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CHAPTER 1

OVERVIEW OF DEMENTIA

Précis

The first step in understanding and addressing behavioral and psychological symptoms of dementia (BPSD) is establishing the cause of dementia. The nature of the symptoms varies based on the cause of dementia; the cause also influences the selection of treatment. For example, patients with dementia with Lewy bodies (DLB) may experience very vivid visual hallucinations, and they can be prone to developing side effects from antipsychotics. The most common cause of dementia is Alzheimer's disease (AD), and most of the research on treating BPSD has been conducted with subjects with AD. Other common dementias include Lewy body disease (DLB and Parkinson disease dementia [PDD]), vascular dementia, and frontotemporal dementia (FTD). The diagnostic evaluation includes identifying comorbid conditions contributing to cognitive impairment, such as depression, hypothyroidism, vitamin deficiency, electrolyte imbalance, alcohol use, and medication side effects. Ideally, the diagnosis will have been determined prior to the onset of BPSD; realistically, the clinician addressing acute BPSD may need to start with a focused diagnostic evaluation, initiate treatment of acute BPSD, and then conduct a more thorough diagnostic evaluation once the patient's distress has improved and safety has been ensured.

BACKGROUND AND TERMINOLOGY

Dementia is a progressive condition that affects cognition and functioning. Most patients with dementia also experience changes in emotion, personality, and behavior. In DSM-5 (American Psychiatric Association 2013), the term *major neurocognitive disorder* is preferred to *dementia*. Both terms are acceptable, and *dementia* is used most often in this book. In DSM-5,

the etiology is then specified as in, for example, "major neurocognitive disorder due to Alzheimer's disease," and then further specified as "with behavioral disturbance" or "without behavioral disturbance."

The *major* in major neurocognitive disorder indicates that the cognitive deficits produce functional impairment and distinguishes it from *mild neurocognitive disorder*, which consists of cognitive decline but not significant functional decline. Patients with mild neurocognitive disorder may experience only slight impairments in activities of daily livings (ADLs), or they may be able to complete all ADLs but have a harder time doing so. Synonyms for mild neurocognitive disorder include *mild cognitive impairment* (MCI) and *cognitive impairment no dementia* (CIND). MCI is used throughout this book. It is probably simplest to think of MCI as the stage prior to dementia; for example, persons with AD progress from cognitive intactness (in which biological markers of AD may be present but there is no evidence of cognitive impairment) to MCI (in which cognition, but not functioning, is beginning to be impaired) to dementia (in which cognition is more impaired and functioning is also impaired). See Figure 1–1 for a graphical representation.

Although the following information is a bit beyond the scope of this book, it is worth noting that there are several subtypes of MCI, which may help with determining the underlying etiology (Petersen et al. 2009). The primary deficit in *amnestic MCI* (aMCI) is memory; people with aMCI are much more likely to "convert" to dementia due to AD than are people with other types of MCI or without MCI. Therefore, aMCI is thought to be an early manifestation of AD, prior to the onset of dementia. *Multiple domain MCI* (mdMCI) may or may not include memory loss, has a much less clear prognosis than aMCI (specifically, some people with mdMCI never progress, and others revert to normal cognition), and has a broader differential diagnosis than aMCI (e.g., cerebrovascular disease, depression).

This would be a good time to explore what exactly is meant by *cognition*. Cognition consists of several domains or functions, each of which has associated dysfunctions:

- *Memory:* The encoding (storing) and retrieving (recalling) of memories, which may be verbal, visual, or procedural (e.g., tying one's shoes). A deficit of memory is called *amnesia. Anterograde amnesia* is a problem with encoding new memories; *retrograde amnesia* is a problem with recalling old memories.
- *Attention:* The ability to maintain focus on a stimulus or task and shifting to a more relevant stimulus when warranted.

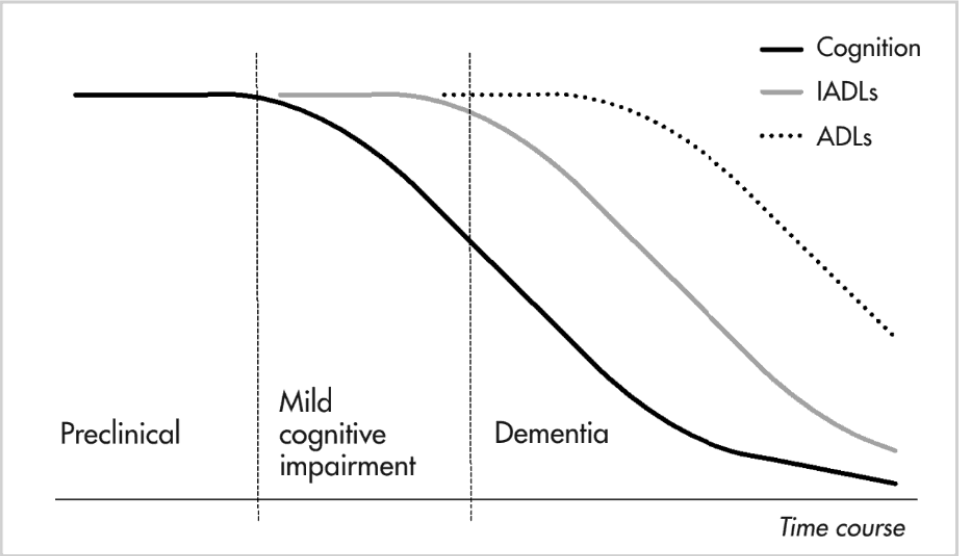

FIGURE 1–1. Course of dementia.
During the *preclinical* phase, cognition is intact and the ability to perform instrumental activities of daily living (IADLs) and activities of daily living (ADLs) is intact; biomarkers of the underlying etiology may be present (see Figure 1–3). In *mild cognitive impairment* (or mild neurocognitive disorder), cognitive abilities begin to decline; although functioning remains intact, more effort may be required to perform IADLs. In *dementia* (or major neurocognitive disorder), both cognition and functioning are impaired; the ability to perform IADLs declines first, followed by the ability to perform ADLs.

- *Language:* The understanding and production of speech and written language. A person with a *receptive* (fluent) *aphasia* has a problem with understanding language, whereas a person with an *expressive* (nonfluent) *aphasia* has difficulty speaking and writing; some people will have both.
- *Visuospatial function:* The processing of visual information, including what an object is and where it is in space. *Hemispatial neglect*, wherein one is unable to attend to visual stimuli on one side, is an example of dysfunction of the visuospatial system. Another example is *agnosia*, which refers to difficulty recognizing objects or faces.
- *Praxis:* The ability to perform complex motor tasks (e.g., buttoning a shirt). *Apraxia* refers to difficulty with complex motor tasks despite otherwise intact sensory and motor systems.
- *Executive function:* The ability to process and act on incoming information. This includes sequencing (e.g., putting on pants before shoes), planning and strategizing, initiating actions, impulse control, judgment, and cognitive flexibility (being able to change plans as circumstances change).

- *Social cognition:* The ability to interact with and understand other people. Abnormalities in interpersonal functioning may include lack of concern about or for others, lack of inhibitions in interactions with others, and inability to appreciate the mental states of others.

Another common cognitive abnormality in dementia is *anosognosia*, or lack of awareness that one has a problem; in a mental health context, this might be called *lack of insight*.

The hallmark of major neurocognitive disorder that distinguishes it from mild neurocognitive disorder is impairment in ADLs. There are two categories of ADLs: instrumental and personal (or basic) (Katz 1983). The instrumental ADLs (IADLs) are higher-order functions that tend to be affected earlier in the course of dementia. The mnemonic SHAFT covers the IADLs (University of Ottawa 2014):

S = Shopping for groceries, clothes, and other household items
H = Housekeeping
A = Accounting—that is, managing one's finances, including paying bills
F = Food preparation
T = Transportation—not necessarily driving, but more broadly the ability to get around, whether by cab or bus or by driving oneself

A person who cannot complete his or her basic or personal ADLs might die without assistance. The mnemonic DEATH is useful for remembering the personal ADLs (University of Ottawa 2014):

D = Dressing oneself
E = Eating—that is, feeding oneself
A = Ambulating
T = Toileting
H = Hygiene

People with dementia may also have a hard time managing their medications, which can hamper the effectiveness of interventions and can result in safety problems. Examples of medication management problems include taking too much medication (perhaps because a patient forgets having already taken it), taking too little medication (forgetting to take it), or taking medication irregularly. (This topic is covered more extensively in Chapter 6.)

Note that a patient with dementia may also have other ailments that affect functioning and compound the impairments associated with dementia. For

example, vision impairment (quite common in older adults, who are prone to glaucoma, cataracts, macular degeneration, and diabetic retinopathy), osteoarthritis (which about half of older adults have), peripheral neuropathy, parkinsonism, depression, anxiety, and alcohol use can also profoundly affect the ability to complete ADLs.

CAUSES OF DEMENTIA

Significant cognitive and functional decline is never due simply to aging. Most commonly, patients with dementia have a neurodegenerative disorder such as AD, Lewy body disease, or FTD. Cerebrovascular disease is another common etiology, often comorbid with a neurodegenerative process. Head injury, normal pressure hydrocephalus, alcohol, anticholinergic medications, electrolyte imbalance, depression, and anxiety also may contribute to cognitive impairment. The major etiologies are compared in Table 1–1.

Establishing the cause of dementia is not simply an academic exercise. In some cases, a reversible etiology may be found—and when this etiology is addressed, the patient's cognition and functioning can improve. The diagnosis influences the presentation of symptoms; for example, patients with Lewy body disease may experience very vivid visual hallucinations, whereas patients with FTD may be disinhibited and physically aggressive. Perhaps most importantly, the treatment plan may vary based on diagnosis. Although it may be tempting to prescribe antipsychotics to try to address hallucinations in a patient with Lewy body disease, this in fact could result in the patient's condition worsening.

The clinician interested in a more in-depth discussion of the causes of dementia should continue reading; other readers should feel free to skip to the next section, "Assessment of Dementia."

Alzheimer's Disease

AD (in DSM-5 parlance, major neurocognitive disorder due to AD) is a neurodegenerative disorder that affects memory, language, visuospatial function, and executive function and that ultimately results in progressive decline in ability to conduct ADLs. The pathological hallmarks of AD are *amyloid plaques* and *neurofibrillary tangles* accompanied by inflammation (Sperling et al. 2011). Amyloid plaques consist of "bad" β-amyloid and form outside of neurons, disrupting neuronal connections. Amyloid precursor protein (APP) is a normal constituent of neuronal cell membranes and normally gets cleaved into nonpathological, soluble β-amyloid. The amyloid hypothesis—namely, that the abnormal cleaving of APP into "bad" β-amyloid

TABLE 1–1. Comparison of the major causes of dementia

Cause of dementia	Course and cognitive symptoms	Behavioral and psychological symptoms
Alzheimer's disease	Slow, progressive decline, typically in this order: memory, language, visuospatial function, executive function	Mild dementia: depression, anxiety, insomnia
		Moderate to severe dementia: hallucinations, delusions, repetitiveness, aggression
Lewy body disease: dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD)	Slow, progressive decline but with fluctuations in cognition reminiscent of delirium; memory deficit; visuospatial dysfunction; motor symptoms precede cognitive impairment in PDD, less significant in DLB; sensitivity to side effects of antipsychotics	Visual hallucinations, delusions, anxiety, rapid eye movement sleep behavior disorder
Vascular dementia	Classically, a stepwise progression (but not always detectable clinically); affected cognitive domains depend on location of vascular lesions	Apathy, amotivation, depression
Frontotemporal dementia, behavioral variant	Relatively rapid decline, affects younger patients (45–64 years old); significant language deficits and executive dysfunction	Disinhibition, verbal repetitiveness, verbal aggression, physical aggression, hyperorality, apathy

is the first step in the pathophysiological cascade of AD—is currently the most widely accepted hypothesis explaining how AD arises (Figure 1–2).

Neurofibrillary tangles are located within neurons and consist of hyperphosphorylated tau protein. Normally, tau protein is associated with microtubules and makes up the skeletal structure of a neuron; when tau gets hyperphosphorylated, it tangles and clumps into neurofibrillary tangles, a process that then results in the death of neurons (Dubois et al. 2007). (For

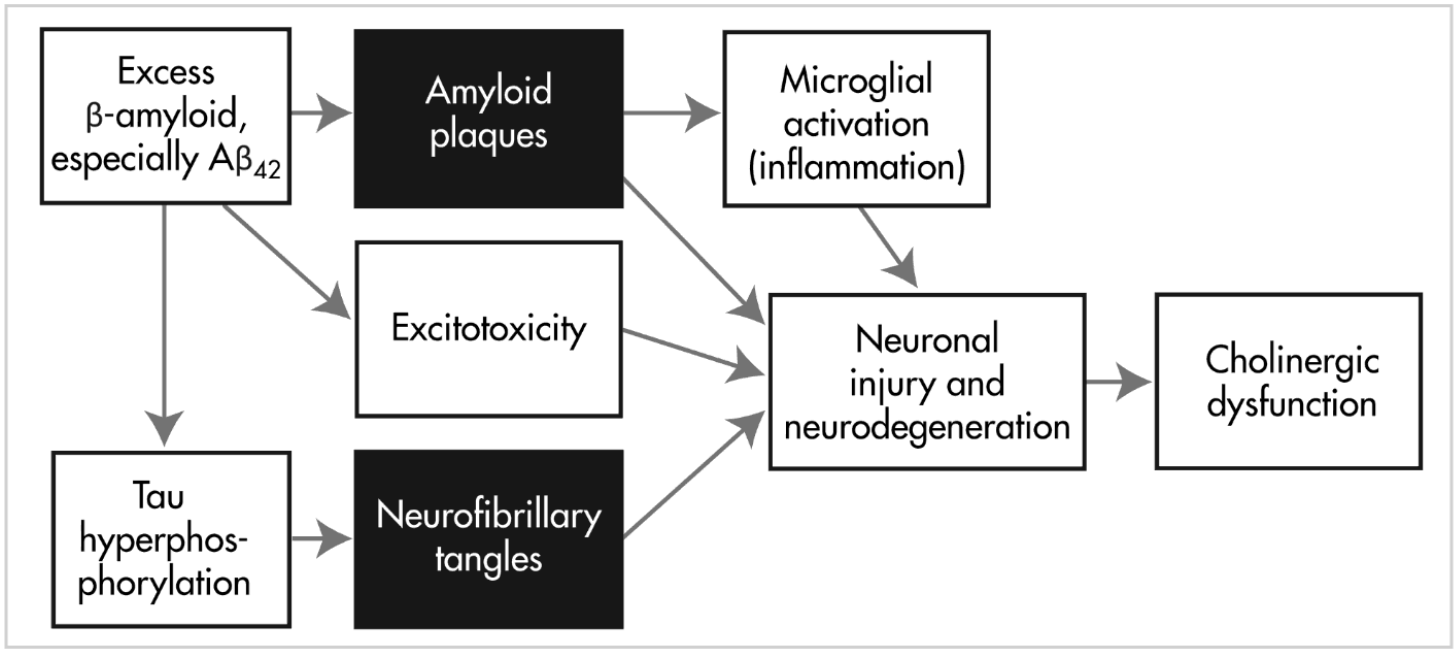

FIGURE 1–2. How Alzheimer's disease (AD) arises.

According to the amyloid hypothesis, excess accumulation of β-amyloid is the first step in the development of AD. $A\beta_{42}$ ("bad" amyloid) aggregates into extracellular amyloid plaques, one of the two neuropathological hallmarks of AD. Plaques are accompanied by an inflammatory response mediated by microglial activation. β-Amyloid may result in hyperphosphorylation of the protein tau (although how this happens is unclear), which in turn aggregates into intracellular neurofibrillary tangles, the other neuropathological hallmark of AD. β-Amyloid is also excitotoxic. All of these factors (plaques, tangles, inflammation, excitotoxicity) lead to neuronal injury and death. A final downstream step is a deficit of cholinergic transmission due to death of cholinergic neurons.

this reason, AD is sometimes referred to as a tauopathy.) It is not clear how the abnormal amyloid and tau processes are related to each other: does one cause the other, or are both the consequences of another process?

Inflammation accompanies the formation of plaques and therefore is essentially a maladaptive response to what are, in effect, foreign bodies (McGeer and McGeer 2001). Microglia, the macrophages of the central nervous system, are responsible for inflammatory responses within the brain: when activated, microglia clear amyloid deposits but also release cytotoxic inflammatory factors, which results in cell death and increases the amount of β-amyloid.

The hippocampus and medial temporal lobes, areas involved in encoding memories, are the first to be affected, specifically by neurofibrillary tangles (Dubois et al. 2007). Therefore, memory deficits arise first. The pathology then spreads to the remainder of the temporal lobes and to the parietal lobes, affecting language and visuospatial function, respectively. Finally, the frontal lobes are affected, resulting in executive dysfunction. Structural neuroimaging (magnetic resonance imaging [MRI] and computed tomography [CT]) can detect this sequence of events, by showing atrophy of gray and white matter and increased cerebrospinal fluid signal (*ex vacuo* changes) (Ahmed et al. 2014). Functional neuroimaging (fluorodeoxyglucose positron emission tomography [FDG-PET]) can detect these changes even earlier by identifying areas of the brain with decreased metabolism. New imaging techniques that would allow for detection of amyloid and tau proteins are being studied (Ahmed et al. 2014).

The pathological changes associated with AD may begin 20 or more years before symptoms first appear. Therefore, the term *Alzheimer's disease* currently encompasses a continuum that includes patients with no clinical findings whatsoever, patients with MCI (cognitive impairment but no functional impairment), and patients with dementia (the end stage of AD). This raises the possibility that medical professionals will be able to identify patients at risk of developing dementia and intervene to reduce this risk.

In fact, a critical area of research in AD is discovering biomarkers to identify people during the preclinical stage of the disease. As best as researchers can tell, markers of abnormal amyloid metabolism appear first, then markers of tau hyperphosphorylation emerge, then comes neuronal injury and neurodegeneration (Sperling et al. 2011) (Figure 1–3). The A/T/N classification system of biomarkers captures this and allows for the description of dementias not due to AD (Jack et al. 2016):

- "A" refers to amyloid biomarkers: the identification of excess amyloid on amyloid PET imaging; low levels of $A\beta_{42}$ in cerebrospinal fluid. Abnor-

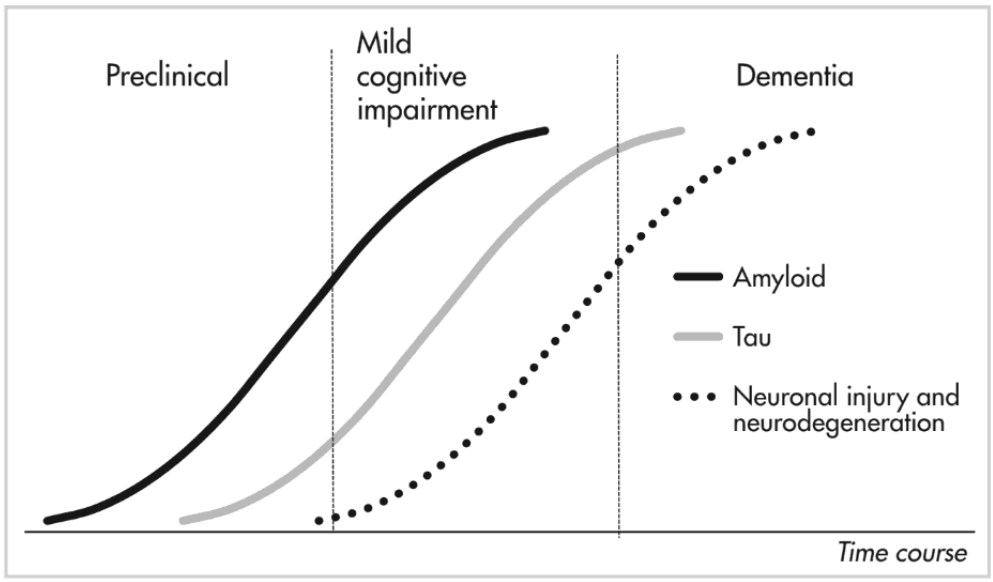

FIGURE 1–3. Biomarkers in Alzheimer's disease.
In Alzheimer's disease, markers of abnormal amyloid metabolism are thought to arise first, followed by markers of tau hyperphosphorylation, and then by markers of neuronal injury and neurodegeneration (e.g., abnormal neuroimaging). See text for details. Note that the divisions between the preclinical phase, mild cognitive impairment, and dementia with respect to biomarkers are approximate, because these states are currently defined clinically (see Figure 1.1) rather than by pathophysiology or pathology.
Source. Adapted from Sperling et al. 2011.

malities in amyloid metabolism may be the earliest findings in AD but are also not necessarily specific to AD.

- "T" refers to tau biomarkers: the identification of tau on tau PET imaging; high levels of phosphorylated tau in cerebrospinal fluid. Phosphorylated tau is quite specific to AD and rarely seen in other causes of dementia.
- "N" refers to neuronal injury and neurodegeneration: high levels of total tau in cerebrospinal fluid (a general marker of neuronal injury, seen in many causes of dementia); hypometabolism demonstrated on FDG-PET; atrophy demonstrated on CT or MRI. In AD, the temporal and parietal lobes are usually affected, whereas other regions are affected in other causes of dementia.

For example, A+/T+/N– means that an asymptomatic person has preclinical AD, with amyloid and tau biomarkers present, but no evidence of neuronal injury or neurodegeneration yet; this person would be at risk of developing MCI and then dementia. Interestingly, many people with Alz-