Neuropathology of the Common Forms of Dementia

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KEYWORDS

• Cardiovascular disease • Cerebrovascular disease • Dementia • Mixed dementia
• Neurodegenerative disease • Resilience • Resistance • Proteinopathy

KEY POINTS

- Dementia is a nonspecific term that corresponds to a group of heterogeneous, mostly age-related neurologic disorders that cause impaired cognition and deterioration of brain functions.
- This neurologic condition is a manifestation of various processes that primarily or secondarily affect the brain organ.
- Underlying neuropathologic substrates encompass various protein inclusions, vascular brain injuries, and cerebrovascular, traumatic, and metabolic brain changes.
- Protein inclusions and metabolic abnormalities accumulate in distinct stereotyped brain regions, whereas trauma and vascular-associated substrates may occur in patchy and/or irregular distribution(s).
- The burden and location(s) of brain lesions influence the type and degree of clinical symptoms, which establish the dementia syndrome.

INTRODUCTION

Dementia is an umbrella clinical term that refers to a range of debilitating neurologic conditions, and its incidence is increasing. Alzheimer disease (AD) dementia is the most common form of dementia.[1] However, a variety of neuropathological lesions are found in persons who succumb with dementia, including AD dementia.[2] Due to the chronic nature of dementing diseases and the range of potential causes and brain lesions, accurate diagnosis of dementia subtypes requires targeted postmortem brain dissection with comprehensive histologic evaluation and incorporation of ancillary testing. However, knowledge on complex causes for dementias also remains

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incomplete and, over the years, neurobiological and epidemiologic evidence have revised criteria used for neuropathologic diagnosis, scoring, and staging schemes. Similarly, neuropathological studies continue to inform on the significance of epidemiologic data and new forms of disease. Therefore, classification of this group of diseases is evolving.

A century of research has shown that various misfolded protein species accumulate in different brain regions and account for distinct proteinopathies that involve different susceptible cell types[1] Here, we explore the range of lesions that are documented within brains of persons who have died with a clinical diagnosis of dementia and summarize the causes, classification, topographies, and staging of these lesions. Although AD pathologic condition is the most common pathologic condition encountered overall, persons with AD type dementia (eg, amnestic dementia) may harbor multiple brain changes including various vascular pathologies and other non-AD neuropathologies, in addition to typical AD lesions. Other common forms of neurodegenerative diseases, such as those characterized by Lewy bodies and transactive response DNA-binding protein 43 kD (TDP-43) pathologic condition, as well as less common processes such as Creutzfeldt-Jacob disease and chronic traumatic encephalopathy (CTE) are described briefly. We also summarize nonproteinopathic diseases and mixed lesions that are linked to dementia syndromes. These other brain "hits" are recognized to lower the threshold for dementia in proteinopathic diseases.[3] Although summarizing current knowledge on dementia pathologies, this review also highlights knowledge gaps and emerging concepts pertaining to cognitive reserve.

PROTEINOPATHIC DISEASES

Proteinopathic diseases, also known as proteopathies or proteinopathies, are a heterogeneous group of protein misfolding disorders that manifest grossly as brain atrophy and histologically as accumulation of aberrant deposits within cortical or subcortical brain regions. These deposits selectively damage vulnerable neurons and/or glial cell populations in distinct brain regions, disturbing neural pathways and thereby altering brain structure and functions. Multiple mechanisms are involved, including neuronal and glial cell death pathways, organelle damage, and secondary physiologic disturbances including reactive astrogliosis and microgliosis.[4] Neuropathologic lesions accumulate chronically over time, thereby precipitating dementia syndromes. Primary diseases are listed in **Table 1** (upper panel) and are summarized below and in **Fig. 1**A, B, D.

Alzheimer Disease

Microscopically, AD neuropathologic change (AD-NC) is defined by the intraparenchymal accrual of 2 abnormal proteins, amyloid-beta (βA) in the form of extracellular plaques and irregularly phosphorylated forms of the microtubule-associated protein tau (MAPT), in the form of intraneuronal neurofibrillary tangles (NFTs).[5,6] On routine stains, these protein aggregates may seem as atypical eosinophilic inclusions within brain gray matter (for βA), or as irregular or flame-shaped intraneuronal inclusions (for NFTs; see **Fig. 1**A). These neuropathologic markers may be imperceptible on routine brain examination but are easily visualized on silver stains (eg, Bielschowsky, Gallyas, and Bodian) and/or via immunohistochemistry panels that incorporate primary antibodies targeted toward the aberrant βA or tau protein (eg, thioflavin S, AT8, Tau; see **Fig. 1**A). The abundance of these aggregates (especially tau protein) generally corresponds with the severity of cognitive impairment because they are related to variable degree of cortical brain atrophy, particularly in vulnerable medial-temporal lobe

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Table 1
Summary of common diseases that lead to neurodegenerative lesions in persons with dementia

Disease	Etiologic Inclusion(s)	Primary Brain Regions(s) Involved
Proteinopathic Diseases Associated with Chronic Cell Loss		
AD-NC	β-Amyloid Tau(3R and 4R)	Cerebral cortex Cerebral cortex
LB Disease	α-Synuclein	Brainstem and limbic region, including substantia nigra
LATE-NC	TDP-43	Hippocampus and temporal lobe
FTLD-Tau	Tau	Frontal and temporal lobes
FTLD-TDP	TDP-43	Frontal and temporal lobes
FTLD-Atypical	Ubiquitin, FUS[b]	Frontal and temporal lobes
PSP	Tau(4R)	Subcortical nuclei and brainstem, including substantia nigra
CBD	Tau(4R)	Cerebral cortex and subcortical nuclei, including substantia nigra
CJD	PrP	Hemispheric gray matter
HD	mHTT	Basal ganglia
PART	Tau	Hippocampus
CTE	Tau	Cerebral cortex
ARTAG	Tau	Cerebral cortex
CAA[a]	β-Amyloid	Cerebral cortex
Hippocampal sclerosis	TDP-43[c]	Hippocampus
Other Diseases Associated with Acute/Subacute or Chronic Cell Loss		
Cardiac and extracranial CVD	N/A	Global/multilobar/lobar, variable
Intracranial CVD (large vessel)	N/A	Global/multilobar/lobar, variable
Intracranial CVD (small vessel)	N/A	Subcortical gray or white matter, variable
Hippocampal sclerosis	N/A[c]	Hippocampus and white matter
Wernicke Korsakoff syndrome	N/A[d]	Mammillary body and white matter
Carbon monoxide poisoning	N/A[e]	Globus pallidus and white matter

[a] CAA may occur with or without AD-NC.
[b] FTLD-Atypical is characterized by FUS, ubiquitin, and neuronal intermediate filament inclusions, or basophilic inclusions.
[c] Hippocampal sclerosis may or may not be associated with TDP-43 and LATE-NC.
[d] The cause of Wernicke-Korsakoff syndrome is vitamin B1 (thiamine) deficiency.
[e] The cause of carbon monoxide poisoning is oxygen deficiency.

structures. Cerebral cortical and subcortical tissue loss leads to variable degree of symmetric sulcal widening, hippocampal atrophy, and lateral ventriculomegaly. AD-NC may also be characterized by the loss of neuromelanin-containing neurons in the locus ceruleus.

Extracellular plaques are formed by the accumulation and aggregation of βA with 40 ($^{1\text{-}40}$βA) or 42 ($^{1\text{-}42}$βA) amino acids. Aβ is a normal peptide product derived from cellular metabolism of the amyloid precursor protein (APP), which may be a neuroprotective molecule although its functions are yet unknown. APP undergoes sequential β-secretase and γ-secretase mediated enzymatic cleavage to produce amyloidogenic isoforms. Based on its accumulation pattern, βA-containing plaques are classified into

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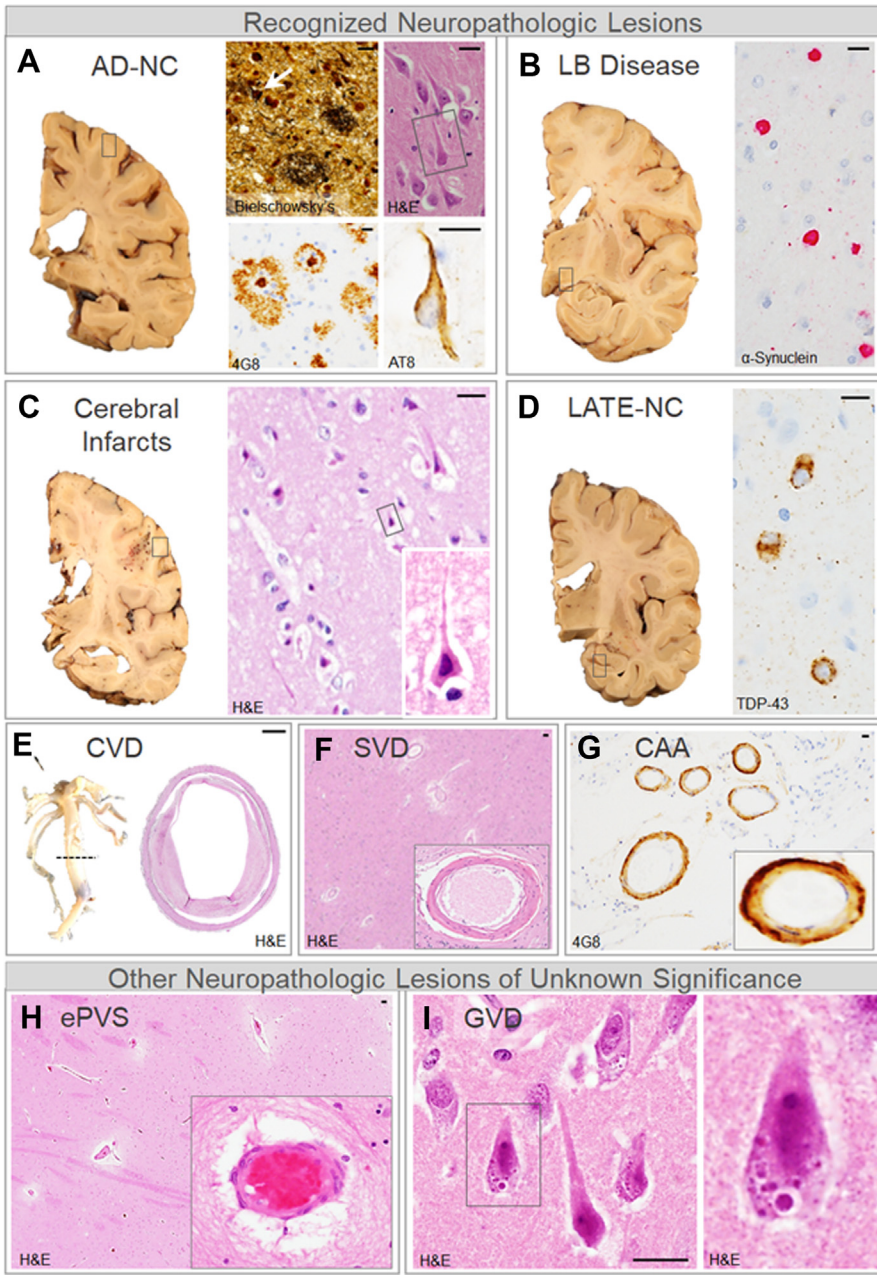

Fig. 1. Histologic features of common neurodegenerative disease lesions. (*A*) AD-NC is classically associated with frontoparietal atrophy (*left*). Etiologic lesions, shown at right (clockwise from *upper left*), include diffuse and neuritic plaques with neurofibrillary tangles (Bielschowsky's silver stain), neurofibrillary tangles (H&E stain), neurofibrillary tangle (phospho-Tau AT8 stain), and diffuse and neuritic plaques (4G8 amyloid stain). (*B*) LB disease is characterized by mild cortical atrophy with evidence of α-synuclein-positive LBs. (*C*) Macroscopic cerebral infarcts are characterized by cerebral edema with reperfusion-related

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either diffuse plaques (DPs) or neuritic plaque (NP) varieties. NPs are composed of aggregated βA protein that may accumulate as dense cores and/or dystrophic neurites, which correspond to degenerated neuronal cell processes.[1–40] βA is enriched in NPs, whereas[1–42] βA is enriched in DPs. In addition to[1–40] βA, NPs also harbor variable numbers of astrocytic and microglial processes. βA NPs usually deposit in layers II–V of the neocortex but in advanced cases can also be noted in neocortical layers I and VI and in subcortical white matter.[7]

Tau protein, which is produced from MAPT gene, supports neuronal microtubule stability and is the primary constituent of NFTs. Alternate splicing of exon 10 generates tau species with either 3 or 4 conserved ~32 amino acid repeats (R), leading to either 3R or 4R tau on biochemical and immunohistochemical characterization. In AD, tau undergoes abnormal phosphorylation that promotes its aggregation into paired helical filaments.[8] These tau inclusions accumulate within neuronal cell soma as large rounded bodies and in neuronal dendrites and axons as neuropil threads.[8] The morphology of NFTs is variable because they acquire the shape of involved neurons. In cortical neurons, NFTs may be flame or triangular shaped (see **Fig. 1**A) but in subcortical or brainstem neurons, they are generally rounded and/or globose. Pre-NFTs exhibit diffuse, low-level tau label within the cytoplasm of intact neurons, whereas mature NFTs exhibit cytoplasmic filamentous tau aggregates that displace neuronal nuclei and extend into dendrites. Late-stage "ghost" NFTs seem entombed within nonviable, nucleus-devoid neurons.[8]

The successive accumulation of NFTs within the aging brain follows a stereotyped pattern that has been depicted in 6 stages.[7] Initially, NFTs are found only in the transentorhinal cortex (stage I and II). With disease progression, they gradually involve the entorhinal cortex and hippocampus (stage III and IV) and neocortical brain regions (stage V and VI; **Fig. 2**A). Similar to NFTs, βA accumulation also follows a stereotyped pattern of brain accumulation that is distinct from tau accumulation and has been described along 5 stages.[9] Initially, βA deposits within neocortex (stage I). With disease progression, they spread into allocortical brain regions such as entorhinal cortex, CA1, and subiculum region of hippocampus (stage II); subcortical nuclei including basal ganglia, thalamus, and hypothalamus (stage III); and, eventually into the medulla oblongata and midbrain colliculi (stage IV); and, finally, into pontine neurons and the cerebellar molecular layer (stage V; see **Fig. 2**A).[9] Although earlier staging schema required AD dementia for pathologic diagnosis of disease, revised guidelines for a diagnosis of AD-NC no longer require the presence of clinical symptoms. Current criteria for AD-NC require the presence of brain βA deposits. A diagnosis of AD is confirmed when there is at least intermediate or high AD-NC, which requires a Braak stage of 3 or more, and a Thal stage of 3. At this stage, most cases will have at least moderate NPs in the neocortex.

Lewy Body Diseases: Lewy Body Demenita and Parkinson Disease Dementia

Lewy body (LB) diseases are characterized by abnormal intracytoplasmic accumulation of alpha-synuclein protein positive LBs.[10] On routine stains, LBs seem as round,

petechial microhemorrhage (*left*) and acute neuronal necrosis (*right*). (*D*) LATE-NC is characterized by cortical atrophy with TDP-43-positive neuronal inclusions. Vascular changes and/or vascular brain injuries may also result from: (*E*) large vessel atherosclerosis, as depicted in the basilar artery; (*F*) SVD, such as arteriolosclerosis; and/or (*G*) CAA. Other neuropathological lesions of unknown significance include enlarged perivascular spaces (ePVS) and granulovacuolar degeneration (GVD), shown in (*H*) and (*I*), respectively. A–I: Boxed/marked area shown in enlarged and/or labeled section. Scale bars: A–D, F–I, 10 μm; E, 1 mm.

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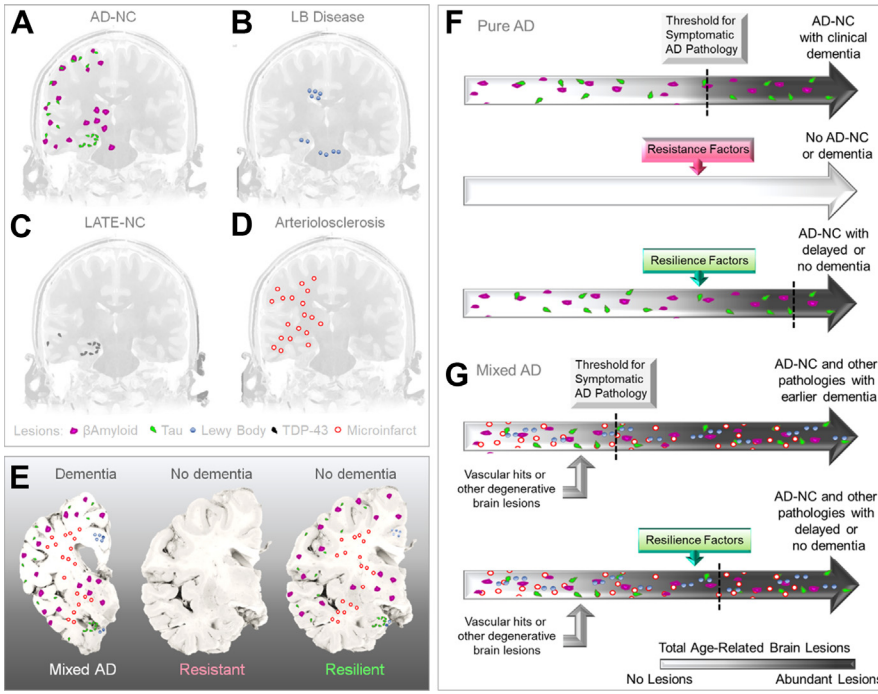

Fig. 2. Topographies and overlap of common proteinopathic and age-related disease substrates and effects on brain function. Topographic distribution of AD-NC (*A*), LB disease (*B*), LATE-NC (*C*), and arteriolosclerosis (*D*), which exhibit different susceptibilities. Mixed pathologic conditions (eg, βA plaques, Tau neurofibrillary tangles, Lewy bodies, TDP-43 inclusions, and/or cerebrovascular lesions) also occur (*E*). Persons who do not develop pathologic condition or do not progress to severe stage of pathologic condition are referred to as "resistant," whereas afflicted persons who do not exhibit dementia are referred to as "resilient." Various effects of AD-NC (*F*) and mixed pathologic conditions (*G*) are shown. Disease resistance refers to the absence of, or lower-than-expected disease burden, whereas resilience refers to the absence of, or delayed onset of cognitive impairment in the face of existing neuropathologies. (Agrawal and Schneider - Neuropathological Underpinnings of the Dementias. In Neuropsychology of Alzheimer's disease and other dementias, Second Edition.)

eosinophilic neuronal cytoplasmic inclusions that may be associated with peripheral halos and are highlighted by immunohistochemistry using antibodies directed to phosphorylated alpha-synuclein (see **Fig. 1**B).[10] When present in substantia nigra and accompanied by evidence of significant neuronal loss, these inclusions confirm a pathologic diagnosis of Parkinson disease (PD). With the involvement of cortical neurons, LBs may cause cognitive impairment and account for 2 recognized dementia syndromes, that is, Parkinson disease dementia (PDD) or LB Dementia (LBD). Although these disorders are similar, PDD is associated with cognitive changes typically occurring years after motor onset of PD, whereas LBD exhibits cognitive and motor (parkinsonism) impairment within a year of each other. Neuropathological data have demonstrated that accrual of LBs may progress along different anatomic pathways. Most frequently, LBs seem to ascend initially in pigmented brainstem nuclei (eg, vagus dorsomedial nucleus, locus ceruleus, and/or substantia nigra), and then along limbic areas (entorhinal cortex and anterior cingulate), and finally progress along neocortical brain tissue (**Fig. 2**B). Although presently unclear whether PD, PDD, and

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LBD are truly distinct disorders or representative of a disease continuum,[11] pathologic condition is currently subclassified based on the regional LB distribution as brainstem, limbic or neocortical-predominant.[12] Postmortem evaluation shows that some brains feature LBs within the amygdala or olfactory bulb, but not brainstem, and these have been described as amygdala-predominant or olfactory types.[12] Spongiform change in entorhinal and other temporal cortical regions, and the presence of alpha-synuclein neurites within hippocampus CA2 sector and areas exhibiting LBs are supporting features of LBD. PDD and LBD may be associated with mild atrophy in affected brain regions. The observation of alpha-synuclein inclusions within glial cells characterizes multiple system atrophy.

Limbic-Predominant Age-Related TDP-43 Encephalopathy

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently characterized proteinopathy that afflicts older persons. LATE-neuropathological change (LATE-NC) is characterized by neuronal and glial TDP-43 inclusions in adults aged older than 80 years (see **Fig. 1**D).[13] LATE-NC includes neuronal loss and astrocytosis in the hippocampus with hallmark features of TDP-43 inclusions involving the limbic structures, olfactory bulb, basal ganglia, neocortex, and occasionally the brainstem. The TDP-43 inclusions initially present only in the amygdala (stage 1) but over time spread gradually to involve the hippocampus (stage 1 and 2) and midfrontal cortex (stage 3; **Fig. 2**C).[13] This neuropathology typically manifests with atrophy in mesial temporal lobe structures, including the hippocampus, and may occur concomitantly with hippocampal sclerosis (HS; described below). Indeed, most cases of HS in aging are associated with TDP-43 proteinopathy. The inferior frontal, and insular cortices, and other cortical regions may be less frequently involved.[13]

Hippocampal Sclerosis

HS is currently broadly defined as severe neuronal loss and gliosis of the hippocampus. In aging, it is most frequently neurodegenerative in origin. The vast majority of HS in aging is characterized by TDP-43 proteinopathy, hippocampal neuronal loss and/or gliosis[14] and thus is often part of LATE. HS is not specific to any other neurodegenerative disease pathologic condition but may be associated with several other classified disease processes, including various age-related neurodegenerative diseases (listed above), hypoxic/ischemic brain injury, and temporal lobe epilepsy.[15] In epilepsy, HS is often referred to as mesial temporal sclerosis. In neurodegenerative and hypoxic/ischemic diseases, HS is frequently characterized by severe neuronal loss and gliosis involving the hippocampus CA1 sector and the subiculum.[16]

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is characterized by cerebral cortical degeneration and is classified into 3 subtypes according to neuronal and glial protein aggregates.[17] FTLD-Tau exhibits hyperphosphorylated tau protein inclusions, whereas FTLD-TDP manifests TDP-43-positive protein inclusions, and FTLD-FUS exhibits fused in sarcoma protein inclusions.[17] FTLD-FUS includes atypical FTLD with only ubiquitin inclusions, neuronal intermediate filament inclusion disease, and basophilic inclusion body disease (BIBD), which are all characterized by FUS inclusions in addition to caudate nuclei atrophy.[15,18] Microscopic examination of brains exhibiting FTLD inclusions often show ballooned neurons, laminar spongiosis involving superficial cerebral cortical layers (ie, I–III), and prominent myelin loss in association with the above neuronal and/or glial cell inclusions.[17] FTLD also includes Pick disease, which is characterized by "Pick bodies" that seem as rounded, basophilic intraneuronal cytoplasmic bodies on routine

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stain and are composed of abnormally phosphorylated tau.[17] Unlike tau of AD-NC, the aberrant tau protein in Pick disease has been shown to form straight helical filaments and aggregates in frontal and temporal cerebral cortical neurons.[17] In addition to Pick bodies, cortical neurons in these regions also display ballooned neurons termed Pick cells.[17] As implied by its name, FTLD causes frontal and temporal lobe atrophy, which when severe is often described at knife-edge atrophy.

Progressive Supranuclear Palsy and Corticobasal Degeneration

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) typically present as atypical parkinsonian disorders but may also present with a dementia syndrome. PSP and CBD are characterized by NFTs involving the substantia nigra but unlike AD-NC, these diseases are characterized by 4R immunoreactive NFTs.[19] In PSP, 4R tau-positive tangles may additionally be found in subcortical regions such as the subthalamic and red nuclei, basal ganglia, and basis pontis.[19] In PSP, the 4R tau inclusions are also present in astrocytes and oligodendrocytes where they characterize so-called tufted astrocytes and coiled bodies, respectively. Tufted astrocytes display fine branching processes and may also be distributed within motor cortex. 4R tau-positive coiled bodies are also seen in subcortical white matter. In CBD, there is also 4R tau-positive tangles involving the substantia nigra but cortical pathologic condition is also prominent, especially in the perirolandic regions of the neocortex. In addition to neuronal tangles, CBD manifests with 4R tau-positive astrocytic plaques and neuritic threads in the cerebral cortex and subcortical basal ganglia, thalamus, and brainstem. Scattered achromatic or ballooned cerebral cortical neurons are typically present in the perirolandic cortices.[19]

Chronic Traumatic Encephalopathy

CTE describes the neuropathology associated with repetitive concussive and/or subconcussive head injuries, such as that which occurs in professional athletes including football and hockey players. This disease is characterized by neuronal NFTs present diffusely throughout the brain, including the hippocampus and brainstem, with accentuated perivascular distribution.[20] Perivascular and subpial glial tau accumulation may also be present. Grossly, CTE brains feature cerebral cortical and subcortical nuclear atrophy with enlargement of the lateral and third ventricles. CTE neuropathology has been shown to progress in 4 stages.[20] Initially, phosphorylated-tau NFTs deposits in perivascular NFT clusters, usually at neocortical sulcal depths (stage 1). Next, they accumulate in discrete clusters in perivascular and superficial cortical layers (stage 2). With subsequent progression, they aggregate multifocally in the medial temporal lobe, hypothalamus, thalamus, nucleus basalis, mammillary bodies, substantia nigra, raphe nuclei, and locus coeruleus (stage 3). Finally, with continued progression, NFTs distribute more widely throughout the brain and are associated with progressive myelin and myelinated axon loss (stage 4).

Huntington Disease

Huntington disease (HD) is a rare neurodegenerative disease that is caused by CAG (polyglutamine) expansion repeats in the huntingtin gene (ie, HTT) on chromosome 4.[21] Huntingtin protein misfolding causes intraneuronal aggregation of mHTT, primarily in striatal regions. Thus, this disease is characterized by striatal degeneration that is associated with secondary ventricular enlargement. HD is a familial dominantly inherited disease.[21] Neuropathological grading criteria used for this disorder is based on ventricle size and degree of striatal pathologic condition and atrophy.[22] Initially, only microscopic evidence of gliosis and neuronal loss is observed without gross

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evidence of striatal atrophy (grade 1). Disease progression features striatal atrophy with minimal changes observed early on in lateral ventricle size (grade 2) but there is increased striatal atrophy and ventriculomegaly with disease progression (grades 3 and 4).[22] Mild cerebral cortical neuronal loss may also be present and involve the frontal cerebral cortices.

Creutzfeldt Jakob Disease

Creutzfeldt Jakob disease (CJD) is a rare disease that is associated with various causes. The disease may be infectious, heritable, sporadic, or iatrogenic in nature.[23] CJD is characterized by intraneuronal prion protein (PrP) inclusions that induce severe and rapidly progressing neuronal loss and gliosis in various brain regions.[23] End-stage disease is usually characterized by severe cerebral cortical spongiform change and corresponding atrophy.[23]

Other Proteinopathies and Unclassified Tissue Changes

Other age-related neuropathologies feature neuronal and/or glial inclusions.[24] Argyrophilic grain disease,[25] aging-related tau astrogliopathy (ARTAG),[26] globular glial tauopathy,[27] and primary age-related tauopathy[28] are also currently classified as separate neuropathologies. However, their epidemiologic significance and link to clinical dementia syndrome(s) is presently unclear. Moreover, the significance of other nonclassified (**Fig. 1**H) but well-recognized lesions such as granulovacuolar degeneration (**Fig. 1**I), which manifest in hippocampal pyramidal neurons of aged persons and commonly coexist with AD-NC, remain undefined.

AGE-RELATED VESSEL CHANGES AND VASCULAR DISEASES

Cerebrovascular pathologic conditions are common with aging and induce vascular and/or brain damage, both of which may contribute to structural brain pathologic condition.[29,30] Cardiac, extracranial and/or intracranial large vessel, and intracerebral small vessel diseases (SVD) may all contribute to dementia syndromes by compromising blood flow, causing subtle multifocal or diffuse neuronal dropout or more discrete, localized brain parenchymal injuries.[31,32] Thereby, these processes indirectly or directly lead to impairment of function in cognitive domains, although they may not directly induce deposition of intracerebral protein aggregates.[33] Although an array of disorders is recognized in this category, some older literature used nonspecific terminology to describe these lesions and no formal criteria exist for their grading or staging. Moreover, many cerebral SVD are only superficially classified, and their true incidences are unknown. A partial list of contributing disorders is summarized in the **Table 1** (lower panel), and described further below and in **Fig. 1**C, E–H.

Cardiac and Extracranial Cardiovascular Diseases

Cardiac diseases and extracranial cardiovascular disease (CVD; eg, structural or functional heart diseases such arrhythmic disorders, coronary artery, valvular, and/or hypertensive diseases, and extracranial carotid artery narrowing, occlusion, and/or emboli) are linked to ischemic phenomena with or without brain hemorrhage.[32] These diseases may lead to vascular brain injuries (VBI) including multifocal or diffuse ischemia with neuronal dropout and/or macroscopic or cystic infarcts (see **Fig. 1**C).[3] Mechanisms of cell depletion may include apoptosis and oncotic necrosis, among other mixed cell death pathways.[33] Although primary or secondary pulmonary or respiratory diseases such as chronic obstructive pulmonary disease, chronic obstructive sleep apnea, chronic bronchitis, and/or pneumonia, asthma, and/or

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pulmonary edema also compromise lung function and may contribute to hypoxia, their overall contribution to dementia syndromes remains controversial in the literature.

Intracranial Cerebral Large Vessel Diseases

Diseases involving the circle of Willis may also lead to VBI. Atherosclerosis (see **Fig. 1**E) and much less commonly large vessel vasculitis and other vasculopathies may cause hemispheric or focal ischemic stroke that leads to macroscopic cerebral infarcts, other macroscopic cystic infarcts, "strategic" infarcts, or contribute to microbleeds.[32] These diseases may also cause acute, subacute, or chronic neuronal dropout from hypoxic-ischemic damage. As with cardiac diseases and extracranial CVD, the mechanisms of cell depletion may include apoptotic, oncotic, and mixed cell death pathways.[37]

Intracerebral Small Vessel Diseases

Diseases involving cerebral small vessels also have potential to cause VBI, and recent studies emphasize the significance of cerebral SVD as a cause for neuronal loss, oligodendrocyte and myelinated fiber depletion, white matter rarefaction, microbleeds, small and microinfarcts, inflammation, and gliosis.[34,35] Arteriolosclerosis is the most common cause of cerebral SVD and causes partial or total fibrous replacement of intracerebral arteriolar smooth muscle cell layers (see **Fig. 1**F), with microbleeds and/or small and microscopic infarcts.[3,36] When widespread, this may lead to subcortical ischemic vascular disease, also known as multi-infarct dementia, Binswanger disease, or vascular dementia of Binswanger type (**Fig. 2**D).[36]

Cerebral amyloid angiopathy (CAA) is also common in older decedents and is characterized by βA deposition within basement membranes and/or smooth muscle cell layer of cerebral arteries and arterioles (see **Fig. 1**G).[37,38] This disease manifests with preferential deposition of $^{1-40}$ βA species and often leads to petechial microhemorrhages and less commonly lobar hemorrhage.[36] Severe forms of SVD results in vessel wall damage with vessel dilation, blood element extravasation, and occasionally vessel occlusion. Several community-based studies demonstrate an association of CAA with cognitive impairment.[39] Clinicopathological evaluations suggest significant associations between moderate and severe, multifocal CAA with ischemic pathologic conditions,[40] although a strong correlation is also noted between CAA and age. CAA commonly, but not always, accompanies AD pathologic condition and may also occur in the absence of significant AD.

Other Intracerebral Vessel Abnormalities

The prevalence of other uncharacterized and subtle vascular changes such as enlarged perivascular spaces [41,42] and blood–brain barrier disruption[43] in persons with dementia is increasingly recognized, although the significance of these changes is presently unclear (see **Fig. 1**H).

METABOLIC, TOXIC, AND OTHER DISEASES

Brain injury is also induced by a host of other diseases. Acute, subacute, and chronic metabolic disturbances are liable to contribute to dementia through various mechanisms. Additionally, metals and other environmental toxins may damage neurons through additional pathways.

Wernicke Encephalopathy and Wernicke Korsakoff syndrome

Wernicke diseases are precipitated by vitamin B1 (thiamine) deficiency.[44] Although recognized most commonly in association with chronic alcoholism, Wernicke

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Korsakoff syndrome (WKS) is also observed in systemic diseases that result in nutrient deficiencies. In the acute phase, Wernicke encephalopathy (WE) is characterized by ophthalmoplegia, mental status changes, and ataxia, whereas the chronic phase of WKS includes confabulation and a dementia syndrome.[44] In WKS, bilateral mammillary body degeneration is observed on gross brain examination and is associated with hemorrhage and neuropil loss. With more extensive disease, WKS may be characterized by progressive involvement, including bilateral diencephalic degeneration.[44]

Carbon Monoxide Poisoning

Carbon monoxide poisoning is caused by inhalation of combustion fumes and binds to blood hemoglobin to form carboxyhemoglobin, which decreases blood oxygen carrying capacity and causes brain tissue hypoxia with preferential necrosis of the globus pallidus and subcortical white matter demyelination.[45,46]

Heavy Metals

Some evidence also suggests that dysregulation of metals such as aluminum, arsenic, and lead may precipitate dementia by causing oxidative stress with axonal and synaptic damage.[45]

AGE CONSIDERATIONS AND MIXED PATHOLOGIES

Among multiple potential causes described above, the most common causes of dementia are AD, CVD, and LB diseases (see **Figs. 1**A–C and **2**A, B, D), but proteinopathies may coexist with each other and with nonproteinopathic CVD/VBI lesions.[47,48] In fact, longitudinal cohort studies demonstrate that mixed pathologies represent the most common form of pathologic condition underlying age-related dementia including AD type dementia.[47,48] LB disease is reported to occur commonly with AD-NC, especially in persons aged younger than 60 years at death[49,50] but is also seen commonly in aging and with AD-NC.[51] As noted above, TDP-43 pathologic condition (see **Fig. 2**C) often coincides with HS and may also co-occur with LB disease.[52] Cohort studies have also shown that, in the oldest old, the incidence of AD-NC plateaus,[51,53] whereas other age-related pathologic conditions, specifically LATE-NC, become more common although the reasons for this are unclear. Despite the detailed diagnostic criteria summarized above for distinct neurodegenerative disease forms of dementia in aging, pure neurodegenerative diseases are relatively rare. Overlapping processes are thought to potentiate the common final pathway of neuronal loss and complex brain inflammation with gliosis that precipitate clinical dementia that is increasingly accepted as a multifactorial and pathologically heterogeneous disorder that occurs along a continuum with a range of phenotypes (**Fig. 2**E).[54] Overall, the location(s) and total burden of various neuropathological substrates determine the clinical dementia syndrome. Thus, the validity and utility of some classification and staging schemes for discrete neuropathologic forms of dementia in aging is presently unclear because mixed pathologic conditions are also recognized as a common cause for atypical clinical presentations. Interestingly, risk factors for dementia are also found to differ by age, with some CVD risk factors appearing to become protective in the oldest-old.[55]

LIMITATIONS OF CURRENT NOMENCLATURES, CLASSIFICATIONS, AND STAGING SCHEMES

Importantly, the above neuropathologies may also be present in persons who are cognitively intact.[56,57] In fact, in persons aged 90 years or older, 40% of individuals without dementia exhibit AD-NC or other neurodegenerative disease lesions.[55] In

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addition to recognition of mixed pathologies and age-related differences in epidemiology, it is increasingly accepted that coexisting proteinopathies and CVD/VBI potentiate dementia severity.[3,55,58] For example, LB, CAA, SVD, and VBI (see **Fig. 2**A–D) in many persons mitigate the burden of AD-NC required for the development of clinical AD-type dementia (**Fig. 2**F,G). Similarly, clinicopathological studies demonstrate that persons with overlapping AD-NC and LATE-NC tend to show more rapid cognitive decline compared with persons with pure disease[17,59] (see **Fig. 2**G). So, while data on the range of potential neurodegenerative disease substrates are advancing, epidemiologic data have also made clear that the presence of neurodegenerative pathologic conditions do not directly equate to dementia syndromes.[55]

During recent years, newer concepts have been introduced in attempt to explain the disconnects that are frequently observed between AD-NC score and degree of cognitive impairment, which presumably represent uncharacterized neuroprotective mechanisms. The term resistant is a heuristic that refers to persons whose brains remain "lesion-proof," or free of structural brain pathologic conditions throughout aging (see **Fig. 2**E, F).[60,61] In contrast, resilient is a term that refers to cognitive preservation, or the paradoxic ability to sustain cognitive function in the face of existing structural brain pathologic conditions[55] (see **Fig. 2**E–G). So-called nondemented individuals with AD neuropathology (NDAN), a.k.a. SuperAgers or asymptomatic AD [62] emphasize the significance of this group of elderly persons who are not prone to develop dementia and remain cognitively intact despite the presence of structural brain pathologic conditions (see **Fig. 2**E–G). Although both resistant and resilient persons have been said to exhibit cognitive reserve, evidence suggest that these are distinct phenomena that refer to unique scenarios, that is, resisting disease development versus compensating for existing disease(s).[61] The causes for these phenomena may include brain maintenance and neurorestorative factors that are presently unknown.[62] Emerging evidence indicate that lifestyle and behavioral factors, along with other metabolic, genetic, environmental, and/or physiologic variables, may influence AD-NC onset and progression, highlighting the importance of advising on nutrition, exercise, social, and cognitive activities, and control of vascular risk factors that may enhance cognitive functioning but are not accounted for in current classification and staging schemes.[21,55]

SUMMARY AND FUTURE DIRECTIONS

Dementia is very common in aging, and although AD pathologic condition (ie, AD-NC) is arguably the most common underlying pathologic condition, other pathologic causes of dementia in aging include Lewy bodies, TDP-43, vascular neuropathologies, and mixed pathologic conditions. Less common pathologic causes should also be recognized. It is important to note that each person has a different threshold for dementia onset. This threshold may be determined by various measures (e.g., the number of existing brain axons and synapses, neuroimmune state, stress level, and genetic and biological factors) and also often changes with age. New concepts and emerging data regarding cognitive reserve support the value of exploring nontraditional and/or nonstructural targets and risk factors for the purpose of preventing or delaying onset and progression of neurocognitive diseases in aging persons. Regarding current classification and nomenclatures, protein aggregates seem to be a final common denominator of many, but not all age-related dementia syndromes. Moreover, vascular mechanisms also play a fundamental role in many dementia syndromes. Indeed, it is notable that dementia syndromes also occur in the absence of protein aggregates, and what causes protein aggregates in the first place is

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incompletely known. With recognition of resistance and resilient factors and mixed pathologic conditions, the boundaries of distinct neuropathological diseases have become more uncertain. For these reasons, some experts have proposed a general neuropathological category of "brain dementia" in aging with specific lesions enumerated secondarily, whereas others suggest revision of current schema although evidence regarding precise revisions is lacking and the current schema continues to evolve.

What is currently known about dementia in aging is that: (1) Dementia represents a looming public health crisis.[1] (2) The brain undergoes various complex age-related structural, physiologic, and biochemical changes and is exposed to heterogeneous environmental stress conditions during the life span that may foster the development and progression, or resistance and resilience toward disease susceptibilities.[55] (3) In patients with dementia, a spectrum of neuropathologies contribute to neurodegeneration and may overlap. (4) Isolated and mixed pathologic conditions result in pruning and loss of neurons and glia and are associated with inflammation in various brain regions that collectively result in synapse and brain volume loss. (5) In persons symptomatic for dementia, the location(s) of neurodegenerative brain changes determine clinical symptomatologies. (6) Heterogeneity among clinical disease phenotypes indicates among other things, the existence of other nonclassified and or nonstructural determinants of disease.[55] Therefore, identification and investigation of potential nonclassified brain pathologic conditions, interactions of different brain pathologic conditions, and currently unrecognized resistant and resilient factors are required because they may not only elucidate hidden contributors to disease but may also uncover potential novel targets for disease prevention.

CLINICS CARE POINTS

- Alzheimer disease neuropathologic change is the most common dementia pathologic condition and manifests with diagnostic lesions of βA plaques and neurofibrillary tangles.
- Other common neuropathological forms of dementia include Lewy body disease, limbic-predominant age-related TDP-43 encephalopathy-neuropathological change, and vascular dementia.
- Additional pathologic conditions related to dementia include frontotemporal lobar degeneration, progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy, and Creutzfeldt Jakob disease, among others.
- Mixed and asymptomatic pathologic conditions are also commonly found in older persons.
- As modifiable risks, vascular diseases and lifestyle factors are important to address in the geriatric population but also show important age-related differences.
- Evidence suggests that traditional brain markers are not fully predictive of clinical disease because other physiologic factors affect the manifestation of dementia syndromes.
- Resistance factors prevent the appearance of neurodegenerative and other brain disease lesions, whereas resilience factors are hypothesized to mask cognitive dysfunction that would otherwise be predicted by the presence of a significant burden of neuropathologic lesions.

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DISCLOSURE

The authors declare no financial or nonfinancial conflicts of interest.

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