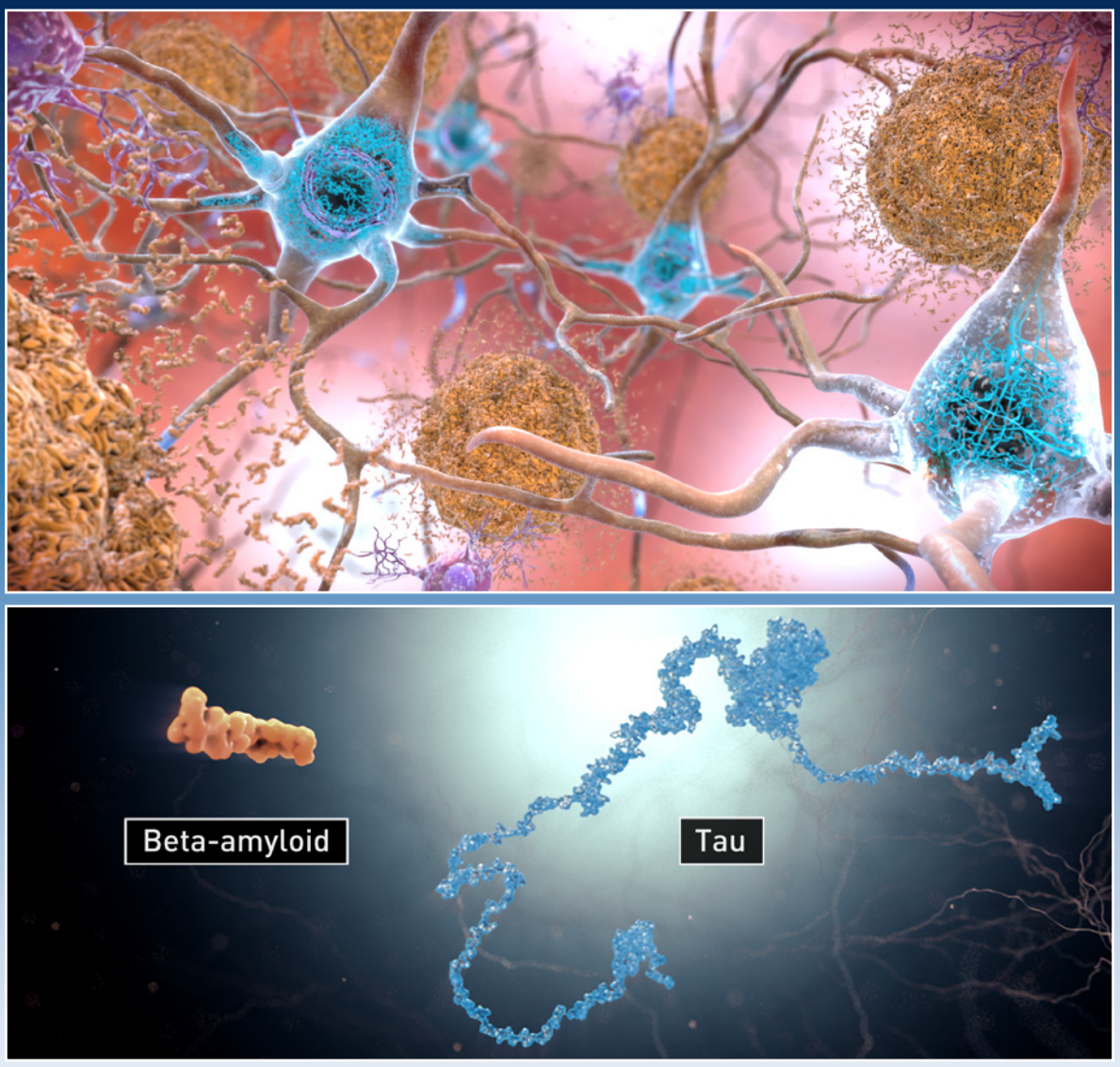

SPECIAL SECTION

THE DEMENTIAS

GUEST EDITOR: JOSEPH H. FRIEDMAN, MD

MAY 2025 VOLUME 108 • NUMBER 5 ISSN 2327-2228

RHODE ISLAND
MEDICAL JOURNAL

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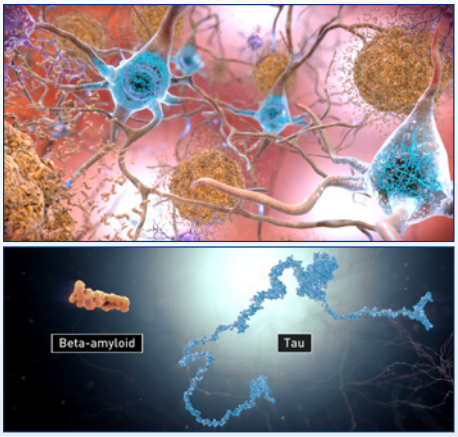

On the cover: Beta-amyloid and Tau in the brain. [IMAGES COURTESY OF THE NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH]

Introduction to the Dementia Issue

JOSEPH H. FRIEDMAN, MD
GUEST EDITOR

With our increasingly aged population, the enormous problem of dementia demands a much greater degree of investment than it has received. Brown University has recently opened its Center for Alzheimer's Disease, which works closely with other neurology research centers at the university, and the University of Rhode Island has its own neurological research center as well, The Ryan Institute for Neuroscience. Despite years of intense research and billions of dollars, we have barely scratched the surface of what needs to be known. In Alzheimer's disease (AD), for the first time, there is hope that new drugs may arrest or slow progression. We are unsure how close we are to this point in the other disorders addressed herein.

This issue of the *Rhode Island Medical Journal* contains articles on AD, the most common cause of dementia in wealthy countries, in **The Alzheimer's Disease Continuum – A New Diagnostic Approach** by **JONATHAN DRAKE, MD**; **SCOTT WARREN, MD, PhD**; **CHUANG-KUO WU, MD, PHD**. The Lewy body dementias, the second most common neurodegenerative causes, are presented in **Dementia with Lewy Bodies and the Lewy Body Dementias: 2/1** by this guest editor, and the frontotemporal dementias (FTDs) are reviewed in **The Diagnostic Landscape of Behavioral Variant Frontotemporal Dementia** by **MEGAN S. BARKER, PhD**; **MASOOD MANOOCHEHRI, BA**; **EDWARD D. HUEY, MD**. While the FTDs are a relatively rare cause, they are of extreme importance for our understanding of all of these neurodegenerative disorders, because these disorders involve tau protein, particularly in AD and FTD, often in dementia with Lewy bodies, Parkinson's disease, and the rare disorders, progressive supranuclear palsy and cortico-basal degeneration syndromes. They may hold the key to major advances. Monoclonal antibody treatments directed against Alzheimer-related amyloid protein are discussed.

Cerebrovascular disease, a frequent cause for dementia and a frequent contributor to the declines seen with the primary brain disorders, is not addressed here, although these patients are treated at the memory clinics as well as by neurovascular specialists.

The issue also contains a review of neuropsychological testing in **Neuropsychology in Aging: Best Practices for Cognitive Screening, When to Refer, and What to Expect From a Comprehensive Evaluation** by **SARAH PRIETO, PhD**; **LOUISA THOMPSON, PhD**. This type of testing is often an important tool in identifying a problem in its earliest stages, as well as helping to classify the disorder when other clinical signs are ambiguous.

Finally, the article, **From Acute Confusion to Chronic Decline: The Cognitive Impact of Delirium in Older Adults** by **FATIMAH HAMEED, MD, MSc**; **VICTORIA SANBORN, PhD**; **CAROLINE NESTER, PhD**; **LORI A. DAIELLO, PharmD, ScM**, reviews delirium, perhaps even more perplexing and challenging than the neurodegenerative disorders, since we lack any pathological starting point, and the clinical data is impossibly varied, making oversimplification unavoidable.

The contributions are all clinically focused, written by members of the Memory and Aging groups at Brown University Health and Butler Hospital. We are fortunate to have their expertise to treat our patients now and help forge a brighter future.

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Disclosures

Royalties: Springer press; Medlink
Consulting: EPI -Q
Expert Witness: Federal Defenders;
Beytin, Mclaughlin, Mclaughlin Attorneys

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The Alzheimer's Disease Continuum – A New Diagnostic Approach

JONATHAN DRAKE, MD; SCOTT WARREN, MD, PhD; CHUANG-KUO WU, MD, PhD

ABSTRACT

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

KEYWORDS: Alzheimer's disease; biomarkers; diagnostic criteria

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

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

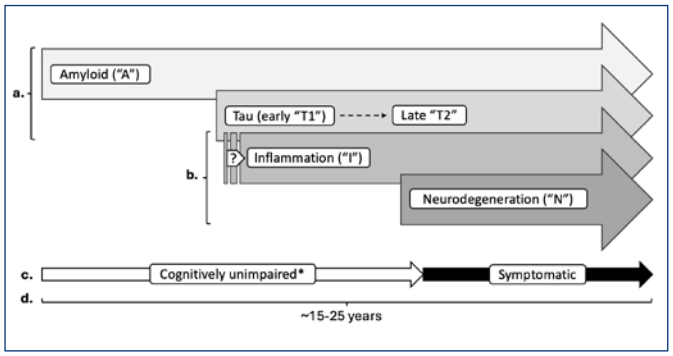

Figure key: A, amyloid; AD, Alzheimer's disease; Aβ, amyloid-beta; I, Inflammation; N, neurodegeneration; T, tau; T1, early-stage tau pathology; T2, later-stage tau pathology

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

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

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

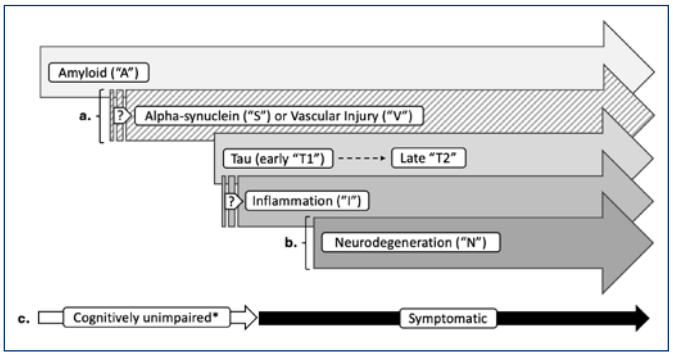

Figure key: AD, Alzheimer's disease; N, neurodegeneration; S, alpha-synuclein; V, vascular brain injury

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

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

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

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

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

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

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

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

Principle 2: The importance of clinical staging

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

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

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

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

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

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

CONCLUSION

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

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Disclosures

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Dementia with Lewy Bodies and the Lewy Body Dementias: 2/1

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KEYWORDS: Dementia with Lewy bodies (DLB); Lewy body dementias (LBD); Parkinson's disease with dementia (PDD)

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia in the Western world.[1] What had been presumed to be a rare disorder when first described,[2] turned out to be more common than expected. That Lewy bodies were found in the brains of 15–25% of cases that came to autopsy was a surprising discovery over 30 years later.[1] However, more recent clinical studies suggest that DLB makes up about 4% of community diagnoses of dementia.[3] While there are clinical criteria that distinguish DLB from Parkinson's disease with dementia (PDD), it is more accurate, as will be explained below, to lump the "Lewy body dementias" (LBD) together, unified both by their clinical signs and by their pathology.[4] PDD is far more common than DLB.

The Lewy body is a proteinaceous sphere (**Figure 1A,B**) found in the cytoplasm of occasional brain neurons, particularly in the brainstem-pigmented nuclei of these two neurodegenerative disorders, but is also found in the neuropil, outside of the cells, presumably a tombstone of a dead neuron. They are the hallmark pathological feature of both disorders required to make the diagnosis. The Lewy body was first described by Fritz Lewy, MD, in 1912. It is primarily composed of an abnormal variant of the protein, alpha-synuclein. While PD was first clinically described in detail in 1817 and was specifically noted by James Parkinson to spare cognition, DLB was first reported in a report by Stanley Aronson, MD, and his group in 1961,[2] with a novel finding of widespread cortical Lewy bodies in two adults with severe dementia and quadriplegia. Of note for this journal, Dr. Aronson, then a prominent neuropathologist in New York, became the founding dean of the medical school at Brown University and was a former Editor-in-Chief of the RIMJ for 10 years.

DEMENTIA WITH LEWY BODIES

The current clinical criteria for the diagnosis of DLB[4] is the fourth iteration since the first international symposium in 1996, and are contained in **Table 1**, unchanged since 2017.

Figure 1A. Lewy body in a substantial nigra cell, surrounded by neuro-melanin granules.

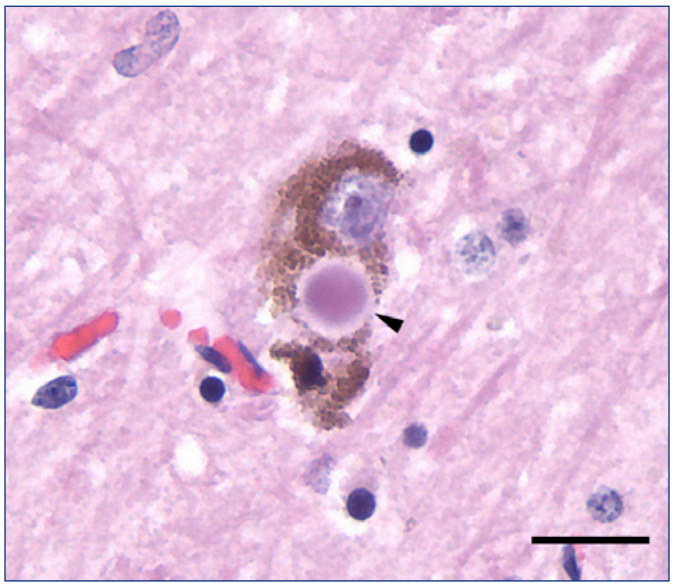
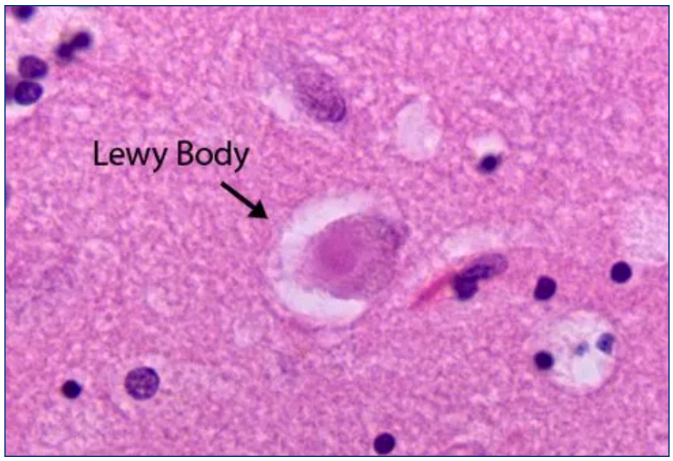


Figure 1B. Lewy body in the cortex.



Clinically, the disorder is often difficult to distinguish from Alzheimer's disease (AD) unless the patient has REM sleep behavior disorder or visual hallucinations, which are rare in AD. Memory disorders' experts miss the diagnosis about half the time when either of these two features are absent, because the other diagnostic criteria, while less common in

Table 1. 2017 Criteria for Dementia with Lewy bodies[4]

I. Required: dementia
II. Core clinical features: 2 required **a**. Fluctuating cognition, attention, alertness; visual hallucinations; REM sleep behavior disorder; parkinsonism
III. Supportive clinical features **a**. Neuroleptic sensitivity (parkinsonism); falls, imbalance; fainting or unresponsive spells; autonomic dysfunction; hyposmia; hypersomnia; non-visual hallucinations; delusions; apathy, anxiety, depression
IV. Indicative biomarkers
V. Abnormal DaT scan or MIBG myocardial scintigraphy; REM sleep w/o atonia
VI. Supportive biomarkers **a**. MR or PET imaging, EEG changes

AD, occur frequently enough to make diagnostic distinction impossible. Fluctuations in cognition or attention,[5] for example, are difficult to interpret and may also occur in AD. Many patients with dementing disorders have sleep disorders, often unrelated to the dementia, which predispose them to cognitive fluctuations due to daytime sleepiness. The vast majority are elderly and often take medications for hypertension, causing orthostatic hypotension, which may also cause cognitive fluctuations. Some parkinsonian features, such as motor slowness, stooped posture, reduced arm-swing, reduced spontaneous movements and imbalance are often part of what are often considered "usual" aging, previously labelled "senile-gait disorder,"[6] a term that has fallen out of favor. Episodes of reduced responsiveness are also not very helpful as AD patients may "tune out" as well, and frank coma is rare in DLB.[7] Although there are differences in the typical neuropsychological profiles of LBD and AD, they often overlap since there is overlap in the pathology in more than half the cases of the LBD, with neurofibrillary tangles being present, in addition to Lewy bodies. When visual hallucinations are present, the diagnosis of DLB is correct over 80% of the time.[8]

The typical cognitive profiles of the LBDs are: early deficits in attention, visual-spatial and executive function, without problems in language function or praxis.[8] These observations led to the commonly used comparison of "sub-cortical" vs "cortical dementias," based primarily on localization deduced from stroke and brain tumor cases. Language and praxis are considered cortical functions since their impairment are typically associated with pathology in the cortex, while executive function, involving planning and multitasking, are generally associated with subcortical or basal ganglia disorders. Early on, even prior to the development of dementia, PD patients decline on neuropsychological testing in these areas. Visual-spatial deficits occur in over 80% of DLB patients, so that its absence raises a red flag about a diagnosis.

In contrast, the typical neuropsychological changes that occur in AD involve language and praxis. The memory impairments are, in general different, too, in that LBD patients may form new memories but have difficulty retrieving them, whereas AD patients will most likely fail to lay down a memory trace at all. In addition, LBD patients are more likely to develop "neuropsychiatric" problems of anxiety, depression, fatigue and apathy early on, often preceding the development of the motor features of PD or even the memory and cognitive changes.

Although the "typical" neuropsychological patterns of the two disorders differ, there is often a significant overlap, which is most likely due to overlapping pathology. More than half of patients with LBD also have significant Alzheimer pathology, particularly neurofibrillary tangles, but also amyloid plaques, and many AD patients have Lewy bodies. What the connections between the two pathological processes are is unknown.[9]

PARKINSON'S DISEASE WITH DEMENTIA (PDD) AND THE TWELVE-MONTH RULE

Although James Parkinson in his famous monograph described the "senses and intellect being uninjured," this is, unfortunately, not usually the case after several years. The standard clinical criteria for diagnosing PD use dementia at onset as exclusionary, but dementia does develop in about 60–80% of PD patients, but usually several years after the onset of motor signs and symptoms. However, in some cases the dementia develops earlier. The guideline for distinguishing DLB from PDD is that if the dementia develops 12 months or more after the onset of motor symptoms, the diagnosis is PDD. If the dementia develops before the motor symptoms or within 12 months, then the diagnosis is DLB. It is often impossible to accurately make this distinction when first meeting a patient.

DIFFERENCES BETWEEN DLB AND PDD

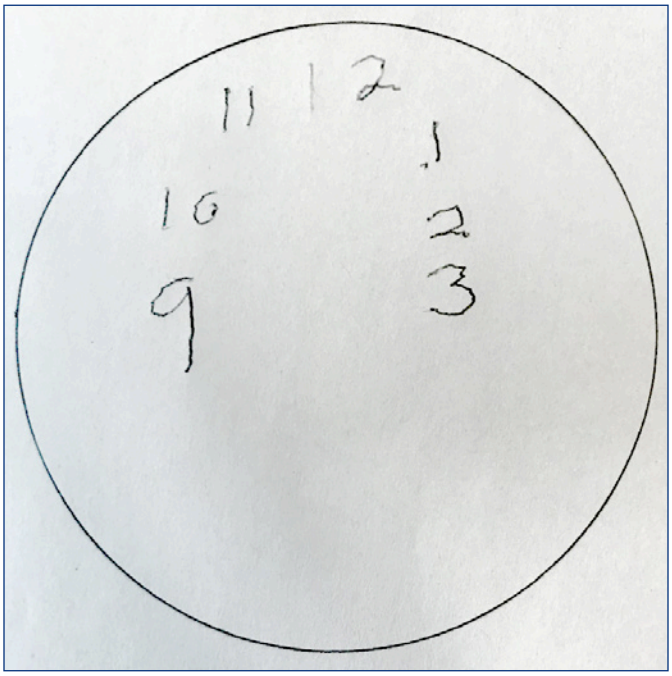
There are two clinical differences between these disorders. Most importantly, by definition, the dementia precedes or accompanies the motor features of PD within 12 months of motor onset. The second is the occurrence of visual hallucinations in DLB that are not associated with PD medication. In resource-wealthy regions, almost all hallucinatory experiences in PD are associated with the PD medications, but, on rare occasion, as in the case below, the hallucinations may occur without medication exposure. There have been no clear pathological differences between the two disorders, so that all authorities believe that the two disorders are very close, and some believe they are variants of the same disease, simply with the dementia beginning early.[10]

In general, DLB progresses more rapidly than AD, but the spectrum is wide.

CLINICAL EXAMPLE OF LBD

An 85-year-old man was evaluated for essential tremor (ET) and a gait abnormality. He had a stooped posture, reduced stride length, absent arm-swing, and mild slowness of movement. His tremor was typical of essential tremor, with no resting tremor. He was cognitively intact. His brain MRI showed a moderate degree of small vessel ischemic change. It was unclear if he had PD in addition to the ET, so a dopamine transporter (DaT) nuclear imaging scan was obtained and was normal. This was strong but not conclusive evidence against a diagnosis of PD. His parkinsonism was then ascribed to the white matter changes on MRI. He returned two years later with resting tremor, worsened bradykinesia, rigidity, and parkinsonian gait and dementia. In filling in a circle with numbers for a clock (see **Figure 2**), he had obvious problems completing the task, but also produced a large halo, particularly at the bottom, classic for PD, although the numbers were large. He also had developed occasional visual hallucinations, without being on any medications, as well as REM sleep behavior disorder.

Figure 2. Fill in the circle with numbers to make it look like a clock.



Because the dementia occurred more that 12 months after the parkinson motor features, he was diagnosed with idiopathic PD with dementia. Had the hallucinations and cognitive dysfunction been present a few months earlier, he would have met criteria for the diagnosis of DLB.

PATHOLOGY

The defining pathology of PD is the Lewy body, found in the pigmented brainstem nuclei locus coeruleus and the substantia nigra. In DLB, these are also seen, but with an increased number of these in the cortex and limbic system. These had not been seen in earlier years because of limited staining capabilities for histopathology. With increased sophistication, greater sensitivity for exposing LB has developed. In addition to the Lewy bodies in the brain, abnormal alpha-synuclein has been found to accumulate in neuronal processes and not just the cell body. These are even seen in peripheral nerves in the skin, which has led to a new diagnostic tool, the skin biopsy. A high percentage of DLB and PDD patients have amyloid plaques and neurofibrillary tangles sufficient to make a pathological diagnosis of concomitant AD.[9] When thinking about the two LBDs, one should keep in mind that the pathologies are identical and the neuropathologist can only make one or the other diagnosis based on the clinical history.

It is unfortunate that review articles on these disorders rarely note that pathologists are currently unable to estimate how many brain cells are lost in these disorders, what regions they are lost from, or what types of neurons they were. Thus, although much is known, we are largely dealing with "unknown unknowns" when we try to understand what goes wrong in the LBD. This will change soon, I believe, with automated techniques.

TREATMENT

As the two disorders are so similar, the treatments for their symptoms are identical as well. Although the cholinergic deficit in the LBD is greater than in AD, the cholinesterase inhibitors, three (donepezil, galantamine and rivastigmine) of the four FDA-approved medications for improving cognitive and memory function in mildly demented people, do not work any better than they do in AD. They are mildly helpful for memory and cognition, but not nearly as helpful for improving cognition or memory as L-Dopa is for mobility. They are mildly but not predictably helpful for reducing hallucinations in either of the LBDs, and have not been reported to improve delusions. The recently approved medications for AD reduce amyloid, which is thought to be important for AD, but is not directly involved in LBD and therefore not known to be useful in the LBD. Treating the parkinson features in DLB is, in most cases, limited to L-Dopa, the single most effective drug, which also has the least likelihood of causing or worsening hallucinations or delusions (and the least expensive). Treatment of motor problems is often limited by the mental side effects of L-Dopa, and, generally better postponed until the psychotic symptoms are controlled. Although no drug is FDA-approved for treating psychotic symptoms in DLB, pimavanserin is approved for this purpose in idiopathic PD. The strongest evidence in support of

an antipsychotic for psychotic symptoms in PD, for both demented and non-demented patients, is for clozapine, while quetiapine is, by far, the most commonly used. Quetiapine has been shown to not worsen motor problems in PD but has failed to show efficacy in three double-blind clinical trials.[11] Unfortunately, the other antipsychotic drugs have all been implicated in worsening motor function. Strong evidence earned olanzapine a Black Box warning for use in PD prior to all antipsychotics being labelled with this stigma. Less strong evidence exists for the dangers of aripiprazole and risperidone. Once psychotic symptoms are controlled, low dose L-Dopa is recommended, with close observation.

COMMENTS

PD is a common disorder, affecting about 1% of Americans over the age of 60. The majority of PD patients, but not all, develop dementia. The variety of clinical signs, their speed and order of progression, have prompted many experts to opine that PD is actually a collection of related diseases.[12] Using this hypothesis as a model, this author believes it makes more sense to consider DLB as one of these in which dementia occurs early, rather than that they are distinct diseases.

It is important to understand that neither the causes of these disorders nor their full pathologies are understood. Many gene abnormalities have been implicated in both sets of disorders. In PD, with the exception of alpha synuclein gene abnormalities, no single gene carries more than a 10% likelihood of producing PD. Furthermore, although Lewy bodies form the identifiable marker of the disease, with a loss of cells in certain locations, this does not account for the shrinkage seen in PDD brains. There have been cases of familial PD in which some affected members, although clinically identical, had LB and others did not, raising obvious questions about the importance of the LB. AD also has variants, the most obvious being the cortico-basal syndrome and the posterior-cortical variant, which are clinically very different than our usual conceptualization of AD.

CONCLUSION

PDD and DLB are disorders that are probably different points on the same spectrum. They are clinically and pathologically indistinguishable, differing only as to when the dementia begins with regards to the motor impairments. Our treatments are symptomatic only, and, unlike the situation with AD, not at a stage where we have reasonable interventions that may reverse disease or slow progression.

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Disclosures

Royalties: Springer press; Medlink

Consulting: EPI -Q

Expert Witness: Federal Defenders;
Beytin, Mclaughlin, Mclaughlin Attorneys

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The Diagnostic Landscape of Behavioral Variant Frontotemporal Dementia

MEGAN S. BARKER, PhD; MASOOD MANOOCHEHRI, BA; EDWARD D. HUEY, MD

ABSTRACT

The behavioral variant of frontotemporal dementia (bvFTD) is a progressive, neurodegenerative disorder, characterized by profound changes in personality, behavior, and social comportment. Diagnosis of bvFTD is challenging, and it is frequently misdiagnosed as an idiopathic psychiatric disorder (e.g., major depressive disorder, bipolar disorder) or another neurodegenerative disease (e.g., Alzheimer's disease dementia). The diagnostic challenge is exacerbated by a lack of reliable in vivo biological markers of disease pathology, which means that, at present, diagnosis relies largely on detailed behavioral and cognitive assessments. In this article, we discuss how clinical diagnostic criteria for bvFTD have evolved over the past three decades, and emphasize the diagnostic uncertainty that can arise when trying to distinguish between bvFTD and primary psychiatric disorders or other neurodegenerative diseases. In highlighting the strengths and limitations of the revised diagnostic criteria, and taking into account current diagnostic predicaments, we provide evidence-based recommendations for clinicians facing this diagnostic question. Finally, we touch on the importance of early (i.e., prodromal) diagnosis, and explain the utility of biomarkers for bvFTD diagnosis, with a nod to exciting research developments in this area.

KEYWORDS: behavioral variant frontotemporal dementia; frontotemporal lobar degeneration; diagnosis; diagnostic uncertainty

GENERAL INTRODUCTION

Frontotemporal dementia (FTD) is the clinical diagnosis most commonly associated with frontotemporal lobar degeneration (FTLD) neuropathology. FTD is a progressive, neurodegenerative disorder with an insidious onset. Based on the initial predominant symptoms, FTD can present as the behavioral variant (bvFTD), or as a language-based disorder, known as primary progressive aphasia (PPA). Of the FTD phenotypes, bvFTD is the most common.[1,2] Considered an "early-onset" dementia, the typical age of symptom onset is between 45–65 years. Survival is highly variable and differs among FTD phenotypes, but for bvFTD, the average survival from symptom onset is estimated to be between four–eight years.[3,4] Approximately 30–50% of patients with FTD will have a strong family history of dementia, and 10–20% will show an autosomal dominant inheritance pattern, with pathogenic variants of the *MAPT, GRN* and *C9orf72* genes accounting for the majority of these cases.[5]

BvFTD, the behavioral variant, is characterized by marked changes in personality and social conduct. It is the prototypical "frontal lobe" dementia, with severe apathetic and disinhibited behavior being two of its hallmark symptoms. Patients tend to show reduced motivation, decreased interest in hobbies and social engagements, a lack of concern for themselves or family members, poor social decorum, risk-taking behavior, repetitive or ritualistic behaviors such as tapping or counting, and binge eating, or an increased preference for sweet food. Cognitively, problems with executive function, such as complex problem solving and planning, are key. On neuroimaging, gross frontal and temporal lobe atrophy is often present, and on neuropathological examination, patients with bvFTD will most commonly show aggregated tau or TDP-43 proteinopathies.

DIAGNOSTIC CRITERIA

The first attempt at reifying clinical diagnostic criteria for FTD was published in a consensus statement from the Lund and Manchester groups in 1994.[6] The core diagnostic features put forth in this paper were extensive, including 10 "behavioral disorder" symptoms, as well as additional affective, speech-related, and physical symptoms, and a lengthy list of 16 exclusion features. Just four years later, in 1998, an updated version of these criteria were published by Neary and colleagues.[7] The Neary et al criteria separated out the FTD phenotypes into a behavioral variant and two language variants, and these diagnostic criteria were quickly adopted by most dementia centers. According to Neary et al, the behavioral syndrome, simply referred to as "FTD," could be considered a disorder of character change and disordered social conduct. Their core features included declines in social interpersonal conduct and in regulation of personal conduct, emotional blunting, and loss of insight, with insidious onset and gradual progression. Supportive diagnostic features included six additional behavioral symptoms, as well as speech/language changes and physical signs. The Neary et al criteria represented an important step forward

in the diagnosis of the behavioral syndrome of FTD, which would later come to be known as bvFTD. However, the limitations of these diagnostic criteria became apparent as the field advanced; primarily, they were criticized for being overly restrictive since all core features had to be present for a diagnosis, and were not well suited to detect impairments at the early stages of disease.

Designed to address these limitations, the most recent consensus criteria for bvFTD were published in 2011 by the International Behavioral Variant FTD Criteria Consortium, informally known as the Rascovsky et al criteria.[8] These criteria include six core features: 1) behavioral disinhibition, 2) apathy or inertia, 3) loss of sympathy or empathy, 4) perseverative, stereotyped, or compulsive/ritualistic behavior, 5) hyperorality or dietary changes, and 6) executive dysfunction with relative sparing of episodic memory and visuospatial functions.[8] For a diagnosis of "possible bvFTD," the individual must have three of the six symptoms present, and the symptoms must show progressive deterioration. For a diagnosis of "probable bvFTD," the individual must additionally have functional decline and evidence of frontal and/or anterior temporal disruption on neuroimaging. "Definite bvFTD" requires histopathological evidence of FTLD or a known pathogenic mutation to be present.

The Rascovsky et al criteria were developed based on explicitly observable symptoms, with the aim to minimize ambiguity and improve inter-rater reliability. This was posited as an advantage over the previous sets of diagnostic criteria, which had included terms that were clinically ambiguous (e.g., "impaired regulation of personal conduct") and required assumptions about the patient's cognitive/emotional state to be made (e.g., loss of insight). The Rascovsky et al approach was also the first data-driven method to develop diagnostic criteria, as the authors conducted a retrospective review of cases with confirmed FTLD pathology on autopsy to define the core characteristics of the bvFTD syndrome. Compared to the 1998 criteria, the 2011 criteria had significantly improved sensitivity – that is, they captured more true cases – at the expense of specificity. However, in relaxing the requirements for diagnosis, there is the potential for more false positive diagnoses, or misdiagnoses.

DIAGNOSTIC UNCERTAINTY

Diagnosis of bvFTD is challenging, as the core impairments are behavioral and overlap with the symptoms of psychiatric and other neurodegenerative disorders. This challenge is intensified by the fact that diagnoses are still primarily clinical; that is, without accurate confirmatory biological markers (biomarkers) of the disease, which we discuss later in this article; bvFTD diagnosis relies almost exclusively on behavioral and cognitive assessment.[9] Despite the multiple attempts at optimizing the diagnosis of bvFTD, misdiagnosis is a common and ongoing issue, which is a stressful experience for patients and families. Indeed, in one survey-based study, more than half of bvFTD patients had to see three or more doctors for a diagnosis to be made.[10] A recent retrospective review of records of patients admitted to an inpatient psychiatric service in Australia found that, compared to other neurodegenerative diagnoses, bvFTD was the most unstable diagnosis.[11] Specifically, almost half of patients who were given a diagnosis of bvFTD had their diagnosis switched at some point.[11] Other research has reported misdiagnosis rates of 25–50%.[10,12,13]

BvFTD is most frequently misdiagnosed as a primary psychiatric disorder, commonly major depression, bipolar disorder, schizophrenia, and anxiety.[12,13] This is unsurprising given the significant overlap in symptoms such as avolition, social withdrawal, risk-taking behavior, and, in some cases, delusions and hallucinations. A key challenge, and flourishing research area, is differentiating bvFTD from primary psychiatric disorders.

Primary Psychiatric Disorders

Despite some evidence suggesting that poorer global cognition and letter fluency scores are more indicative of bvFTD,[14] at mild stages, cognitive testing has not proven particularly helpful in distinguishing bvFTD from primary psychiatric disorders. Tests of social cognition have also shown some promise and may become more important in clinical practice in future years.[9] While social cognition deficits can be present in psychiatric disorders such as depression, schizophrenia, and bipolar disorder, the impairments are usually more profound in bvFTD.[15] One study found that tasks of emotion recognition (e.g., Ekman faces) can differentiate bvFTD from other major psychiatric disorders,[16] but research directly comparing bvFTD to specific psychiatric disorders is lacking.

Psychiatric interview tools, such as the Neuropsychiatric Inventory (NPI),[17] help to characterize psychiatric symptoms in dementia, but are not sufficient to exclude a diagnosis of a primary psychiatric disorder.[9] Instead, careful and detailed clinical phenotyping, including phenomenological descriptions of symptoms that may have important diagnostic value, is needed.[9] One example of this is apathy. Apathetic behavior, such as watching television all day, which is commonly reported by bvFTD patients, may signal a diagnosis of major depression; however, in bvFTD the apathy lacks the concomitant feelings of sadness or hopelessness characteristic of depression.[18]

In current practice, the most reliable way to distinguish bvFTD from idiopathic psychiatric disorders is by monitoring symptom progression. Generally, psychiatric disorders will show stability or even improvement over time, whereas in bvFTD symptoms are progressive. However, this is complicated by the high incidence of mid-life dementia in schizophrenia,[19] as well as logistic factors (e.g., inconsistent access to a specialist clinician to monitor symptoms). Thus,

developing assessment tools to differentiate bvFTD from psychiatric disorders is essential.

Recently, there have been important advancements in this arena. Ducharme and colleagues identified 17 clinical features that are more strongly associated with either primary psychiatric disorders or bvFTD, and created a bedside checklist with an impressive discriminatory ability.[20] The checklist includes items such as "was the patient self-referred?" which are more likely in psychiatric disorders, as well as symptoms more common in neurodegeneration, such as, "are there abnormalities on elemental neurological examination?" A score ≥11 is indicative of bvFTD, with specificity over 93%, while scores ≤8 are indicative of a psychiatric disorder, with specificity higher than 91%.[20] Prospective studies comparing the checklist features between bvFTD and psychiatric disorders are ongoing.[21]

It is critical to highlight the nature of the clinical features in this checklist. Of the 17 features, seven of them relate to the patient's insight into or understanding of the situation, ("Is the patient aware of or concerned about cognitive or behavioral changes?") or blunted/distressed emotional responses ("Is the patient emotionally distressed by the current situation?"). Loss of insight and emotional blunting were two core features of the 1998 Neary et al diagnostic criteria,[7] but were removed in the 2011 Rascovsky et al revision,[8] due to the focus on overtly observable symptoms. Based on the work by Ducharme et al,[9,20] it appears as though these two symptoms may in fact be some of the most valuable features to discriminate bvFTD from primary psychiatric disorders, and could be at the center of why Rascovky et al do not discriminate well between bvFTD and primary psychiatric disorders.[22] Future research should focus on reintegrating these features into the diagnostic criteria for bvFTD, and improving measurement of these somewhat nebulous symptoms.

Phenocopy Syndrome

The relative stability of psychiatric disorders vs. the progressive nature of bvFTD in distinguishing the two is further complicated by the bvFTD "phenocopy syndrome." A portion of patients meet clinical criteria for bvFTD but do not have evidence of FTD on imaging and do not decline functionally.[23] It has been proposed that this represents a bvFTD "phenocopy syndrome." Some suggest that this is a psychiatric disorder rather than true bvFTD, as at least a portion of patients with this phenocopy syndrome do not have FTLD neuropathology on autopsy.[24] Nevertheless, there are reports of the bvFTD phenocopy syndrome in carriers of the *C9orf72* pathogenic expansion, who would be expected to have FTLD pathology given their genetic status.[23,25] It remains unclear whether the phenocopy syndrome represents a psychiatric disorder or belongs on the bvFTD spectrum, and currently the only way to ascertain whether a patient has true or phenocopy bvFTD is to monitor them longitudinally.

Other Neurodegenerative Disorders

When distinguishing bvFTD from other neurodegenerative disorders, the two most common differential diagnoses are early-onset Alzheimer's disease (AD) and dementia with Lewy Bodies (DLB), which can also occur in those younger than 65 years. Poor insight is not as useful in parsing out these neurodegenerative diagnoses from each other as it is in the psychiatric disorder vs. bvFTD differential diagnosis, as it may be present in other dementias.[26,27] Cognitively there is significant overlap, as executive dysfunction is common across dementias; however, executive impairments tend to be more severe in bvFTD,[28] and some executive function tests are better at discriminating bvFTD from AD than others.[29] Traditionally, poor performance on episodic memory testing would be suggestive of AD, and indeed impaired episodic memory has typically been viewed as incongruent with bvFTD, but mounting evidence of episodic memory impairments in bvFTD has challenged this.[30–32] Neuropsychiatric symptoms, such as apathy, are often present in other neurodegenerative disorders, and characteristic features of DLB, such as psychosis and parkinsonism, have been observed in bvFTD.

Perhaps the most difficult neurodegenerative diagnosis to clinically differentiate from bvFTD is the behavioral variant of Alzheimer's disease (bvAD). BvAD is a rare, non-amnestic form of AD, where prominent behavioral problems are caused by Alzheimer pathology. The first diagnostic criteria for the clinical syndrome of bvAD were published recently,[33] and all five of the Rascovsky et al bvFTD behavioral features are represented in the core bvAD phenotype. There are, however, some very subtle clinical differences; for example, on average, patients with bvAD exhibit milder behavioral impairments than bvFTD patients at a similar disease stage, including less compulsivity and hyperorality.[33] One recent study showed more significant visuospatial impairments in bvAD compared to bvFTD,[34] but direct comparison studies are lacking. Currently, the only way to distinguish bvAD from bvFTD is by the presence of AD biomarkers (e.g. β-amyloid pathology in CSF or PET) or known pathogenic genetic variants.

PRODROMAL DIAGNOSIS

An important issue for all neurodegenerative diseases, which has recently gained traction in the bvFTD field, is that of early or "prodromal" diagnosis. The disease prodrome is the phase when mild symptoms are present, before the disease becomes fully manifest. This is a critical stage, as it is the phase during which interventions are likely to be most effective, and clinical trials would seek to enroll participants. In AD, this phase is known as Mild Cognitive Impairment (MCI). In FTD, various research groups have tackled the question of prodromal diagnosis in different ways.

At the earliest stages of disease, when symptoms are mild and have large overlap with normal populations, the

trade-off between sensitivity and specificity becomes paramount. High sensitivity means that there is a low bar for diagnosis, and therefore most cases are captured, but there is a risk of false positives. High specificity means that the requirements for diagnosis are stricter, so false positive diagnoses are minimized, but there is a risk of missing true cases. In developing criteria for the diagnosis of prodromal FTD, most research groups have prioritized sensitivity. Criteria by Benatar et al to diagnose FTD in the context of motor neuron disease[35] only require one or two cognitive tests to be impaired for a diagnosis. Benussi et al cast a broad net of many neuropsychiatric, cognitive, and motor symptoms for prodromal diagnosis, but did not include any clinical control groups against which to compare their results.[36] Barker et al published the only criteria to diagnose the prodrome of the behavioral variant, rather than any variant, of FTD,[18] and found good specificity against an AD control group. Importantly, the priorities of this trade-off differ, depending on the circumstances; for example; a clinical trial for a high-risk drug may require excellent specificity, so that individuals without the disease are not inadvertently enrolled, whereas a yoga intervention could afford to enroll as many participants as possible as the risk is low, so high sensitivity would be key. But this flexibility needs to be weighed against the complexity of using several different sets of criteria for prodromal bvFTD. The development of in vivo FTLD biomarkers will be important for accurate early diagnosis.

BIOMARKERS

Currently, the diagnosis of bvFTD is hampered by the absence of specific in vivo biomarkers for the two most common FTLD pathologies, intraneuronal insoluble aggregates of either the tau or TDP-43 proteins (the exception to this is when a specific autosomal dominant genetic mutation is present, as this directly implicates a specific FTLD – either tau or TDP-43 – pathology). More commonly, neuroimaging can aid diagnostic confidence by examining gross neuroanatomic changes. A pattern of focal frontal and/or anterior temporal gray matter atrophy is characteristic of bvFTD, while FDG-PET or SPECT scans are used to identify hypometabolism in these same areas, which may be detectable prior to gray matter atrophy.[37] These imaging findings warrant a diagnosis of probable (rather than possible) bvFTD according to Rascovsky et al criteria,[8] but each modality has its limitations. MRI findings have good specificity but are not very sensitive, as it is not uncommon for mildly impaired patients to not exhibit atrophy by visual inspection.[38] FDG-PET or SPECT are more sensitive, but other syndromes, including psychiatric disorders, can be associated with diffuse or frontal hypometabolism.[38] Findings of global atrophy or hypometabolism on MRI and PET/SPECT, respectively, can be consistent with bvFTD as well as with AD or other forms of dementia. There are efforts underway to use machine learning to increase the diagnostic power of imaging exams.[39]

Testing for AD biomarkers, through amyloid PET scans and CSF amyloid or CSF hyperphosphorylated tau, has been a mainstay of research centers and some clinics to rule out the involvement of AD pathology in an apparent bvFTD syndrome. Accurate and less burdensome blood-based biomarkers of AD have been developed recently and are poised to become more widely used.[40] While not yet in routine clinical use, researchers have also identified neurofilament light chain (NfL) as a potential biomarker of FTLD. NfL is a protein marker of axonal injury and neuronal loss that is detected across many neurodegenerative disorders.[41] Emerging evidence suggests a potential utility in cases where a differential diagnosis of bvFTD vs. a primary psychiatric disorder is being considered, but is likely of lower utility to distinguish FTLD from other neurodegenerative illnesses.[42] Exciting work to identify even more specific blood-based biomarkers particular to tau and TDP-43 pathologies is in progress, including through examinations of proteins present in plasma extracellular vesicles.[43]

CONCLUSION

The diagnostic landscape of bvFTD is complex, compounded by a general lack of understanding of the disorder within the medical and broader community. The diagnostic criteria have undergone several revisions, generally moving from strict to more liberal, and with a focus on observable symptoms rather than internal states of the patient, with the benefit of higher rates of diagnosis but the downside of more false diagnoses. Future research should consider revising the criteria to re-introduce specific symptoms that show good diagnostic value but were removed in the most recent iteration, such as emotional blunting. Until accurate in vivo biomarkers become available, diagnosing bvFTD is challenging and requires a multidisciplinary effort and multifaceted assessment, including detailed phenotyping and phenomenological descriptions of behavioral symptoms.

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Disclosures

The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgment/funding

The researchers have no funding to acknowledge.

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Neuropsychology in Aging: Best Practices for Cognitive Screening, When to Refer, and What to Expect From a Comprehensive Evaluation

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KEYWORDS: Cognition; Neuropsychology; Cognitive screening; Assessment; Dementia

INTRODUCTION

Recent census estimates indicate that older adults (i.e., 65 years and older) currently make up 17.5% of the United States population[1] and are projected to make up a quarter of the population by 2060.[2] Given these demographic trends, it is important to understand factors that contribute to negative outcomes in the context of aging, while supporting older adults' health and well-being. Normal aging is associated with declines in cognitive functioning, including processing speed, working memory, reasoning, spatial visualization, and memory.[3,4] Furthermore, neurodegenerative conditions (i.e., dementia) are common. Recent estimates suggest that one in nine older adults has Alzheimer's disease dementia.[5] The estimated cost for Alzheimer's Disease and Related Dementias (ADRD) care is $360 billion in the United States.[5] Early detection can identify reversible causes of cognitive impairment and help plan for the inevitable declines with the progressive causes.

UTILITY OF COGNITIVE SCREENERS

Cognitive screeners aim to provide an overview of a patient's cognitive functioning and are particularly helpful within medical settings because they can be administered quickly (i.e., within three to 15 minutes), do not require extensive training to administer, and may help identify individuals who would benefit from a more detailed cognitive evaluation. Cognitive screeners may be particularly helpful in evaluating individuals who are members of groups at risk of cognitive dysfunction (e.g., older adults). Using these screeners aligns well with recommendations encouraging evaluation in primary care settings (e.g., Medicare Annual Wellness Visits[6]), where patients are most likely to present with concerns. If time constraints limit the feasibility of screening tools, providers can ask their patients if they have concerns about their memory and consider scheduling a separate follow-up visit to focus on cognitive screening and care planning, if appropriate. Normalizing conversations around brain aging may help patients feel comfortable bringing up concerns if they do notice an issue in the future.

Frequently used brief cognitive screeners include the Mini-Mental State Examination (MMSE),[7] Kokmen Short Test of Mental Status (STMS),[8] and the Montreal Cognitive Assessment (MoCA).[9] Despite their utility, limitations of cognitive screeners include their inability to capture specific patterns of impairments or severity of dysfunction.[10] Screeners are thought to be less sensitive when used on individuals with higher levels of education,[11] low literacy,[11,12] or among individuals from historically marginalized backgrounds.[12] Although poor performance on a cognitive screener suggests that referral for a rigorous, neuropsychological evaluation may be helpful, the converse is not necessarily true. Neuropsychological assessment may still be warranted in cases of intact screening performance, for example, if a patient reports cognitive symptoms are interfering with daily functioning, or there is a significant family history of dementia.[11] Newer digital assessment tools are increasingly available[13,14] and, when appropriately validated for clinical use, may help address some of the barriers of traditional paper-and-pencil screening measures through features such as automated administration and scoring as well as electronic medical record (EMR) integration.[15]

CLINICAL NEUROPSYCHOLOGY

Clinical neuropsychologists are doctoral-level psychologists who use their expertise of brain-behavior relationships to evaluate, diagnose, and provide tailored treatment recommendations for individuals experiencing cognitive dysfunction.[16] In the context of referrals for older adults, clinical neuropsychologists can aid in assisting with the formulation of an accurate differential diagnosis, clarifying disease progression, and evaluating a patient's decision-making capacity.[17,18] Referrals from healthcare providers may be appropriate in several instances: 1) A patient presents with concerns (ideally corroborated by a family member or friend and confirmed with a cognitive screening); 2) A discrepancy between cognitive screening and self-reports of cognitive functioning emerges; 3) A focal cognitive impairment is identified; 4) The patient's cognitive functioning may be affected by multiple factors, such as chronic medical illness, psychiatric distress, pain, or a neurodegenerative process, that require further evaluation; 5) Mapping trajectory of cognitive functioning may be helpful with suspected mild cognitive impairment (MCI). Appointments include an in-depth clinical interview (typically 60 minutes), neuropsychological assessment (90–120 minutes), and feedback session (60 minutes).

CLINICAL INTERVIEW

During the clinical interview, the neuropsychologist takes comprehensive stock of the patient's developmental, academic, medical, psychiatric history, and social factors (e.g., social support). Interviews may also include care partners (e.g., family members, like a spouse or adult children) who know the patient well. Neuropsychologists glean information about the onset and course of cognitive symptoms and determine whether difficulties have interfered with activities of daily living (ADLs) through a comprehensive clinical interview. Instrumental ADLs include the patient's ability to manage finances, prepare meals, and manage medications, while basic ADLs include feeding, dressing, and personal hygiene.[19] Assessing ADLs is particularly important because the diagnosis of a major neurocognitive disorder (i.e., dementia) requires a significant decline in one or more cognitive domains, with the stipulation that these deficits interfere with ADLs. Taken together, these interviews can help clarify the severity of cognitive dysfunction that the patient is experiencing, assist with differential diagnosis, and help with the development of a care plan, if needed.

ASSESSMENT

Following the clinical interview, neuropsychologists use a battery of reliable, valid measures to assess a patient's cognitive strengths and weaknesses. While some neuropsychologists utilize a fixed battery approach, others use a flexible approach to construct a neuropsychological battery. Fixed batteries use the same, standardized assessments regardless of the patient's history, referral question, or presenting symptoms. However, most neuropsychologists adhere to a flexible evaluation approach that maintains a fairly standardized set of measures, with some flexibility to tailor evaluations based on the referral question, suspected neurodegenerative process, severity of impairment, and performance on the evaluations.[20] Typically, at least two tests are given for each of the following cognitive domains: attention and processing speed, executive functioning, language (comprehension, fluency, repetition, naming), visuospatial, learning and memory, and motor abilities. Testing is helpful for gaining a comprehensive understanding of current mood symptoms and psychiatric distress in a quantitative way by assessing symptoms of depression, anxiety, posttraumatic stress disorder, etc. on validated questionnaires.

RESULTS

Following the clinical interview and assessment, the neuropsychologist then integrates information from the evaluation with available medical records into a comprehensive report that is submitted to the referring provider. Using norm-based comparisons, neuropsychologists are able to glean an individual patient's performance compared to others of a similar demographic (e.g., age, sex, education) group.[21] Neuropsychologists take time to integrate the influence of important sociocultural, linguistic, and situational factors into how patients may present during the evaluation as well as consider the limitations of single timepoint assessment.[22]

A determination will be made regarding whether the patient meets criteria for a neurocognitive disorder based on the Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM–5-TR).[23] Severity and a listing of reasonable etiologies is generated.

RECOMMENDATIONS

Neuropsychologists provide comprehensive, tailored recommendations based on the patient's diagnosis, projected disease progression, impact on daily functioning, comorbid medical and psychiatric conditions, and personal values. Neuropsychologists may provide compensatory strategies to mitigate deficits in cognitive functioning. Rather than attempting to restore function, compensatory strategies are used to optimize patients' quality of life.[24] Results from one survey indicated that the vast majority of neuropsychologists (i.e., 85.7–100% of surveyed neuropsychologists) provide compensatory strategies across different clinical presentations, including dementia.[25] Patients may be encouraged to break complex tasks into smaller steps, write notes in a reliable location (e.g., a notebook kept in pocket), use a calendar to keep track of appointments, stick to a fixed schedule, etc.

Neuropsychologists also provide recommendations to target potentially reversible causes of cognitive dysfunction, including psychosocial stressors, psychiatric distress, poor sleep, chronic pain, or polypharmacy. For example, neuropsychologists may suggest an appointment to discuss medication reconciliation in the context of high anticholinergic burden, or talk to patients about sleep or headache hygiene. Addressing modifiable factors of dysfunction is of paramount importance since targeting them can improve cognitive outcomes and quality of life substantially. For individuals with dementia, recommendations may include discussing the benefits of having a trusted person to assist with making sound financial, medical, and legal decisions, as well as exploring long-term care options, such as family support, in-home assistance, or placement in a long-term care facility. When a patient's prognosis or cognitive trajectory is unclear or likely to change substantially in the future, a repeat evaluation may also be recommended.

RHODE ISLAND

It is essential that the healthcare landscape accommodates to the shifting demographics as the population of older adults in the United States rapidly grows. Neuropsychologists are specialists trained to assess, diagnose, monitor, and provide treatment recommendations related to healthy and unhealthy brain aging. Utilizing this resource may be of particular importance for Rhode Island residents, since Rhode Island has the highest proportion of adults aged 85 and older of any state.[26] Rhode Island, like many states, currently faces

a shortage of primary care providers and long wait times for neuropsychological evaluations. Optimizing early detection and management of mild cognitive impairment and dementia requires a multipronged approach, including patient and family education to reduce disease stigma and promote brain health awareness, provider education, and resources to ensure that basic steps can be made to address patient or family members concerns about cognitive decline. Although dementia due to neurodegenerative disease is always a progressive illness, many aspects of care can be managed by general practitioners similar to other common conditions in aging, such as diabetes and heart disease.

Articles that may be helpful:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3341654/pdf/DialoguesClinNeurosci-14-91.pdf
- https://practicalneurology.com/articles/2021-june/clinical-approach-to-dementia
- https://practicalneurology.com/articles/2021-june/neuropsychologic-approaches-to-dementia
- https://academic.oup.com/acn/article/32/5/541/3852214
- https://academic.oup.com/acn/article/34/3/418/5126782
- https://www.sciencedirect.com/science/article/abs/pii/0887617786900211
- https://www.sciencedirect.com/science/article/abs/pii/B9780080450469009967?via%3Dihub
- https://www.kaerbrain.org/
- https://familymedicine.uw.edu/cpc/clinical-tools/

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Disclosures

The authors have no conflicts of interest relevant to this article to disclose.

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From Acute Confusion to Chronic Decline: The Cognitive Impact of Delirium in Older Adults

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ABSTRACT

Delirium is prevalent in healthcare settings, leaving susceptible older adults at risk for persistent cognitive impairment, prolonged care needs, morbidity, and mortality. In older adult patients, delirium often arises from acute medical illnesses, infections, medications, and comorbidities, with age and underlying dementia increasing susceptibility. Its complex pathophysiology involves systemic inflammation, neurotransmitter dysregulation, disrupted brain metabolism, and physiological cycle disturbances. While delirium causes acute cognitive impairments, patients are often left with persistent dysfunction. Moreover, patients with pre-existing cognitive impairment are at higher risk for developing dementia or accelerated cognitive decline in the wake of a delirium episode. Delirium also worsens long-term quality of life, increasing risk for functional disability and need for institutional care. Prevention and management strategies focus on prophylaxis, early intervention, multicomponent programs, and pharmacological interventions, while ongoing research seeks to identify biomarkers and improve delirium detection and long-term management.

KEYWORDS: delirium, dementia, cognitive impairment, geriatric

INTRODUCTION

Delirium is a common medical condition that disproportionately affects older adults. Among hospitalized older adults, the incidence of delirium ranges from 10% on general medical floors, 20 to 45% following major surgeries, and up to 85% of patients in intensive care units.[1,2] When delirium occurs in the emergency department, 57–83% of cases are missed and often misattributed to dementia or psychiatric illness, and 25% of these patients are discharged home.[3] Known sequelae of delirium include increased risk of morbidity and mortality, prolonged hospital stays, increased hospital-acquired infections, poorer quality of life, and increased admissions to short- and long-term post-acute care facilities.[4]

Historically, delirium has been conceptualized as an acute confusional state associated with psychomotor disturbances and its cognitive effects were believed to be fully reversible. However, increasing reports of persistent post-delirium cognitive impairment in the medical literature of the mid-1980s motivated researchers to question the "transient" impact of delirium on the aging brain. Current evidence suggests that persistent cognitive dysfunction following an episode of delirium is not infrequent among susceptible older patients, particularly for those with pre-existing dementia. In one study, only 4% of patients who experienced delirium while hospitalized demonstrated full resolution of symptoms at discharge, and 60% experienced persistent symptoms six months later.[4,5] Given the potentially long-lasting impact of delirium on cognitive and functional outcomes, prevention, early identification, and treatment of delirium remains paramount for patients, families, caregivers, and healthcare systems, and may play a pertinent role in dementia prevention. Therefore, the primary objective of this paper is to summarize current knowledge of the acute and long-term cognitive impacts of delirium.

DIAGNOSTIC CRITERIA AND SUBTYPES

Delirium, defined by the *Diagnostic and Statistical Manual, 5th edition, Text Revision* (DSM-5 TR), is characterized by a disturbance in attention and accompanied by reduced awareness of the environment (Criterion A), occurring acutely with frequent fluctuations in severity (Criterion B) with additional disturbances in memory, orientation, language, visuospatial ability, or perception (Criterion C), which are not better explained by a pre-existing, established, or evolving neurocognitive disorder (Criterion D). Likewise, there is more evidence for a direct physiological consequence of another medical condition, toxin, substance, or multiple etiologies (Criterion E).[6]

Delirium has been classified into four phenotypes based on psychomotor/physical activity and level of arousal; these include hypoactive, hyperactive, mixed, and subsyndromal.[1,3,7] Hypoactive delirium is characterized by diminished motor activity and speech output, hypersomnolence, and lethargy, with or without perceptual disturbances.[3,7] As such, this subtype is often misattributed to medication effects, depression or fatigue. Hyperactive delirium typically presents with increased activity, (e.g., wandering, hypervigilance, restlessness, paranoia, agitation), sometimes accompanied by euphoria, and hyperverbal and pressured speech.

Although hyperactive delirium is slightly less prevalent than the hypoactive subtype,[7] it is more commonly recognized by clinicians. Mixed delirium features alternations between hypoactive and hyperactive episodes, leading to the classic "waxing and waning" presentation associated with delirium.[7] Patients with subsyndromal delirium exhibit one or more diagnostic features of delirium, but do not meet standard criteria. Subsyndromal delirium often goes unrecognized; leaving patients at elevated risk for negative outcomes post-discharge relative to hospitalized patients without delirium.[1]

Although this phenotypic construct is most utilized in delirium research, evidence suggests potential application for clinical prognostication as well. Of clear clinical relevance, variation in pathological mechanisms, precipitants, risk, and etiologic factors among delirium subtypes has been reported. Likewise, phenotypic prognoses may vary; hypoactive delirium, relative to hyperactive and mixed phenotypes, has been associated with the most detrimental prognosis, including higher short- and long-term mortality rates.[3,8] Amongst all phenotypes, delirium severity is correlated with increased length of hospitalization, likelihood of nursing home placement, increased re-admission within 30 days, worsened functional impairment, and overall morbidity.[3,9,10]

COGNITIVE IMPACT OF DELIRIUM

Associations between delirium and subsequent cognitive dysfunction have been observed across research populations, with and without premorbid cognitive disorders.[11] In longitudinal studies, cognitively unimpaired older adults who develop delirium show greater rates of decline and increased risk for progression to dementia than their peers who did not develop delirium.[12,13] For example, a large prospective study of cognitive aging in people 85 years or older found that participants who developed delirium during follow- up experienced a faster rate of decline in MMSE scores, relative to those without a history of delirium.[14] Results of a subgroup analysis of participants without cognitive impairment at baseline showed that delirium was associated with a nearly nine-fold increased risk of incident dementia. Likewise, Mohanty et al reported that postoperative delirium was associated with substantially elevated odds of a new dementia diagnosis (odds ratio [OR] 13.9; 95% confidence interval (CI), [12.2–15.7]) in the year following a major elective surgery.[15] More recently, a 2020 meta-analysis that included 24 observational studies of cognitive outcomes in older adult, general medical or surgery patients found that delirium was associated with worse post-discharge cognitive performance at three months or longer, across all studies.[16]

Factors influencing post-delirium outcomes

Premorbid cognitive function is arguably the most consistent and robust predictor of incident delirium, as well as post-delirium cognitive outcomes. While delirium has been identified as an independent risk factor for developing new-onset dementia, it is also strongly associated with accelerated cognitive decline among those with cognitive disorders, including mild cognitive impairment (MCI), Alzheimer's Disease (AD), and other neurodegenerative dementias.[11,14,17]

Compared to hospitalized patients with delirium, but no baseline cognitive impairment, patients with pre-existing dementia experienced more severe long-term cognitive and functional decline following delirium, as well as a 2.6-fold increase in risk of dying.[11,18] Researchers have also hypothesized that individuals with AD dementia may be particularly vulnerable to prolonged post-delirium cognitive deficits.[19] Associations of delirium with accelerated cognitive decline in AD have been shown to be independent of dementia severity, demographic factors, and pre-delirium rate of cognitive decline in some studies.[20]

The often-subtle cognitive deficits associated with MCI are rarely recognized or documented in clinical settings,[21,22] so it is not unexpected that relatively little is known about the impact of delirium. Notably, a recently proposed longitudinal study, MDDCohort (Mild Cognitive Impairment Delirium Dementia), will evaluate the rate of coversion from MCI to dementia following delirium.[23] Findings from a subgroup analysis of patients with MCI in a large prospective study of older adults undergoing major elective surgeries, demonstrated that patients with MCI developed postoperative delirium at twice the rate of those with normal cognition (adjusted relative risk (RR)=1.9, 95% confidence interval (CI) [1.3, 2.7]), and were at highest risk for moderately severe (RR=2.3, 95% CI [1.1–4.6]) or severe delirium (RR=4.6, 95% CI[2.0, 10.8]), compared to those without MCI or delirium.[24] Furthermore, patients with MCI and delirium were less likely to be discharged home, and at one month after surgery, this group was more likely to have developed new impairments in tasks associated with higher-level cognitive functions (e.g., handling finances, cooking, managing medications).

Last, recent results from the U.K. Delirium and Population Health Informatics Cohort (DELPHIC), a community-based study of cognitive aging, suggests that relationships between baseline cognitive function and long-term outcomes after delirium may be more complex than previously appreciated. As reported by Tsui et al, participants with strong baseline cognitive abilities had a lower risk of incident delirium, shorter duration, and lower delirium severity; however, this group experienced a larger post-delirium drop in cognitive scores, and were more likely to develop MCI during follow-up than those without delirium.[20,25]

Delirium: cause or catalyst of cognitive decline?

Taken together, the current literature suggests the potential for a bidirectional relationship between delirium and

cognitive impairment, such that presence of either may increase the incident risk of the other.[26] However, the question of whether post-delirium cognitive sequalae represent the unmasking of unrecognized dementia, an accelerant of preclinical neurodegeneration, or a direct cause of new onset of cognitive impairment, cannot be completely resolved with observational data. Advances in neurobiology research contribute additional insights into the nature of these relationships.

OVERVIEW OF DELIRIUM NEUROBIOLOGY

The underlying pathophysiology and associated neurologic and cognitive changes of delirium are complex, and multiple theories have been proposed.[4] Evidence supports the involvement of several potential mechanisms, including inflammation, immune response, abnormal brain energy metabolism, disruption in neurotransmitter function, cellular-signaling, and network connectivity, and neuronal injury and degeneration.[4,11,27] One systematic review across 32 studies examined markers of inflammation in delirium and found consistently elevated levels of serum CRP, TNF-α, IL-8, and IL-6.[28,29] The association between incident delirium and inflammatory markers may be due to the powerful cascade effect of the systemic inflammatory response resulting in the release of cytokines and leukocytes, reduced integrity of the blood-brain barrier, and risk for perivascular swelling, neuroinflammation, decreased oxygen perfusion, ischemia, and neuronal apoptosis.[4,29-31] Acetylcholinesterase deficiency and increased serum anticholinergic levels have also been associated with increased risk and severity of delirium, with improved levels associated with delirium resolution.[3,32,33] One hypothesis posits that a cumulative effect of neurotransmitter dysfunction and hampered brain network connectivity may reduce sensory processing and integration, resulting in delirium.[1] This may explain why the use of medications that alter neurotransmission, like opioids, may induce delirium.[29] Abnormalities in the above mechanisms, as well as alterations in melatonin and cortisol levels, may also explain why disruptions in sleep-wake cycles and heightened physiological stress are also implicated in cognitive changes and delirium onset.[4,31,34,35]

Several neurobiological mechanisms overlap between delirium and dementia. One pertinent and thorough review by Fong & Inouye[27] summarizes the current evidence for several shared mechanisms, including neuroinflammation, neuronal injury, neuroanatomical structural abnormalities, and AD-specific biomarkers. Novel research is being conducted on the potential use of related biomarkers for early detection or prediction of delirium, including apolipoprotein E isoforms, cortisol signaling, pro-inflammatory cytokines, neurodegenerative marker S100B, copeptin and 6-sulfatoxymelatonin levels, neurofilament light, and MRI-based brain atrophy.[36-38] Other unique approaches for prediction and detection of delirium include EEG and transcranial doppler.[27] The substantial overlap in mechanisms shared by delirium and dementia supports observations of frequent cooccurrence and mutual exacerbation.

NEUROPSYCHOLOGY OF DELIRIUM

Though acute change in cognitive functioning is a key characteristic of delirium, full neuropsychological evaluation is not typically pursued during acute episodes. Due to the nature of delirium, it is challenging to accurately evaluate higher-level cognitive abilities that require intact attention (e.g., problem solving). Other factors common in delirium (e.g., agitation, drowsiness) and inpatient settings (e.g., distracting noises, cognitive effects of medications) can also confound cognitive test performance. However, clinicians may use brief cognitive testing or simplified test measures to assess basic domains of cognitive impairment and track changes over time.

Many assessment tools are available to characterize diagnosis, subtype, symptom severity, and relevant risk factors for delirium,[39] including the Confusion Assessment Method,[40] Family Confusion Assessment Method,[41] Memorial Delirium Assessment Scale,[42] Delirium Rating Scale Revised-98,[43] and Mini-Mental Status Exam (MMSE).[44] These assessments are relatively easy to administer and, except for the MMSE, they are publicly available for clinical use. The first four utilize clinical observation or collateral report to evaluate for relevant symptoms and show moderate to strong sensitivity and specificity for identifying delirium (CAM 94%, 89%; FAM-CAM 74%, 91%;[45] DRS-R98 83–88%, 79–88%; MDAS 71%, 94%).[42,46] The MMSE can be used to assess severity and domain-specific cognitive impairments during delirium (e.g., language, attention, and memory). However, the MMSE has poor specificity for differentiating cognitive impairment due to delirium from other causes.[47] Impairment on such cognitive screeners without improvement following resolution of acute delirium symptoms may warrant further neuropsychological evaluation. Before attempting cognitive assessment with an individual with suspected delirium, clinicians should determine patient engagement to ensure accuracy of test findings. Though no formal tests of engagement have been developed for delirium specifically, clinicians can use behavioral observation and informal approaches. For example, assessing quality and nature of performance on certain MMSE items, including basic orientation questions, object identification, phrase repetition, and simple command following, may help gauge the patient's capacity to engage in more comprehensive assessment.

Attention, memory, language, and visuospatial abilities are commonly impaired in delirium and some simple bedside tasks can be administered to better gauge these abilities.[48] Attention can be assessed in delirium using a range of tasks, including digit span, spatial span, vigilance, serial

7s, and months of the year backwards (MOTYB).[48-50] Clinicians may also assess for deficits in expressive and receptive language using tasks of confrontation naming, and comprehension.[51]Interestingly, impaired written signature is quite specific to impairments in visual perception and visuospatial abilities are often reported in delirium, and patients may perform significantly worse.[52,53] Short- and long-term tests of memory can also be administered; however, it can be difficult to determine.[48]

Considering the significant overlap in cognitive symptoms between delirium and dementia,[54] there is no one task that can differentiate the two. However, subtle differences have been found on tests of verbal memory (dementia<delirium) and visual perception, and test combinations may be even more accurate (e.g., vigilance, MOTYB). The Cognitive Test for Delirium (CTD) was also specifically designed to evaluate cognitive abilities in patients with delirium and involves tasks of orientation, memory, comprehension, and vigilance. Patients with delirium perform significantly worse on the CTD (Total Score 9.5 ± 5.0) than patients with dementia (Total Score 24.5 ± 1.9) suggesting good discriminability.[55] Although often infeasible, cognitive evaluation before and after delirium may be the most useful to track post-delirium cognitive changes and guide decision-making concerning future treatments and support.

DELIRIUM PREVENTION AND MANAGEMENT

Since the cognitive and functional effects of delirium may persist long after the acute episode has resolved, taking measures to prevent and ameliorate delirium are critical. Risk for delirium has been associated with several factors, including older age, preexisting cognitive impairment, certain medical and psychiatric comorbidities, acute medical events, polypharmacy, certain medications and medical interventions, and treatment setting.[25,27,30,56-59] Though some of these risk factors are unalterable (e.g., age), several are modifiable and should be addressed to prevent or mitigate the effects of delirium. Non-pharmacological approaches include tailoring hospital environments (e.g., consistent reorientation to time using calendars), having a family member present, promoting physical functioning (e.g., ensuring use of visual and hearing devices), confirming proper hydration and nutrition, and preventing common complications (e.g., falls, urinary incontinence, and feeding disorders), all of which may increase delirium risk.[60,61] Additionally, the utilization of brief cognitive screeners (i.e., MMSE, MoCA) may help predict heightened delirium risk and establish a neurocognitive baseline. Serial cognitive monitoring may therefore promote early detection of delirium as well as dementia.

Drug toxicity and polypharmacy may precipitate delirium or prolong its duration, particularly in older adults with pre-existing health conditions. Anticholinergic medications, antipsychotics, benzodiazepines, and opioids have long been recognized as key triggers for delirium, although the frequency of association varies across different studies. Deprescribing deliriogenic medications and assessing medication withdrawal sequelae are recommended approaches to decrease delirium risk.[30,62] Pharmacologic prophylaxis of delirium has also been investigated, though not formally recommended since evidence from randomized trials is sparse and interpretation of effectiveness is challenging due to heterogeneity across treatment settings and patient populations. One meta-analysis of 58 studies showed favorability for the use of ramelteon, as well as promise for olanzapine, risperidone, and dexmedetomidine to reduce delirium incidence.[63] Evidence for use of medications to ameliorate acute delirium is also mixed. Some research has found that use of haloperidol plus lorazepam and alpha-2 agonist dexmedetomidine (depending on the patient population) may improve delirium outcomes;[62,64] however, various other studies have not found haloperidol to be superior to placebo for treatment of delirium on all-cause, post-hospitalization, or short-term mortality.[65,66] In general, findings on the general use of antipsychotics, opioids, benzodiazepines, statins, serotonin agonists, and cholinesterase inhibitors to mitigate delirium are unclear,[64] and as such, the deprescription of medications should be of primary consideration.[64-66]

CONCLUSIONS

Although delirium may be an acute medical event, the residual effects of delirium can be long-lasting and have significant implications for daily functioning and cognitive outcomes. The neurobiological mechanisms underpinning cognitive consequences of delirium and associated neurological diseases are multifaceted, complex, and, seemingly, overlapping. Patients with preexisting cognitive impairment, including those with MCI and dementia, are at greater risk for incident delirium, and episodes of delirium can exacerbate or incite new cognitive impairments. Presently, there are several measures that clinicians can take to reduce risk and screen for delirium, including integration of non-pharmacological and pharmacological approaches to patient care, and use of well-validated measures to detect and track delirium symptoms. Though completing neuropsychological testing before and after delirium is rarely feasible, subsequent outpatient evaluations can help track future changes and provide additional insights for treatment and support. Future research pursuing additional insights into the neurobiological mechanisms of delirium will hopefully support the development and implementation of additional approaches for prevention, detection, and treatment.

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Disclosures

Funding: This work was supported in part by the National Institutes of Health (R01 AG058648 to Lori Daiello)

Conflicts of Interest: None

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