

Chapter 15: Mild Cognitive Impairment and Dementia

Supplemental Materials

Definition and Classification

Cultural factors may impact self- and informant-report of cognitive history (e.g., hesitancy to report decline), as well as the manifestation of neuropsychiatric symptoms. Importantly, neuropsychologists must remain sensitive to cultural factors during the evaluation by focusing on establishing rapport, selecting appropriate measures/norms, respecting cultural values, promoting transparency related to cultural factors, and recognizing the limitations of the assessment within the conceptualization and written report. Also, psychometric characteristics of each measure and norms must be considered when interpreting low scores to avoid misdiagnosis. Repeat assessment is especially helpful with diverse older adults to inform progression of neurodegeneration (Rivera Mindt et al., 2019). Demographically adjusted norms may help to reduce false-positive diagnostic errors. Importantly, sociocultural measures of educational quality and acculturation should be used to contextualize findings. When norms are used with individuals who differ from the reference group on sociocultural factors, the risk of diagnostic error increases dramatically (Byrd & Rivera-Mindt, 2022). Race-based norms and regression parameters have been developed for research (Sachs et al., 2020; Wang et al., 2021). However, the use of demographically adjusted norms (especially when race is considered a proxy for sociocultural factors that impact neuropsychological performance) also raises a complex set of issues. In this context, Possin et al. (2021) recommended the use of a regression-based normative approach adjusting for social determinants of brain health; however, the normative epidemiological database to support such an approach remains to be developed.

Functional Neuroanatomy and Neuropsychological Evaluation

Vascular Cognitive Impairment and Dementia

Following a vascular event (e.g., stroke), an abrupt onset and stepwise or fluctuating decline is common. However, many individuals will show a gradual onset and slow progression when the etiology is due to ischemic small vessel disease (Sachdev et al., 2014). Although a single neuropsychological profile cannot be determined due to the heterogeneity of underlying vascular causes, deficits in attention, processing speed, working memory, executive functioning, phonemic fluency, and motor programming commonly occur with small vessel disease and are thought to result from ischemic interruption of frontosubcortical circuits (Cullum et al., 2018). A recent metanalysis found that individuals with cerebral small vessel disease (cSVD) performed below controls across assessed areas of cognition, with processing speed being the most consistent deficit (Salvadori et al., 2023). These authors also noted the lack of sufficient data for differentiation of cognitive changes in cSVD versus other neurodegenerative conditions.

In general, the underlying pathogenesis of vascular dementia (VaD) may involve cardioembolic, atherosclerotic, ischemic, hemorrhagic, or genetic processes such as: (1) small vessel disease resulting in microinfarction, leukoencephalopathy, and/or lacunar infarctions; (2) large-vessel occlusive disease; and (3) micro/macro-hemorrhagic lesions. The majority of individuals with vascular cognitive disorders have a combination of cortical and subcortical lesions (Sachdev et al., 2014). However, vascular disease may be exclusively subcortical (i.e., *subcortical vascular dementia*), and caused by widespread lacunes and/or white matter lesions in deep white matter. Subcortical vascular dementia has previously been referred to as *Binswanger's disease*, a term rarely utilized at present (Sachdev et al., 2014).

Cerebrovascular disease (CVD) and Alzheimer's disease (AD) often co-occur (Kapasi et al., 2017). Notably, one or both *APOE* ϵ 4 alleles elevates risk for VaD, although to a lesser

extent than for AD (Rohn, 2014). Generally, the greater the evidence of CVD, the greater the likelihood that cognitive impairment is due, at least in part, to vascular underpinnings. With substantial vascular contributions, a diagnosis of mixed dementia may be considered. Rare genetic cerebrovascular disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) increase the risk of a vascular cognitive disorder to probable certainty (Sachdev et al., 2014). Risk factors for VCI include, but are not limited to, lifestyle factors (e.g., alcohol intake, diet, obesity, smoking), physiological risk factors (e.g., hypertension, diabetes, hyperlipidemia), and vascular disease (e.g., coronary artery disease, atrial fibrillation; Sachdev et al., 2014).

Parkinson's Disease Dementia

Dementia prevalence estimates in Parkinson's disease (PD) vary dramatically from 8 percent to 93 percent, depending on study design. The most rigorous studies, however, have reported a Parkinson's disease dementia (PDD) prevalence of approximately 25 percent among individuals with PD (Tröster & Abbott, 2019). The likelihood of developing dementia increases as the number of years with PD increases (Galvin, 2019). The mean time from onset of PD to dementia is approximately 10 years (Galvin, 2019). Most people with idiopathic PD develop symptoms at 50 years of age or older, while Young Onset Parkinson's disease (YOPD) occurs before age 50 (Parkinson's Foundation, n.d.).

For a PD diagnosis, Postuma et al. (2015) detail: (1) parkinsonism, defined as: bradykinesia (slowness of movement and reduced amplitude in continuous movement) and either (a) rigidity (stiffness, which may include cogwheeling) and/or (b) resting tremor; and (2) supportive criteria of clear beneficial response to dopaminergic treatment, levodopa-induced dyskinesia, resting tremor of a limb, and/or either olfactory loss or cardiac sympathetic

denervation. Resting tremor in PD is initially unilateral (presumably due to asymmetric dopaminergic degeneration), and can progress to other limbs, but typically remains asymmetrical (Greenland & Barker, 2018). Other supportive signs of PD include hypophonia, micrographia, shuffling gait, and postural instability (Greenland & Barker, 2018).

Cognitive areas that are typically impaired in PD include processing speed, working memory, sustained attention, executive functioning, visuospatial functioning and constructional praxis, and encoding/retrieval deficits with intact retention (Tröster & Abbott, 2019).

Neuropathology includes dopaminergic neuronal loss in the substantia nigra, which is theorized to be related to mitochondrial dysfunction and alpha-synuclein pathology (Surmeier, 2018), and presents mainly in dorsolateral regions; this is compared to dementia with Lewy bodies (DLB) in which medioventral regions are most affected. Aggregation of alpha-synuclein proteins in the form of Lewy bodies and neurites occur in PD, PDD, and DLB. In PD, inclusions are restricted to the brainstem and limbic regions, whereas in PDD and DLB, pathology extends to the neocortex. In PDD, as compared to DLB, pathology is particularly notable in the striatum (Walker et al., 2019).

Risk factors for PDD include advanced age, male sex, greater severity of motor symptoms, hallucinations, rapid eye movement (REM) sleep behavior disorder, and cardiovascular risk factors (e.g., hypertension; Xu et al., 2016). About 15 percent to 20 percent of individuals with PD have a clear family history of PD. Early onset and a strong familial history of PD are often linked to genes (e.g., *SNCA*, *PARK2*, *PINK1* and *LRRK2*; Nuytemans et al., 2010; Parkinson's Foundation, n.d.). Dopamine transporter (DaT) imaging using single proton emission computed tomography (SPECT) helps to identify dopaminergic deficit (Tröster & Abbott, 2019). F-Dopa PET imaging offers additional benefits (e.g., improved spatial

resolution, shorter scan time, and lower radiation burden). Anxiety and depression are commonly co-morbid in PDD (Tröster & Abbott, 2019). Fluctuating attention, visual hallucinations, and REM sleep behavior disorder are frequent in PDD and DLB (Walker et al., 2019). Notably, fluctuating attention and visual hallucinations are more frequent in DLB (Jellinger & Korczyn, 2018).

Parkinsonism and Parkinson's Plus Syndromes. *Parkinsonism* is a general term used to describe any condition that causes movement abnormalities seen in PD such as bradykinesia, rigidity, or resting tremor. Parkinsonism can have a variety of causes, such as medications, brain lesions, metabolic disorder, or neurodegenerative disease (Mayo Clinic, 2019). *Parkinson's Plus Syndromes* and *atypical PD/parkinsonian disorders* are terms used to describe neurodegenerative syndromes that have some motor features of PD, include other symptoms, and either do not respond to levodopa or do so for only a short time. These syndromes include DLB, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and multiple system atrophy (MSA; Johns Hopkins Medicine, n.d.-a; University of Michigan Health, 2020).

Progressive Supranuclear Palsy

PSP was originally called Steele-Richardson-Olszewski syndrome, then PSP, and is now termed Richardson Syndrome (PSP-RS; Alster et al., 2020). It has become increasingly recognized, however, that multiple clinical syndromes aside from PSP-RS may result from PSP pathology (Coughlin & Litvan, 2020), also referred to as PSP-tau (Ling, 2016). PSP-RS is the most common PSP subtype (estimated at 72 percent) and PSP-parkinsonism (PSP-P) is the second most common subtype (estimated at 14 percent; Mahale et al., 2021). Other clinical syndromes associated with PSP pathology are rare and include pure akinesia with gait freezing (PAGF), corticobasal syndrome, bvFTD, progressive non-fluent aphasia, cerebellar ataxia,

primary lateral sclerosis, progressive apraxia of speech or speech/language, ocular motor dysfunction, and postural instability (Höglinger et al. 2017; Ling et al. 2016; Stamelou et al., 2021). Disease onset is in the mid-sixties for PSP-RS and PSP-P, with approximately six to nine years of survival, respectively (Williams et al., 2005).

The combination of early-onset postural instability and falls (typically backwards and presumably due to axial rigidity) with vertical ocular motor dysfunction reflects PSP-RS (Ling, 2016; Williams et al., 2005). In PSP-RS, predominant cognitive deficits occur in processing speed (Lee et al., 2018), complex attention, and executive functioning (Schoenberg & Duff, 2011), as well as immediate memory capacity and learning (Pillon et al., 1994). Höglinger et al. (2017) proposed diagnostic criteria for seven other subtypes.

PSP-tau pathology is a 4R tau with neuronal and glial lesions found in the basal ganglia, diencephalon, brainstem, and cerebellum (Dickson et al., 2010; Stamelou et al., 2021). *MAPT* is the strongest genetic link; however, PSP is usually sporadic (Boxer et al., 2017; Höglinger et al., 2011); see Coughlin and Litvan (2020) as well as Stamelou et al. (2021) for more information about genetic factors. During clinical examination of PSP-RS, it is often possible to elicit an *appliance sign*, which is an indicator of impaired motor control due to frontal dysfunction (i.e., perseverative clapping despite instruction to clap only once; Borroni & Alberici, 2016). Striking midbrain atrophy on MRI is also typically observed in PSP-RS (e.g., *hummingbird*, *mickey mouse*, or *morning glory* signs; Whitwell et al., 2017).

Corticobasal Syndrome

Although CBS and corticobasal degeneration (CBD) have been used interchangeably in the past, CBS is more recently understood to be a rare clinical syndrome that is caused by several pathologies, including but not limited to CBD (a specific 4R tauopathy pathologic diagnosis) or

other tauopathies of PSP or FLTD-tau, AD pathology, or FTLD-TDP-43. CBD most commonly results in CBS but can cause other clinical presentations such as PSP-RS, Frontal Behavioral-Spatial Syndrome, nfvPPA, and a range of neurological symptoms (Constantinides et al., 2019; Parmera et al., 2016; Wilson et al., 2021). Disease onset is typically in the sixties (Armstrong et al., 2013) and average survival in CBS is seven to eight years (Wilson et al., 2021).

In CBS, there is a range of cognitive, behavioral, and motor symptoms, though patients usually present with cognitive deficits before the onset of motor symptoms (Parmera et al., 2016). According to Armstrong et al. (2013), *probable* CBS is characterized by an asymmetric presentation with at least two of: [a] (a1) limb rigidity or akinesia, (a2) limb dystonia, (a3) limb myoclonus; and two of the following: [b] (b1) orobuccal or limb apraxia, (b2) cortical sensory deficits, (b3) alien limb phenomena. *Possible* CBS, by contrast, describes asymmetric or symmetric presentation with one supportive feature from each of the above groups (a and b). Speech and language deficits are the most common cognitive problem (predominantly reduction in fluency with deficits in grammar and motor functioning; Mathew et al., 2011), while executive functioning, visuospatial, and memory deficits (primarily encoding and retrieval) also may occur (Kertesz & McMonagle, 2010; Mathew et al., 2011). The pathologies that produce CBS show a consistent pattern of cortical damage. MRI reveals asymmetric cortical atrophy in frontal and parietal areas, and this pattern is observed on SPECT/PET as hypoperfusion/hypometabolism with basal ganglia involvement (Hassan et al., 2011).

Multiple Systems Atrophy

MSA is rare and includes a diverse combination of cerebellar ataxia, autonomic dysfunction, and extrapyramidal and pyramidal motor symptoms. Although dementia has been considered as nonsupport for MSA and cognitive impairment is not mentioned in widely used

guidelines (Gilman et al., 2008), dementia and cognitive impairment have each been reported in approximately 32 percent of MSA cases. Cognitive impairment is usually mild but can range to severe (Koga et al, 2017; Stankovic et al., 2014). Symptoms tend to appear in the fifties and increase rapidly over five to 10 years, with progressive loss of motor function. Death tends to occur in the later stages due to cardiac or respiratory issues (National Institute of Neurological Disorders and Stroke [NINDS], 2014).

MSA is divided into subtypes based on initial symptoms: a parkinsonian subtype (MSA-P; 80 percent of cases) and a cerebellar type (MSA-C; 20 percent of cases). Individuals with MSA-P exhibit more symptoms common in PD (e.g., bradykinesia, rigidity, and postural instability), whereas those with MSA-C commonly exhibit cerebellar ataxia (Lee et al., 2019; Tröster & Garrett, 2018). Cerebellar ataxia can include oculomotor (over/undershoot of saccades, nystagmus), limb (over/undershoot of limb movements, action tremor, poor coordination), and balance/gait (slowness in alternating movement, sway when sitting/standing, instability) dysfunction (Marsden, 2018). Common autonomic symptoms include gastrointestinal dysfunction (Lee et al., 2019), genitourinary dysfunction, orthostatic hypotension, and sleep disorders (REM sleep behavior disorder; Palma et al., 2018). Within a few years, difficulties with balance, speech, and coordination progress rapidly (Palma et al., 2018). Frontal-executive dysfunction is the most common neuropsychological presentation (including attention and working memory), while deficits in memory and visuospatial functions also may occur (Stankovic et al., 2014).

The term MSA was initially introduced to describe three neurologic conditions: Shy–Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy, as these conditions are all considered to be multisystem degenerations with unique oligodendroglial

cytoplasmic inclusions. Shy-Drager syndrome is an outdated term that used to refer to MSA generally; striatonigral degeneration now corresponds MSA-P and olivopontocerebellar atrophy now corresponds to MSA-C (Fanciulli & Wenning, 2015; Wenning et al., 2004). Although there are familial cases of MSA-C, MSA is considered sporadic. Accumulations of alpha-synuclein protein occur in the central and peripheral autonomic nervous systems, primarily in oligodendroglial cells, which form glial cytoplasmic inclusions (Palma et al., 2018). Cell loss and gliosis tend to occur in the striatum, particularly in the putamen, substantia nigra pars compacta, and pons. There is also loss of pontocerebellar fibers and reduction in the size of the middle cerebellar peduncle. Pathology is primarily nigrostriatal in MSA-P and olivopontocerebellar in MSA-C (Tröster & Garrett, 2018). An additional clue of MSA may be *Pisa syndrome*, an abnormal posture in which the body appears to be leaning to one side, akin to the Leaning Tower of Pisa (NINDS, 2014).

Huntington's Disease

Huntington's disease (HD) is a fatal genetic neurodegenerative disease caused by a single-gene mutation associated with huntingtin protein. This defect causes abnormal cytosine, adenine, and guanine (CAG) trinucleotide repeats. The longer the CAG repeat, the younger the age of motor-symptom onset and death (Keum et al., 2016). Like in early-onset familial (genetic) AD, HD has autosomal dominant transmission, meaning that if an individual has a parent with the gene mutation, the individual has a 50 percent chance of inheriting the mutation. The presence of the mutation on either allele leads to the disease, and, if inherited, disease is certain to develop. If the gene mutation is not inherited, HD will not develop or pass to future generations. Onset of clinical symptoms is typically between the ages of 30 and 50 (NINDS, 2019b), though cases in individuals as young as eight have been documented (Patra & Shirolkar,

2015). Death occurs within 10 to 30 years following symptom onset and is typically due to infection (often pneumonia) or fall-related injuries (NINDS, 2019b). HD is characterized by motor, cognitive, and psychiatric disturbances. Motor symptoms include chorea, dystonia, myoclonic jerks, tics, and, as the disease progresses, bradykinesia, akinesia, rigidity, and impaired postural reflexes. Psychiatric symptoms can include depression, anxiety, obsessive-compulsive behavior, or apathy, and psychosis occasionally occurs in late stages (Ghosh & Tabrizi, 2018). Cognitive deficits occur in processing speed, attention, visuospatial integration, and executive functioning (Ghosh & Tabrizi, 2018; Tröster & Garrett, 2018). In fact, cognitive and psychiatric changes may precede motor symptoms by 15 years (Paulsen, 2011). Because a diagnosis of HD should include genetic testing (NINDS, 2019b), genetic counseling is needed. Atrophy of the striatum is a hallmark on MRI but may be absent in early stages (Zamora et al., 2022). PET has been helpful in showing progressive changes in striato-thalamic and cortical metabolic activity (Tang et al., 2013).

Other Causes of Cognitive Impairment in Older Adults and Relevant Topics

Creutzfeldt-Jakob Disease

A rare and rapidly progressing dementia, Creutzfeldt-Jakob disease (CJD) results from a transmissible spongiform encephalopathy, otherwise known as *prion disease*, caused by an infectious form of proteins (*prions*). Onset is approximately 60 years of age with a very rapid course of one year or less for the majority of individuals. There are three types of CJD: (1) sporadic CJD/sCJD in approximately 85 percent of cases; (2) hereditary CJD in 10 percent to 15 percent of cases; and (3) acquired CJD in less than 1 percent of cases. Acquired CJD occurs by exposure to affected brain/nervous system tissue or CSF, typically through medical procedures (NINDS, 2021a). In rare instances, variant (vCJD) can be acquired by eating meat from cattle

with a similar bovine spongiform encephalopathy and may be transmitted through blood. Infections, such as pneumonia, often lead to death (NINDS, 2021a). Symptoms tend to include cognitive deficits (i.e., disorientation, memory, judgment), visual problems, ataxia, myoclonus, muscle tone abnormalities, visual/auditory hallucinations, and delusions (NINDS, 2021a; Zerr & Parchi, 2018). vCJD begins primarily with psychiatric symptoms, usually occurs in younger individuals, and has a longer disease duration. Neuropathology includes aggregated prion protein, spongiform changes, neuronal loss, and gliosis (Zerr & Parchi, 2018). Confirmation of CJD should include brain biopsy/autopsy; however, a diagnostic CSF test (i.e., Real Time-Quaking-Induced Conversion) may be used. MRI and electroencephalogram (EEG) are also informative (NINDS, 2021a). For sCJD, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) are preferred and implicate damage to focal or diffuse cortical areas and basal ganglia, particularly the striatum (Fragoso et al., 2017); cortical ribbon enhancement (*cortical ribboning*) on DWI is a sensitive marker of the disease.

HIV-Associated Neurocognitive Disorder

HIV-associated neurocognitive disorder (HAND) is divided into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). Despite combination antiretroviral (cART) treatment, HAND affects about half of individuals with HIV (Smail & Brew, 2018). Prior to cART, infection severity markers such as decreased CD4 cell count inform the likelihood of HAD. After cART, however, it is important to consider the duration and severity of infection and central nervous system (CNS) infiltration that occurred prior to cART, age, and vascular or neurodegenerative comorbidities (Smail & Brew, 2018). The clinical presentation of HAND is primarily frontosubcortical and includes slowed processing speed and difficulties with attention, working memory, and executive

functioning; gait unsteadiness and clumsiness also tend to occur (Smail & Brew, 2018). Psychiatric effects of HAND include apathy, depression, or hypomania (Smail & Brew, 2018). HAND develops due to HIV and inflammation in the CNS. Neuronal dysfunction and loss ultimately occur, particularly in subcortical structures such as the basal ganglia and white matter fiber tracks. Hippocampal dysfunction and atrophy can also occur, though the memory deficits are primarily of encoding, and are believed to be associated with frontosubcortical dysfunction (Smail & Brew, 2018). Rumbaugh and Tyor (2015) provide a succinct diagnostic table based on the work of Antinori et al. (2007), who outlined research criteria for a diagnosis of HIV-associated neurocognitive disorders. Briefly, ANI includes impairment in at least two domains (≥ 1 SD), no impairment in ADL, no evidence of delirium/dementia, and no other preexisting cause of ANI such as depression. MND includes impairment in at least two domains (≥ 1 SD), mild interference in ADL, no evidence of delirium/dementia, and no other preexisting cause of ANI such as depression. HAD includes impairment in at least two domains (≥ 2 SD), marked impairment in ADL, no evidence of delirium, and no other preexisting cause for dementia.

Normal Pressure Hydrocephalus

There are two forms of normal pressure hydrocephalus (NPH): (1) idiopathic (*primary*; iNPH) in which the cause is unknown; and (2) symptomatic (*secondary*), which occurs in response to neurological insult such as brain infection, hemorrhage, or TBI. iNPH impacts older adults primarily, while secondary NPH impacts all age groups. Both types are non-obstructive (or *communicating*). In addition, the term *normal pressure* has been challenged because intracranial pressure is not always within normal limits (Das & Biagioni, 2021). iNPH is considered a potentially reversible dementia, occurring insidiously over six months, and accounting for approximately 6 percent of dementia cases with symptoms initially occurring

around age 70 (Das & Biagioni, 2021; Relkin et al., 2005). Clinically, individuals present with gait disturbance (magnetic or shuffling), urinary incontinence (or in earlier stages increased frequency or urgency), and cognitive impairment; however, not all three symptoms may be present (Ravdin et al., 2019). Gait disturbance is the most common symptom and is required for a diagnosis, along with either urinary or cognitive symptoms (Das & Biagioni, 2021).

Cognitively, a frontosubcortical pattern of cognitive impairment has been described including slowed processing speed and impairments in attention, executive function, and retrieval (Kazui, 2008); other aspects of memory (i.e., retention) and visuospatial abilities may also be impacted (Saito et al., 2011). Psychiatric symptoms include anxiety, agitation, and depressive symptoms (Ravdin et al., 2019; Relkin et al., 2005). International guidelines recommend the classification of iNPH based on onset, imaging support, and clinical symptoms, see Relkin et al. (2005).

iNPH is due to impaired reabsorption of CSF, among other specific causes, but the exact pathophysiology is unclear (Das & Biagioni, 2021). A diagnosis should include imaging and CSF drainage, which help determine shunt treatment prognosis. The procedure involves removal of CSF (~50 cc) to assess improvement in gait, and ideally includes neuropsychological assessment prior to and following the CSF removal to evaluate change in cognition (Ravdin et al., 2019). Measures of psychomotor speed are especially sensitive to change, such as the line tracing test and serial dotting test (see Ravdin et al., 2019). Success of shunt placement (typically a shunt catheter drains CSF from either lateral ventricle to the abdominal cavity; *ventriculoperitoneal shunt*) is impacted by co-morbid neurodegenerative disease. However, quality of life may be enhanced by gait improvements alone, even if cognition is not expected to improve (Ravdin et al., 2019). MRI is especially helpful in showing ventricular enlargement, among other supportive findings, and the Evans Index (ratio of maximal frontal horn width

divided by transverse inner diameter of the skull) is helpful in identifying ventricular enlargement if ≥ 3 (Das & Biagioni, 2021).

Encephalitis in Older Adults

Encephalitis refers to inflammation of the brain parenchyma caused by infectious (e.g., herpes simplex virus, varicella-zoster virus, enteroviruses, Epstein-Barr virus, human herpesvirus-6, arboviruses) or non-infectious etiologies such as autoimmune conditions (e.g., anti-NMDA receptor encephalitis, anti-AMPA, or other autoimmune limbic encephalitis conditions; Venkatesan et al., 2013). Autoimmune encephalitis can be associated with cancer in the body (i.e., paraneoplastic). Individuals with encephalitis often show mild flu-like symptoms and may develop problems with speech/hearing, diplopia, hallucinations, and/or personality changes. Other complications include sensory loss, muscle weakness, partial paralysis, seizures, and cognitive symptoms including impaired memory and judgment (NINDS, 2021b). Graus et al. (2016) present diagnostic criteria of autoimmune encephalitis, which includes subacute onset (rapid progression of less than three months) of working memory deficits, altered mental status, and/or psychiatric symptoms. Anti-NMDA and anti-AMPA encephalitis conditions are often associated with ovarian teratomas, especially in young women (Dutra et al., 2018); however, it is important to consider encephalitis when unexplained psychiatric and cognitive symptoms occur at any age. Brain biopsy is informative but often avoided due to invasiveness; thus, clinical, laboratory (bloodwork and CSF analysis for antibodies), electroencephalographic, and neuroimaging data are critical (Venkatesan et al., 2013). Treatments for encephalitis include antiviral medications for viral infections, antibiotics for bacterial infections, and immunotherapy (e.g., steroids, intravenous immune globulin, or plasma exchange) for autoimmune conditions (Johns Hopkins Medicine, n.d.-b).

Encephalopathy

Although the blood-brain barrier is lined with various cells (i.e., endothelial, pericytes, astrocytes, microglia) that protect the CNS, pathogens may enter via several mechanisms: (1) *paracellular*, in which microorganisms cross between two endothelial cells; (2) *transcellular*, in which microorganisms cross through the endothelial cells, and/or; (3) *"Trojan horse"/infected phagocytes*, in which microorganisms infect phagocytic white blood cells that are permeable to the blood-brain barrier (Evans, 2020). Encephalopathy refers to the clinical state of altered mental status, behavioral changes, or other cognitive changes and occurs with or without brain inflammation. Encephalopathy has various causes such as infection (bacteria, virus, or prion), metabolic or mitochondrial dysfunction, brain tumor, increased intracranial pressure, prolonged exposure to toxic elements, and hypoxia (NINDS, 2019a; Venkatesan et al., 2013). Blood tests, CSF examination, imaging studies, and EEG, are helpful in determining the cause of encephalopathy (NINDS, 2019a).

COVID-19. Encephalopathy has been a reported neurological manifestation of the SARS-CoV-2 viral infection. For example, encephalopathy was estimated in approximately 32 percent of consecutive COVID-19 cases in a U.S. hospital (Liotta et al., 2020). Cognitive dysfunction following SARS-CoV-2 infection is often described as “brain fog” (Nalbandian et al., 2021). There is evidence that COVID-19 preferentially affects the frontal lobes/networks, presenting with fronto-temporal hypoperfusion on MRI, frontal hypometabolism on PET imaging, and frontal slowing on EEG (Toniolo et al., 2021). Patients may present with delirium and/or exhibit long-term cognitive and varied neurological or psychiatric symptoms. Although more research is needed, the cognitive pattern associated with COVID-19 has shown reductions in frontal-mediated processes such as attention, processing speed, executive functioning, and

encoding (Jaywant et al., 2021; Nalbandian et al., 2021; Vanderlind et al., 2021; Whiteside et al., 2021; Wilson et al., 2020). Older adults are also at increased risk of developing AD in the year following SARS-CoV-2 infection (Wang et al., 2022).

Hippocampal Sclerosis of Aging

Hippocampal sclerosis of aging (HS-Aging) is a neuropathologic diagnosis based on neuronal loss and gliosis in the hippocampal formation (often with TDP-43 immunoreactivity) that is out of proportion to AD neuropathologic changes in these areas. Brain autopsy research has shown that 5 percent to 30 percent of older adults over 90 years of age have HS-Aging pathology; notably, it is often comorbid with other pathologies such as AD, FTLN, and LBD (Cykowski et al., 2017; Nelson et al., 2013).

Limbic-Predominant Age-Related TDP-43 Encephalopathy Neuropathological Change

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is a TDP-43 proteinopathy, with or without coexisting hippocampal sclerosis, observed in older adults (especially after the eighth decade). It often occurs with comorbid amyloid beta plaques and tauopathy and is associated with an amnestic dementia syndrome (“AD-mimic”). LATE-NC is currently a neuropathological diagnosis based primarily on immunohistochemistry from amygdala, hippocampus, and middle frontal gyrus tissue; however, atrophy is observable on imaging in the medial temporal lobes and frontal cortex, among other regions. Genes associated with increased risk include *GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE* (Nelson et al., 2019).

Chronic Traumatic Encephalopathy

Chronic traumatic encephalopathy (CTE) is a neuropathologic diagnosis (Alzheimer’s Association, 2022) that is currently understood as a tauopathy that results from repetitive brain

injury and is often associated with participation in contact sports (Barr & Karantzoulis, 2019). Researchers have found p-tau accumulation associated frontal-temporal atrophy in autopsy-confirmed CTE cases (Alosco et al., 2021). Clinically, CTE has been associated with wide-ranging cognitive, mood, behavioral, and/or motor symptoms; however, there are no widely accepted consensus guidelines (Barr & Karantzoulis, 2019). Controversy over CTE exists due to modest data and methodological flaws of existing studies (e.g., excluding control subjects), and limits conclusions about the incidence, cause, and characteristics of the condition (Barr & Karantzoulis, 2019). It is hoped that robust *in vivo* biomarkers will be developed to enable longitudinal studies of the development and progression of CTE (Alosco et al., 2021; Ruprecht et al., 2019).

Remote Assessment of Older Adults

It is important to consider the ethical use of telehealth neuropsychology services for older adult patient care. A recent study found adequate validity support for remote assessment using cognitive screening and measures of language (visual confrontation naming, verbal fluencies), basic attention/working memory, and verbal memory with older adults (Marra et al., 2020). However, many factors are required to ensure ethical and valid remote assessment. For example, the clinician must consider the individual's access to and fluency with electronic devices (Hewitt et al., 2020). Prior to engaging in remote assessment, informed consent is necessary; see Bilder et al. (2020) for specific guidance. Health Insurance Portability and Accountability Act (HIPAA)-compliant platforms are required to secure protected health information. At the start of the session, it is crucial to obtain and confirm the individual's direct phone number, address, and contact information in case of emergency (Hewitt et al., 2020). To maintain test security, patients/families should be asked to refrain from recording information during the evaluation and

any information written should be disposed of in a secure manner. Many publishers have provided electronic stimuli and guidelines for administration, though most have not granted permission to photocopy/scan protocols (Hewitt et al., 2020). It is critical to be aware of any potential confounds during administration such as poor display/resolution during visual tasks, transmission lag during speeded tasks, and written notes during memory tasks. To minimize such problems, patients should have their hands visible and the clinician should confirm the quality of the connection prior to speeded tasks; one may even consider conducting speeded tasks by phone (while maintaining video). Other practical recommendations include using a private room without people or pets present, silencing electronic devices, using headphones, muting alerts, and ensuring that sensitive information is not visible if screen-share function is engaged (Bilder et al., 2020; Hewitt et al., 2020).

Compensatory Strategies

The development of compensatory strategies with the guidance of a therapist (sometimes called “cognitive remediation”) can help improve functional status in those with cognitive impairment (Tuokko & Smart, 2018). Alternatively, practicing skills/games to improve specific cognitive areas (often called “cognitive training”) may be more useful for healthy older adults and those with SCD. Cognitive training, however, has limited generalizability to everyday functions (Tuokko & Smart, 2018).

Disclosing Diagnosis

The disclosure of an MCI or dementia diagnosis should be approached with compassion. Before a disclosure, the neuropsychologist can discuss the benefits and drawbacks of knowing a diagnosis and inquire about preferences related to hearing the details of the evaluation results, as well as who should be present. Sometimes family members may ask to withhold the diagnosis

from the patient due to potential emotional impact. In these cases, the neuropsychologist should explore the concerns and whether the information can be shared with supports in place. During disclosure, clear and simple language, frequent pauses to allow for questions, pacing of information to patient/family needs, checking for comprehension, and providing written and verbal information are all recommended. After disclosure, the clinician may check again for understanding, leave sufficient time for questions, and present recommendations (Carpenter & Glooblar, 2018). Disclosure of an MCI diagnosis should include validation of the patient/family concerns via objective data, psychoeducation about possible causes and risks for dementia, supportive recommendations, and shared decision-making. If additional diagnostic work up (i.e., imaging and biomarkers) is considered, clinicians should discuss limitations. For example, a positive amyloid PET scan does not only indicate AD pathology or that cognition will decline definitively. Moreover, a negative PET scan reduces the likelihood of underlying AD pathology, but does not definitely rule out the future development of clinical AD or other dementia (Grill et al., 2017).

Identifying Abuse

Abuse of older adults unfortunately impacts hundreds of thousands of older adults in the United States every year. The nature of abuse can be physical, emotional, sexual, financial, or related to neglect or abandonment. Signs may include unkempt appearance, unexplained bruises or cuts, lacking needed aides (e.g., walker, dentures), or report of unpaid bills (National Institute on Aging, 2020). It is also important to note that older adults have increased susceptibility to fraud (United States Senate Special Committee on Aging, 2018).

Relevant Legal Terminology and Capacity

An *advance directive* is a legal document that provides provision for future health care decisions in the event that an individual is unable to make such decisions. These vary by states in the U.S. and region/country. In New York, for example, there are three types: (1) health care proxy form, (2) living will, and (3) do not resuscitate order (DNR; New York State Office of Attorney General, n.d.). Individuals may appoint a health care agent, such as a trusted family member or friend, to make decisions regarding medical treatment on their behalf (New York State Department of Health, 2017). Sometimes “proxy” is used interchangeably with “power of attorney for health care” and “agent” is used interchangeably with “proxy” or “representative.” A living will is a written statement that details the wishes of an individual regarding medical treatment and is to be followed if the individual is unable to provide instructions during the time that the medical decision needs to be made (New York State Department of Health, 2017). Lastly, a power of attorney is a financial planning document that gives another person the legal power to act on the behalf of an individual to manage financial assets (New York State Office of Attorney General, n.d.). Ideally, advance directives are in place before the patient becomes incapacitated; when they are not, a caregiver may need to petition for guardianship (see CaringKind, n.d., formerly Alzheimer's Association NYC Chapter). *Guardianship* is a court-appointed relationship in which one person or entity is deemed as a “guardian” of another person and given the legal duty to make decisions (personal- or property-related) for that person if the court finds that the person lacks capacity to make decisions for him or herself (American Bar Association Commission on Law and Aging, 2006).

Capacity

Although the terms *capacity* and *competence* have been used interchangeably, *competency* should be restricted to legal settings to describe the ability to participate in legal

proceedings. Conversely, *capacity* may be used in legal or clinical settings, referring to one's functional ability to make decisions in a particular area (e.g., medical and financial capacities among others; American Bar Association [ABA] & American Psychological Association [APA], 2008; Libby et al., 2021). A primary component of capacity assessment includes a mental status exam (i.e., brief assessment of appearance/behavior, motor activity, speech, mood, affect, thought process/content, perceptual disturbances, sensorium, cognition, insight/judgment; Libby et al., 2021).

Capacity to Make Healthcare Decisions. Informed consent in medical situations requires clinicians to obtain voluntary and well-informed agreement to medical interventions (ABA & APA, 2021). Four relevant standards are commonly recognized: (1) *understanding*, or the ability to comprehend diagnostic and treatment-related information; (2) *appreciation*, or the ability to relate treatment information to one's personal situation such as inferring the possible benefits of treatment; (3) *reasoning*, or the ability to rationally explain one's position or to process information logically; and (4) *expression of a choice*, or communication of a treatment choice (ABA & APA, 2021; see also ABA & APA, 2008; Grisso & Appelbaum, 1998). The following are suggested questions for clinical interview to assess these domains: (1) *understanding*: “tell me what your understanding is of the nature of your condition, the recommended treatments, the benefits and risks of those treatments?” and “how likely are the benefits and risks to occur?”; (2) *appreciation*: “what do you believe will happen if you are not treated?”; (3) *reasoning*: “why does treatment A seem better than treatment B?”; and (4) *expression of a choice*: “have you decided whether to follow your doctor's suggestions for treatment?” (ABA & APA, 2008). Subsequently, this information is used to determine if the patient is able to make the decision to participate in the medical procedure.

Financial Capacity. Financial capacity involves the performance of financial tasks (e.g., writing checks, paying bills), as well as judgment ability to support one's best financial interest (ABA & APA, 2021). Ghesquiere et al. (2019) provides a review of measures relevant to financial capacity. Although assessment of financial capacity is particularly relevant to a question of guardianship or power of attorney in forensic settings, it could be helpful to assess an individual's level of functioning in the clinical interview. For example, the clinician can ask questions such as "are you in any debt?" or "are you able to save for the future?" (ABA & APA, 2008).

Driving

Both physical and cognitive abilities affect the ability to drive safely. Relevant aspects of driving ability include sensorimotor functioning, reaction time, knowledge of driving rules and regulations, appreciation of pertinent medical diagnoses that may impact driving, and judgment (ABA & APA, 2008). It is also important to inquire about prior accidents, frequency of current driving and typical distance traveled, and any difficulties while driving. Referral for a formal driving evaluation may be helpful when the ability to drive safely is in question. Laws that require a healthcare provider to report a patient with neurological or cognitive disorders vary by state. For example, a voluntary Physician's Report Form may be completed and sent to DMV in some states within the U.S.

Relevant Ongoing Aging Research

- The National Institute on Aging (NIA)-sponsored Alzheimer's Disease Neuroimaging Initiative (ADNI) has focused on the longitudinal characterization of MCI and AD dementia, including neuropsychological and imaging/biomarker profiles, as well as outcome measurements (Veitch et al., 2021; Weiner et al., 2017).

- The Dominantly Inherited Alzheimer's Network (DIAN; Moulder et al., 2013) focuses on the observational study and clinical trials for AD.
- The Longitudinal Early-onset Alzheimer's Disease Study (LEADS; Apostolova et al., 2021) is devoted to the study of sporadic Early Onset Alzheimer's Disease (EOAD).
- A useful resource is MarkVCID, a National Institutes of Health-sponsored consortium focused on the identification and validation of biomarkers for small vessel diseases associated with cognitive impairment (Lu et al., 2021; Wilcock et al., 2021).
- An active research area involves use of polygenic risk scores (PRS) to identify the combined genetic risk for AD and other disorders (Chasioti et al., 2019). Use of PRS coupled with diagnostic biomarkers is likely to be a key element of precision medicine for AD and related dementias.

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