REVIEW
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Dementia

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ABSTRACT

Dementia is any decline in cognition that is significant enough to interfere with independent, daily functioning. Dementia is best characterized as a syndrome rather than as one particular disease. The causes of dementia are myriad and include primary neurologic, neuropsychiatric, and medical conditions. It is common for multiple diseases to contribute to any one patient's dementia syndrome. Neurodegenerative dementias, like Alzheimer disease and dementia with Lewy bodies, are most common in the elderly, while traumatic brain injury and brain tumors are common causes in younger adults. While the recent decade has seen significant advancements in molecular neuroimaging, in understanding clinico-pathologic correlation, and in the development of novel biomarkers, clinicians still await disease-modifying therapies for neurodegenerative dementias. Until then, clinicians from varied disciplines and medical specialties are well poised to alleviate suffering, aggressively treat contributing conditions, employ medications to improve cognitive, neuropsychiatric, and motor symptoms, promote evidence-based brain-healthy behaviors, and improve overall quality of life for patients and families.
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KEYWORDS: Clinical care; Cognitive impairment; Dementia; Major neurocognitive disorder; Neurodegenerative disease

INTRODUCTION

Dementia is any disorder where significant decline from one's previous level of cognition causes interference in occupational, domestic, or social functioning. Generally, dementia should be considered to be an acquired *syndrome*, with multiple possible causes, rather than a specific *disease* itself. For example, the dementia *syndrome* of progressive decline in language can be caused by various *diseases*, such as Alzheimer disease, a tumor in the language cortex, or frontotemporal lobar degeneration. Global estimates of dementia prevalence are up to 7% of individuals above the age of 65 years, with a slightly higher prevalence (8%-10%) in developed countries due to longer life spans.[1] Advancing age, genetic profile, and systemic vascular disease are major risk factors for developing dementia.[2]

A classic way to conceptualize dementia is to consider 2 broad categories of disease: those that are "neurodegenerative" (originally called "irreversible") and non-neurodegenerative (potentially "reversible") (see **Table 1**). This dichotomy is a helpful heuristic but is limited by simplicity. For example, patients with dementia can, and often do, have multiple diseases that can be neurodegenerative (eg, dementia with Lewy bodies) and non-neurodegenerative (eg, cerebrovascular disease), which cumulatively account for the impairment.[3] Diseases can also impair cognition without leading to a decline in daily functioning, either at diagnosis or subsequently. Mild neurocognitive disorder (from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition)[4] and mild cognitive impairment are used variously to characterize these states.

Most dementia in the elderly is caused by some degree of neurodegeneration. Some common degenerative dementias in the elderly are Alzheimer disease, dementia with Lewy bodies, vascular dementia, frontotemporal lobar degeneration, and Parkinson disease.

Common causes of non-neurodegenerative mild cognitive impairment and dementia that can occur across the lifespan

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include vitamin deficiencies (eg, B12, thiamine), hypothyroidism, normal pressure hydrocephalus, chronic alcohol abuse, chemotherapy-related cognitive dysfunction, infections (eg, human immunodeficiency virus), intracranial masses (eg, subdural hematomas, brain tumors), traumatic brain injury, and psychiatric illness (profound depression/anxiety).

EVALUATION AND DIAGNOSIS

The initial evaluation and diagnosis of dementia should include at least the following 4 elements: 1) thorough clinical history; 2) neurological examination, with an emphasis on the assessment of mental status; 3) selective labs to screen for selected metabolic/physiologic abnormalities (eg, basic chemistries, thyroid panel, B12, Vitamin D); and 4) a structural brain scan, with magnetic resonance imaging (MRI) preferable to computed tomography whenever possible (see **Table 2**). In certain patients, sending serological studies like antinuclear antibody, erythrocyte sedimentation rate, *Treponemal pallidum* antibody or venereal disease research laboratory, human immunodeficiency virus-ab, and heavy metal screen are warranted.

CLINICAL SIGNIFICANCE

- Dementia is a heterogeneous syndrome that may be caused by many different neurological and medical diseases.
- Neurodegeneration, vascular injury, and nutritional and metabolic disorders are some major causes of dementia.
- The global prevalence of dementia is approximately 7% of individuals age 65 years or older.
- Alzheimer disease and frontotemporal lobar degeneration are 2 diseases with early-onset variants.
- Psychosocial interventions, multidisciplinary care, symptom-focused medications, and treating all contributions are essentials of management.

Emphasis in the clinical interview should be placed on determining the pace of symptom onset (eg, sudden vs gradual) and symptom progression (eg, decline over months, or over years).[5] For example, human prion diseases, such as Creutzfeldt-Jakob disease, typically have a rapid progression over weeks to months. Diseases like Alzheimer disease and frontotemporal lobar degeneration, on the other hand, usually progress gradually over years.

A detailed mental status examination should assess multiple domains of mental function, including basic attention, memory, visuospatial abilities, executive function, and sociobehavioral aptitude (see **Table 3**). The 30-point Mini-Mental Status Examination[6] remains a helpful tool to screen for and assess dementia severity, although it is probably less informative in some populations, like high-functioning elders and those with low formal education. Other tests, like the Montreal Cognitive Assessment,[7] offer a broader assessment of cognitive domains and can be more sensitive than the Mini-Mental Status Examination for the early detection of neurodegenerative disease.[8] Further testing, including neuropsychological evaluation, may be helpful in cases where screening tests or clinical impression is equivocal.

Table 1 Examples of Selected Cognitive Impairment/Dementia Syndromes, Divided into Two Broad Categories: Neurodegenerative and Non-neurodegenerative

Neurodegenerative	Non-neurodegenerative
Alzheimer disease	Vascular dementia (multi-infarct dementia, small-vessel ischemic disease, chronic/subacute subdural hematomas, hypoxic/ischemic encephalopathy)
Dementia with Lewy bodies, Parkinson disease dementia	Normal pressure hydrocephalus
Frontotemporal lobar degeneration	Metabolic causes (hypothyroidism, chronic uremia, malnutrition, Cushing syndrome)
Multiple system atrophy	Autoimmune causes (limbic encephalitis, Hashimoto encephalopathy, voltage-gated potassium channel encephalopathy)
Non-Parkinsonian movement disorders (Huntington disease, Wilson disease, Dentatorubral-pallidoluysian atrophy)	Depression, bipolar disorder (historically called "pseudo-dementia")
Alcoholic cognitive impairment/dementia	Neoplastic/paraneoplastic causes (NMDA-receptor and CRMP-5-antibody encephalopathy, brain tumor)
Chronic traumatic encephalopathy	Infectious causes (syphilis, HIV-associated neurocognitive disorder)
Prion disease (Creutzfeldt-Jakob disease, fatal familial insomnia)	Toxic causes (lead, arsenic, organophosphate pesticides)
Dementia related to multiple sclerosis	Vasculitides (primary vasculitis of the central nervous system, Behçet disease, SLE-related)
Motor neuron disease (Amyotrophic lateral sclerosis, Primary lateral sclerosis)	Vitamin deficiency (B12, thiamine, niacin, folic acid)

CRMP = collapsin response-mediator protein; HIV = human immunodeficiency virus; NMDA = *N*-methyl-D-aspartate; SLE = systemic lupus erythmatosus.

Table 2 Clinical "Pearls" for the Diagnosis of Selected Dementias

Common Clinical Sign/Symptom	Suggestive Diagnosis
Progressive memory impairment	Alzheimer disease
Stepwise cognitive decline, sensorimotor signs, vascular risk factors	Vascular cognitive impairment
Hallucinations, mental status fluctuations, parkinsonism	Dementia with Lewy bodies
Behavioral disinhibition, loss of empathy, hyperphagia/hyperorality, ± aphasia	Behavioral variant frontotemporal dementia
Multiple falls, axial rigidity, vertical gaze palsy, levodopa unresponsiveness	Progressive supranuclear palsy syndrome
Asymmetric motor examination, apraxia, alien limb syndrome	Corticobasal syndrome
Recent fall or head acceleration/deceleration, psychomotor slowing	Subdural hematoma
Urinary incontinence, "magnetic" gait, cognitive impairment	Normal pressure hydrocephalus
Headache, malaise, behavioral changes	Vasculitis (systemic lupus erythematosus, primary central nervous system vasculitis)
Psychiatric episodes, chorea, personality change	Huntington disease
Polypharmacy (especially tricyclic antidepressants, oxybutynin, topiramate, famotidine, metronidazole)	Toxic dementia (polypharmacy)

NEURODEGENERATIVE DEMENTIAS

Alzheimer Disease

Alzheimer disease is the most common neurodegenerative dementia from middle age to the elderly. Alzheimer disease has a prevalence of 5%-6% of all individuals age 65 years and above, and up to 30% in those over age 85.[9] About 5% of all Alzheimer disease occurs prior to age 65, which is conventionally termed "early-onset."[10] The disease typically begins with slowly progressive memory decline, although behavioral, visuospatial, or language symptoms dominate in less common variants. The mean survival after symptom onset in Alzheimer disease tends to be 10-12 years.

Current models of Alzheimer disease include a "preclinical" stage, which is characterized by the gradual accumulation of beta-amyloid rich neuritic plaques and neurofibrillary tangles, beginning at least 20 years prior to symptom onset[11,12] (**Figure 1**). Early on patients may show subtle forgetfulness or occasionally repeat stories and can also exhibit irritability, apathy, or low mood. Patients or family members often first notice symptoms before any functional decline occurs, a stage that has been termed prodromal Alzheimer disease or mild cognitive impairment.[13,14] As the disease advances, brain MRI can show medial temporal lobe atrophy, involving the hippocampi and surrounding structures. A fluorodeoxyglucose-positron emission tomography (PET) scan classically shows bilateral temporoparietal hypometabolism and amyloid-PET reveals plaque deposition in multiple regions.[15]

Cerebrospinal fluid biomarkers demonstrate decreased levels of the 42-residue long beta-amyloid protein and increased levels of phosphorylated tau protein in the preclinical phase.[16] Tau protein is the major component of "neurofibrillary tangles" and beta-amyloid protein for neuritic plaques (**Figure 2**). These 2 findings constitute the pathologic diagnosis of Alzheimer disease.

To date, there are no disease-modifying, pharmacologic treatments for Alzheimer disease. Recent clinical and translational research has focused on early detection and therapeutic targeting of the underlying histopathology.[17] Cholinesterase inhibitors (ie, donepezil, rivastigmine, galantamine) and an *N*-methyl-D-aspartate receptor antagonist (memantine) are the currently used medications. Although they do not alter the overall course of decline, these medications may improve cognitive and behavioral symptoms for periods of 6 months to several years.[18,19] Evidence suggests that regular aerobic exercise, adherence to a Mediterranean-style diet, and participation in socially and cognitively stimulating activities can decrease one's risk of Alzheimer disease and impact the rate of progression along the disease continuum.[20,21]

Frontotemporal Lobar Degeneration

The frontotemporal dementias are a group of neurodegenerative diseases linked by selective degeneration of the frontal and

Table 3 Important Domains to Assess in the Cognitive Examination*

Mental Function/Domain	Explanation/Ideas for Testing
Arousal level	Response to light physical or verbal stimulation
Basic attention	Maintaining focus and being able to concentrate on examiner
Executive function	Multi-tasking; interpreting similarities and idioms; inhibiting automatic responses
Memory	Learning new information and recalling past events and facts
Language	Understanding and following complicated commands; writing and reading a sentence; speaking fluently
Visuospatial ability	Interpreting a complicated visual scene; copying basic and complex shapes
Social/behavioral	Ability to interpret and respond to verbal and non-verbal social cues during conversations

*Adequate levels of arousal and basic attention are necessary to perform other higher-order functions.

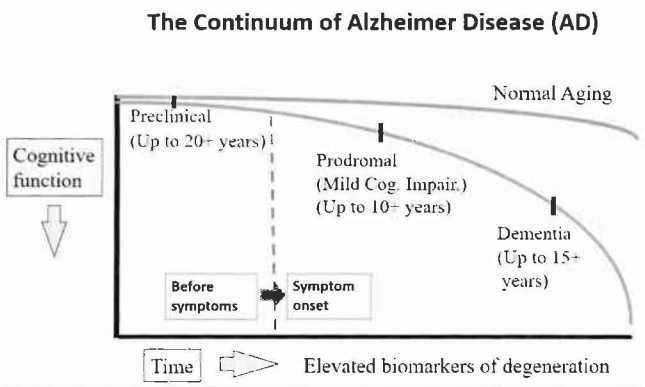

Figure 1 The continuum of Alzheimer disease, current consensus. The preclinical phase, prior to symptom onset (purple line), may last for up to 20 years. Note the inherent variability of time in each disease "phase." Neurodegenerative biomarkers can be detected in cerebrospinal fluid and brain PET scans. *Figure is original;* concept introduced by Sperling et al.[80]

temporal lobes. They can be unified under the pathological term frontotemporal lobar degeneration, which includes at least 3 distinct histologic subtypes: Transactive responsive DNA-binding, tau protein, and fused in sarcoma.[22,23] The most common clinical syndromes arising from these subtypes are: the behavioral variant of frontotemporal dementia; the "language variant," known as primary progressive aphasia; corticobasal syndrome; and progressive supranuclear palsy syndrome.[24] Less commonly, patients show signs/symptoms of both a frontotemporal lobar degeneration syndrome and amyotrophic lateral sclerosis, which constitutes a frontotemporal dementia/amyotrophic lateral sclerosis "spectrum" syndrome.[25]

Behavioral variant frontotemporal dementia is characterized by early personality changes (ie, decline in social comportment and empathy), disinhibited or compulsive behaviors, and executive dysfunction (ie, mental inflexibility).[26] Patients with primary progressive aphasia initially develop speech and language problems, which could be gross articulatory speech errors, impairments in syntax, the loss of word meaning, or "word finding" or pauses in conversation.[27] MRI can show focal frontal or temporal lobe atrophy (**Figure 3**). In corticobasal syndrome, which usually arises from either frontotemporal lobar degeneration-tau subtype or Alzheimer disease, the initial symptoms frequently include asymmetric parkinsonism (eg, limb rigidity, slowed movements), limb apraxia, executive dysfunction, and behavioral changes, and, in subsequent years, aphasia, "alien limb" phenomenon, frequent falls, and gait decline.[28] Progressive supranuclear palsy syndrome is usually characterized by axial rigidity, postural instability with early falls, and vertical gaze palsy, with subsequent progressive motor and cognitive decline.[29] Some subtypes of progressive supranuclear palsy can also have prominent cerebellar ataxia and apraxia of speech.

The frontotemporal dementias are probably the third most common type of degenerative dementia in the elderly, behind Alzheimer disease and dementia with Lewy bodies, respectively.[30] In patients younger than age 65 years, the frontotemporal dementias are the second most common dementia after Alzheimer disease, accounting for close to 20% of all cases.[30] Medical treatment for the frontotemporal dementias is supportive, with a focus on relieving neuropsychiatric and motor symptoms with antidepressants and dopamine-modulating therapy, respectively; response to dopaminergic medications is usually poor.[31]

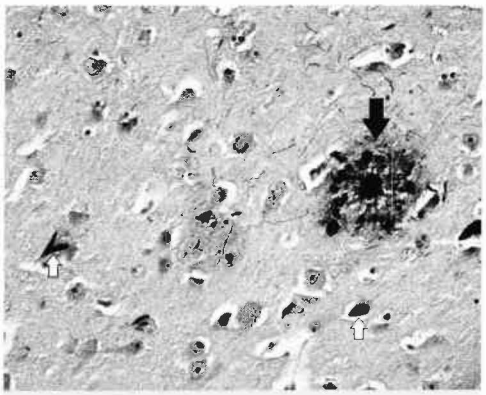

Figure 2 The defining histopathology of Alzheimer disease: hippocampus. Shown is a neuritic plaque (black arrow) rich with beta-amyloid protein, and neurofibrillary "tangles" (white arrows), which contain tau-protein aggregates. (Bielschowsky silver stain). Courtesy: Gad A. Marshall. MD, Brigham and Women's Hospital, Boston, Mass.

The Alpha-Synucleinopathies

Several neurodegenerative diseases are characterized by the pathologic accumulation of alpha-synuclein aggregates in neurons and other nervous system cells.[32] These diseases include dementia with Lewy bodies, Parkinson disease, and multiple system atrophy.

Dementia with Lewy bodies is probably the second most common degenerative dementia after Alzheimer disease.[33] Its core clinical features include: fluctuating cognition with pronounced variations in attention and alertness, recurrent well-formed visual hallucinations, dream enactment behaviors during rapid eye movement sleep, and one or more features of parkinsonism (ie, bradykinesia, tremor at rest tremor, or rigidity).[34] Importantly, these motor, cognitive, and sleep symptoms can also be features of the dementia associated with Parkinson disease (Parkinson disease dementia). Conventionally, Parkinson disease dementia should be used to describe dementia that develops in the setting of well-established Parkinson disease and should occur at least 1 year after the onset of parkinsonism.[34] Atypical antipsychotics should be used sparingly or avoided in dementia with Lewy bodies and Parkinson disease dementia, as they can worsen motor and behavioral symptoms and sometimes cause serious neuroleptic sensitivity reactions.[35,36]

Multiple system atrophy is a rarer alpha-synucleinopathy that manifests with any combination of parkinsonism,

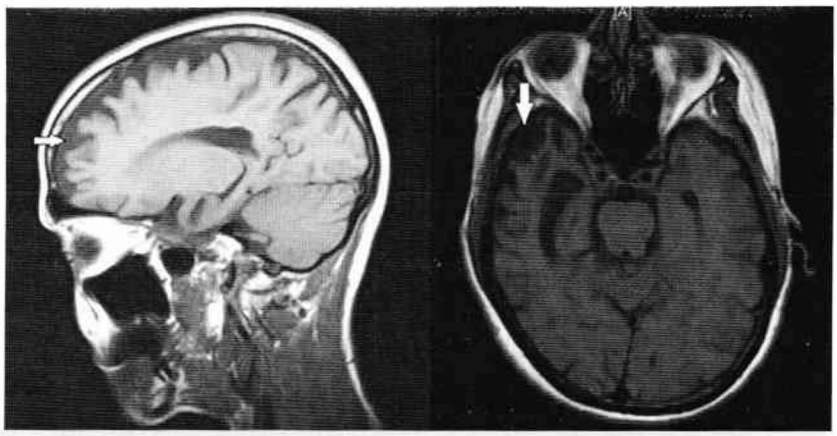

Figure 3 Frontotemporal lobar degeneration. **Left**: Brain magnetic resonance image of a 58-year-old woman with 1.5 years of personality change, loss of social graces, and behavioral disinhibition. Note the global atrophy, with frontal lobe predominance (white arrow), characteristic of behavioral-variant frontotemporal dementia **Right**: Evidence of focal anterior temporal lobe atrophy (downward white arrow), characteristic of a subtype of primary progressive aphasia caused by frontotemporal lobar degeneration. Courtesy: Seth Gale, MD (author), personal archive.

cerebellar signs, pyramidal signs, and dysautonomia.[37] Severe forward neck flexion (antecollis), as well as hand or foot dystonia, is common. More than half of patients with multiple system atrophy develop nonmotor symptoms months or years prior to motor symptoms, including inspiratory stridor, dysautonomia (ie, sexual dysfunction, orthostatic hypotension), and rapid eye movement sleep behavior disorder.[38] Dysautonomia is also common in dementia with Lewy bodies and Parkinson disease. Although cognitive difficulties may be minimal or negligible in multiple system atrophy, at least some impairment is present in up to half of patients. Deficits are predominantly in executive function and less commonly involve memory, apraxia, and spatial difficulties.[39]

Parkinsonism is common among many dementias, and thus, associated symptoms and clinical history are key to the diagnosis. Parkinsonism is driven either by the "primary" pathology, as in the alpha-synucleinopathies, corticobasal syndrome, and progressive supranuclear palsy, or arises secondary to other brain injuries, including cerebrovascular disease or repeated concussion or traumatic brain injury (as in chronic traumatic encephalopathy) (see **Table 4**). The clinical syndrome of chronic traumatic encephalopathy usually begins years after repetitive concussions, is progressive for more than 2 years, and, along with parkinsonism, often includes cognitive decline, behavioral changes with violence and suicidality common, and emotional dysregulation.[40]

NON-NEURODEGENERATIVE COGNITIVE IMPAIRMENT/DEMENTIAS

Nutritional

Dementia can arise when patients develop a deficiency or derangement of vitamin levels or nutrients. Severe thiamine (vitamin B1) deficiency can cause a disease called Wernicke encephalopathy in its earliest phases and Korsakoff syndrome if it converts to a chronic memory disorder.[5] It is most commonly seen in chronic alcoholics and those with poor nutritional intake. Wernicke encephalopathy usually presents abruptly as neurons deficient in thiamine undergo necrosis. Classically, the clinical triad includes gait ataxia, delirium, and ophthalmoplegia, but <20% of patients present with all 3 signs.[41] Korsakoff syndrome may become apparent weeks later when the delirium of Wernicke encephalopathy subsides with severe anterograde amnesia and less prominent retrograde amnesia.[42] The treatment for Wernicke encephalopathy is intravenous thiamine, which must be administered prior to glucose, as glycolysis itself consumes B1.[43]

There is epidemiologic evidence that even relative vitamin D deficiency is associated with a higher incidence of all dementia syndromes.[44-46] Other nutritional deficiencies that can rarely lead to dementia include folic acid deficiency (which can also arise from malabsorption with chronic phenytoin or primidone use) and niacin deficiency (pellagra).

Toxic

Any medication taken in excess or in combination with particular other medications can cause cognitive deficits; this occurs by either direct or indirect neurotoxic effects.[47] Medications with strong anticholinergic properties, like some tricyclic antidepressants, cyclobenzaprine, and oxybutynin, are particularly implicated. Exposure to toxic chemicals (eg, organophosphate pesticides), pollutants, and heavy metals can all cause dementia syndromes that often are nonprogressive,[48] but may also increase the risk of developing neurodegenerative dementia over years.[49,50] Lead, mercury, arsenic, and manganese poisoning have all been implicated in dementia syndromes.[51,52]

Table 4 Selected Dementias with Parkinsonism*

Disease	Clinical Symptoms	Pathology/Imaging	Clinical "Pearls"
Primary neurodegenerative			
Dementia with Lewy bodies	Cognitive fluctuations, visual hallucinations, symmetric parkinsonism	- Deposition of Lewy bodies (alpha-synuclein deposits) throughout cortexsubcortex - PET/SPECT may show hypometabolism in temporoparietal/visual cortex	- Cognitive improvement with cholinesterase inhibitors - Increased sensitivity to atypical neuroleptics, with markedly increased parkinsonism
Parkinson disease	Asymmetric rest tremor, rapid eye movement sleep behavior disorder, limb rigidity, shuffling gait, later-onset dementia	- Dopaminergic neuron loss in substantia nigra (midbrain), Lewy bodies (alpha-synuclein deposits) - MRI can have overall mild atrophy	- Cognitive deficits can improve with levodopa - Deep-brain stimulation (DBS) improves motor symptoms, variable impact on cognition
Progressive supranuclear palsy syndrome, frontotemporal lobar degeneration	Multiple early falls, axial rigidity, eye movement abnormalities, dysarthria, dementia	- Tau protein inclusions in brainstem, cortex - MRI often with midbrain atrophy	- Differentiate from Parkinson disease by early gait difficulties, erect posture, eye movements
Corticobasal basal syndrome, frontotemporal lobar degeneration	Progressive, asymmetric rigidity and apraxia, limb dystonia, myoclonus, alien limb phenomenon, mild cognitive impairment	- Tau protein inclusions in neuropil threads, and astrocytic plaques in cortex, basal ganglia, brainstem (called corticobasal degeneration) - MRI can have asymmetric, cortical atrophy in parietal lobe	- Has both cortical (apraxia, alien limb) and extra-pyramidal (rigidity, dystonia) signs
Secondary parkinsonism			
Chronic traumatic encephalopathy	Early decreased attention, depression/mood swings, irritability; later incoordination, tremor, pyramidal and extrapyramidal signs;	- Superficial cortical layers with neurofibrillary (tau) tangles - MRI can show diffuse axonal injury, diffuse atrophy, petechial hemorrhages	- Follows repeated traumatic brain injury from boxing, contact sports, blast injuries - Early intervention for mood disorder, cognitive rehab.
Vascular parkinsonism	Often has leg > arm rigidity; may have emotional incontinence (pseudobulbar palsy), pyramidal signs (hyperreflexia)	- MRI with large strategic or multiple small lacunar infarcts in basal ganglia/circuits	- Risk increases with chronic hypertension, hypoxic-ischemic brain injury

*A summary of common clinical symptoms, pathology, imaging, and clinical "pearls."

Metabolic

Hypothyroidism can contribute to or be the primary cause of cognitive impairment or, rarely, dementia.[53,54] Symptoms of hypothyroidism can include apathy, memory and attention problems, and depression. Severe hyperthyroidism or autoimmune thyroiditis can present with psychosis, psychomotor slowing, and lethargy.[55] Metabolic disorders such as chronic uremia, hepatic disease of various etiologies, parathyroid disorders, chronic hemodialysis (so-called "dialysis dementia"), and hypercortisolism/Cushing syndrome can all cause varying degrees of cognitive deficits.[56-58] In addition, patients with chronic respiratory insufficiency, congestive heart failure, chemotherapy exposure, severe obstructive sleep apnea, cancer or paraneoplastic disease, and hematologic conditions, such as sickle cell anemia, can all lead to disabling cognitive impairment.[59-62]

Vascular Cognitive Impairment

Cerebrovascular disease of differing etiologies is a common cause of cognitive impairment. These different vascular causes can be subsumed under the broad label of vascular cognitive impairment.[63] Vascular cognitive impairment that leads to a loss of autonomy in daily functioning is called vascular dementia.

Etiologies are myriad and include: clinically evident stroke or multiple strokes, small-vessel ischemic disease (historically known as Binswanger disease), rare hereditary diseases like cerebral autosomal dominant arteriopathy with subcortical infarcts, and cerebral amyloid angiopathy.[64] Vascular cognitive impairment probably accounts for between 15% and 35% of all dementia, including degenerative and nondegenerative, making it likely the second most common cause behind Alzheimer disease.[65,66] If we consider all

"mixed-type" dementias, where vascular cognitive impairment co-occurs with Alzheimer disease or other diseases, the prevalence is substantially higher. Systemic vascular risk factors, such as hypertension,[67,68] diabetes,[68] smoking,[69] and hypercholesterolemia[64] are also major risk factors for vascular cognitive impairment. Coronary artery disease, atrial fibrillation, and myocardial infarction are also independent risk factors for developing vascular cognitive impairment.[70,71]

A major etiology is poststroke (or multi-infarct) vascular cognitive impairment. Cognitive deficits may start abruptly after the stroke or appear more subacutely, and often will plateau after weeks or months. If recurrent clinical, or new covert ("silent") strokes occur, the impairment will worsen, a consequence of accumulated brain injury. Sensorimotor signs, like lateralized weakness or a visual field deficit, can be accompanying clues in the multi-infarct etiology. In small-vessel ischemic disease, the small arterioles in the deep white matter occlude over many years,[72] demonstrated by confluent hyperintense lesions on MRI. Symptoms manifest insidiously without overt neurologic events and often include slowed processing speed, dysarthria or subtle speech changes, memory difficulty, and sometimes psychomotor slowing or apathy.[73] Severe small-vessel ischemic disease can lead to urinary incontinence, lower extremity-predominant parkinsonism, and significant functional decline.[74]

Cerebral amyloid angiopathy denotes the pathologic accumulation of amyloid protein in cerebral vessels, which causes microbleeds and lobar hemorrhages.[75] This diagnosis is often made by MRI, and sometimes after a cerebral bleed causes focal neurologic signs or symptoms. Cerebral amyloid angiopathy can also cause recurrent, transient ischemic attack-like symptoms, including weakness, numbness, or paresthesias, often experienced as moving through contiguous body regions.[76] Cognitive impairment in cerebral amyloid angiopathy is directly correlated with the number and distribution of bleeds; patients with more than one microbleed have up to a 70% risk of developing vascular dementia in 5 years or less.[75] The co-incidence of cerebral amyloid angiopathy and Alzheimer disease may be 90% or higher, with autopsy studies showing moderate to frequent neuritic plaques (Alzheimer disease) in most patients with cerebral amyloid angiopathy.[77] Vigilance in treating systemic vascular risk factors and using neuropharmaceuticals, like acetylcholinesterase inhibitors, are the mainstay in vascular cognitive impairment management.

Discussion: Mixed-Dementia and Cognitive Burdens

Despite much advancement in clinico-pathologic correlation, it remains difficult in most dementia evaluations to account for all underlying etiologies. Most dementia syndromes are complex and arise from a mixture of pathologies, whose effects are likely additive to the neurocognitive decline.[78,79]

For example, it is common for an elderly dementia patient who exhibits only the slowly, progressive memory decline of Alzheimer disease, with no overt signs or symptoms of vascular dementia or dementia with Lewy bodies, to show some pathologic burden of all 3 diseases on autopsy. Furthermore, dementia patients of all ages and all causes are particularly vulnerable to additional brain insults. These include sleep disorders like obstructive sleep apnea, medications with cognitive side effects, concussions, and depression.

For all of these reasons, it is paramount to aggressively treat all known and even suspected underlying contributions to address all medical-psychiatric conditions and to be vigilant about promoting brain health behaviors.

CONCLUSION

Cognitive impairment and dementia continue to be major contributors to the global burden of disease. In this brief review, we highlight selected dementia syndromes from among dozens of different diseases. Efforts to preserve daily functioning abilities and quality of life should be the driving aim of dementia management across the lifespan. Dementias are chronic diseases that require longitudinal care, ongoing counseling, and psychosocial support for patients and families by dedicated clinicians. While we await disease-modifying therapies for degenerative dementias, clinicians are positioned, now, to understand and treat a range of neurologic and neuropsychiatric symptoms that can improve the quality of life for patients.

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