Behavioral Neurology

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26.1 Introduction

In order to successfully interact with the world, we make use of fundamental cognitive and behavioral skills. If we lose some of these capabilities, as occurs with dementing conditions, previously familiar activities such as driving, cooking, taking care of finances or social engagement become difficult. Brain disorders in older adults jeopardize functional independence due to the associated cognitive decline. The World Alzheimer Report 2015 estimates that every 3 seconds someone in the world developed dementia and 46.8 million people live with dementia [1]. The prevalence of dementia doubles every 5 years in individuals between the ages of 65 and 85 years and continues increasing after the age of 90 years [2]. The vast majority of cases are caused by neurodegenerative diseases, like Alzheimer's disease (AD), but there is also a high prevalence of cerebrovascular disease as a single or mixed etiology. In a small number, we find reversible causes of cognitive impairment [2–5].

Clinicians who are knowledgeable about cognitive impairment are able to provide better care for their geriatric patients. Early detection can lead to implementation of medical and lifestyle interventions as a potential way to delay or reduce cognitive decline [6, 7] and allows for the evaluation of reversible causes such as infections (HIV, syphilis), metabolic changes (hypothyroidism, hypercalcemia), or vitamin deficiencies (B12) [8]. Accurate and timely diagnosis helps guide treatment management and facilitates guidance for advance care planning. When diagnosis is determined early in the illness, it maximizes the likelihood that patients participate meaningfully in decision-making [9]. Discussion of what to expect is particularly important in neurodegenerative diseases. Knowing the expected clinical progression helps families and patients provide context to conversations and when decision-making is necessary, it allows the individual to guide management over the course of their illness, even after they have lost cognitive skills.

26.2 Cognitive Aging, Mild Cognitive Impairment, and Dementia

Even early in the illness, cognitive changes can be present in one or more domains, such as memory, attention, executive function, language, visuospatial abilities, and behavior (refer to Tables 26.1 and 26.2 for examples). If a patient or family member expresses concern regarding any of these domains, the symptoms require formal evaluation as they often reflect the beginning of a neurodegenerative condition. Yet, according to the World Alzheimer Report in 2019 almost 62% of health-care providers worldwide think that dementia is part of normal aging [10]. For this reason, we begin by describing some of the nonpathological age-related cognitive changes.

Cognitive aging is a lifelong process of gradual, ongoing, yet highly variable changes in cognitive functions that occur as people age [11]. Some of the most common patterns of age-related changes include slower processing speed, decreased attention (selective and divided, i.e., multitasking), and working memory (ability to temporarily hold information in one's mind while it is processed or used), slower learning process, and effortful retrieval [11, 12]. By contrast, autobiographical memory, semantic knowledge, and emotional processing remain relatively stable as we age [13]. Some components of the clinical history help to discern if the reported concerns are due to cognitive aging or represent a neurodegenerative condition. For example, many healthy people have infrequent and nondisruptive memory lapses, such as the occasional inability to remember a word or a name and, while common at all ages, this is even more common with healthy aging [14]. Asking patients if their deficits are comparable to their peers can be useful, although self-awareness of deficits is often absent with dementias [15]. Hence, obtaining information from a knowledgeable informant is critical, whenever possible. Administration of brief

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Table 26.1 Cognitive domains

Cognitive domain	Common complaints
Memory	Forgetting recent events and important conversations Difficulty keeping track of appointments or medications Repetitiveness Misplacing objects frequently
Attention	Distractible Attentional fluctuations
Executive functions	Slower cognitive processing speed Difficulty planning or organizing Poor judgment and problem-solving
Language	Word finding difficulties Decreased speech output Effortful speech Word substitutions or speech sound errors Grammatical errors in verbal or written language Impaired reading or comprehension
Visuospatial skills	Topographical disorientation Getting lost in familiar places Difficulty recognizing objects or faces

Table 26.2 Behavior, sleep, and autonomic symptoms

Domain	Common complaints
Motor & coordination	Difficulty walking Imbalance Frequent falls Muscle weakness Involuntary movements like tremor, muscle jerking (myoclonus), and muscle twitching (fasciculations) Changes in handwriting or fine motor movements Swallowing difficulty
Behavior & mood	Irritability/lability Emotional blunting Apathy Disinhibition Delusions Hallucinations Agitation/aggression Depression, anxiety, restlessness Decreased empathy Changes in eating habits and weight Repetitive behaviors and compulsions
Sleep	Insomnia Hypersomnia Snoring and apneas Dream enactment behavior Poor reparative sleep and sleeping throughout the day
Dysautonomia	Lightheadedness/orthostatic hypotension Constipation Anosmia

cognitive assessments (refer to the next section) can help identify cognitive impairment. When patients have high scores on cognitive screening but, a subtle dementia is suspected, a full neuropsychological battery can provide an objective measure of cognitive deficits by comparing results to normative data accounting for age and education differences. We recommend performing a thorough evaluation before concluding that a change is due to normal cognitive aging. When there is uncertainty regarding whether there is progressive decline, a second evaluation, 6–12 months later, should be considered.

While the separation of *mild cognitive impairment (MCI)* from normal cognitive aging can be difficult, MCI is characterized by progressive decline associated with cognitive deficits in one or more domains without significant loss of function in the ability to perform activities of daily living. MCI can be subdivided into amnestic and nonamnestic subtypes, depending on whether or not memory is the predominant deficit [16]. When cognitive difficulties have progressed to a point when a person needs assistance in order to be able to function in daily life, we categorize them as suffering from *dementia* or from a *major neurocognitive disorder*, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [17, 18]. The differentiation between MCI and dementia is based on an accurate description of daily affairs, which needs to be corroborated with a reliable informant.

Predicting dementia progression in patients with MCI is complex but important for the development of early therapeutic interventions. While some patients with MCI do not progress to dementia and a few even improve, most progress, and with the advent of biomarkers like amyloid imaging, the ability to determine whether the MCI is due to Alzheimer's disease (AD) is possible [19, 20]. Longitudinal studies suggest that the annual rate of conversion to dementia ranges from 8% to 15%, with amnestic-MCI carrying the highest risk of progressing to Alzheimer's disease [21, 22]. A meta-analysis that included approximately 15,000 participants from 16 countries revealed that certain risk factors predicted progression from MCI to AD: atrophy of the hippocampus, medial temporal lobe, and entorhinal cortex, presence of APOEε4 allele, abnormal CSF p-tau and total-tau, depression, and diabetes [23].

26.3 Cognitive Testing

Multiple brief cognitive assessments have been developed to detect cognitive impairment. Two of the most commonly used are the Mini-Mental State Examination (MMSE) [24] and the Montreal Cognitive Assessment (MoCA) [25]. It is important to mention that these are screening tests (Table 26.3) and are not a substitution for a full neuropsychological evaluation, particularly in cases where there is diagnostic uncertainty.

The clinician should anticipate some factors that can affect the patient's performance or influence the interpretation of

Table 26.3 Cognitive testing

Screening instruments	Notes
MMSE: Mini-Mental State Examination	One of the most well-known tests Does not include executive function items
MoCA: Montreal Cognitive Assessment	Available in various versions and languages Certification enforced by developers
RUDAS: Rowland Universal Dementia Assessment Scale	Well studied cross-culturally
SLUMS: Saint Louis University Mental Status	Studied in US veterans
Memory Alteration Test (M@T)	Well studied in a low-literacy population
CSI-D: Community Screening Interview for Dementia	Useful in a low-literacy population. Includes informant interview and cognitive testing

results. For example, accommodating for sensory impairment when necessary, particularly for vision and hearing by ensuring that glasses or hearing amplifiers are available. Educational attainment should always be considered before interpreting results, and more recently some evidence exists that also early-life educational quality and literacy in late life explain race-related disparities in late-life cognitive function [26].

When evaluating older adults who belong to an ethnic minority and have a low educational attainment or illiteracy, the clinician should use a test that has less cultural, language, and educational bias. Some instruments that have been validated in these scenarios include the Rowland Universal Dementia Assessment Scale (RUDAS) studied cross-culturally [27–30] and the Memory Alteration Test (M@T) in populations with low literacy [31, 32], as well as instruments that combine a cognitive test and an informant interview like the Community Screening Interview for Dementia (CSI-D) [33].

Box 26.1 Vignette

A 74-year-old man presented with 6 years of progressive memory problems. Initially, he noticed difficulty at work when trying to remember information from documents and needed to rely on notes to keep up with plans. This made his work difficult, and he decided to retire. Over the year prior to assessment, his memory continued to worsen, and he developed mild word-finding difficulties. He acknowledged more irritability and difficulty staying asleep, frequently awakening in the middle of the night. He was quite concerned about his memory problems, but his wife believed his problems were mild and not much worse than other people his age. She noticed that he had problems troubleshooting on the computer and poorer planning skills, but he successfully carried on with all activities of daily living. His MMSE was 21/30 with points deducted for orientation, delayed recall, and missing 1 step out of 3 on a three-step command. A geriatric depression scale score was low at 5/30 with a few points for cognitive items and worry. Neuropsychological testing revealed severe deficits in visual and verbal memory as well as executive function below expected for age. Magnetic resonance imaging (MRI) showed disproportionate atrophy of medial temporal lobe, including hippocampi. He was diagnosed with amnestic-MCI, with concern for underlying Alzheimer's disease pathology. A year later, he was diagnosed with Alzheimer's type dementia.

This case illustrates the importance of objective evaluation by cognitive assessment after a report of cognitive concern, whether the complaint comes from the patient or the caregiver. Generally, there is congruence of appraisal for cognitive deficits between the informant and the patient during earlier stages of the illness. As cognitive deficits worsen, the emergence of higher informant concern, compared to patient's awareness, has been found to occur particularly at later stages [34, 35]. Yet, sociocultural differences in perceptions of early cognitive decline and education may influence the informant's report. It has been reported that among African Americans, informants may underestimate mild cognitive changes as compared to their Caucasian counterparts. No differences were found between groups, when patients were at a dementia stage [36, 37]. One of the two studies attributed the difference to the informant's lower educational attainment, and we should always keep in mind that race serves as proxy for social determinants of health that often explain disparities, and may have not been explicitly described or assessed.

26.4 Causes of Dementia and Underlying Neuropathology

Dementias are classified clinically into syndromic categories which predict with different degrees of certainty the underlying neuropathology. Diagnostic criteria have been introduced and updated for Alzheimer's disease (AD) [17, 38, 39], dementia with Lewy bodies (DLB) [40], behavioral variant frontotemporal dementia (bvFTD) [41], primary progressive aphasia (PPA) [42], progressive supranuclear palsy (PSP) [43], corticobasal syndrome (CBS) [44], and prion disease [45, 46]. There is greater controversy regarding the criteria

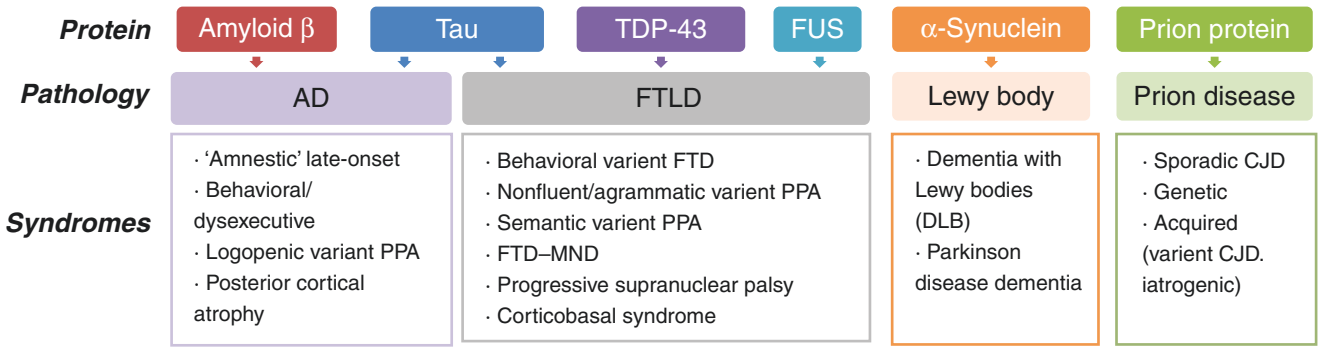

Fig. 26.1 Clinicopathological spectrum of neurodegenerative diseases. (Modified with permission from: Elahi and [49]). AD Alzheimer's disease, CJD Creutzfeldt-Jakob disease, FTD frontotemporal dementia, FTD-MND FTD with motor neuron disease, FTLD frontotemporal lobar degeneration, PPA primary progressive aphasia

for vascular dementia, and it is well accepted that vascular dementia often coexists with Alzheimer's disease and other degenerative conditions [47, 48]. The degenerative dementias can be categorized according to the pathological changes and the accumulation of abnormal protein aggregates in specific regions of the brain (Fig. 26.1) [49].

Typically, the process of protein aggregation precedes the appearance of clinical deficits by years. For example, with Alzheimer's disease it is now accepted that amyloid deposition begins 20 years before the onset of symptoms [50]. Also, in the old and very old, autopsy studies show that people with or without dementia often have multiple comorbid pathologies [51–53]. How is it that some individuals develop symptoms while others do not? This brings up the concept of *cognitive reserve,* defined as the "adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult." Differences in cognitive reserve are determined by the interaction of innate individual differences (e.g., in utero, or genetically determined) and lifetime exposures (educational and occupational attainment, general cognitive ability or intelligence, and engagement in activities that are cognitively, socially, and physically stimulating) [54, 55]. The concept of cognitive reserve is critically important because if we could better understand the factors that allow an individual to resist the neurodegenerative process, it could help with the design of novel therapies.

26.5 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia worldwide and makes up 60%–80% of all dementia cases [3, 14]. The neuropathological hallmark is the dual accumulation of extracellular aggregates of amyloid protein (neuritic plaques) and intracellular aggregates of hyperphosphorylated tau protein (neurofibrillary tangles) in the brain [49]. Some risk factors associated with developing AD include cerebrovascular disease, diabetes, smoking, obesity, traumatic brain injury, the presence of ApoE e4 allele, and having a first-degree relative with AD [3, 56]. Often, AD presents with an amnestic syndrome, characterized by progressive deficits in episodic memory (memories of events and their temporal-spatial relations). This can manifest with difficulty remembering recent conversations or events, repetitive questioning, or misplacing items frequently (see Table 26.1). Cognitive testing will show early weaknesses in delayed recall and category fluency (i.e., generating lists of animals) and as the disease progresses, difficulties in visuoconstruction and executive function [57]. Other presentations of AD are characterized by early changes in behavior or executive function (behavioral/dysexecutive AD) [58], language deficits, particularly with word retrieval (logopenic primary progressive aphasia (lvPPA)) [42] and visuospatial deficits (posterior cortical atrophy). The last two are more common in early-onset AD, meaning before age 65 [59].

Neuroimaging shows disproportionate atrophy of hippocampi, precuneus, and posterior cingulate cortex in classic amnestic AD syndrome and posterior-predominant atrophy (i.e., precuneus and posterior cingulate) is generally a feature across all AD syndromes [60, 61] (Fig. 26.2). The use of AD biomarkers for detection of tau and amyloid in positron emission tomography (PET) imaging is expensive and, therefore, currently it applies mainly to research. Cerebrospinal fluid (CSF) biomarkers are available for clinical use and can be used to rule in a diagnosis of AD. AD is characterized by low amyloid beta-42 and high tau in the CSF. Keeping in mind that roughly a third of cognitive normal older adults in their late 70s have amyloid positivity [50, 62]. New blood-based biomarkers for both amyloid and tau are emerging and also appear to have great promise for affirming the diagnosis of AD [63, 64].

Recently, a new disease entity that causes an amnestic syndrome in the oldest old has been described to cause a very similar presentation to AD, but with a different underlying pathology: Limbic-predominant age-related TDP-43 encephalopathy or "LATE" [65]. Currently, there is no way to confirm this diagnosis in vivo, but this should be considered by clinicians, since it is likely to have implications for treatment in the future.

Although older adults experience age-related *sleep changes* due to circadian rhythm disruptions (earlier bedtime and awakening times, inability to fall asleep or remain asleep), patients with neurodegenerative diseases frequently experi-

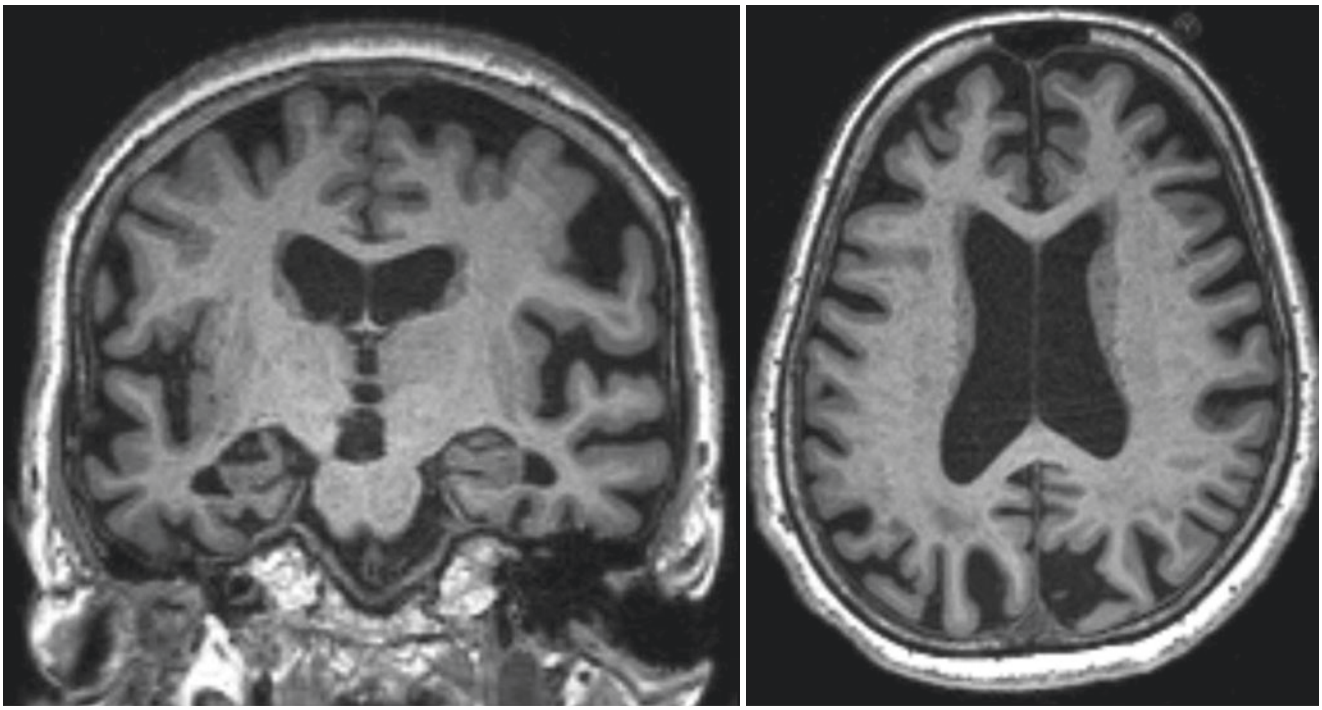

Fig. 26.2 Magnetic resonance imaging (MRI) of classic Alzheimer's disease (AD). MRI of a 74-year-old woman with 5 years of short-term memory loss, followed by navigational, planning, and organization difficulties. Predominant atrophy of dorsoparietal cortex, moderate atrophy of bilateral hippocampi, and mild dorsofrontal atrophy

ence more severe sleep disruptions. In AD, patients can present with an irregular sleep-wake rhythm disorder, with lack of a clear 24-hour sleep-wake pattern, usually with long periods of wakefulness during the night and irregular bouts of sleep throughout the day. This worsens as the disease progresses. Physiologically, wake-promoting neurons (WPNs) and sleep-promoting neurons compete for dominance through mutual inhibition, creating a systematic "switch" that results in either sleep or awake state. It has been found that tau protein accumulates in the brainstem and subcortical regions early in the disease trajectory of AD [66], where WPNs are located, and they have been found to be highly vulnerable in AD as compared to other neurodegenerative diseases [67, 68] which could explain the early sleep changes in AD.

It is well accepted that patients with underlying dementia have an increased risk of seizures, particularly in Alzheimer's disease [69, 70]. Often these seizures appear early in the course of illness and can even be the presenting sign of AD. Seizures are more common in the genetic forms of AD and with early age of onset [71–73]. The predominant seizure subtype in AD is a nonmotor complex partial seizure [74]. Fluctuations in awareness, cognition, or behavior may be the only clue that seizures are occurring. Given that its presence can hasten cognitive decline, the clinician should be aware of this correlation, to offer a timely diagnosis and treatment. When seizures are suspected, a 24-hour electroencephalogram (EEG) should be considered.

Box 26.2 Vignette

A 75-year-old-man with a history of hypothyroidism, obstructive sleep apnea (OSA), and depression and anxiety since his mid-40s, previously hypertensive now off medication due to orthostatic hypotension. He presented with 4 years of behavioral and cognitive changes. Family initially noted apathy, and he had decreased interest in playing golf and reading. He had progressive memory complaints that led to his retirement. He then developed increased irritability, anxiety, and new panic attacks. He had navigational problems and difficulty seeing things in front of him and described the appearance of shadowy figures just behind his field of view (extracampine hallucinations). His wife reported dream enactment behavior 2 years before his appearance in the clinic. On examination, he had signs of parkinsonism with decreased blink rate, axial rigidity, and mild bilateral upper extremity bradykinesia. Tremor was not present. Gait was wide based with decreased left arm swing and inability to do tandem walk. His MMSE was 18/30 with points deducted for orientation, world backward, delayed recall, pentagons, and repetition. A full neuropsychological battery revealed primarily visuospatial and executive function weaknesses.

26.6 Alpha-Synucleinopathies: Parkinson's Disease Dementia (PDD) and Dementia with Lewy Bodies

DLB and PDD lie along a clinicopathological spectrum, characterized by intracellular α-synuclein aggregates (Lewy bodies) in the brainstem, cortex, and substantia nigra, with the main difference between the two, the temporal relationship of parkinsonism relative to cognitive and neuropsychiatric changes. DLB should be diagnosed when dementia or visual hallucinations and fluctuation in attention occur before or within a year of appearance of parkinsonism [40]. DLB accounts for about 5% of all dementia cases in older adults [75]. DLB and PDD have a slightly increased male-to-female ratio [76, 77]. Having a first-degree relative with Parkinson's disease (PD) increases the risk, particularly if the family member had younger onset PD [77, 78]. Pesticide exposure is linked to PD and is a risk factor for PDD and DLB [49]. The core clinical features of DLB are recurrent visual hallucinations (typically of people or animals) [79], attentional fluctuations, rapid eye movement (REM), sleep behavior disorder (RBD), and parkinsonism. Supportive clinical features include autonomic dysfunction and neuropsychiatric symptoms like apathy, anxiety, and depression (refer to Table 26.4 for diagnostic criteria) [40]. Interestingly, like in the case of vignette 2, there has been some evidence that mood disorders presenting after age 45 might signal a neurodegenerative movement disorder [80]. The patient in the clinical vignette 2 clearly met the criteria for DLB and had a typical neuropsychological profile with disproportionate executive function, attentional, and visual processing deficits relative to memory and naming, as compared to AD [81], although memory deficits are usually evident with progression. Brain MRI of patients with DLB may not be diagnostically informative, as patients often have diffuse mild cortical atrophy with no distinct regional pattern; however, preservation of the medial temporal lobe can help differentiate from AD [61]. Clinicians can consider a polysomnography when the bed-partner reports dream enactment behavior, particularly if there is concern for obstructive sleep apnea (OSA), given that severe OSA can be a mimicker for RBD [82].

Table 26.4 Clinical diagnostic criteria for most common neurodegenerative disorders

Probable Alzheimer's disease dementia (Adapted from McKhann et al. [17])
Meets the criteria for dementia and has the following characteristics:
A. Insidious onset (gradual over months to years).
B. Clear-cut history of worsening of cognition by report or observation.
C. Initial and most prominent cognitive deficits by history and examination in one of the following:
(a) Amnestic: impairment in learning and recall of recently learned information. Deficits in other cognitive domains should be present.
(b) Nonamnestic:
(i) Language presentation: most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
(ii) Visuospatial presentation: most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
(iii) Executive dysfunction: most prominent deficits are impaired reasoning, judgment, and problem-solving. Deficits in other cognitive domains should be present.
Possible diagnosis of Alzheimer's disease dementia
Atypical course: has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline.
Etiologically mixed presentation: evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.
Dementia with Lewy bodies (DLB) (Adapted from McKeith, et al. 2017)
Meets criteria for dementia.
Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
Core clinical features (probable DLB 2 or more; possible DLB 1 core feature)
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically well formed and detailed
REM sleep behavior disorder, which may precede cognitive decline
One or more spontaneous cardinal features of parkinsonism: bradykinesia, resting tremor, or rigidity.
Supportive clinical features
Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, urinary incontinence); hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease.
DLB is less likely, if parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

Table 26.4 (continued)

Behavioral variant frontotemporal dementia (bvFTD) (Adapted from Rascovsky et al. [41])

I. Neurodegenerative disease

Progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant) must be present.

II. Possible bvFTD

At least three of the following features (symptoms must be persistent or recurrent, rather than single or rare events)

A. Early[a] behavioral disinhibition [one of the following]:

A.1. Socially inappropriate behavior

A.2. Loss of manners or decorum

A.3. Impulsive, rash, or careless actions

B. Early apathy or inertia

C. Early loss of sympathy or empathy

C.1. Diminished response to other people's needs and feelings OR

C.2. Diminished social interest, interrelatedness, or personal warmth

D. Early perseverative, stereotyped, or compulsive/ritualistic behavior [one of the following]:

D.1. Simple repetitive movements

D.2. Complex, compulsive, or ritualistic behaviors

D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following]:

E.1. Altered food preferences

E.2. Binge eating, increased consumption of alcohol or cigarettes

E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following]:

F.1. Deficits in executive tasks

F.2. Relative sparing of episodic memory

F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

Possible bvFTD + significant functional decline + imaging supported

Frontal and/or anterior temporal atrophy OR hypoperfusion or hypometabolism on PET/SPECT

Exclusion criteria:

Deficits are better accounted for by other nondegenerative nervous system or medical disorders, or by a psychiatric diagnosis.

If biomarkers are strongly indicative of Alzheimer's disease or other neurodegenerative processes, can only be "possible bvFTD" and not probable.

[a]As a general guideline "early" refers to symptom presentation within the first 3 years

Primary progressive aphasia (PPA) (Adapted from Gorno-Tempini et al. [42])

To meet the criteria for PPA, all of the following need to be present:

1. Difficulty with language is the most prominent clinical feature.
2. These deficits are the principal cause of impaired daily living activities.
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease.

Exclusion criteria:

Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders, or by a psychiatric diagnosis

Prominent initial episodic memory, visual memory, and visuoperceptual impairments

Prominent, initial behavioral disturbance

Semantic variant PPA (svPPA)

1. Impaired confrontation naming AND
2. Impaired single-word comprehension

PLUS, three of the following:

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

Imaging-supported svPPA: predominant anterior temporal lobe atrophy

Nonfluent/agrammatic variant PPA (nfPPA)

1. Agrammatism in language production OR
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

PLUS, two of the following:

1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

Imaging-supported nfPPA predominant left posterior fronto-insular atrophy

Logopenic variant PPA (lvPPA)

1. Impaired single-word retrieval in spontaneous speech and naming AND
2. Impaired repetition of sentences and phrases

PLUS, three of the following:

1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism

Imaging-supported lvPPA: predominant left posterior perisylvian or parietal atrophy

Box 26.3 Vignette

A 70-year-old woman presented with 4 years of behavioral and cognitive changes. Her family initially noticed social withdrawal, and she spent most of her time using her iPad or watching TV, instead of engaging with her grandchildren. Later on, when visiting her daughter who lived out of town, she seemed disinterested in activities she would have previously enjoyed and stayed at home and watched TV. Her daughter started to feel that she was not as interested in her life, and on one occasion during a time she was crying, the patient laughed.

She exhibited poor judgment and social disinhibition. She hit a parked car and left the scene of the accident and drove home. Her husband noticed a dent in the car, and when confronted, she answered "I hit somebody." At this point, the family insisted that she stop driving. She cut in line at the store and tried to take off her shirt in public when she became hot. On a few occasions, she walked out unexpectedly from a restaurant. She developed mental rigidity and obsessive behavior, becoming regimented in her routines and meal schedule. She insisted on eating the same food every day and watched the same episode of certain TV shows over and over again. She became obsessed about the weather, providing exact details about the forecast. She started *hoarding* cans of tomatoes. She became *disorganized*, which was very uncharacteristic of her. She had *difficulty balancing her checkbook*, missed payments, and could not calculate a tip at a restaurant. Later on, her family also noticed some *memory problems*, such as difficulty following a story line and remembering events. Her MMSE was 21/30, missing points for orientation (season, floor, and county), delayed recall, and spelling world backward (working memory). A full neuropsychological evaluation showed predominantly impairment in executive function, and working memory, although she also had poor verbal memory. During her examination, she showed poor insight into her deficits, and she was filing her nails during the interview. Her brain MRI showed out-of-proportion frontal atrophy and insula as well as mild degree of atrophy of the temporal and parietal lobes.

26.7 Frontotemporal Dementias

The frontotemporal dementias (FTDs) are a group of disorders characterized by predominant deficits in behavior and language. The three core syndromes are behavioral variant FTD (bvFTD) and two primary progressive aphasias (PPAs), nonfluent/agrammatic variant PPA (nfPPA) and semantic variant PPA (svPPA) [83, 84]. FTD is a leading cause of early-onset dementia, but it can also be seen in the geriatric population. Studies have reported that about one in four FTD cases has late-onset presentation (at age 65 or later) [85, 86]. Additionally, diagnosis is often made 2.5 years into the disease trajectory [87]. Almost 40% of patients have a significant family history of dementia. Nonetheless, heritability varies between FTD subtypes, including genes with autosomal dominant inheritance [88].

Progressive disturbance in personality, social comportment, and cognition is the hallmark of bvFTD [41], as seen in vignette 3. To meet diagnostic criteria, these features need to be present: behavioral disinhibition; apathy or inertia; loss of empathy or sympathy; perseverative, stereotyped, or compulsive/ritualistic behavior; hyperorality and dietary changes; and a neuropsychological profile that is primarily dysexecutive, sparing of memory and visuospatial skills (refer to Table 26.4). Not surprisingly, bvFTD is misdiagnosed as a psychiatric disease in up to 50% of cases [89]. Brain MRI can aid in diagnosis, if there is disproportionate atrophy of frontotemporal structures such as insula, anterior cingulate, anterior temporal lobes, striatum, amygdala, and thalamus [61, 90]. Although in advanced stages, the disease will affect areas of hippocampi and parietal lobes [91] (Fig. 26.3).

Language-predominant FTD syndromes include svPPA and nfPPA. Word-finding difficulties tend to be a common complaint in PPA, but a careful history and evaluation will show other problems as well. Patients with svPPA have problems with semantic memory (the organized knowledge we possess about words, objects, facts about the world, their meaning and referents, like a verbal and visual thesaurus essential for communication) and present with anomia and single-word comprehension deficits, initially for low-frequency words, for example they might have difficulty thinking of the difference between a slug and a snail. Although not part of the diagnostic criteria, oftentimes they have behavioral disturbances including compulsions and decreased empathy. Predominant anterior temporal lobe atrophy is characteristic on a brain MRI. In contrast, nfPPA presents with effortful speech (slow and labored speech production) and/or agrammatism (use of short, simple phrases and omissions of grammatical morphemes) in their written and verbal communication. Predominant left posterior fronto-insular atrophy on MRI is characteristic. A third type of PPA, mentioned earlier, "logopenic" is an atypical presentation of Alzheimer's disease, hence not part of FTD spectrum disorders (see Table 26.4 for diagnostic criteria). FTD-related syndromes that have motor predominant symptoms include progressive supranuclear palsy (PSP) syndrome [43] and corticobasal syndrome (CBS) [44, 92] (refer to Table 26.5 for more details).

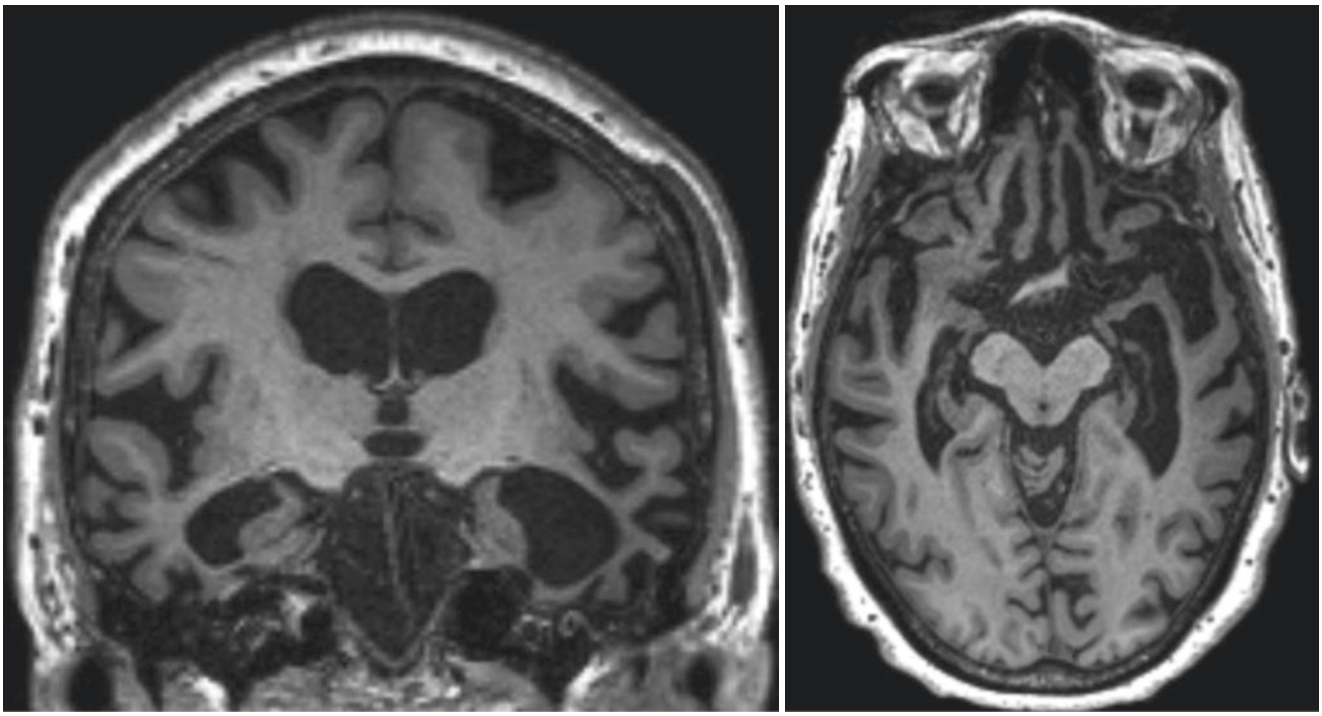

Fig. 26.3 Magnetic resonance imaging (MRI) of an 82-year-old patient with behavioral variant FTD. Predominant focal atrophy in the anterior and inferior temporal, orbitofrontal, and insular regions, right worse than left. Orientation is neurological (right-hand side of the figure is the right side of brain)

Table 26.5 FTD spectrum with prominent motor features

FTD-MND (1)	Overlap FTD + ALS Behavioral symptoms Upper motor neuron signs (hyperreflexia, spasticity, and slow speech) AND Lower motor neuron signs (fasciculations, muscle atrophy, and weakness) Frequently: pseudobulbar affect
PSP (2)	Postural instability (frequent falls) Oculomotor dysfunction Atypical parkinsonism Cognitive dysfunction Frequently: early dysphagia and dysarthria Behavioral symptoms: apathy, impulsivity, inattention, personality changes Depression is common Sleep disturbances: insomnia Brainstem atrophy
CBS (3)	Motor signs (limb dystonia, rigidity, akinesia, or myoclonus) AND Cortical signs (apraxia, cortical sensory loss, and alien limb phenomena).

FTD-MND frontotemporal dementia-motor neuron disease, *ALS* amyotrophic lateral sclerosis, *PSP* progressive supranuclear palsy, *CBS* corticobasal syndrome
(1) Lomen-Hoerth [139]; (2) Armstrong et al. [44]; (3) Höglinger et al. [43]

All of these clinical presentations belong to the frontotemporal lobar degeneration (FTLD) spectrum, a pathological entity characterized by neurodegeneration of cortical and subcortical structures within frontal and temporal regions of the brain, which have diverse molecular pathologies with the majority caused by intracellular aggregates of tau or TDP-43 protein [49] (Fig. 26.1).

26.8 Vascular Cognitive Impairment

Vascular cognitive impairment (VCI) encompasses MCI and dementia associated with cerebrovascular disease. Identifying a temporal relationship between a vascular event with the onset of cognitive deficits makes a diagnosis of VCI clearer, although it is not necessary. As long as there is evidence of vascular injury by neuroimaging, a diagnosis of possible VCI can be considered. In many occasions, mixed pathology contributes to the deficits with VCI [47]. Vascular dementia is the second most common cause of dementia. Studies have shown that up to 30% of patients develop a major neurocognitive impairment within 3 months after a stroke [4]. VCI can be caused not only by a large vessel disease (cortical infarcts), but also by a small vessel disease (subcortical), as well as ischemic and/or hemorrhagic etiologies [93], and it can be sporadic or occasionally inherited, with CADASIL syndrome being the most frequent within this category.

Small vessel disease (SVD) is the most common cause of VCI. Classical brain MRI features include white matter hyperintensities on T2FLAIR and lacunar infarcts (cavitating lesions

typically in the white matter or subcortical gray matter on T1 sequence) [61]. White matter abnormalities of SVD typically affect frontostriatal circuits, correlating with observed deficits in attention, processing speed, and executive function [4]. Choosing an instrument that appropriately assesses these cognitive skills is an important consideration, and for this reason, the MMSE has been shown to be relatively insensitive in detecting VCI [94]. Hence, when administering only a brief assessment, the MoCA or another instrument that has more items of executive function is preferred. Noncognitive symptoms are often seen in patients with VCI, such as irritability, apathy, and depression. Clinical features that are supportive of VCI found during neurological examination include the presence of focal findings from a previous vascular insult, extrapyramidal signs "vascular parkinsonism," and motor deficits observed in gait [95].

26.9 Rapidly Progressive Dementia

Although there is no clear definition of rapidly progressive dementia (RPD), the term is accepted when dementia develops in less than 1 year from the onset of first symptom [96]. Confirming this timeframe after taking a careful history and ruling out delirium are key first steps. Also, it is important to perform a full review of symptoms and medications used. The vast majority of RPDs are nonprion neurodegenerative diseases; the second most common cause varies among studies reporting prion disease and secondary/reversible dementias [97–99]. Diagnostic accuracy is important given the possibility of a potentially treatable cause, such as immune-mediated disorders, infections, metabolic disorders, and malignancy [96, 100], but also for providing guidance to the family and patient, if the cause is deemed incurable. Prion disease or CJD (Creutzfeldt-Jakob disease) is a neurodegenerative disease with very poor prognosis. It is caused by the conversion of the normal prion protein into an abnormal form in the brain by three mechanisms: spontaneous (sporadic), genetic (familial), and acquired (transmitted). Sporadic CJD is the most common type, with a median age of presentation at 67 (55–75 years), and it has a mean survival of 6 months. Ninety percent of patients die within a year [101]. The classic clinical presentation involves not only cognitive/behavioral abnormalities, but also ataxia (usually gait), extrapyramidal features, and, eventually, myoclonus.

An initial RPD screen includes a routine work-up for cognitive impairment (complete blood count, comprehensive metabolic panel, TSH, vitamin B12 level, folate, as well as HIV and RPR) and neuroimaging. A brain MRI can help identify findings typical of CJD such as cortical ribboning and deep nuclei restricted diffusion (Fig. 26.4), or abnormalities consistent with encephalitis, vasculitis, infarcts, tumors, etc. The CSF analysis can provide clues to diagnosis by detecting pleocytosis, inflammation, or positive tests of rapid neuronal injury (total-tau). Particular tests can be ordered, depending on the clinical scenario, for example, EEG when seizures are suspected, RT-quIC in CSF if CJD is in the differential, or autoimmune encephalopathy panel in blood and serum, if an autoimmune encephalopathy is suspected (typically has a subacute onset ~3 months), among other toxic/metabolic and infectious workup depending on the clinical case [96, 102].

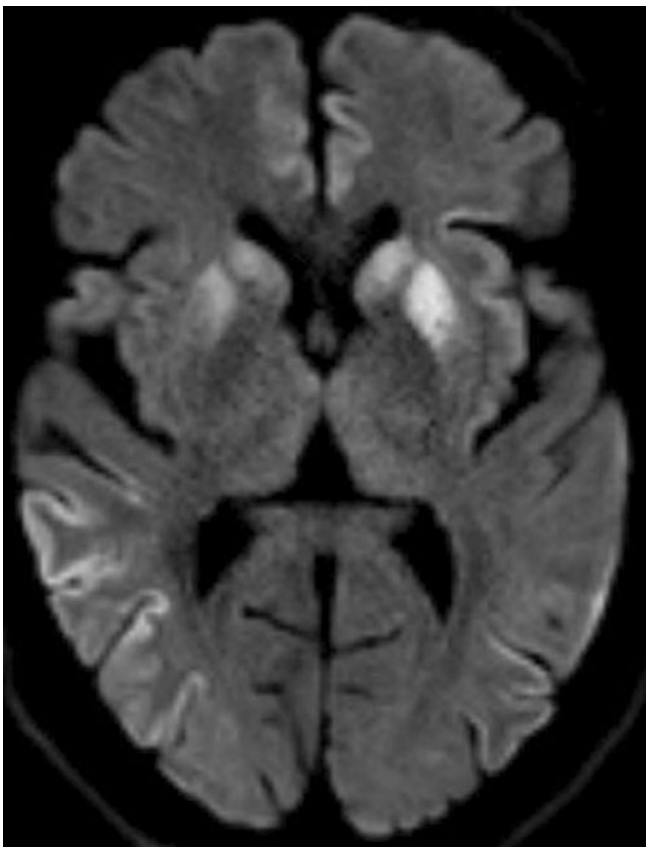

Fig. 26.4 Magnetic resonance imaging (MRI) of sporadic CJD. A 71-year-old woman with 1 year of memory loss, worsening executive dysfunction, and gait difficulties. Gait ataxia and mild parkinsonism on examination. DWI images show cortical ribboning of multiple cortical structures and hyperintensity of the deep nuclei bilaterally

26.10 Neuropsychiatric Symptoms of Dementia

Nearly all patients with dementia and more than 50% of patients with MCI have at least one neuropsychiatric symptom during the course of the disease [103, 104]. These include delusions, hallucinations, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behavior, and changes

in appetite/eating. These symptoms are associated with decreased quality of life, functional decline (independent of cognition), nursing home placement, increased caregiver burden as well as caregiver stress, regardless of patient's residence [105–107].

Although agitation/aggression is highly prevalent in patients with dementia [104, 108], apathy is the most common neuropsychiatric symptom across different forms and stages of dementia [109, 110]. Depression and apathy are the most frequent symptoms in both MCI and dementia and are often confused. Apathy is characterized by diminished motivation in self-initiated goal-directed behavior (like in vignettes 2 and 3), cognitive goal-directed behavior (paucity of ideas and curiosity), or emotional goal-directed behavior. Approach to neuropsychiatric symptoms will be discussed in the next section.

26.11 Prevention and Management of Cognitive Impairment

It is estimated that approximately 40% of worldwide dementias could be prevented or delayed by addressing 12 modifiable risk factors during a person's life-course. Forty percent! These risks include less education, hearing impairment, hypertension, obesity, excessive alcohol consumption (>21 units/week, equivalent to 12 standard drinks/week, since 1 unit = 8 g of pure alcohol), traumatic brain injury (TBI), air pollution, low physical inactivity, social isolation, smoking, diabetes, and depression [111]. Modifying the last six risk factors even after age 65 can have a positive impact. Starting with physical activity, the WHO recommends at least 150 minutes of moderate-intensity aerobic exercise throughout the week and a Mediterranean-like diet to adults with normal cognition and MCI to reduce the risk of cognitive decline. We recommend this goal, but patients can try to be as active as physical ability allows. Additionally, appropriate management of vascular risk factors is always recommended to promote brain health and decrease further decline. Doing a good review of medications and discontinuing any that could be contributing to cognitive deficits is important. Common offenders are first-generation antihistamines that have an anticholinergic effect, like diphenhydramine or sedating medications like benzodiazepines.

Patients with cognitive impairment often live with multimorbidity and have difficulty managing their health and navigating the health-care system, eventually relying on their caregivers for these responsibilities. For this reason, care in the continuum of cognitive impairment requires a holistic and multidisciplinary approach that addresses medical and psychosocial needs of the patient to optimize health and well-being, as well as providing support to caregivers [112]. The prototypical Comprehensive Geriatric Assessment (CGA) can be particularly useful in dementia, given that a multidimensional evaluation process identifies the needs of the patient, followed by multidisciplinary interventions that foster a personalized care plan, incorporating the patient's circumstances and caregiver's support [113, 114].

In terms of disease-specific medications, currently there are no disease-modifying treatments that can be offered to patients with a neurodegenerative disease, but extensive research efforts continue. Medical management has focused on symptomatic treatment that is FDA approved for patients with Alzheimer's dementia. Cholinesterase inhibitors, like donepezil and rivastigmine, boost levels of the neurotransmitter acetylcholine and have small benefits for cognitive function, activities of daily living, and clinician-rated global clinical state at all stages of the disease [115–117]. Significant benefits have also been observed in patients with DLB and Parkinson's disease dementia with positive impact on behavioral disturbances and cognitive function (particularly with attention) [118–120]. In our experience, we always recommend this medication when AD and DLB is in the differential diagnosis, unless the patient has intolerable side effects. Some of the side effects include gastrointestinal (nausea, diarrhea), vivid dreams, and bradycardia. Rivastigmine should be given as a patch rather than a pill, due to less gastroinstestinal side effects in this form. Memantine, an NMDA-receptor antagonist, reduces clinical deterioration in moderate-to-severe AD [121], and there is some evidence that it has some benefit in diminishing behavioral disturbances in AD [122]. In FTD, cholinesterase inhibitors have been mostly associated with worsening of cognitive and behavioral symptoms, and memantine has shown no benefit [123, 124].

Treatment of behavioral disturbances can be the most challenging, and the first-line approach should be a nonpharmacological intervention, except when the risk of harm to patients or caregivers is present. In behaviors that are severe and have a risk for injury, we start with an atypical antipsychotic in parallel with nonpharmacological strategies. The first step is to understand the behavior in question and possible triggers by doing a good semiology of the symptom. Following the DICE approach can be very helpful [106], this acronym stands for Describe, Investigate, Create, and Evaluate. A good example is "agitation" which can mean a myriad of things for people. Understanding the behavior by asking the questions who, what, when, and where can be enlightening. Careful history-taking and observation is key as it allows the provider to identify possible modifiable causes that might be related to patient (pain, illness, medication changes, etc.), caregiver (i.e., communication styles, unrealistic expectations), and/or environment (i.e., over- or understimulating environment). Knowing the level of distress of caregivers and patients will also guide the plan. For example, if low levels of distress

are associated with a symptom like nonbothersome hallucinations, no further intervention is needed other than reassurance. A personalized plan for each dyad (patient-caregiver) should be created to address the particular behavior and follow-up should happen soon after to evaluate if it was beneficial or further interventions are needed. In general, caregiver education and referral to support groups are always warranted, as well as ensuring that the patient has a schedule that provides engaging activities.

When medications for behavior are needed, antidepressant SSRIs have been associated with a reduction in symptoms of agitation, when compared to placebo [125]. These studies have included sertraline and citalopram. Empirically, escitalopram is likely to provide the same benefit as citalopram, with likely a safer cardiac profile. The FDA has a maximum recommended dose of citalopram of 20 mg/day for people older than 60 years of age due to the risk of QT interval prolongation, which may limit its use. There is currently a clinical trial to evaluate the safety and efficacy of escitalopram for agitation. As mentioned earlier, atypical antipsychotics are sometimes necessary; however, it is important to discuss with families their side effect profile, including somnolence and risk of gait problems, and that they carry a FDA black box warning of increased risk of death and cerebrovascular adverse events [126, 127]. Some of the drugs commonly used in this group, include risperidone, olanzapine, and quetiapine. Compared to quetiapine, risperidone has more extrapyramidal symptoms, hence it should be used judiciously or avoided in patients with DLB. Trying the lowest dose possible with the desired benefit is highly recommended [128].

Sleep disturbances are also common, and it is important to first rule out and treat other causes that could be contributing, like nocturia or obstructive sleep apnea, as well as implementing known recommendations for sleep hygiene. Use of melatonin is controversial, but generally considered innocuous. Hence, it can be tried, and if sleep difficulties continue to be problematic, low-dose trazodone should be considered [129]. One of the advantages of trazodone is that it does not interfere with deep sleep which is the time when memories are consolidated and when tau and amyloid are cleared from the brain. Benzodiazepines and nonbenzodiazepine hypnotic "Z drugs," such as zolpidem, should be avoided, as they are in the Beers criteria for potentially inappropriate medication in older adults and interfere with deep sleep [130].

It is important to discuss with the patient and their family safety measures and advance care planning. As part of a safety assessment, providers should inquire about wandering behavior and risk of getting lost, cooking and fire hazard, driving adequacy [131], use of heavy machinery or appliances that could cause harm, and access to firearms [132]. Screening for social isolation and loneliness (perceived isolation) is important in this patient population, due to its association with poor outcomes. If present, interventions to increase social support, such as referral to available community resources, are recommended [133, 134]. Unfortunately, patients with cognitive impairment are vulnerable to financial scams, and implementing measures to protect their assets by educating them and their caregivers is necessary, so that they can be proactive about financial planning. Lastly, advance care planning should always be discussed with patients and their families. Due to the progressive nature of neurodegenerative diseases, patients will lose their cognitive capabilities and with time will be less able to communicate their wishes. Hence, the earlier this discussion takes place, the better [9]. Prognosis varies depending on the type of neurodegenerative disease and the clinical severity [85, 87, 135, 136] (refer to Table 26.6), and universally, patients with dementia eventually develop swallowing difficulties. It is well accepted that tube feeding in persons with advanced dementia does not offer any benefits. Hence, it is not recommended [137]. Estimating survival in advanced dementia is difficult; however, a study that included nursing home patients with dementia showed that the presence of pneumonia, febrile episodes, and eating problems were associated with high 6-month mortality [138]. When available, patients with advanced dementia who have a life expectancy of 6 months or less can be offered hospice services. The provider can use the functional assessment staging tool (FAST) to have a sense of the clinical severity of the illness. Some of the benefits that have been observed with use of hospice include lower risk of dying in the hospital or being hospitalized in the last 30 days of life. Also, this approach is associated with a higher frequency of treatment for pain and dyspnea, and families report have greater satisfaction with patient care [137].

Table 26.6 Survival estimates of neurodegenerative diseases from symptoms' onset

Alzheimer's disease	6.6 years[a] (age dependent)
Dementia with Lewy bodies	6.1[a]
Behavioral variant FTD	8.7[a]
Semantic variant PPA	11.9[a]
Nonfluent/agrammatic variant PPA	9.4[a]
FTD-MND	3 years[a]
PSP	5.1 years[b]
CBS	6.8 years[b]
Sporadic CJD	6 months[b] (4–17 months)

FTD frontotemporal dementia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *FTD-MND* frontotemporal dementia-motor neuron disease, *CBS* corticobasal syndrome, *CJD* Creutzfeldt-Jakob disease

[a]Median; [b]Mean

References: Wolfson et al. [135]; Mueller et al. [136]; Johnson et al. [85]; Coyle-Gilchrist et al. [87]; Geschwind [101]

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