

Dementia

Article 1: Late-onset Alzheimer Disease

Gil D. Rabinovici, MD. Continuum (Minneapolis, Minn). February 2019; 25 (1 Dementia):14–33.

ABSTRACT

PURPOSE OF REVIEW:

Alzheimer disease (AD) is the most common cause of late-onset dementia. This article describes the epidemiology, genetic and environmental risk factors, clinical diagnosis, biomarkers, and treatment of late-onset AD, defined by age of onset of 65 years or older.

RECENT FINDINGS:

An estimated 5.7 million Americans are living with AD dementia, with the number of affected individuals growing rapidly because of an aging population. Vascular risk factors, sleep disorders, and traumatic brain injury are associated with an increased risk of AD, while increased cognitive and physical activity throughout the lifespan reduce the risk of disease. The primary genetic risk factor for late-onset AD is the apolipoprotein E (APOE) ϵ 4 allele. AD typically presents with early and prominent episodic memory loss, although this clinical syndrome is neither sensitive nor specific for underlying AD neuropathology. Emerging CSF and imaging biomarkers can now detect the key neuropathologic features of the disease (amyloid plaques, neurofibrillary tangles, and neurodegeneration) in living people, allowing for characterization of patients based on biological measures. A comprehensive treatment plan for AD includes use of symptomatic medications, optimal treatment of comorbid conditions and neuropsychiatric symptoms, counseling about safety and future planning, and referrals to community resources.

SUMMARY:

AD is very common in older neurologic patients. Neurologists should set the standard for the diagnosis and care of patients with AD and should be familiar with emerging biomarkers that have transformed AD research and are primed to enter the clinical arena.

KEY POINTS

- Alzheimer disease is the most common cause of dementia, affecting an estimated 5.7 million Americans. The number of affected individuals is expected to triple by 2050 because of an aging population.
- Vascular risk factors, sleep disturbances, and traumatic brain injury increase the risk of Alzheimer disease. Increased years of education and greater cognitive and physical activity throughout the lifespan decrease the risk of Alzheimer disease.
- The estimated heritability of late-onset Alzheimer disease is approximately 60% to 80%. The primary genetic risk factor for sporadic late-onset Alzheimer disease is the apolipoprotein E (APOE) ϵ 4 allele.

- The clinical evaluation of patients with cognitive symptoms should first and foremost exclude reversible causes based on history, examination, and laboratory testing.
- Mild cognitive impairment is defined as objectively confirmed cognitive decline that does not interfere with independent function. When cognitive decline interferes with independent function, patients meet criteria for dementia.
- Late-onset Alzheimer disease typically presents with progressive decline in episodic memory, with variable involvement of other cognitive domains. Progressive memory impairment can also be caused by other neurodegenerative processes affecting the medial temporal lobes.
- Common neuropsychiatric symptoms in Alzheimer disease include depression, anxiety, mild apathy, irritability, and sleep disturbances.
- MRI findings in Alzheimer disease include medial temporal lobe and posterior-predominant cortical atrophy. Iron-sensitive sequences should be performed to assess for hemorrhages associated with cerebral amyloid angiopathy.
- The neuropathology of Alzheimer disease is defined by the presence of senile amyloid plaques and tau neurofibrillary tangles. The burden and distribution of these two lesions define the degree of Alzheimer disease neuropathologic changes.
- Late-life dementia is often associated with multiple brain pathologies. The most common are Alzheimer disease, Lewy bodies, vascular brain injury, hippocampal sclerosis, and TDP-43 inclusions.
- Amyloid plaques and tau tangles can be detected in living people based on changes in CSF levels of amyloid- β and phosphorylated tau or by using positron emission tomography radiotracers that selectively bind amyloid- β or tau aggregates.
- A comprehensive care plan for patients with Alzheimer disease includes treatment with Alzheimer disease-specific medications, treatment of relevant comorbid conditions, counseling about safety and future planning, and referrals to community resources.
- Acetylcholinesterase inhibitors are approved for the treatment of mild to severe Alzheimer disease dementia. Memantine is approved for the treatment of moderate to severe Alzheimer disease dementia.
- Difficult behaviors in Alzheimer disease should be addressed primarily with nonpharmacologic approaches, use of Alzheimer disease symptomatic drugs, and judicious use of antidepressants. Use of neuroleptics should be avoided, if possible, because of increased morbidity and mortality.

Article 2: Early-onset Alzheimer Disease and Its Variants

Mario F. Mendez, MD, PhD, FAAN. *Continuum (Minneapolis)*. February 2019; 25 (1 Dementia):34–51.

ABSTRACT

PURPOSE OF REVIEW:

Early-onset Alzheimer disease (AD) is defined as having an age of onset younger than 65 years. While early-onset AD is often overshadowed by the more common late-onset AD, recognition of the differences between early- and late-onset AD is important for clinicians.

RECENT FINDINGS:

Early-onset AD comprises about 5% to 6% of cases of AD and includes a substantial percentage of phenotypic variants that differ from the usual amnesic presentation of typical AD. Characteristics of early-onset AD in comparison to late-onset AD include a larger genetic predisposition (familial mutations and summed polygenic risk), more aggressive course, more

frequent delay in diagnosis, higher prevalence of traumatic brain injury, less memory impairment and greater involvement of other cognitive domains on presentation, and greater psychosocial difficulties. Neuroimaging features of early-onset AD in comparison to late-onset AD include greater frequency of hippocampal sparing and posterior neocortical atrophy, increased tau burden, and greater connectomic changes affecting frontoparietal networks rather than the default mode network.

SUMMARY:

Early-onset AD differs substantially from late-onset AD, with different phenotypic presentations, greater genetic predisposition, and differences in neuropathologic burden and topography. Early-onset AD more often presents with nonamnestic phenotypic variants that spare the hippocampi and with greater tau burden in posterior neocortices. The early-onset AD phenotypic variants involve different neural networks than typical AD. The management of early-onset AD is similar to that of late-onset AD but with special emphasis on targeting specific cognitive areas and more age-appropriate psychosocial support and education.

KEY POINTS

- Early-onset Alzheimer disease, which makes up about 5% to 6% of all cases of Alzheimer disease, is distinct from late-onset Alzheimer disease in a number of clinical, genetic, neurobiological, and management features.
- Early-onset Alzheimer disease is the most common cause of early-onset neurodegenerative dementia.
- Many clinical, neuropathologic, and management differences exist between early-onset and late-onset Alzheimer disease.
- One major difference between early-onset and late-onset Alzheimer disease is that one-third or more of patients with early-onset Alzheimer disease present with language, visuospatial, or other phenotypes rather than the usual amnestic disorder seen in late-onset Alzheimer disease.
- MRI of patients with early-onset Alzheimer disease shows more widespread cortical atrophy, particularly in the parietal cortex, compared to the more limited atrophy affecting temporal regions in patients with late-onset Alzheimer disease.
- Fludeoxyglucose positron emission tomography shows greater parietal hypometabolism in early-onset Alzheimer disease compared to greater bilateral temporal hypometabolism in late-onset Alzheimer disease.
- Amyloid positron emission tomography is positive in most patients with early-onset Alzheimer disease who would not be expected to have age-associated brain amyloid deposition and can be useful in diagnosis of the disorder.
- Tau positron emission tomography has promise for future use in early-onset Alzheimer disease, particularly in correlating localization of changes with clinical symptoms.
- CSF analysis in early-onset Alzheimer disease is similar to late-onset Alzheimer disease, showing the characteristic low amyloid- β_{1-42} and high total tau and phosphorylated tau levels but with some variations.
- The vast majority of patients with early-onset Alzheimer disease have a nonfamilial, or sporadic, form.
- Only 11% or less of those with early-onset Alzheimer disease (about 0.6% of the total of all patients with Alzheimer disease of any age) have familial Alzheimer disease associated with one of the three known autosomal dominant mutations in *APP*, *PSEN1*, or *PSEN2*.
- An active area of genetic research is the recognition of a polygenic risk for sporadic early-onset Alzheimer disease from a number of susceptibility genes.
- On neuropathology, patients with early-onset Alzheimer disease (especially with the variants) are more likely to have hippocampal sparing with increased neocortical tau pathology, particularly in the parietal cortex and, to a lesser extent, the frontal cortex, than patients with late-onset Alzheimer disease.
- On neuropathology, tau and neurofibrillary tangles, more than amyloid- β_{1-42} and neuritic plaques, correspond with the features of early-onset Alzheimer disease, with a relatively greater tau burden in early-onset Alzheimer disease than in late-onset Alzheimer disease.

- Phenotypic variants of early-onset Alzheimer disease include those that present with language impairment (known as *logopenic variant primary progressive aphasia*), those that present with visuospatial or visuoperceptual impairments (known as *posterior cortical atrophy*), frontal or behavioral/executive variants, a number of parietal syndromes (such as the acalculia variant of early-onset Alzheimer disease), and a subgroup of patients with corticobasal syndrome.
- Phenotypic variants of early-onset Alzheimer disease may involve alternative frontoparietal neural networks rather than the posterior default mode network implicated in late-onset Alzheimer disease.
- Logopenic variant primary progressive aphasia, the most common nonamnestic phenotypic variant of early-onset Alzheimer disease, presents with a progressive decline in language with relatively spared memory and cognition due to focal Alzheimer neuropathology in temporoparietal language areas in the left hemisphere, especially the superior/midtemporal gyrus, angular gyrus, and midfrontal cortex.
- In logopenic variant primary progressive aphasia, neuroimaging and CSF studies usually reveal abnormalities consistent with early-onset Alzheimer disease, including focal atrophy and decreased metabolism in the left temporoparietal junction.
- Posterior cortical atrophy, the second most common early-onset Alzheimer disease variant, presents with progressive and disproportionate loss of visuospatial or visuoperceptual functions, usually due to Alzheimer neurodegeneration of posterior visual cortical regions.
- The frontal variant of Alzheimer disease, now known as *behavioral/dysexecutive Alzheimer disease*, presents with features suggestive of frontotemporal lobar degeneration but most commonly with apathy or abulia.
- Less common phenotypic variants of early-onset Alzheimer disease may have prominent parietal lobe symptoms and signs, exemplified by the acalculia variant from early Alzheimer neuropathology in the left inferior parietal lobule, particularly the intraparietal sulcus.
- Acetylcholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, are indicated in the management of patients with early-onset Alzheimer disease, with the usual precautions and titration schedules.
- The management of early-onset Alzheimer disease may differ from late-onset Alzheimer disease when targeting the management of specific cognitive and behavioral deficits.
- Management of patients with early-onset Alzheimer disease must also consider providing genetic counseling if patients are to be evaluated for familial Alzheimer disease when the family history is suggestive of an autosomal dominant disorder.
- The provision of age-appropriate psychosocial support is important in the management of early-onset Alzheimer disease.

Article 3: Posterior Cortical Atrophy

Jonathan M. Schott, BSc, MD, FRCP, FEAN, SFHEA; Sebastian J. Crutch, PhD, CPsych. Continuum (Minneapolis, Minn). February 2019; 25 (1 Dementia):52-75.

ABSTRACT

PURPOSE OF REVIEW:

This article presents an overview of the clinical syndrome of posterior cortical atrophy (PCA), including its pathologic underpinnings, clinical presentation, investigation findings, diagnostic criteria, and management.

RECENT FINDINGS:

PCA is usually an atypical form of Alzheimer disease with relatively young age at onset. New diagnostic criteria allow patients to be diagnosed on a syndromic basis as having a primary visual (pure) form or more complex (plus) form of PCA and, when possible, on a disease-specific basis using biomarkers or underlying pathology. Imaging techniques have demonstrated that some

pathologic processes are concordant (atrophy, hypometabolism, tau deposition) with clinical symptoms and some are discordant (widespread amyloid deposition). International efforts are under way to establish the genetic underpinnings of this typically sporadic form of Alzheimer disease. In the absence of specific disease-modifying therapies, a number of practical suggestions can be offered to patients and their families to facilitate reading and activities of daily living, promote independence, and improve quality of life

SUMMARY:

While rare, PCA is an important diagnostic entity for neurologists, ophthalmologists, and optometrists to recognize to allow for early accurate diagnosis and appropriate patient management. PCA provides an important opportunity to investigate the causes of selective vulnerability in Alzheimer disease.

KEY POINTS

- A striking feature of posterior cortical atrophy is that the majority of affected individuals have an unusually early age at disease onset, typically presenting between 50 and 65 years of age.
- Most patients with posterior cortical atrophy have underlying Alzheimer disease.
- The core features of posterior cortical atrophy include visuospatial and perceptual deficits as well as features of Gerstmann syndrome (acalculia, left-right disorientation, finger agnosia, and agraphia), Balint syndrome (ocular motor apraxia, optic ataxia, and simultanagnosia), alexia, and apraxia.
- Patients with posterior cortical atrophy may have a history of repeated visits to optometrists and ophthalmologists and multiple unsuccessful changes in eyeglasses or surgical procedures in an attempt to correct acuity.
- Over time, difficulties with reading emerge in the vast majority of patients with posterior cortical atrophy.
- Patients with posterior cortical atrophy often become anxious about riding on escalators, particularly when going down; can be cautious when crossing the road because of difficulties in judging the speed of traffic; and can have difficulty with revolving doors.
- Combinations of visual problems and dyspraxia in patients with posterior cortical atrophy have significant functional consequences, including difficulty in getting dressed; cooking; and using cell phones, remote controls, and computers.
- Simultanagnosia (the inability to interpret the entirety of a visual scene) can often be demonstrated by asking an individual to describe a complex picture; rather than describing it in its entirety, individuals with posterior cortical atrophy will often hone in on specific features and fail to see the picture as a whole.
- A particularly striking and very common feature of posterior cortical atrophy is the presence of an apperceptive agnosia.
- Visual disorientation (likely reflecting combinations of simultanagnosia and optic ataxia), when present, is a striking sign in patients with posterior cortical atrophy.
- When performing neuropsychological testing in posterior cortical atrophy, it is important that the testing psychologist is aware of the patient's difficulties with vision, ensuring that test material is, whenever possible, presented in verbal rather than visual form.
- In the presence of a typical history for posterior cortical atrophy, the absence of marked parietooccipital volume loss should not exclude the diagnosis.
- Fludeoxyglucose positron emission tomography may be extremely valuable in demonstrating hypometabolism within the parietooccipital cortices.
- While amyloid positron emission tomography has a role in confirming the presence or absence of amyloid pathology, it is not useful in distinguishing between Alzheimer disease syndromes.
- Tau positron emission tomography, which is currently only available in a research setting, often shows very striking posterior cortical deposition of tau pathology.
- Posterior cortical atrophy due to Alzheimer disease is a sporadic condition, and routine testing for the autosomal dominant forms of the disease is not usually indicated.

- For most patients with posterior cortical atrophy due to Alzheimer disease, treatment with acetylcholinesterase inhibitors or memantine, as would be standard treatment for Alzheimer disease, is appropriate.
- The mainstay of management of patients with posterior cortical atrophy (as with typical Alzheimer disease) is the provision of practical and psychological support to affected patients and their caregivers.
- Most patients with posterior cortical atrophy will not be fit to drive. Establishing driving safety is of paramount importance.

Article 4: Behavioral Variant Frontotemporal Dementia

William W. Seeley, MD. *Continuum (Minneapolis, Minn)*. February 2019; 25 (1 Dementia):76-100.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical, anatomic, genetic, and pathologic features of behavioral variant frontotemporal dementia (bvFTD) and discusses strategies to improve diagnostic accuracy, emphasizing common pitfalls to avoid. Key aspects of management and the future of diagnosis and care for the disorder are highlighted.

RECENT FINDINGS:

BvFTD is a clinical syndrome, not a disease. Patients with the syndrome share core symptoms that reflect degeneration within the most consistently affected brain regions, but accompanying features vary and reflect the precise topography of regional degeneration. The clinician must distinguish a bvFTD syndrome from psychiatric illness and other neurodegenerative syndromes that feature a prominent behavioral component. Antemortem prediction of pathologic diagnosis remains imperfect but improves with careful attention to the clinical details. Management should emphasize prevention of caregiver distress, behavioral and environmental strategies, symptom-based psychopharmacology, and genetic counseling.

SUMMARY:

BvFTD is an important and challenging dementia syndrome. Although disease-modifying treatments are lacking, clinicians can have a profound impact on a family coping with this disorder. Treatment trials are under way for some genetic forms of bvFTD. For sporadic disease, pathologic heterogeneity remains a major challenge, and ongoing research seeks to improve antemortem molecular diagnosis to facilitate therapeutic discovery.

KEY POINTS

- Behavioral variant frontotemporal dementia (bvFTD) is an important disorder that can be difficult to recognize, in part because of the wide normative variation in social-emotional functions and the long list of disorders that affect those functions.
- BvFTD is a syndrome, not a disease, and clinicians who diagnose bvFTD should generate a differential diagnosis.
- BvFTD presents with slowly progressive decline in social and emotional functions.
- BvFTD core diagnostic features reflect degeneration of networked structures, typically including the anterior insula, anterior cingulate and adjacent medial prefrontal cortices, amygdala, striatum, and thalamus.
- Features that develop less frequently in patients with bvFTD reflect variable involvement of additional brain regions.

- Patients with bvFTD often develop prominent motor deficits of various types later in the course of the syndrome.
- BvFTD is the result of a known pathogenic variant in 15% to 20% of patients.
- Expansions in *C9orf72* are the most common genetic cause of bvFTD and are commonly accompanied by motor neuron disease.
- BvFTD results from a diverse array of neuropathologic entities, most of which are classified as frontotemporal lobar degeneration.
- Accurate bvFTD diagnosis requires a methodical stepwise approach that relies heavily on the clinical history.
- Both neurodegenerative and non-neurodegenerative causes should be considered in all patients with bvFTD.
- Structural MRI and, increasingly, molecular biomarkers play a key role in predicting pathology in patients with a bvFTD syndrome.
- Occasionally, patients with bvFTD have severe early memory loss or a normal MRI.
- Executive dysfunction is common in bvFTD but also in other disorders and should not be used as an indicator of bvFTD unless accompanied by signature social-emotional features.
- Model care for bvFTD involves contributions from a multidisciplinary team that supports both patient and caregiver.
- BvFTD caregivers are at high risk for burnout.
- Nonpharmacologic approaches are often the best way to manage troublesome behavioral symptoms in bvFTD.
- Pharmacologic management of bvFTD should target specific symptoms, such as overeating, compulsivity, severe agitation, or psychosis.
- Selective serotonin reuptake inhibitors are first-line therapy for overeating and compulsivity symptoms in bvFTD.
- Acetylcholinesterase inhibitors have shown no benefit in bvFTD and may worsen behavioral symptoms.

Article 5: Primary Progressive Aphasias and Apraxia of Speech

Hugo Botha, MBChB; Keith A. Josephs, MD, MST, MSc. *Continuum (Minneapolis)*. February 2019; 25 (1 Dementia):101–127.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews two of the primary progressive aphasias (PPAs), disorders characterized by the early and predominant impairment of language, and primary progressive apraxia of speech, a degenerative motor speech disorder that is closely related to PPA. An outline of the history and controversy surrounding how these disorders are classified is provided before the article focuses on each disorder's clinical and imaging features.

RECENT FINDINGS:

Over the past decade, the classification of degenerative speech and language disorders has been refined. Clinical, imaging, and pathologic evidence suggests that primary progressive apraxia of speech is a distinct degenerative disorder. Furthermore, multiple lines of evidence have highlighted issues with nonfluent/agrammatic variant PPA, which complicates the diagnosis, prognosis, and study of this disorder. Semantic variant PPA, while not without controversy, remains one of the most well-defined disorders, with good clinicopathologic correlation.

SUMMARY:

Accurate classification and diagnosis of these degenerative speech and language disorders is crucial in clinical practice and ongoing research efforts. For nonfluent/agrammatic variant PPA, the authors suggest emphasizing agrammatism as the core inclusion criterion and taking care not to include patients with isolated or predominant apraxia of speech. Isolated apraxia of speech can be the manifestation of a degenerative disease and, based on the different prognosis, should be recognized as distinct from PPA. Finally, it is important to recognize that some patients with semantic dementia, despite sharing the same pathologic associations, may not meet criteria for PPA.

KEY POINTS

- *Primary progressive aphasia* refers to a group of neurodegenerative diseases characterized by early and prominent language impairment occurring in the relative absence of cognitive impairment, behavioral disturbance, or motor symptoms.
- Three canonical variants of primary progressive aphasia (PPA) are recognized, of which two (nonfluent/agrammatic variant PPA and semantic variant PPA) are classified as frontotemporal dementia syndromes while the other (logopenic variant PPA) is most commonly viewed as an atypical variant of Alzheimer disease.
- Apraxia of speech is a motor speech disorder thought to result from impaired planning and programming of the movements required for speech production.
- The most widely accepted current classification scheme and diagnostic criteria for primary progressive aphasia consists of two stages. First, a root diagnosis of primary progressive aphasia is considered. Second, criteria for the three main variants are considered, each with a set of mandatory and supportive features.
- While motor speech disorders such as dysarthria and apraxia of speech often co-occur with aphasia, these are clearly not language impairments that would, on their own, qualify a patient for a diagnosis of primary progressive aphasia.
- The relative dominance of phonetic impairment (sound level errors, such as distorted substitutions or additions) or prosodic impairment (such as slow rate or segmented speech) is the primary source of heterogeneity in apraxia of speech.
- Primary progressive apraxia of speech refers to cases in which apraxia of speech is the sole initial manifestation of a neurodegenerative disease.
- In primary progressive apraxia of speech, it is crucial to ask about writing or typing, as preservation of these forms of communication is often striking despite severe speech impairment.
- Cases in which apraxia of speech dominates over aphasia appear to have clinical and imaging features that are more like those seen in primary progressive apraxia of speech than nonfluent/agrammatic variant primary progressive aphasia.
- Patients with primary progressive apraxia of speech typically score well within the normal range on bedside cognitive testing and may continue to do so in the later disease stages, provided written responses are allowed.
- The most helpful parts of the speech examination for primary progressive apraxia of speech are those that demand the production of motorically complex utterances: conversational or narrative speech, alternating motion rates, sequential motor rates, and repetition of increasingly complex words and sentences.
- About two-thirds of patients with primary progressive apraxia of speech have a coexisting nonverbal oral apraxia, which can be assessed at the bedside by asking the patient to perform simple movements such as smacking their lips, clicking their tongue, coughing, or blowing.
- Gray and white matter atrophy of the motor, premotor, and supplementary motor areas bilaterally has been reported in primary progressive apraxia of speech at group level, but it is worth noting that this may be fairly asymmetric at the single patient level.

- Approximately 40% of patients with primary progressive apraxia of speech develop a progressive supranuclear palsy/corticobasal syndrome–like disorder, which has been termed *progressive supranuclear palsy–apraxia of speech*, approximately 5 years into their illness.
- The overwhelming majority of autopsied cases of primary progressive apraxia of speech reported in the literature were found to have an underlying 4-repeat tauopathy, with corticobasal degeneration pathology being the most common.
- While some patients or informants may volunteer examples of impaired grammar or syntax, focused questioning is often necessary to reveal early problems.
- When assessing language ability, it is important to bear in mind that aphasia typically involves all aspects of language to varying degrees, and thus the primary progressive aphasia classification depends on the relative impairment.
- When evaluating patients for nonfluent/agrammatic variant primary progressive aphasia, it is helpful to review samples of written language, such as emails, as they frequently contain errors involving word order or functional morphemes.
- The rest of the neurologic examination is typically unrevealing in nonfluent/agrammatic variant primary progressive aphasia, although mild ideomotor apraxia and parkinsonism are possible.
- The anterior portions of the language network appear to be most vulnerable in nonfluent/agrammatic variant primary progressive aphasia, including Broca areas 44 and 45.
- The subset of nonfluent/agrammatic variant primary progressive aphasia cases with apraxia of speech are more likely to have underlying 4-repeat tau.
- Semantic dementia results from a breakdown in semantic memory, the amodal and time-independent knowledge store, in contrast to the episodic memory system, which is involved with recall of specific events or experiences.
- About 70% of cases of semantic dementia have predominant left-sided involvement (ie, would be viewed as semantic variant primary progressive aphasia), while the remaining 30% present with predominant right-sided involvement.
- Nouns are typically most difficult for patients with semantic variant primary progressive aphasia, which may result in circumlocution, the use of a more general or category label, or the use of nonspecific filler words.
- Testing for prosopagnosia is usually done by showing patients pictures of celebrities or other famous people and asking them to either identify the famous face among distractors or to provide some information to prove that they have correctly recognized the person.
- Whereas patients with nonfluent/agrammatic variant or logopenic variant primary progressive aphasia typically benefit greatly from cueing on unnamed items, patients with semantic variant primary progressive aphasia often fail to choose the correct word from a small list.
- A supportive, albeit not specific, feature of semantic variant primary progressive aphasia is trouble with reading (surface dyslexia) and writing (surface dysgraphia) of irregularly spelled words, such as *yacht*, *colonel*, and *debt*.
- Focal anterior temporal pole involvement is characteristic of semantic dementia.
- Semantic dementia appears to be the frontotemporal dementia syndrome with the lowest risk of an underlying genetic cause.
- The majority (>80%) of semantic dementia cases are associated with the accumulation of TDP-43 Type C.
- Even in unclassified or mixed cases of primary progressive aphasia, the presence of certain features (eg, apraxia of speech) may still influence management and can still be predictive of the underlying pathology.
- The lack of pharmacologic options to treat speech and language disorders should not dissuade the physician or patient from seeking therapeutic options, and referral to a speech and language pathologist is highly recommended when a degenerative speech and language disorder is considered.

Article 6: Lewy Body Dementias

Melissa J. Armstrong, MD, MSc, FAAN. *Continuum (Minneapolis, Minn)*. February 2019; 25 (1 Dementia):128–146.

ABSTRACT

PURPOSE OF REVIEW:

This article describes current diagnostic criteria relating to the diagnosis of Lewy body dementia, highlights diagnostic controversies, and reviews treatment approaches.

RECENT FINDINGS:

Clinical diagnostic criteria for both Parkinson disease and dementia with Lewy bodies have been recently updated. These criteria result in overlap between individuals diagnosed with Parkinson disease and those with dementia with Lewy bodies. Although clinical features and symptomatic treatment overlap, differences remain in epidemiology and expected progression. The high prevalence of cognitive impairment in Parkinson disease supports regular screening for cognitive changes and counseling patients and families regarding what to expect. Treatment for Lewy body dementia involves avoiding medications that may cause or exacerbate symptoms; prescribing pharmacologic agents to address bothersome cognitive, behavioral, movement, and other nonmotor symptoms; recommending physical exercise and therapy; and providing education, counseling, caregiver support, and palliative care.

SUMMARY:

Lewy body dementia includes both dementia with Lewy bodies and Parkinson disease dementia, overlapping clinicopathologic entities with differences relating to diagnosis and expected progression. Treatment is symptomatic and thus largely overlapping for the two conditions.

KEY POINTS

- Lewy body dementia is an umbrella term that includes the clinical diagnoses of both Parkinson disease dementia and dementia with Lewy bodies.
- According to current diagnostic criteria from the Dementia With Lewy Bodies Consortium, probable dementia with Lewy bodies is diagnosed in the context of a dementia consistent with the dementia with Lewy bodies phenotype and either two or more core clinical features or the presence of one core clinical feature and at least one indicative biomarker.
- In dementia with Lewy bodies, visual processing, attention, and executive functioning are typically more impaired than memory and naming.
- Individuals with a history of rapid eye movement sleep behavior disorder are 6 times more likely to have autopsy-confirmed dementia with Lewy bodies than other neurodegenerative dementias.
- Parkinson disease psychosis includes a broad range of experiences, including hallucinations in various modalities, sense of presence or passage, illusions, and delusions.
- The American Academy of Neurology Parkinson disease quality measurement set includes a measure identifying the percentage of patients with Parkinson disease who were assessed for cognitive dysfunction in the past 12 months using a recommended screening tool or neuropsychological assessment.
- The diagnosis of Parkinson disease–mild cognitive impairment should prompt clinicians to identify potentially modifiable risk factors for cognitive impairment, perform serial evaluations to monitor for changes in cognitive status, assess functional capabilities, and counsel patients and families to discuss long-term planning topics.

- In a 2016 study examining cause of death in Lewy body dementia, dementia was described as a contributor to death 71% of the time, followed by circulatory (45%) and respiratory (38%) contributors, consistent with reports that pneumonia is the most common cause of death in Parkinson disease dementia (25%).
- Treating individuals with Lewy body dementia and their families should include querying safety concerns and driving safety, assessing pain, screening for and managing behavioral and psychiatric symptoms, discussing pharmacologic and nonpharmacologic treatment approaches, encouraging advance care planning, and providing palliative care counseling and caregiver education and support.
- The first step in successfully treating an individual with Lewy body dementia is to identify medications that could contribute to symptoms or are best avoided in older adults with dementia.
- Cognitive symptoms in Lewy body dementia are treated with cholinesterase inhibitors, with use supported by multiple systematic reviews and meta-analyses.
- Pimavanserin was approved by the US Food and Drug Administration for Parkinson disease psychosis in 2016 based on a single randomized controlled trial, and it is the only approved treatment for this indication. While high-level efficacy data are lacking, quetiapine and clozapine are also commonly used to treat psychosis in the context of Parkinson disease and Lewy body dementia as these are safer than alternative antipsychotics. All antipsychotic agents have a boxed warning regarding increased risk of death in patients with dementia-related psychosis.
- Melatonin is first-line treatment for rapid eye movement sleep behavior disorder in the context of Lewy body dementia, but clonazepam is often cautiously tried if melatonin is not sufficiently helpful.
- Physical therapy, occupational therapy, and speech-language pathology assessments (addressing both speech and swallowing) are important interdisciplinary considerations for care of patients with Lewy body dementia. Therapy sessions will usually include both patients and caregivers to compensate for patients' cognitive limitations and also to teach caregiver-specific skills (eg, assistance in transfers and fall reduction).

Article 7: Vascular Cognitive Impairment

Jonathan Graff-Radford, MD. Continuum (Minneapolis, Minn). February 2019; 25 (1 Dementia):147-164.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of vascular cognitive impairment; discusses its epidemiology, subtypes, and associations with other neurodegenerative diseases; and reviews the diagnostic evaluation and management of these disorders.

RECENT FINDINGS:

Cerebrovascular disease is a common cause of dementia and frequently coexists with neurodegenerative causes. The heterogeneity of mechanisms leading to vascular cognitive impairment makes developing unifying clinical and research criteria difficult. Recognizing the neuroimaging hallmarks of different forms of vascular cognitive impairment can allow for individualized treatment and management. In individuals with mild vascular cognitive impairment, aerobic exercise appears to be a promising treatment but requires further investigation.

SUMMARY:

Vascular cognitive impairment can be caused by several mechanisms. While treating vascular risk factors is rational to prevent worsening of cognitive impairment, well-designed studies are needed to demonstrate efficacy.

KEY POINTS

- Vascular cognitive impairment represents a spectrum of vascular disorders that cause cognitive impairment.

- No single neuropsychological pattern distinguishes vascular cognitive impairment from other etiologies of cognitive impairment; however, patients with vascular cognitive impairment tend to perform worse on tests of executive function compared to memory function.
- In the community setting, cerebrovascular disease commonly occurs with neurodegenerative diseases.
- Both clinical and so-called “silent” strokes are significant risk factors for the development of dementia.
- Neuroimaging biomarkers may allow for identification of different mechanisms leading to small vessel disease. For example, deep cerebral microbleeds are suggestive of hypertensive arteriopathy, and lobar cerebral microbleeds are suggestive of cerebral amyloid angiopathy.
- Several strategic brain regions have been associated with the development of dementia after an infarct, including the angular gyrus, thalamus, caudate and putamen, basal forebrain, posterior cerebral artery (ie, hippocampus), and anterior cerebral artery territories.
- While multi-infarct dementia was once considered synonymous with vascular dementia, it is now recognized that multi-infarct dementia represents a subset of individuals with vascular cognitive impairment.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic cerebral small vessel disease caused by mutations in the *NOTCH3* gene. Cognitive impairment is common in CADASIL, as are migraine headaches and stroke.
- T2 hyperintensity involvement of the anterior temporal lobes on MRI may suggest CADASIL as a possible diagnosis.
- Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) occurs due to mutations in the *HTRA1* gene and is associated with alopecia and spondylosis in addition to the cerebral small vessel disease.
- Microinfarcts are increasingly recognized as an important contributor to cognitive decline. Recent advances in MRI techniques have allowed a subset to be imaged in vivo.
- Treatment of vascular risk factors in midlife, aerobic exercise, and a Mediterranean diet are promising treatments to prevent and treat vascular cognitive impairment but require further investigation.

Article 8: Normal Pressure Hydrocephalus

Neill R. Graff-Radford, MBBCH, FRCP, FAAN; David T. Jones, MD. *Continuum (Minneapolis)*. February 2019; 25 (1 Dementia):165–186.

ABSTRACT

PURPOSE OF REVIEW:

Since it was first described in 1965, normal pressure hydrocephalus (NPH) has been a controversial subject. New studies have shed light on its epidemiology and pathogenesis and provided objective ways to measure outcome in patients with NPH. Neuroimaging has improved and allows better recognition of both NPH and the presence of overlapping diseases

RECENT FINDINGS:

Several recent epidemiologic studies confirm that NPH is a rare disease, but the presence of large ventricles is a common finding with aging. NPH may be multifactorial, including congenital causes, vascular disease, and impaired CSF absorption. MRI features of NPH include enlarged ventricular size and CSF fluid collection outside the ventricles not due to atrophy. The term *disproportionately enlarged subarachnoid space hydrocephalus* (DESH) has been used to describe prognostic MRI features in NPH, including a “tight high convexity” and enlargement of CSF spaces in the sylvian fissure. DESH has been included in the Japanese guideline for the

diagnosis and treatment of NPH. A new NPH scale has been published that provides an objective framework for evaluating patients with NPH before and after shunt placement. Programmable shunts can noninvasively manage overdrainage complications. Surgical outcome has been improving over time. Recent studies have led to improved recognition of overlapping diseases such as Alzheimer pathology, which co-occurs in about 30% of NPH cases. Fludeoxyglucose positron emission tomography (FDG-PET) is a promising imaging modality for diagnosing NPH and detecting concomitant degenerative disease.

SUMMARY:

A systematic approach to patients with possible NPH allows recognition of the subset of patients who will respond to shunt surgery and identification of those with alternative diagnoses.

KEY POINTS

- Hydrocephalus can occur as fluid accumulation both inside and outside the ventricles.
- Factors associated with so-called idiopathic normal pressure hydrocephalus include impaired CSF absorption, vascular disease, and congenital hydrocephalus. All these factors may alter CSF dynamics in a way that can lead to increased CSF content in the cranial vault while maintaining a relatively normal average CSF pressure.
- Normal pressure hydrocephalus is an uncommon disease, but large ventricles are commonly seen in persons older than 70 years of age.
- No pathognomonic individual or combination of clinical features exists for normal pressure hydrocephalus. Comorbid diseases are common and should be evaluated.
- The triad of gait abnormality, incontinence, and cognitive impairment seen in normal pressure hydrocephalus may possibly be related to periventricular frontal cortical–basal ganglia–thalamocortical circuitry. Most often, patients with normal pressure hydrocephalus do not have the full triad of symptoms, and gait abnormality usually presents first.
- Cognitive features of normal pressure hydrocephalus include psychomotor slowing, decreased attention and concentration, impaired executive functions, and apathy. Anomia suggests the presence of a cortical dementia and is a poor prognostic factor when deciding about shunt placement.
- The differential diagnosis of gait abnormalities in the elderly is broad and should be reviewed in detail when evaluating patients for normal pressure hydrocephalus.
- A focused history and examination should be performed looking for diseases that can co-occur or mimic the symptoms of normal pressure hydrocephalus and looking for factors that may influence management.
- In the assessment of patients for NPH, establish that there is ventriculomegaly; look for congenital factors such as aqueductal stenosis or webbing; and recognize the features of disproportionately enlarged subarachnoid space hydrocephalus (DESH), not mistaking DESH for atrophy.
- The two best diagnostic tests for normal pressure hydrocephalus are evaluating the MRI for the characteristic features, and performance of a high-volume lumbar puncture, measuring gait features objectively before and within 30 minutes after the lumbar puncture.
- Overlapping chronic diseases are common in persons being considered for shunt surgery because their average age is about 74 years. At this age, 30% of cognitively normal persons have Alzheimer disease pathology. Fludeoxyglucose positron emission tomography may help reveal a concomitant degenerative disease.
- In idiopathic normal pressure hydrocephalus, most metabolic proteins are low in the CSF, so Alzheimer biomarkers (eg, amyloid- β_{1-42} and phosphorylated tau) are also low and are not helpful in distinguishing Alzheimer disease from idiopathic normal pressure hydrocephalus.
- Surgical complications following shunt surgery are common but have decreased over the decades. Adjustable shunts allow treatment of overdrainage without surgical intervention.
- Objective measurements to assess patient change with shunt placement are very helpful in management.

- Surgical outcome is improving, and patients who are seen in follow-up 3 years after shunt surgery have a good chance of remaining improved.

Article 9: Chronic Traumatic Encephalopathy

Katherine W. Turk, MD; Andrew E. Budson, MD. *Continuum (Minneapolis)*. February 2019; 25 (1 Dementia):187–207.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a discussion on the current state of knowledge of chronic traumatic encephalopathy (CTE), with an emphasis on clinical features and emerging biomarkers of the condition.

RECENT FINDINGS:

The results of several large brain bank case series among subjects with a history of contact sports or repetitive head trauma have indicated that a high frequency of CTE may exist in this population. However, the true prevalence of CTE among individuals with a history of head trauma remains unknown, given that individuals who experienced cognitive, behavioral, and mood symptoms during life are more likely to have their brains donated for autopsy at death and epidemiologic studies of the condition are lacking. Neuropathologic consensus criteria have been published. Research-based clinical criteria have been proposed and are beginning to be applied, but the definitive diagnosis of CTE in a living patient remains impossible without effective biomarkers for the condition, which is an active area of study.

SUMMARY:

The field of CTE research is rapidly growing and parallels many of the advances seen for other neurodegenerative conditions, such as Alzheimer disease decades ago.

KEY POINTS

- Chronic traumatic encephalopathy is a pathologically defined neurodegenerative disorder associated with repetitive concussive or subconcussive head injury.
- The frequency, severity, and total exposure to head trauma and the exact pathophysiologic mechanism by which blows to the head result in chronic traumatic encephalopathy are active areas of research.
- Head injury is an important but nonsufficient risk factor in the development of chronic traumatic encephalopathy; other exposure and genetic risk factors are under investigation.
- Currently, no validated clinical diagnostic criteria for chronic traumatic encephalopathy exist, although research diagnostic criteria have been developed.
- Concussion is a clinical syndrome of impaired brain function, typically impacting memory and orientation, with or without loss of consciousness that results from head injury.
- Chronic traumatic encephalopathy is defined by neuropathology: perivascular aggregation of phosphorylated tau protein within neurons and astrocytes that begins in the depths of sulci and progresses to involve the medial temporal lobes and other parts of the brain.
- Chronic traumatic encephalopathy deficits involve progressive cognitive, behavior, and mood changes as well as possible motor deficits.
- The most common cognitive difficulties in patients with chronic traumatic encephalopathy involve memory and executive function.

- Four traumatic encephalopathy syndrome subtypes have been described: (1) a behavioral/mood variant, occurring in younger patients; (2) a cognitive variant, which occurs later in life; (3) a mixed variant; and (4) a dementia form.
- The classification of patients into the diagnostic categories probable, possible, and unlikely chronic traumatic encephalopathy relies, in part, on results of potential research-based biomarker findings, thus diagnoses are for use in research, not clinical settings.
- The evaluation for possible chronic traumatic encephalopathy should include asking about a history of repetitive head trauma, with or without concussion, including exposures during contact sports, military service, domestic abuse, assault, and motor vehicle accidents.
- The differential diagnosis for chronic traumatic encephalopathy often includes frontotemporal dementia and Alzheimer disease.
- No disease-modifying or symptomatic treatments for chronic traumatic encephalopathy are US Food and Drug Administration approved. All medication management is off-label and symptom-based, and can include acetylcholinesterase inhibitors, selective serotonin reuptake inhibitors, and memantine.
- The incidence and prevalence of chronic traumatic encephalopathy is unknown because of a lack of epidemiologic data. However, the frequency of chronic traumatic encephalopathy is potentially increased within the professional contact sports community and others exposed to head trauma.
- The age of clinical onset of traumatic encephalopathy syndrome/chronic traumatic encephalopathy symptoms is delayed by several years or decades following exposure to head injuries and is currently estimated to be between 30 and 65 years of age.
- Posttraumatic stress disorder and traumatic brain injury often co-occur in military veterans and may share a common pathophysiology.
- Posttraumatic stress disorder, postconcussive disorder, and chronic traumatic encephalopathy share many common symptoms, including difficulty with concentration, changes in mood, memory problems, irritability, and sleep disturbances.
- Chronic traumatic encephalopathy frequently involves TDP-43 pathology, but TDP-43 is not necessary for pathologic confirmation.
- Chronic traumatic encephalopathy can co-occur pathologically with other neurodegenerative conditions, including motor neuron disease, Alzheimer disease, Lewy body disease, and frontotemporal dementia.
- The main genetic risk factor investigated in association with head injury and chronic traumatic encephalopathy is the *APOE* ϵ 4 allele.
- The *APOE* ϵ 4 allele may lower the threshold for an individual to develop cognitive deficits following repeated head injury.
- Nongenetic potential risk factors for chronic traumatic encephalopathy include cognitive reserve, age of first exposure, and cumulative exposure to head injuries.
- Serum tau concentration elevations may indicate the existence of prior head injury but have not been found to correlate with cognitive function.

Article 10: Hippocampal Sclerosis, Argyrophilic Grain Disease, and Primary Age-Related Tauopathy

Gregory A. Jicha, MD, PhD; Peter T. Nelson, MD, PhD. *Continuum* (Minneapolis, Minn). February 2019; 25 (1 Dementia):208–233.

ABSTRACT

PURPOSE OF REVIEW:

Hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy are common Alzheimer disease mimics that currently lack clinical diagnostic criteria. Increased understanding of these pathologic entities is important for the neurologist who may encounter patients with an unusually slowly progressive degenerative dementia that may appear to meet criteria for Alzheimer disease but who progress to develop symptoms that are unusual for classic Alzheimer disease

RECENT FINDINGS:

Hippocampal sclerosis has traditionally been associated with hypoxic/ischemic injury and poorly controlled epilepsy, but it is now recognized that hippocampal sclerosis may also be associated with a unique degenerative disease of aging or may be an associated pathologic finding in many cases of frontotemporal lobar degeneration. Argyrophilic grain disease has been recognized as an enigma in the field of pathology for over 30 years, but recent discoveries suggest that it may overlap with other tau-related disorders within the spectrum of frontotemporal lobar degeneration. Primary age-related tauopathy has long been recognized as a distinct clinical entity that lies on the Alzheimer pathologic spectrum, with the presence of neurofibrillary tangles that lack the coexistent Alzheimer plaque development; thus, it is thought to represent a distinct pathologic entity.

SUMMARY:

Despite advances in dementia diagnosis that suggest that we have identified and unlocked the mysteries of the major degenerative disease states responsible for cognitive decline and dementia in the elderly, diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy demonstrate that we remain on the frontier of discovery and that our diagnostic repertoire of diseases responsible for such clinical symptoms remains in its infancy. Understanding such diagnostic confounds is important for the neurologist in assigning appropriate diagnoses and selecting appropriate therapeutic management strategies for patients with mild cognitive impairment and dementia.

KEY POINTS

- Several clinically uncharacterized neuropathologic disease states are found at high frequency in the elderly population and may contribute to the observed inaccuracy of clinical diagnostic criteria in clinicopathologic correlation studies in dementia.
- Recent and ongoing work over the past several decades has brought to light the importance and high prevalence of diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy as common mimics of Alzheimer disease and other dementing disorders, largely because their own clinical phenotype has been poorly elucidated to date.
- The prevalence of diseases such as hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy can be as high as 20% of normal controls and higher than 50% in individuals with clinical dementia.
- It is now recognized that hippocampal sclerosis occurs not only in “pure” or isolated forms but is frequently found to be a comorbid process, coexisting with other neurodegenerative pathologies such as Alzheimer disease, dementia with Lewy bodies, progressive supranuclear palsy, and amyotrophic lateral sclerosis.
- The presence of hippocampal sclerosis should always be suspected in patients diagnosed with frontotemporal dementia who demonstrate appreciable anterograde amnesic signs and symptoms, irrespective of other associated clinical features or diagnoses.
- The extent of TDP-43 pathology seen in hippocampal sclerosis of aging can frequently extend well beyond the medial temporal lobe to include neighboring regions of the frontal and temporal cortices as well as subcortical regions, demonstrating that hippocampal sclerosis of aging is not confined to the medial temporal lobe structures but instead can be associated with more widespread pathology.

- The “coiled bodies,” “ballooned” neurons, and “tufted” or “thorny” astrocytes seen in argyrophilic grain disease all involve accumulation of phosphorylated tau protein, suggesting its central role in the pathogenesis of the disease. At the time of their original description, it was understood that they were associated with an increased frequency of clinical dementia, but their presence is not an absolute determinant of clinical dementia.
- Biochemical differences stemming from discoveries in postmortem brain tissue have not yet been translated into antemortem serum or CSF biomarkers for argyrophilic grain disease. At present, argyrophilic grain disease remains a diagnosis that can only be made and confirmed at autopsy.
- In brains with primary age-related tauopathy pathology, neuritic amyloid plaques are not detected, but tau neurofibrillary tangles are observed.
- By definition, the neurofibrillary tangles of primary age-related tauopathy are not associated with underlying frontotemporal lobar degeneration or chronic traumatic encephalopathy, differentiating this entity from other degenerative disease states characterized by predominant tau-related pathology.
- Despite the near-identical molecular and structural nature and anatomic distribution of neurofibrillary tangles between primary age-related tauopathy and early Alzheimer disease, the neuroanatomic extent of neurofibrillary tangle pathology in primary age-related tauopathy appears largely restricted to the temporal lobes, unlike in Alzheimer disease, in which the distribution of neurofibrillary tangles can be more widespread cortically.
- In large autopsy series, the distribution of primary age-related tauopathy pathology has been shown to be associated with antemortem cognitive impairment, and primary age-related tauopathy is also implicated in subjective memory symptoms and mild cognitive impairment.
- Prospective testing of multimodal use of antemortem biomarkers remains to be confirmed but holds much promise for the antemortem detection of pathologic diseases such as primary age-related tauopathy.
- Hippocampal sclerosis of aging, argyrophilic grain disease, and primary age-related tauopathy all have a predilection for medial temporal lobe and hippocampal involvement, present in a common phenotype as an early amnesic syndrome, and can be associated with medial temporal lobe atrophy. These clinical characteristics make them indistinguishable from Alzheimer disease using routine clinical diagnostic tests and MRI.
- Hippocampal sclerosis of aging and argyrophilic grain disease (but not primary age-related tauopathy) have strong associations with the genetic, biochemical, neuroanatomic, and clinical presentations of frontotemporal lobar degeneration syndromes. These data suggest that frontotemporal lobar degeneration–associated features are common in the aging population.
- Data acquired over the past decade have advanced our understanding of hippocampal sclerosis of aging, argyrophilic grain disease, and primary age-related tauopathy and may begin to allow the development of clinical trials for both symptomatic therapeutics and disease-modifying agents.

Article 11: Reversible Dementias

Gregory S. Day, MD, MSc. *Continuum (Minneapolis, Minn)*. February 2019; 25 (1 Dementia): 234–253.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical features that suggest a reversible cause of dementia.

RECENT FINDINGS:

Substantial variability exists in the presenting features and clinical course of patients with common neurodegenerative causes of dementia, but the response to available therapies and

eventual outcomes are often poor. This realization has influenced the evaluation of patients with dementia, with diagnostic approaches emphasizing routine screening for a short list of potentially modifiable disorders that may exacerbate dementia symptoms or severity but rarely influence long-term outcomes. Although a standard approach to the assessment of dementia is appropriate in the vast majority of cases, neurologists involved in the assessment of patients with dementia must recognize those rare patients with reversible causes of dementia, coordinate additional investigations when required, and ensure expedited access to treatments that may reverse decline and optimize long-term outcomes.

SUMMARY:

The potential to improve the outcome of patients with reversible dementias exemplifies the need to recognize these patients in clinical practice. Dedicated efforts to screen for symptoms and signs associated with reversible causes of dementia may improve management and outcomes of these rare patients when encountered in busy clinical practices.

KEY POINTS

- Neurologists involved in the diagnosis and management of patients with dementia should recognize the symptoms and signs that suggest a reversible cause of dementia.
- Truly reversible causes of dementia account for a small proportion of cases in outpatient clinics.
- Patients with rapidly progressive dementia warrant an expedited assessment, with the goal of rapidly identifying and remedying reversible causes of and contributors to dementia.
- Younger than expected age at symptomatic onset is a well-recognized marker of secondary causes of dementia, warranting careful evaluation and screening for reversible causes.
- Autoantibody testing should be considered in all patients meeting criteria for possible autoimmune encephalitis and in patients 60 years of age or older with characteristic central nervous system syndromes, even if neuroimaging and CSF findings do not suggest an underlying autoimmune disease.
- Toxic-metabolic disturbances, medications, untreated sleep disorders (including obstructive sleep apnea), and psychiatric illnesses may all present with prominent fluctuations in cognition.
- Transient epileptic amnesia is associated with acute and transient memory disruptions lasting minutes (typically less than an hour) that are often accompanied by fluctuations in attention.
- Anticholinergic medications may be especially problematic in patients with Alzheimer disease–associated degeneration of acetylcholine-producing basal forebrain cells.
- If promptly recognized, the life-threatening effects of thiamine deficiency may be counteracted by administration of high doses of parenteral thiamine.
- The high potential for response to appropriate treatment, high cost of delayed diagnosis, and low risk of complications associated with parenteral thiamine supplementation justify expedited treatment in all patients with possible nutritional deficiency and features consistent with Wernicke encephalopathy.
- Syphilis testing should be considered in patients with dementia from endemic regions within and beyond the United States and in those with a past or present history of high-risk behaviors.
- A thorough history, including screening for past or present high-risk behaviors, is imperative when investigating patients with unusual presentations of cognitive impairment.
- The discovery of abnormal neurologic findings—whether subtle or pronounced—warrants consideration of atypical causes of dementia, including reversible causes.
- Detection of features of the triad of progressive memory loss, gait apraxia, and urinary incontinence warrants screening for causes of normal pressure hydrocephalus and high-pressure hydrocephalus.
- Performance on cognitive testing that is substantially better or worse than expected from the clinical history should trigger investigations for reversible causes of dementia.
- Sleep dysfunction, attributable to obstructive sleep apnea or other causes, is increasingly identified as a contributor to cognitive impairment.