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Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment

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Synopsis

Clinicians can diagnose the syndromes of dementia (major neurocognitive disorder) and mild cognitive impairment (mild neurocognitive disorder) based on history, examination, and appropriate objective assessments, using standard criteria such as DSM-5. They can then diagnose the etiological subtypes of these syndromes using standard criteria for each of them. Brain imaging and biomarkers are gaining ground for the differential diagnoses among the different disorders. Treatments for the most part are still symptomatic.

Keywords

Neurocognitive disorder; Mild Cognitive Impairment (MCI); Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); National Institute on Aging- Alzheimer's Association (NIA-AA) Guidelines; diagnosis; risk factors; biomarkers; Alzheimer's disease

INTRODUCTION

When older patients and their families report symptoms of "memory loss," experienced clinicians know that these concerns refer to a range of cognitive abilities or to general cognitive decline, and not just memory. However, some degree of cognitive slowing is typical of normal aging.

The clinician's first challenge, therefore, is to identify the cognitive changes that are clinically significant. **Dementia** is typically diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning. **Mild cognitive impairment (MCI)** is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities.

We will describe these entities and their diagnoses using the framework of the recently published fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) (Table 1).[1] Briefly, the DSM-5 diagnosis of Major Neurocognitive

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Disorder, which corresponds to dementia, requires substantial impairment to be present in one or (usually) more cognitive domains. The impairment must be sufficient to interfere with independence in everyday activities. The diagnosis of Mild Neurocognitive Disorder, corresponding to MCI, is made when there is modest impairment in one or more cognitive domains. The individual is still independent in everyday activities, albeit with greater effort. The impairment must represent a decline from a previously higher level and should be documented both by history and by objective assessment. Further, the cognitive deficits must not occur exclusively in the context of a delirium or be better explained by another mental disorder.

The clinician's second challenge is to determine the cause(s) of the cognitive impairment, i.e., to identify the underlying etiology. DSM-5 also provides diagnostic criteria for the most common etiologic subtypes of the neurocognitive disorders in all age groups. Here we focus on the neurocognitive disorders of older adults.

Impact of Dementia

Neurocognitive disorders, particularly major neurocognitive disorders (dementias), have tremendous consequences for individuals, their families, the healthcare system, and the economy. In the United States, Alzheimer's disease (AD) is a leading cause of death,[2] hospital admissions, skilled nursing facility admissions, and home health care. The costs of health services and the informal costs of unpaid caregiving for individuals with dementia are high and growing. Family caregivers also experience increased emotional stress, depression, and health problems.[3] In absolute numbers, 35.6 million people worldwide were estimated to be living with dementia in 2010, a number expected to reach 115.4 million people by 2050.[4]

Dementia in the Population

Prevalence, defined as the proportion of people with an illness in a given population at a given time, is an index of the burden of disease in the population. Incidence is the rate at which new disease occurs in a given population, i.e., the proportion of new cases in that population over a given period of time. Incidence is therefore an index of the risk of disease in that population. Prevalence is a function of both incidence and duration. Since most dementias are not curable, their duration reflects how long individuals live with their dementia. Thus, the public health burden of dementia depends both on the development of new cases and on the survival of those cases after onset; holding incidence constant, groups with longer life expectancy will have higher prevalence.

Prevalence

Prevalence of dementia increases exponentially with increasing age[5], and doubles every five years of age after age 65. In higher income countries, prevalence is 5–10% in those aged 65+ years, usually greater among women than among men, in large part because women live longer than men. Within the US, higher prevalence has been reported in African American and Latino/Hispanic populations than in White nonHispanic populations. Global systematic reviews and meta-analyses suggest that prevalence of dementia is lower in sub-Saharan Africa and higher in Latin America than in the rest of the world [Table 2]. The prevalence of

MCI is at present difficult to pin down as it depends on the precise definitions and subtypes of MCI being studied.[6]

Life expectancy is increasing across the planet, with population aging rising the most rapidly in the low- and middle-income countries, where the prevalence of dementia is therefore expected to increase.[7] Emerging studies suggest that prevalence may be leveling off or even decreasing in the high-income countries.[8 9]

Incidence

The incidence of dementia increases steadily until age 85 or 90, and then continues to rise but less rapidly. It is either similar in men and women or slightly higher in women. Annual age-specific rates ranged from 0.1% at age 60–64 to 8.6% at age 95.[5 18]

Risk and Protective Factors

Risk factors are factors associated with an elevated incidence rate of disease, higher odds of developing disease, or earlier onset of disease, depending on the type of statistical analysis that is performed. Protective factors represent the converse. An observed risk factor does not necessarily cause disease; a protective factor does not necessarily prevent disease and almost certainly will not treat the disease. The observed effects can potentially reflect selection or survival bias or confounding, or sometimes reverse causality. They may also depend on the timing and duration of exposure to the factor, with mid-life often being the critical period.

Demographic risk factors

Increasing age is not only the strongest risk factor for dementia, but also the only risk factor consistently identified after the eighth decade of life. While prevalence is consistently higher among women, incidence is not; thus, the higher prevalence may largely be a function of longer life-expectancy in women. Lower educational levels have been found associated with higher prevalence. Within the US, prevalence has been reported as elevated in African American and Latino populations; some authors have attributed these findings to lower education and higher cardiovascular morbidity in those populations.

Genetic factors

Few dementias are caused by deterministic autosomal dominant genes; these are discussed later under the specific disorders. While several genes have been identified as increasing susceptibility for Alzheimer's disease, the best-established is the Apolipoprotein E (*APOE*) polymorphism on Chromosome 19. The *APOE*4* allele, associated with higher risks of hypercholesterolemia and heart disease, is also associated with dementia due to Alzheimer's and Parkinson's diseases, Dementia with Lewy Bodies, vascular dementia, and frontotemporal dementia in men.[19 20 21 22 23] Individuals homozygous for *APOE*4* are at greater risk of dementia than those who are heterozygous. The *APOE*2* appears to have a protective effect. *APOE*4* is a risk factor, not a diagnostic marker for Alzheimer's disease. It is neither necessary nor sufficient for diagnosis, and its effect on risk appears to wear off by the eighth decade, i.e. individuals who are older than 80 years, *APOE*4* positive, and do not yet have dementia, are at no greater risk of developing dementia than those who are *APOE*4* negative.

Medical risk factors

Cardiovascular disease is increasingly recognized as not just a risk factor for vascular dementia but also for degenerative dementias, particularly AD. Heart disease has been associated with both dementia of the Alzheimer's type, and vascular dementia.[24] Risk factors in midlife, including hypertension, high cholesterol, high body mass index (BMI), and diabetes mellitus are associated with increased risk of dementia in late life, demonstrating the importance of risk exposures decades earlier.[25 26] Heart failure and atrial fibrillation are risk factors for cognitive impairment and dementia.[27 28 29] Cardiac disease can cause or worsen cerebral hypoperfusion, creating a cellular energy crisis setting off a cascade of events leading to the production of toxic proteins.[30] In cognitively normal older adults, elevated pulse pressure has recently been found associated with alterations in biomarkers suggestive of AD.[31]

Inflammation and alterations in inflammatory markers [interleukins, cytokines, C-reactive protein] have been reported in Alzheimer's and vascular dementias.[32 33] Multiple mechanisms have been proposed for the role played by inflammation in the neuropathology of AD.[34 35 36]

Obstructive sleep apnea, associated with hypertension, heart disease, stroke risk[37] and white matter change,[38] is also associated with an increased risk of dementia.[39]

Stroke increases risk of dementia.[40 41]

Psychiatric risk factors

Depression has a complex and likely bi-directional association with dementia. Recurrent major depression in earlier adulthood appears to increase risk of dementia in later life.[42] Depression with late life onset is believed to be an early sign of the vascular or degenerative disease causing the dementia.[43 44] Late-life anxiety is associated with cognitive impairment and decline.[45] Post-traumatic stress disorder has been reported as increasing risk of dementia.[46] Lifelong traits of harm avoidance and lesser sense of purpose have been reported as harbingers of AD.[47]

Head injury

Head injury is associated with increased risk of dementia, in particular AD,[48] and the severity of injury appears to heighten this risk.[49 50] Neurocognitive disorders can occur immediately after a traumatic brain injury or after the recovery of consciousness at any age.[1] However, chronic traumatic encephalopathy (previously termed dementia pugilistica) is diagnosed years after repeated concussive or subconcussive blows to the head, with a clinical presentation similar to AD or frontotemporal lobar degeneration.[51]

Lifestyle and environmental risk factors

Many environmental and occupational exposures have shown varying associations with neurodegenerative diseases.[52] Smoking has been associated with an elevated risk of dementia;[53] although some studies have found an apparentprotective effect which could reflect survival bias (competing risks)[54] or possibly cholinergic action as also seen

in Parkinson's disease.[55] Heavy consumption of alcohol increases odds of developing dementia.[56 57] Parkinson's disease risk is associated with exposure to pesticides, for which a molecular mechanism has been established.[58]

Protective Factors

Protective factors are those associated with a reduced incidence rate or reduced odds of dementia, or with delayed onset of dementia.

The concept of "reserve" was proposed to explain why some individuals remain cognitively intact despite the presence of neuropathology typically associated with dementia.[59] Brain reserve refers to structural capacity and integrity of the brain (e.g. brain mass, preserved large neurons),[60] whereas cognitive reserve refers to its functional capacity, specifically the ability to utilize alternative neural networks and compensatory strategies.[61]

Education and cognitive activity

Where educational opportunities are universal, higher education may reflect innate reserve; the process of education may also promote the development of reserve through mechanisms such as increased dendritic branching. Education may also reflect general socioeconomic status and thus also represent quality of environmental factors like nutrition, or health care. Regardless of mechanism, higher education is associated with lower prevalence of dementia.[62]

Bilingualism has been associated with delayed onset of dementia,[63] independent of education, and may specifically protect against declines in attention and executive functioning.[64]

Cognitive activity: Lifelong occupations that do not require higher education or skilled vocational training appear to be associated with a higher risk of dementia.[65 66] Several popular leisure activities have been found associated with lower risk of dementia.[67] Cognitively stimulating activities appear to have both protective and enhancing effects on cognition.[68]

Pharmacological factors

Several therapies for other conditions have been found in long-term observational studies to be associated with a reduced risk of dementia. However, in clinical trials, these drugs have not been found to prevent dementia. Timing and duration of the exposure might partly explain these discrepancies, as the protective effects were seen with prolonged use multiple years before dementia onset. While some studies have found a protective relationship with the use of non-steroidal anti-inflammatory drugs (**NSAIDs**),[69 70 71] a 2005 meta-analysis determined that many of the positive results seen in the 25 studies reviewed were due to various forms of bias.[72] Despite mixed reports of the effects of the lipid-lowering HMG Co-A reductase inhibitors ("**statins**"), pooled results in a recent review as well as in a 2013 meta-analysis indicate a protective effect against dementia.[73 74]

As regards **estrogen** therapy, the WHIMS trial in older women showed no protection and possibly an increased risk from combination hormone therapy.[75 76] A 2013 meta-analysis

of any use versus no use concluded that hormones had no effect on dementia.[77] However, a long-term observational study suggests that the timing of hormone therapy, at menopause, may be the critical factor.[78 79 80]

Lifestyle factors

As with cardiovascular disease, population based studies have found that mild to moderate alcohol consumption is associated with reduced risk of cognitive impairment and dementia.[56 57 81 82] Adherence to a Mediterranean diet was associated with better cognitive functioning, lower rates of cognitive decline and a reduced risk of AD.[83] High physical activity levels are associated with reduced risk of neurodegenerative diseases.[84] Smoking shows a consistently protective effect against Parkinson's disease, potentially involving nicotine effects on cholinergic receptors.[55]

Elderly women with larger social networks,[85] and who participate in mental, social or productive activities, have shown lower incidence of dementia.[86] Social, mental and physical lifestyle components appear important,[87] although reverse causality cannot be ruled out, given that the neuropathology often begins decades before symptom onset.

CLINICAL ASSESSMENT

Assessment is easier for the clinician when patients themselves and/or their family members or other caregivers spontaneously express concern about cognitive difficulties. In other cases, neither patient nor caregiver report concerns but may acknowledge them if asked. Alternatively, the patient denies any difficulty, and there is no reliable informant, but the clinician observes cognitive impairment, this being more likely when the clinician knows the patient well. Sometimes the clinician, or a member of the clinic staff, is tipped off by a patient forgetting to keep appointments or fill prescriptions, or being confused by simple instructions. Experienced clinicians also recognize vagueness and evasiveness in patient's responses, or catastrophizing of minor problems, as clues to failing cognition. Occasionally, the initial complaint will not be of cognitive loss but of changes in mood or behavior, such as apathy, anxiety, or depression.

Subjective assessment

Whenever possible, history should be obtained both from the patient and also from a family member, caregiver, or other reliable informant. In some mild cases, the patient is more aware of the deficits than the relative. The clinician should focus on changes in cognitive functioning as manifested in everyday activities. Early deficits are frequently noted in managing finances and medications. Over-learned, routine activities may be preserved but problems may be occurring in problem-solving, multi-tasking, and dealing with new situations. Table 3 lists the cognitive domains recognized by DSM-5 and everyday activities that tap those domains.[1]

Many patients and families accept cognitive decline as part of normal aging, and will declare themselves normal on the grounds that they are no worse than others their age. Others may magnify the significance of relatively minor changes and express fears of developing AD. Despite the value of systematic and disciplined clinical observations, clinicians' impressions

can be clouded by personal expectations of what is normal for a given patient. Subjective concerns alone are therefore insufficient for diagnosis.

Objective assessment

The objective assessment requires the administration of one or more standardized tests. Neuropsychological assessment of specific cognitive domains is preferred both for detecting mild impairments and for differential diagnosis (Table 4). Details of such assessments are beyond the scope of this chapter but are readily available from other sources. If neuropsychological assessment is unavailable, objective testing can consist of a global screening scale, such as the well-known Mini-Mental State Examination (MMSE),[88] the Montreal Cognitive Assessment (MoCA),[89] or the Mini-Cog.[90] Such tests are usually sensitive enough to detect dementia but not necessarily MCI. It is critically important that a patient's test performance be interpreted in accordance with norms for that patient's age and educational level, and preferably for his/her cultural/linguistic group and region as well.

Additional assessments

A general physical and neurological examination, and appropriate laboratory investigations, should be performed both to rule out treatable causes of cognitive impairment (even if they only partially explain the impairment) and to aid in differential diagnosis.

We present here the etiologic subtypes most likely to be seen in geriatric psychiatry settings.

Alzheimer's Disease

Alzheimer's disease (AD) is the single most common neurodegenerative disease, characterized by progressive loss of synapses and neurons, with the accumulation of amyloid plaques, and neurofibrillary tangles, and prominent cholinergic deficits. It is typically diagnosed in the eighth or ninth decades of life, but early onset forms of the disease may be diagnosed as early as the fifth decade. Average duration of survival is about 10 years after the onset of dementia, but varies widely depending on the age of onset, the severity of cognitive impairment, the presence of comorbid diseases, and other factors.[91 92]

In DSM-5,[1] AD is listed an etiologic subtype of both Major and Mild Neurocognitive disorders. Criteria for this subtype harmonize with the latest expert guidelines for Dementia and MCI due to AD, as published by the National Institute on Aging – Alzheimer Association (NIA-AA) Work Group.[93] Unlike the NIA-AA guidelines, the DSM-5 criteria are intended primarily for clinical rather than research use, and do not include pre-clinical AD. The diagnosis of Dementia (Major NCD) in Alzheimer's disease requires evidence of decline to the level of substantial impairment in at least two cognitive domains, one of which must be memory. To diagnose MCI (Mild NCD) in Alzheimer's disease, decline to the level of modest impairment must be observed in memory and potentially in additional domains as well. The cognitive decline should be of insidious onset with gradual and steady progression. Impairments in memory and executive functions typically develop earlier in the disease course, while impairments in visuoconstructional/ perceptual-motor functions, language functions, and social cognition occur later. However, non-amnestic presentations also do occur. Depression and apathy may occur throughout the

clinical spectrum. In the middle to later stages, psychotic features, irritability, agitation, combativeness and wandering may occur, and very late in the illness, gait disturbances, dysphagia, incontinence, myoclonus and seizures may be evident.[1]

For neurocognitive disorders to be attributed to Probable AD, there should either be evidence of autosomal dominant familial AD, or no evidence of mixed etiology, i.e., no other contributing neurological, psychiatric, or systemic disorder that could explain the cognitive decline. Otherwise, the diagnosis of Possible AD is appropriate.[1]

Genetics of AD

Autosomal dominant mutations which cause rare cases of early onset familial AD are the amyloid precursor protein (APP) gene on Chromosome 21, the Presenilin 1 (PS1) gene on Chromosome 14, and the Presenilin 2 (PS2) gene on Chromosome 1. Individuals with Down's Syndrome, caused by Trisomy 21, inevitably develop Alzheimer's neuropathology if they live long enough. The *APOE*4* gene, as noted under Risk Factors, increases risk of dementia but is not diagnostic.

Biomarkers for AD

Evidence of cerebral amyloid deposition, such as positron emission tomographic (PET) brain scans with amyloid tracers, and reduced levels of amyloid beta 42 in the cerebrospinal fluid (CSF), have been proposed as research biomarkers. Evidence of neuronal injury, such as hippocampal atrophy on magnetic resonance imaging (MRI) brain scan, temporoparietal hypometabolism on fluorodeoxyglucose (FDG) PET scans, and elevated total tau and phospho-tau levels in CSF, are less specific to AD but have also been proposed as research biomarkers.[1] They have not been officially validated or approved for clinical diagnostic use.

Unlike DSM-5, the NIA-AA guidelines also describe a stage of asymptomatic preclinical Alzheimer's disease, in which the pathology of the disease is present as evidenced by biomarkers and subclinical cognitive decline detectable only by objective testing.[94]

Vascular Dementia (Vascular Neurocognitive Disorder)

In Major and Mild Vascular Neurocognitive Disorders,[1] the cognitive deficits are principally attributed to cerebrovascular disease. Variously referred to as arteriosclerotic dementia, multi-infarct dementia, vascular cognitive impairment and vascular cognitive disorder,[95] it is the second most common cause of dementia and is frequently present in combination with AD ("mixed dementia"). It can result from both large and small vessel disease, with the location of the lesions more important than the volume of destruction.[95] Given the variability of lesions and locations, the presenting symptoms and time course are often variable. The progression of the neurocognitive decline can be in an acute stepwise pattern, show a more gradual pattern, or can be fluctuating or rapid in its course.[1]

To diagnose vascular neurocognitive disorder, there should either be a clear history of stroke or transient ischemic attacks temporally related to the cognitive decline, or neurological deficits consistent with sequelae of previous strokes. Cognitive decline is usually seen in the domains of complex attention and executive functions. Gait disturbance, urinary

symptoms, and personality or mood changes (including emotional lability) are common.[1] The depression associated with vascular neurocognitive disorder may have a late-life presentation and be coupled with psychomotor slowing and executive dysfunction, the so called vascular depression.[96]

Neuroimaging

Neuroimaging (CT or MRI) evidence of significant parenchymal injury attributable to cerebrovascular disease can include one or more large vessel infarcts, a single large or strategically located infarct or hemorrhage, extensive lacunar infarcts outside the brainstem, or extensive white matter lesions.

Genetics

There are rare autosomal dominant cerebrovascular disorders, such as CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy), which is a form of hereditary stroke caused by Notch-3 mutations on Chromosome 19.

Frontotemporal lobar degeneration (Fronto-temporal Dementia)

Frontotemporal dementia (FTD), the third most prevalent degenerative dementia, is characterized by prominent atrophy of the frontal and temporal lobes, with the predominant neuropathological proteins containing inclusions of hyperphosphorylated tau or ubiquitin protein.

With mean onset in the sixth decade, FTD is a common cause of early-onset dementia although 20–25% of individuals with this disorder are over age 65.[1] The duration of survival is 6–11 years after symptom onset, and 3–4 years after diagnosis.[97] With insidious onset and gradual progression, the clinical subtypes (behavioral and language variants) of FTD correspond to specific areas of brain atrophy.

In the **Behavioral Variant**, changes in personality and behavior are most prominent, with loss of interest in personal affairs and responsibilities, social withdrawal, loss of awareness of personal hygiene, and socially disinhibited behavior.[97] Perseverative or compulsive motor behaviors, as well as hyperorality and dietary changes may also be evident.[1] These patients are often initially seen in psychiatric settings and can be misdiagnosed as major depressive or bipolar disorder. In addition to the Behavioral Variant, there are three **Language Variants**: **(i)** the **Semantic** type which appears as a fluent aphasia with impoverished content and paraphasic errors, with intact syntax and prosody; emotional blunting, loss of empathy, and rigid behaviors may also be seen,[97] (ii) **Progressive Nonfluent Aphasia**, and (iii) the **Logopenic** subtype.

Genetics

In familial FTD, mutations have been associated with genes encoding proteins affecting a number of fundamental cellular functions, including microtubule-associated protein tau (MAPT), granulin (GRN), C9ORF72, transactive response DNA- binding protein of 43 kDa, valosin-containing protein, chromatin modifying protein 2B, and fused in sarcoma protein.

Neuroimaging

Structural MRI or CT can show distinct patterns of regional cortical atrophy which correlate with the clinical variants of FTD.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia. The underlying disease is primarily characterized by alpha-synuclein misfolding and aggregation within the pathognomonic Lewy bodies, which are also found in Parkinson's disease. Onset of symptoms is between the sixth and ninth decades, and average survival is 5–7 years.[1]

With insidious onset and gradual progression, the cognitive deficits are most prominent in the domains of attention, visuospatial and executive functioning. Additional core features include fluctuating cognition, recurrent visual hallucinations, and parkinsonism.[1] The key distinction between DLB and dementia of Parkinson's disease is based on the temporal sequence of the cognitive impairment and the movement disorder. In DLB, cognitive impairment precedes the onset of parkinsonism, while in the latter, the cognitive impairment occurs in the context of established Parkinson's disease.

Suggestive features of DLB include REM sleep behavior disorder and severe neuroleptic sensitivity. Low dopamine transporter (DaT) uptake in basal ganglia demonstrated by SPECT or PET imaging has been proposed as a suggestive feature. Supportive clinical features include repeated falls and syncope, transient and unexplained loss of consciousness, severe autonomic dysfunction, hallucinations in other modalities, systematized delusions and depression.[98]

Neuroimaging

To help differentiate Lewy-body related dementias (DLB and Dementia in Parkinson's disease) from other dementias, dopamine transporter (DaT) PET scans may be useful. Generalized low uptake on SPECT and fluorodeoxyglucose PET with reduced occipital activity also suggests DLB. Additional testing supportive of DLB include low uptake MIBG myocardial scintigraphy, suggesting synaptic denervation, as well as prominent slow wave activity on EEG with temporal lobe transient sharp waves.[98]

Neurocognitive Disorders due to Parkinson's Disease

These disorders are diagnosed when there is gradual cognitive decline in the presence of a well-established diagnosis of Parkinson's disease. Over the course of their disease, approximately 75% of individuals with Parkinson's disease will develop a major neurocognitive disorder.[1] The pattern of cognitive deficits is variable but often affects the executive, memory, and visuospatial domains, with a slowing of information processing that suggests a "subcortical" picture. Associated features include psychiatric symptoms such as depressed or anxious mood, apathy, hallucinations, delusions, or personality change, as well as rapid eye movement sleep behavior disorder and excessive daytime sleepiness.[1]

Neurocognitive Disorder due to Huntington's Disease

Huntington's disease is a neurodegenerative disease caused by an autosomal dominant mutation consisting of CAG repeats on Chromosome 4. The neurotoxic Huntingtin (HTT) protein begins by damaging the striatum of the basal ganglia but eventually affects the entire brain. Although adult onset Huntington's disease usually manifests in the fourth or fifth decades, patients have a median survival of 15 –20 years after diagnosis, and can thus present to geriatric services. A few patients develop their first symptoms at older ages in the absence of a family history. Progressive cognitive impairment to eventual dementia is inevitable. Although cognitive deficits (executive function) and behavioral symptoms (depression, anxiety, apathy, obsessive-compulsive symptoms, and psychosis) often emerge before the motor abnormalities (bradykinesia and chorea), clinical diagnosis is rarely made on the basis of cognitive symptoms alone. A family history of the disease should alert clinicians to the possibility, and genetic testing for the HTT mutation is diagnostic.[1]

Neurocognitive Disorder due to Prion Disease

These are neurocognitive disorders due to spongiform encephalopathies caused by transmissible misfolded protein particles called prions. The human prion disorders include kuru, sporadic Creutzfeldt-Jacob disease (CJD), familial CJD, iatrogenic CJD, Gerstmann-Stäussler-Scheinker disease, fatal insomnia, and new variant CJD. Human transmission has been reported due to infected growth hormone injection and corneal transplantation; cross-species transmission is exemplified by bovine spongiform encephalopathy ("mad cow disease.") These illnesses progress rapidly and combine neurocognitive decline and motor features such as myoclonus and ataxia. Variant CJD may present with low mood, withdrawal, and anxiety. Individuals are typically diagnosed in their seventh and eighth decades, and the course is rapidly progressive, with survival typically under one year.[99] Diagnosis can only be confirmed by biopsy or autopsy. However, MRI scanning with diffusion weighted imaging or fluid-attenuated inversion recovery may show multifocal gray matter hyperintensities in the subcortical and cortical areas. Tau or 14-3-3 protein may be found in the cerebrospinal fluid; characteristic triphasic waves may be seen on the electro-encephalogram. Genetic testing may be useful in the 15% of cases who have a family history suggesting an autosomal dominant mutation.[1]

TREATMENT

Etiology-specific treatment

If a neurocognitive disorder is diagnosed as wholly or partly due to a treatable condition, treatment specific to that condition is clearly the first line of defense. At this time, no disease-modifying therapies are available for any of the neurodegenerative diseases. However, symptomatic and supportive treatments are usually of value.

Symptomatic Treatment

Cholinesterase inhibitors increase cholinergic transmission at the synaptic cleft, potentially benefiting patients with cholinergic deficits as in AD. Three such drugs are currently available in the US: donepezil, rivastigmine, and galantamine. For dementia due to AD,

a systematic review determined that all three drugs are comparable in efficacy and, on average, provide modest improvements in cognitive function and everyday activities and behavior in Alzheimer's disease.[100] Although approved for use in severe dementia, many practitioners question its value in advanced disease. Evidence is mixed on the effects of these drugs on long-term outcomes, e.g., slowing of the rate of decline in everyday functions, and delay of institutionalization.[101]

Rivastigmine is also approved for dementia in Parkinson's disease. A large double-blind placebo-controlled trial of rivastigmine showed meaningful improvements in cognition and everyday functioning.[102 103]

While there is expert consensus that cholinesterase inhibitors are more effective in DLB than in AD, for both cognitive and behavioral effects,[104] evidence from large controlled trials is lacking.

In vascular dementia, evidence is mixed for the cholinesterase inhibitors. They are often prescribed in vascular dementia because of the frequent co-occurrence of cerebrovascular and neurodegenerative disease.[105]

In frontotemporal dementia, there is no convincing evidence of benefits from these drugs, and there are reports that they worsen behavior symptoms.[106 107]

There is inadequate evidence on the use of cholinesterase inhibitors in other neurocognitive disorders.

In contrast, a systematic review has found minimal evidence of benefit from these drugs in mild cognitive impairment, either with symptom relief or delay in progression to dementia. Further, this weak evidence was overwhelmed by the risk of adverse effects, particularly gastrointestinal effects.[108]

NMDA receptor antagonist

One such agent, memantine, is approved for the treatment of moderate to severe dementia due to Alzheimer's disease. It is believed to be neuroprotective against excitoxicity in the cortex and hippocampus. An advantage of memantine is that it is well tolerated.

A systematic review showed that memantine had a small beneficial effect on cognition at six months in moderate to severe AD, marginal effect on mild to moderate AD, and a small but clinically undetectable effect in mild to moderate vascular dementia.[109]

In frontotemporal dementia, memantine has shown mixed results.[106] There is preliminary evidence of benefits in DLB and Dementia in Parkinson's disease; however, there have been reports of worsening delusions and hallucinations in DLB.

Serotonergic agents

SSRI antidepressants can produce benefits for behavioral /psychiatric symptoms in frontotemporal dementia, without concomitant improvements in cognition.[110]

Dopamine blocking agents

Neuroleptic (antipsychotic) drugs should be prescribed in dementia with due attention to the risk of adverse cerebrovascular events.[111] They should be avoided or used with extreme caution in patients with DLB, given their sensitivity to these agents. When necessary the second-generation antipsychotics are preferred.[104] If the patient is taking a dopaminergic (anti-parkinsonian) drug, lowering its dose would be the preferred first step before introducing a dopamine-blocking agent.

Benzodiazepines

In general, benzodiazepines are to be avoided in the neurocognitive disorders because of the risk of paradoxical agitation as well as of falls and further diminished cognition. An exception may be the treatment of REM Sleep Behavior Disorder in DLB.

Further discussion of the pharmacologic, psychosocial, and environmental management of neurocognitive disorders is provided elsewhere in this volume.

SUMMARY

Clinicians should be knowledgeable about the various neurocognitive disorders which are common and devastating in older adults. Diagnosis requires careful history-taking and skilled clinical assessment, followed by appropriate laboratory investigations. Diagnostic imaging can be useful when interpreted by experts familiar with these conditions. Biomarkers for most of these disorders are still being validated and are not yet recommended for clinical use. Referral to specialists can be valuable for specific purposes, e.g., neuropsychologists for objective cognitive testing and interpretation; neurologists for diagnosis, particularly of the less common disorders; geriatric psychiatrists when there are psychological or behavioral challenges. Drug treatments at present provide symptomatic relief. Psychosocial and other supportive therapies are essential.

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Key Points

1. Clinicians should be knowledgeable about the various neurocognitive disorders which are common and devastating in older adults.
2. Diagnosis requires careful history-taking and skilled clinical assessment, followed by appropriate laboratory investigations.
3. Diagnostic imaging can be useful when interpreted by experts familiar with these conditions.
4. Biomarkers for most of these disorders are still being validated and are not yet recommended for clinical use.
5. Referral to specialists can be valuable for specific purposes, e.g., neuropsychologists for objective cognitive testing and interpretation; neurologists for diagnosis, particularly of the less common disorders; geriatric psychiatrists when there are psychological or behavioral challenges.
6. Drug treatments at present provide symptomatic relief. Psychosocial and other supportive therapies are essential.

Table 1

Neurocognitive Disorders as Diagnosed in DSM-5

Diagnostic Criteria	**Major Neurocognitive Disorder/Dementia**	**Mild Neurocognitive Disorder/MCI**
A	Significant cognitive decline in one or more cognitive domains, based on:	Modest cognitive decline in one or more cognitive domains, based on:
	1. Concern about significant decline, expressed by individual or reliable informant, or observed by clinician.	1. Concern about mild decline, expressed by individual or reliable informant, or observed by clinician.
	2. Substantial impairment, documented by objective cognitive assessment.	2. Modest impairment, documented by objective cognitive assessment.
B	Interference with independence in everyday activities.	No interference with independence in everyday activities, although these activities may require more time and effort, accommodation, or compensatory strategies
C	Not exclusively during delirium.	
D	Not better explained by another mental disorder.	
E	Specify one or more etiologic subtypes, “due to”	
	• Alzheimer’s disease • Cerebrovascular disease (Vascular Neurocognitive Disorder) • Frontotemporal Lobar Degeneration (Frontotemporal Neurocognitive Disorder) • Dementia with Lewy Bodies (Neurocognitive Disorder with Lewy Bodies) • Parkinson’s disease • Huntington’s disease • Traumatic Brain Injury • HIV Infection • Prion Disease • Another medical condition • Multiple etiologies	

Adapted from: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013

Table 2

Prevalence of Dementia: Overall and Subtypes

Authors	Country	Study type	Age	Regions		Overall Dementia	Alzheimer'S dementia	Vascular dementia	Parkinson'S dementia	Dementia with Lewy Bodies	Fronto-temporal dementia
Prince *et al., 2013*[4]	Global	Meta-analysis + systematic review	>=60	Latin America		8.5%					
				Sub-Saharan Africa		5.0—7.0%					
				Other world regions		2.0– 4.0%					
*Matthews *et al., 2013*[9]	UK	Population survey	65+	Cambridgeshire, Newcastle, and Nottingham		6.5%					
Gurland *et al., 1999*[10]	USA	Population survey	65+	Hispanic/Latino	65–74	7.5%					
					75–84	27.9%					
					85+	62.9%					
				African American	65–74	9.1%					
					75–84	19.9%					
					85+	58.6%					
				Non-Hispanic White	65–74	2.9%					
					75–84	10.9%					
					85+	30.2%					
*Hall *et al., 2009*[11]	USA	Population survey	70+	African Americans in Indianapolis		7.45%	6.77%				
Plassman *et al. 2007*[12]	USA	Population survey	71–79	Nationally representative sample		4.97%	2.32%	0.98%			
			80–89			24.19%	18.1%	4.09%			
			90+			37.36%	29.7%	6.19%			
*Graves *et al., 1996*[13]	USA	Population survey	65+	Japanese Americans		6.32%	3.46%	1.41%			
*CSHA Working Group, *1994*[14]	Canada	Population survey	65+	Nationally representative sample		8%	5.1%	1.5%			
Aarsland *et al.,2005*[15]	Multi-national	Systematic review	65+						0.15–0.5%		
Zaccai et *al.,2005*[16]	Multi-national	Systematic review	65+							0–5%	
Rosso *et al.,2003*[17]	Netherlands	Population survey									Per 100,000

Authors	Country	Study type	Age	Regions	Overall Dementia	Alzheimer'S dementia	Vascular dementia	Parkinson'S dementia	Dementia with Lewy Bodies	Fronto-temporal dementia
			50–59							3.6
			60–69							9.4
			70–79							3.8

In all studies, prevalence % increases with age.

*Age-specific prevalence is reported in the original articles but omitted from this table.

Table 3

Functional limitations associated with impairment in different cognitive domains

Cognitive domain	Examples of changes in everyday activities
Complex attention	Normal tasks take longer, especially when there are competing stimuli; easily distracted; tasks need to be simplified; difficulty holding information in mind to do mental calculations or dial a phone number
Executive functioning	Difficulty with multi-stage tasks, planning, organizing, multi-tasking, following directions, keeping up with shifting conversations
Learning and memory	Difficulty recalling recent events, repeating self, misplacing objects, losing track of actions already performed, increasing reliance on lists, reminders
Language	Word-finding difficulty, use of general phrases or wrong words, grammatical errors, difficulty with comprehension of others' language or written material
Perceptual-motor/ visuospatial function	Getting lost in familiar places, more use of notes and maps, difficulty using familiar tools and appliances
Social cognition	Disinhibition or apathy, loss of empathy, inappropriate behavior, loss of judgment

Adapted from: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013

Table 4

Examples of objective cognitive assessments, as noted in DSM-5

Cognitive domains	**Objective Assessment**
Complex Attention	*Maintenance of attention*, e.g., press a button every time a tone is heard, over a period of time. *Selective attention*, e.g., hear numbers and letters, but count only the letters. *Divided attention*, e.g., tap rapidly while learning a story. *Processing speed*: carry out any timed task.
Executive Functioning	*Planning:* e.g., maze puzzles, interpret sequential pictures or arrange objects in sequence. *Decision making* with competing alternatives, e.g., simulated gambling. *Working memory:* hold information for a brief period and manipulate it, e.g. repeat a list of numbers backward. *Feedback utilization:* Use feedback on errors to infer rules to carry out tasks. *Inhibition:* Override habits; choose the correct but more complex and less obvious solution, e.g., read printed names of colors rather than naming the color in which they are printed. *Cognitive flexibility*: Shift between sets, concepts, tasks, rules, e.g., alternate between numbers and letters.
Learning and Memory	*Immediate memory*: Repeat a list of words or digits. *Recent memory:* Free recall: recall as many items as possible from, e.g., a list of words, or a story, or a diagram. Cued recall: with examiner providing cues, e.g., “recall as many food items as you can from the list.” Recognition: with examiner asking, e.g., “was there an apple on the list?” *Semantic memory:* recall well-known facts. *Autobiographical memory:* recall personal events. *Implicit (procedural) memory:* recall skills to carry out procedures.
Language	*Expressive language:* confrontation naming of e.g., objects or pictures; fluency for words in a given category (e.g. animals) or beginning with a given letter, as many as possible in one minute. *Grammar and syntax*: omitting or incorrectly using articles, prepositions, helper verbs. *Receptive language*: comprehend /define words, carry out simple commands.
Perceptuomotor functioning	*Visuoconstructional: e.g.*, Draw, copy, assemble blocks. *Perceptuomotor: e.g.*, Insert blocks or pegs into appropriate slots. *Praxis:* Mime gestures such as “salute” or actions such as “use hammer.” *Gnosis:* e.g., recognize faces and colors.
Social cognition	*Recognize emotions*: Identify pictures showing e.g., happy, sad, scared, angry faces. *Theory of mind:* Consider another person’s thoughts, intentions when looking at story cards, e.g., “why is the boy sad?”

Adapted from: American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013