REVIEW ARTICLE

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Neuropathology of Dementia Disorders

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ABSTRACT

PURPOSE OF REVIEW: **This article provides an overview of the neuropathology of common age-related dementing disorders, focusing on the pathologies that underlie Alzheimer disease (AD) and related dementias, including Lewy body dementias, frontotemporal dementia, vascular dementia, limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), and mixed-etiology dementias. This article also discusses the underlying proteinopathies of neurodegenerative diseases (eg, amyloid-β, paired helical filament tau, α-synuclein, and TDP-43 pathology) and vascular pathologies, including tissue injury (eg, infarcts, hemorrhages) with or without vessel disease.**

RECENT FINDINGS: **New criteria for AD pathologic diagnosis highlight amyloid-β as the *sine qua non* of AD; they require molecular markers of amyloid and establish a minimum threshold of Braak neurofibrillary tangle stage 3. Pathologic diagnosis is separated from clinical disease (ie, pathologic diagnosis no longer requires dementia). TDP-43 pathology, a major pathology in a frontotemporal dementia subtype, was found as a central pathology in LATE, a newly named amnestic disorder. Multiple pathologies (often co-occurring with AD) contribute to dementia and add complexity to the clinical picture. Conversely, Lewy body, LATE, and vascular dementias often have accompanying AD pathology. Pathology and biomarker studies highlight subclinical pathologies in older people without cognitive impairment. This resilience to brain pathology is common and is known as *cognitive reserve*.**

SUMMARY: **The pathologies of dementia in aging are most commonly amyloid, tangles, Lewy bodies, TDP-43, hippocampal sclerosis, and vascular pathologies. These pathologies often co-occur (mixed pathologies), which may make specific clinical diagnoses difficult. In addition, dementia-related pathologies are often subclinical, suggesting varying levels of resilience in older people.**

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INTRODUCTION

The most common neurodegenerative pathologies underlying dementias that occur in aging include amyloid-β (Aβ) and paired helical filament tau tangles in Alzheimer disease (AD), Lewy bodies in dementia with Lewy bodies (DLB) and Parkinson disease (PD) dementia, and transactive response DNA-binding protein 43

(TDP-43) in limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathologic changes. Frontotemporal dementia (FTD) is less common, and a complex array of pathologies may underlie the syndrome, most commonly frontotemporal lobar degeneration (FTLD)–tau or FTLD-TDP. Vascular cognitive impairment and vascular dementia are most commonly caused by ischemic tissue injury in the form of brain infarcts and may include other forms of hypoxia and hemorrhage. The location of the tissue injury (brain atrophy or damage) from these pathologic changes underlies the presentation and clinical phenotype of the dementia, including atypical presentations; heterogeneity within the disease process (eg, posterior cortical atrophy with AD pathology) may also be related to atypical presentations. Behavioral and language phenotypes of FTD (ie, nonfluent/agrammatic variant primary progressive aphasia, logopenic variant primary progressive aphasia, and semantic dementia) often have underlying FTLD (most commonly FTLD-tau or FTLD-TDP), but AD pathology has also been implicated, especially in the primary progressive aphasias. Another common cause for atypical presentations in age-related dementias is the presence of mixed pathologies. The most common mixed pathologies include AD pathology and vascular pathologies, but AD with TDP and AD with Lewy bodies are also common. All of these pathologies may be present in individuals who are not cognitively impaired. This subclinical pathology may be present decades before the onset of cognitive impairment. Evidence exists that cognitive resilience for accumulating brain pathologies in aging is related to a myriad of pathologic, genetic, and environmental factors.

KEY POINTS

- **Alzheimer disease (AD) neuropathologic changes are defined by the accumulation of two key abnormal proteins, amyloid-β in the form of extracellular plaques and abnormally phosphorylated microtubule-associated protein tau in the form of neuronal neurofibrillary tangles.**
- **The primary component of plaques is amyloid-β protein.**

ALZHEIMER DISEASE

AD neuropathologic changes are defined by the accumulation of two key abnormal proteins, Aβ in the form of extracellular plaques and abnormally phosphorylated microtubule-associated protein tau in the form of neuronal neurofibrillary tangles. Plaques and tangles were first described by Alois Alzheimer in 1906 in a middle-aged woman with memory loss and behavioral changes who died after 8 years of progressive illness. Her brain at autopsy showed atrophy with microscopic neuronal loss and gliosis. Using special stains and microscopic analysis, Dr Alzheimer found extracellular plaques and intraneuronal neurofibrillary tangles in multiple cortical brain regions. These special stains, called *silver stains*, are still used today in the pathologic diagnosis of AD, especially to distinguish the more toxic neuritic plaque from the more benign diffuse plaques.

The primary component of plaques is Aβ protein. This abnormal protein is cleaved from a much larger 695-amino acid amyloid precursor protein, which is the predominant isoform expressed in neurons. The amyloid precursor protein is a transmembrane protein, which can be processed via two pathways, amyloidogenic and nonamyloidogenic. The nonamyloidogenic pathway begins with α-secretase enzyme, which releases soluble amyloid precursor protein-α into the extracellular space.[1] The remaining intramembrane fragment is cleaved by γ-secretase, releasing a small nonamyloidogenic fragment. Alternatively, amyloid precursor protein is cleaved by β-secretase, resulting in release of soluble amyloid precursor protein-β into the extracellular space. Cleavage of the remaining fragment embedded in the plasma membrane by γ-secretase results in the production of the highly amyloidogenic β fragment, the Aβ protein, which

accumulates and deposits in the brains of individuals with AD. Two major subtypes of the amyloid-β protein exist, which differ in C-terminal length: Aβ40 and Aβ42. Aβ42 is more amyloidogenic than Aβ40, whereas Aβ40 accumulates more often in neuritic plaques and exclusively comprises the amyloid within the blood vessels in cerebral amyloid angiopathy (CAA).

It is well recognized that adults with trisomy 21, or Down syndrome, commonly have brain accumulation of AD pathology beginning in the fifth decade of life or earlier.[2] Although the extra copy of the *APP* gene encoded on chromosome 21 plays a central role in the increase in Aβ levels, triplication of other genes on chromosome 21 may also play a role in promoting aggregation and deposition of Aβ.[3] Autosomal dominant forms of AD explain about 5% to 10% of early-onset cases (and less than 1% of all AD cases), which are most commonly caused by highly penetrant mutations in presenilin 1 (*PSEN1*) but may also be caused by mutations in *APP* and presenilin 2 (*PSEN2*). The pathogenic mutations either result in overproduction of the Aβ protein or cause a greater ratio of Aβ42 to Aβ40.[4] Interestingly, both PSEN1 and PSEN2 are proteins of the γ-secretase complex.[4] These proteins are involved in the proteolytic cleavage of amyloid precursor protein into Aβ.

By contrast, amyloid deposition associated with sporadic forms of AD may be more varied and heterogeneous, possibly because of a combination of upstream or downstream factors. The most common genetic polymorphisms increasing risk of AD in the community occur in the *APOE* gene, a cholesterol transport protein secreted primarily from astrocytes and affecting neurons mostly through the low-density lipoprotein family of receptors.[5] Human *APOE* has three main variants, ε2, ε3, and ε4. Most people have two copies of the ε3 variant, but about 25% of population harbor at least one copy of the ε4 allele, which increases the risk of AD. Pathologically, people with the ε4 allele have a greater accumulation of brain amyloid than those with other alleles, and people with the less common ε2 allele have less Aβ than those with the ε3 allele. Multiple less common genetic polymorphisms in the population also increase the risk of AD. Many of these polymorphisms involve complex cellular functions such as the immune system, synaptic functioning, and lipid metabolism. Axonal transport, cytoskeletal function, regulation of gene expression, apoptosis, and autophagy have also been implicated.[4]

Most, but not all, experts believe that the cerebral deposition of amyloid is the earliest stage in AD pathogenesis. Amyloid accumulation begins in the neocortex and, over time, progresses to the hippocampus, basal ganglia, midbrain, and cerebellum. Amyloid deposition is required for any level of AD pathologic changes to occur.[6] Multiple pathologic studies have suggested that amyloid accumulates presymptomatically in those without cognitive impairment[7]; this has been confirmed with in vivo positron emission tomography (PET) using amyloid ligands that shows that the accumulation of amyloid begins many years to decades before the onset of symptoms.[8] In hemispheric cortical regions, two types of plaques are seen depending on the presence or absence of abnormally distended neurites: diffuse and neuritic. Plaques that have thickened processes that disrupt the brain neuropil, best seen on by silver stains, are called *neuritic plaques*. Plaques without these thickened neuritic processes are referred to as *diffuse plaques*. Diffuse plaques are commonly seen with neuritic plaques in the cerebral cortex, but they are typically the exclusive plaque type in subcortical and brainstem regions.

Neuritic plaques are associated with a pathologic diagnosis of AD and dementia.[6] An early set of pathologic criteria to confirm a clinical diagnosis of AD, the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) criteria,[9] used the density of neocortical neuritic plaques to determine the likelihood that the clinical diagnosis of dementia was due to AD. In addition to the density of neuritic plaques, these earlier criteria for a pathologic diagnosis of AD also used age and clinical diagnosis to determine whether the pathology confirmed a final diagnosis of AD in a person with dementia.[9]

Neurofibrillary tangles are the other essential pathologic feature of AD. Like amyloid plaques, they accumulate during the course of AD, but the progression and pattern differ from that of amyloid plaques. Where amyloid is extracellular in location, neurofibrillary tangles are intracellular, residing in the neuronal cytoplasm. Neurofibrillary tangles are composed of abnormally phosphorylated tau protein in the form of paired helical filament neuronal tangles. Normal tau is a protein coded by the microtubule associated protein tau (*MAPT*) gene on chromosome 17q21.[10] Tau is essential for microtubule structure and function, especially axonal transport. In aging and disease, the phosphorylation of tau and the formation of neurofibrillary tangles result in loss of the ability to perform these and other pivotal cellular functions. Neurofibrillary tangles are not specific to AD but also occur in normal aging and more than 30 different diseases.[11] In the context of dementia, tauopathy in other major neurodegenerative diseases includes subtypes of FTLD, such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick disease, and FTD with parkinsonism due to *MAPT* mutations. Although most tauopathies have the accumulation of abnormally phosphorylated tau in neurons, an accumulation of tau in glial cells is also seen in aging and disease.[12]

In aging and AD, neurofibrillary tangles typically begin to accumulate in the mesial temporal lobe, specifically the entorhinal and hippocampal cortices. Neurofibrillary tangle accumulation in aging and AD has been described by Braak[13] in six stages. In AD, neuronal neurofibrillary tangles progressively accumulate in the mesial temporal lobe structures, followed by accumulation in the neocortical association regions. The progression as described by Braak shows stages 1 through 4 are largely restricted to the mesial temporal lobe, whereas stages 5 and 6 are widespread in the neocortex (**FIGURE 9-1**).[14] Three patterns of neurofibrillary tangles in AD have been described.[15] In typical AD, neuronal neurofibrillary tangles are found in both limbic and neocortical regions; in limbic-predominant AD, the tangles are most prominent in the mesial temporal cortex with little involvement of neocortex. In some cases, the neurofibrillary tangles predominate in the neocortex, the so-called limbic-sparing AD. People with limbic-sparing AD tend to be younger and more often male.[15]

Neocortical neurofibrillary tangles tend to involve association cortices while sparing primary cortical regions (eg, visual, motor, auditory cortices) until late in the course of the pathologic progression of AD (Braak stage 6). Neurofibrillary tangle deposition is more closely aligned than amyloid with progression of regional atrophy and clinical symptomatology. Paired helical filament tau, the primary component of neurofibrillary tangles, also accumulates in some, but not all, of the distended neurites of neuritic plaques, which is the other characteristic feature of AD (ie, the CERAD neuritic plaque score).[9]

Criteria for the pathologic diagnosis of AD have evolved over the past few decades. Although older criteria incorporated age and clinical diagnosis in

KEY POINTS

- **Adults with trisomy 21, or Down syndrome, commonly have brain accumulation of AD pathology beginning in the fifth decade of life or earlier.**
- **Pathologically, people with the *APOE* ε4 variant have a greater accumulation of brain amyloid than those with other variants, and people with the less common ε2 variant have less amyloid-β than those with the ε3 variant.**
- **In hemispheric cortical regions, two types of plaques are seen depending on the presence or absence of abnormally distended neurites: diffuse and neuritic. Plaques that have thickened processes that disrupt the brain neuropil are called *neuritic plaques*. Plaques without these thickened neuritic processes are referred to as *diffuse plaques*.**
- **Diffuse plaques are commonly seen with neuritic plaques in the cerebral cortex, but they are typically the exclusive plaque type in subcortical and brainstem regions.**
- **Neurofibrillary tangles, composed of abnormally phosphorylated tau protein in the form of paired helical filament neuronal tangles, are an essential pathologic feature of AD.**

KEY POINT

- Current AD pathologic diagnosis also newly incorporates molecular pathology into traditional neuritic plaque and/or neurofibrillary tangle classifications. Specifically, the new National Institute on Aging–Alzheimer's Association criteria for pathologic diagnosis of AD requires Thal amyloid phase in addition to Braak tangle stage and CERAD neuritic plaque stage.

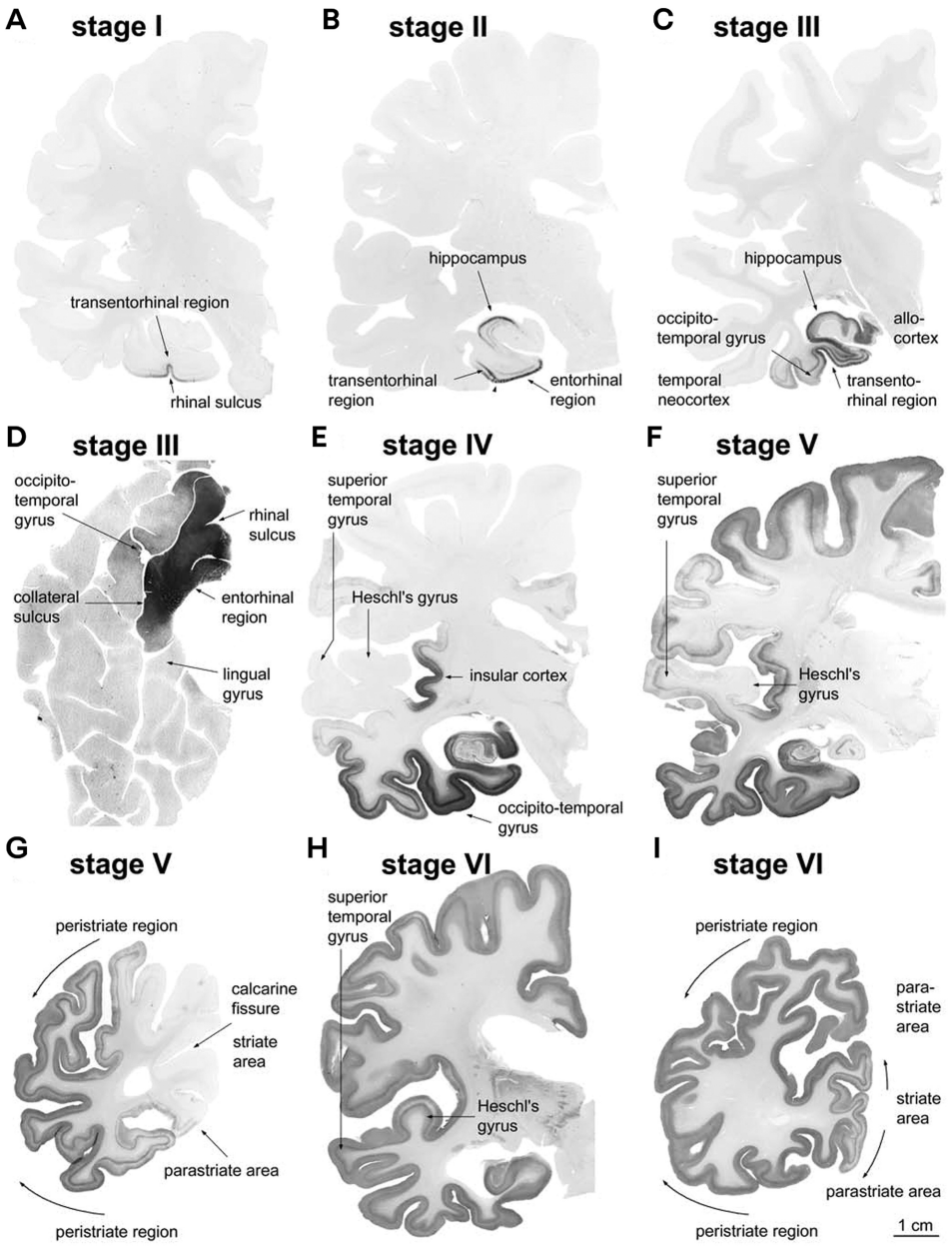

FIGURE 9-1

Braak staging of neurofibrillary tangles. Stages 1 through 4 are largely restricted to the mesial temporal lobe, whereas stages 5 and 6 are widespread in the neocortex.

Reprinted with permission from Braak H, et al, Acta Neuropathol.[14] © 2006 Springer-Verlag.

determining the likelihood that a dementia was caused by AD pathology,[6,16] current criteria are agnostic to age and clinical diagnosis.[5] Current AD pathologic diagnosis also newly incorporates molecular pathology into traditional neuritic plaque and/or neurofibrillary tangle classifications. Specifically, the new National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for the pathologic diagnosis of AD require Thal amyloid phase in addition to Braak tangle stage and CERAD neuritic plaque score (TABLE 9-1[17]).[5] The Thal phase describes the progression of amyloid from the neocortex (phase 1) to the

hippocampus (phase 2), diencephalon (phase 3), brainstem (phase 4), and cerebellum (phase 5). People without dementia typically have a Thal phase of 0, 1, 2, or 3, whereas those with dementia have a Thal phase of 3, 4, or 5. For the new criteria that use an ABC score, this is further simplified into A score: A0 = no amyloid, A1 (Thal phase 1 or 2), A2 (Thal phase 3), and A3 (Thal phases 4 and 5). Braak scores are simplified as B0 (Braak 0), B1 (Braak 1/2), B2 (Braak 3/4), and B3 (Braak 5/6). Braak score is most strongly related to cognitive function, with lower scores typical in cognitively normal older adults and higher scores typical of individuals with Alzheimer dementia. The CERAD neuritic plaque score uses semiquantitative scoring of neocortical plaques: none (C0), sparse (C1), moderate (C2), and frequent (C3). The CERAD neuritic plaque score is correlated with cognitive impairment such that moderate neuritic plaques are typically needed to explain a dementia syndrome. New to this pathologic framework is the criterion that the presence of amyloid is required even to diagnose low levels of AD pathology. By contrast, neurofibrillary tangles in the absence of amyloid are not consistent with AD pathology but rather indicative of primary age-related tauopathy (PART) or another tauopathy.[11] AD neuropathologic changes are described by an ABC score (TABLE 9-2[18]) and further categorized as none or a low, intermediate, or high level of

Alzheimer Disease Neuropathologic Change[a]

TABLE 9-1

Classification

Alzheimer disease neuropathologic change should be ranked along three parameters (**A**myloid, **B**raak, **C**ERAD) to obtain an ABC score:

- **A** Aβ plaque score (modified from Thal, et al.[17]):
  - **A0** No Aβ or amyloid plaques
  - **A1** Thal phases 1 or 2
  - **A2** Thal phase 3
  - **A3** Thal phases 4 or 5
- **B** NFT stage (modified from Braak for silver-based histochemistry[13] or phosphorylated tau immunohistochemistry[14])
  - **B0** No NFTs
  - **B1** Braak stage I or II
  - **B2** Braak stage III or IV
  - **B3** Braak stage V or VI
- **C** Neuritic plaque score (modified from CERAD[9])
  - **C0** No neuritic plaques
  - **C1** CERAD score sparse
  - **C2** CERAD score moderate
  - **C3** CERAD score frequent

Aβ = amyloid-β; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NFT = neurofibrillary tangle.

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AD neuropathologic changes. Intermediate and high AD neuropathologic changes are consistent with a pathologic diagnosis of AD. It is important to note that in these new criteria, a clinical diagnosis of dementia is not required for a pathologic diagnosis of AD. As previously noted, it is now well recognized that AD pathology may be subclinical.

LEWY BODY PATHOLOGY

Lewy bodies are intracytoplasmic neuronal inclusions and are commonly found in the aging brain. The presence of these inclusions together with the presence of significant substantia nigra neuronal loss are the defining feature for a pathologic diagnosis of idiopathic Parkinson disease. It is now well recognized that Lewy bodies may also localize in cortical neurons, where they are strongly related to cognitive impairment and dementia. Lewy bodies in both cortical and subcortical

TABLE 9-2 **Level of Alzheimer Disease Neuropathologic Change[a,b]**

A: Amyloid-β/ amyloid plaques score (Thal phases)[c]	C: Neuritic plaque score (CERAD)[d]	B: NFT SCORE (Braak stage)[e]		
		B0 or B1 (None or I/II)	B2 (III/IV)	B3 (V/VI)
A0 (0)	C0 (none)	Not[f]	Not[f]	Not[f]
A1 (1/2)	C0 or C1 (none to sparse)	Low	Low	Low[g]
	C2 or C3 (moderate to frequent)[h]	Low	Intermediate	Intermediate[g]
A2 (3)	Any C	Low[i]	Intermediate	Intermediate[g]
A3 (4/5)	C0 or C1 (none to sparse)	Low[i]	Intermediate	Intermediate[g]
	C2 or C3 (moderate to frequent)	Low[i]	Intermediate	High

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NFT = neurofibrillary tangle.

[a] Reprinted with permission from Hyman BT, et al, Alzheimers Dement.[6] © 2012 The Alzheimer's Association.

[b] Alzheimer disease (AD) neuropathologic change is evaluated using an ABC score that derives from three separate four-point scales: amyloid-β (Aβ)/amyloid plaque score by Thal phases (A), NFT score by Braak stages (B), and neuritic plaque score by CERAD stage (C). The combination of A, B, and C scores receives a descriptor of Not, Low, Intermediate, or High AD neuropathologic change. Intermediate or High AD neuropathologic change is considered sufficient explanation for dementia.

[c] Aβ/amyloid plaque score should be determined by the method of Thal, et al.[17]

[d] Neuritic plaque score should be determined by the method of CERAD.[9]

[e] NFT stage should be determined by the method of Braak.[13,14]

[f] Medial temporal lobe NFTs in the absence of significant Aβ or neuritic plaques occur in older people and may be seen in individuals without cognitive impairment, with mild impairment, or with cognitive impairment from causes other than AD.[18] Consider other diseases when clinically or pathologically indicated.

[g] Widespread NFTs with some Aβ/amyloid plaques or limited neuritic plaques are relatively infrequent, and when they occur, other diseases, particularly tauopathies, should be considered. Such cases may not fit easily into a specific Braak stage, which is intended for categorization of AD-type NFTs.

[h] Presence of high levels of neuritic plaques in setting of low Thal phase is a rare occurrence and should prompt reconsideration of neuritic versus diffuse plaques and the possible contribution of other diseases to cognitive impairment or dementia.

[i] Higher levels of Aβ or neuritic plaques with low Braak stage should prompt consideration of contribution by comorbidities such as vascular brain injury, Lewy body disease, or hippocampal sclerosis. Also, consider additional sections as well as repeat or additional protocols to demonstrate other non-AD lesions.

neurons are intraneuronal cytoplasmic inclusions that are eosinophilic, round, and, when subcortical, often have a clear halo on hematoxylin and eosin (H&E) stains. The defining protein of Lewy bodies is the phosphorylated α-synuclein protein. The two dementia syndromes characteristic of Lewy body pathology are PD dementia and dementia with Lewy bodies (DLB). Other synucleinopathies include multiple system atrophy and pantothenate kinase-associated neurodegeneration (PKAN).[19] The pathologic diagnoses of PD dementia and DLB are determined by validated consensus criteria.[20] In addition, many older people have cortical Lewy bodies contributing to their dementia when mixed with other pathologies, especially AD.[21] The degree of concomitant AD or other pathologies alters the clinical presentation in individuals with both cortical Lewy bodies and AD pathology.[20] With little AD pathology, it is likely that the cortical Lewy bodies will be associated with a specific DLB syndrome that features hallucinations, cognitive fluctuations, and parkinsonism. With increasing AD pathology, however, this clinical syndrome may be obscured, so that the prevalence of Lewy bodies as a contributing feature to an AD dementia may be underrecognized.[20] The pathologic progression of Lewy body pathology may take two or three different pathways, but most commonly the pathology ascends in the brainstem pigmented nuclei (eg, dorsomedial nucleus of the vagus, locus ceruleus, substantia nigra), followed by involvement of the limbic area (entorhinal cortex and anterior cingulate) and finally the neocortex.[22] Over the years, the pathologic criteria for confirming the diagnosis of DLB have remained relatively stable; DLB is classified as nigral type disease, limbic predominant, or neocortical based on the presence and/or severity of Lewy bodies in each of these regions. Additional pathologic features of DLB pathology are spongiform change (especially in the entorhinal cortex and other temporal cortical regions) and α-synuclein neurites (especially in regions where Lewy bodies are observed as well as in neurites in the CA2 sector of the hippocampus). Brains with Lewy body disease often have some level of AD pathology, and it is common for those with AD pathology to have coexisting Lewy bodies. The distinction between PD dementia and DLB is based on clinical information, with DLB showing cognitive changes before the motor symptoms and PD dementia starting with motor findings and later-onset cognitive impairment.

LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY

TDP-43 proteinopathy was first described in FTLD/amyotrophic lateral sclerosis, but it was quickly revealed that TDP-43 pathology was also a prominent pathology in aging, often (but not always) accompanied by AD pathology. In aging and AD, the predominance of the TDP pathology is in the limbic regions, and no associated lobar atrophy or layer 2 spongiform change is seen. Unlike FTLD, TDP in aging is associated with an amnestic disorder that can be mistaken for AD. The acronym LATE was introduced in 2017 to highlight and increase recognition of the role of TDP-43 in amnestic disorders of aging.[23] A clinical diagnosis of LATE is currently uncommon except in tertiary and specialty care centers because of the lack of a clear LATE-specific biomarker and because concomitant AD is common. However, as the use of AD biomarkers increases, the absence of amyloid and tau biomarkers in the presence of an amnestic syndrome and hippocampal atrophy most likely signals a diagnosis of LATE.[24] Isolated LATE-associated cognitive decline progresses more slowly than in AD. When TDP and AD are concomitant, accelerated cognitive

KEY POINTS

- Two dementia syndromes characteristic of Lewy body pathology are Parkinson disease dementia and dementia with Lewy bodies.
- Over the years, the pathologic criteria for confirming the diagnosis of dementia with Lewy bodies have remained relatively stable; dementia with Lewy bodies is classified as nigral type disease, limbic predominant, and neocortical based on presence and/or severity of Lewy bodies in each of these regions.
- TDP-43 proteinopathy was first described in frontotemporal lobar degeneration (FTLD)/amyotrophic lateral sclerosis, but it was quickly revealed that TDP-43 pathology was also a prominent pathology in aging, often (but not always) accompanied by AD pathology.
- The pathologic progression of limbic-predominant age-related TDP-43 encephalopathy (LATE) is divided into three stages. More than 90% of cases of hippocampal sclerosis of aging are associated with LATE.

decline is seen.[25] The pathologic progression of LATE is divided into three stages. In stage 1, TDP-43 pathology is in the amygdala. Currently, no evidence indicates that associated cognitive deficits are present in this early stage. Over time, TDP-43 progresses to involve the entorhinal, hippocampus, and dentate cortex (stage 2). The final stage 3 of LATE is neocortical. Both LATE stage 2 and stage 3 are associated with cognitive impairment with predominant amnestic changes, but other domains of cognitive function are also involved, especially language. Many individuals with LATE also have brain atrophy, especially significant and accelerated atrophy of the hippocampus; more than 90% of cases of hippocampal sclerosis of aging are associated with LATE.[26]

HIPPOCAMPAL SCLEROSIS

Hippocampal sclerosis is a nonspecific pathologic term for severe neuronal loss and gliosis in the hippocampus. The term is not descriptive of one disease but may be associated with one of several different pathologic processes, including temporal lobe epilepsy, hypoxic/ischemic brain injury, and neurodegenerative diseases of aging. In hypoxic/ischemic brain injury and neurodegenerative disease, hippocampal sclerosis commonly involves severe neuronal loss and gliosis in the CA1 sector of the hippocampus and the adjacent subiculum. In aging and neurodegeneration, hippocampal sclerosis is most commonly associated with TDP-43 pathology (LATE neuropathologic changes) with or without concomitant AD or Lewy body disease pathology. Hippocampal sclerosis is also observed in some cases of FTLD. Hippocampal sclerosis characterizes some cases of temporal lobe epilepsy; in much of the imaging literature, it is referred to as *mesial temporal sclerosis*. The hippocampal sclerosis of temporal lobe epilepsy has unique histopathologic features, including significant involvement of CA3/CA4 sectors of the hippocampus, granule cell dispersion, the presence of extensive mossy fiber sprouting, and no association with TDP-43.[27] Both hippocampal sclerosis and LATE neuropathologic changes are strongly related to old age, and, unlike AD pathologic changes, these changes do not plateau in the ninth decade of life.[28]

VASCULAR PATHOLOGIES

The nomenclature used to refer to dementia related to vascular disease is heterogeneous. Currently, most experts refer to the dementia related to ischemic or hemorrhagic tissue injury as vascular dementia or vascular cognitive impairment. Other terms include multi-infarct dementia, strategic infarct dementia, and Binswanger disease. No specific criteria are currently available for a pathologic diagnosis of vascular dementia. The pathologic substrates include gross (lacunar or cystic) or microscopic infarcts and/or hemorrhages (lobar, deep, and microbleeds). Other vascular pathologies include enlarged perivascular spaces and white matter lesions, which are best visualized on MRI. The likelihood of dementia from ischemic or hemorrhagic tissue injury is dependent on multiple factors, including the size, location, and number of vascular lesions. The tissue changes are often, but not always, accompanied by small vessel (arteriolosclerosis, cerebral amyloid angiopathy [CAA]), intracranial large vessel (atherosclerosis), or extracranial vessel diseases. Most older people have some combination of vessel pathologies and tissue injury in their brain.[29] Other vessel pathologies, such as ruptured aneurysms and vascular malformations, are less common substrates. Cardiac

and noncardiac systemic causes of brain ischemia or hemorrhage, such as embolic infarcts and global hypoxic/ischemic injury, are also well-known causes of vascular dementia.

Small Vessel Disease

Small vessel disease is a term that often refers to some combination of arteriolosclerosis or CAA, often with associated white matter changes and small or microinfarcts. Interestingly, although the small and microscopic infarcts are related to arteriolosclerosis, intracranial atherosclerosis (large vessel disease) is also independently associated with microinfarcts and therefore contributes to what is considered small vessel disease.[30] Small vessel disease is the most common underlying pathologic substrate for vascular cognitive impairment and dementia in aging. Age, diabetes, and hypertension are strong risk factors for arteriolosclerosis and associated infarcts and white matter damage. Although midlife elevations in blood pressure are a strong risk factor, high blood pressure in later life is also related to more severe small vessel disease.[31] Small vessel disease pathology, including arteriolosclerosis and microinfarcts, is also common in the watershed regions of the brain, suggesting low-flow states may also be important in the pathogenesis of tissue injury in aging.[32] Additional factors involved in vascular cognitive impairment in aging and AD include disruption of the blood-brain barrier and neurovascular unit and impaired clearance mechanisms.

Arteriolosclerosis

Arteriolosclerosis refers to the concentric hyalinized thickening of small arterioles. Changes are prominent in the deep gray matter (basal ganglia and thalamus) and white matter of the brain. Arteriolosclerosis is also common in the basis pontis and cerebellar white matter. Typically, arteriolosclerosis is accompanied by loss of smooth muscle actin in the vascular wall, and concomitant luminal constriction is seen. These vessel wall changes are common in aging, diabetes, and hypertension and are related to white matter hyperintensities and microbleeds seen on MRI. Arteriolosclerosis has also been implicated in brain atrophy. Clinically, arteriosclerosis is related to AD, vascular, and mixed dementias; it also plays a role in age-related parkinsonism.

Cerebral Amyloid Angiopathy

Unlike most age-related vascular diseases that are associated with vascular risk factors, such as hypertension and diabetes, CAA is associated with risk factors for AD, including the accumulation of the Aβ protein. Although Aβ-CAA is related to AD pathology in aging, not all people with AD pathology have CAA and severe CAA with hemorrhage is rarely associated with clinical AD. Similar to AD, *APOE* ε4 is a risk factor for CAA, but unlike in AD, the *APOE* ε2 allele also confers risk of CAA. Hereditary forms of CAA with the accumulation of Aβ are well known, with the *APP* Dutch variant mutation being the best characterized. Interestingly, familial forms of Aβ-CAA are caused by missense mutations within the part of the *APP* gene that codes for Aβ, whereas *APP* mutations outside of the Aβ coding region are characteristic of chromosome 21 dominantly inherited AD.[33] Small and medium-sized vessels of the cortical parenchyma and overlying meninges are predominantly involved in CAA, and an occipital predilection exists for more severe accumulation. CAA is associated with hemorrhages, infarcts, and cognitive

KEY POINTS

- The term *hippocampal sclerosis* is not descriptive of one disease but may be associated with one of several different pathologic processes, including temporal lobe epilepsy, hypoxic/ischemic brain injury, and neurodegenerative diseases of aging.
- In aging and neurodegeneration, hippocampal sclerosis is most commonly associated with TDP-43 pathology (LATE neuropathologic changes) with or without concomitant AD or Lewy body disease pathology.
- The pathologic substrates of vascular dementia include gross (lacunar or cystic) or microscopic infarcts and/or hemorrhages (lobar, deep, and microbleeds).
- Small vessel disease is the most common underlying pathologic substrate for vascular cognitive impairment and dementia in aging.

CASE 9-1

An 80-year-old woman presented with memory loss. Her history was obtained from her daughter, who reported that her mother began having gradually progressive difficulties after the death of her husband about 4 years earlier, but in the previous year her memory had suddenly declined more rapidly. She noted that her mother had been having trouble remembering their telephone conversations and had been missing appointments and other events. She thought her mother might be "depressed," as she had been very quiet during family gatherings. The patient had no fluctuations, behavior issues, or history of stroke. She did, however, have some difficulty remembering names. She had a past medical history of hypertension, stage I breast cancer treated with lumpectomy and radiation, and hypothyroidism. She was on amlodipine and levothyroxine. She had no family history of Alzheimer disease (AD) or dementia. She lived by herself and had no other neurologic symptoms.

On examination, the patient's blood pressure was 140/90 mm Hg. She acknowledged that she was having some problems with her memory but "nothing too bad," stating that "all my friends have the same problems." Her general physical examination was unremarkable. Neurologic examination was remarkable for a left pronator drift and left Babinski sign. Sensory examination showed loss of vibration at the toes. Coordination was normal. On cognitive examination, her Mini-Mental State Examination (MMSE) score was 16, showing moderate loss of episodic memory and some mild language difficulties. MRI and laboratory tests were unremarkable. The patient was diagnosed with AD and started treatment. Her symptoms progressed over the next few years, and she died at the age of 83.

COMMENT

At autopsy, this patient's brain showed diffuse atrophy, especially in the hippocampus and temporal lobes. Histopathologic examination showed an intermediate level of AD pathology, Thal amyloid stage of 3 (A2), moderate neocortical neuritic plaques (C2), and Braak score of 4 (B2), resulting in an ABC score of A2B2C2 (TABLE 9-2). In addition, the amygdala and hippocampus showed transactive response DNA-binding protein 43 (TDP-43) pathology consistent with limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathologic changes stage 2 and a lacunar infarct in the right posterior thalamus with moderate arteriolosclerosis (small vessel disease). The final pathologic diagnoses were AD, LATE neuropathologic changes, and infarct pathologies consistent with a mixed etiology dementia, including both neurodegenerative and vascular pathologies.

impairment. The hemorrhages may be large and lobar (especially occipital) but are more commonly incidental microbleeds seen on imaging as small cortical hemorrhages. Superficial siderosis is also a common imaging finding in CAA. Cognitive impairment may manifest as an AD dementia with or without transient neurologic symptoms. Rarely, CAA may be associated with pathologic inflammation and edema and cause a potentially reversible encephalopathy.[34]

MIXED PATHOLOGIES

AD is often considered the most common underlying pathology of dementia in aging; however, in the vast majority of older people with dementia, the etiology of the underlying dementia is related to the accumulation of multiple pathologies, including neurodegenerative (amyloid, paired helical filament tau neurofibrillary tangles, cortical Lewy bodies, and TDP-43 inclusions) and vascular pathologies. The term *mixed dementia* is often used to refer to the combination of AD and vascular pathologies; however, in reality, all of the aforementioned pathologies commonly co-occur.[35] Indeed, much of what clinicians call "Alzheimer disease" is an amnestic clinical syndrome related to the accumulation of multiple neurodegenerative and vascular pathologies (CASE 9-1). Each of the pathologies, when in sufficient severity, contributes to cognitive impairment and dementia. Because multiple pathologies in the aging brain often contribute to cognitive impairment, most neuropathologists will report on all of the pathologies that potentially can be contributing to dementia. Separating the terminology of AD pathology (amyloid and tangles) from AD dementia (a multidomain amnestic dementia), as recommended within the proposed NIA-AA Research Framework,[36] provides a mechanism to improve on the clarity of dementia nomenclature.

FRONTOTEMPORAL LOBAR DEGENERATION

FTLD is a distinct pathologic entity that is typically linked to a clinical diagnosis of FTD. FTD is an uncommon clinical syndrome with early behavioral and/or language impairment. The distribution of the pathology, as the name implies, is frontal and temporal and often spares the hippocampus early in the disease, consistent with the lack of early memory impairment. Individuals with FTLD often have stark severe focal atrophy of the frontal and temporal lobes, which is sometimes referred to as *knife-edge atrophy*. Underlying this atrophy is severe cortical degeneration with neuronal loss and gliosis. The neocortex also shows superficial vacuolization, called *layer 2 spongy change*. The two main pathologic types of FTLD are FTLD-TDP and FTLD-tau; as the names imply, the proteinopathies are associated with distinct forms of FTLD called TDP-43 and abnormally phosphorylated tau protein, respectively. The TDP-43 protein was recently found to be a major component of FTLD and amyotrophic lateral sclerosis with ubiquitin-positive inclusions, nonspecific inclusion types. A hexanucleotide repeat expansion in *C9orf72* is the most common cause of FTD and amyotrophic lateral sclerosis. This repeat induces the formation of aberrant stress granules and phosphorylated TDP-43 inclusions.[37] A neuropathologic hallmark is the intracellular accumulation of RNA foci. Mutations in the progranulin gene (*GRN*) are associated with FTLD-TDP. Genetic polymorphisms in *TMEM106* are a risk factor for both familial and sporadic FTLD-TDP. Another familial form of FTLD is FTD with parkinsonism

KEY POINTS

- AD is often considered the most common underlying pathology of dementia in aging; however, in the vast majority of older people with dementia, the etiology of the underlying dementia is related to the accumulation of multiple pathologies, including neurodegenerative and vascular pathologies.
- Because multiple pathologies in the aging brain often contribute to cognitive impairment, most neuropathologists will report on all of the pathologies that potentially can be contributing to dementia.
- FTLD is a distinct pathologic entity that is typically linked to a clinical diagnosis of frontotemporal dementia.
- The distribution of the pathology in frontotemporal dementia, as the name implies, is frontal and temporal and often spares the hippocampus early in the disease, consistent with the lack of early memory impairment.
- The two main pathologic types of FTLD are FTLD-TDP and FTLD-tau.
- Depending on age and other cohort characteristics, about one-third of older individuals have a pathologic diagnosis of intermediate or high AD neuropathologic changes in their seventh decade of life despite having normal cognition proximate to death.

linked to chromosome 17, which maps to the *MAPT* locus and has tau pathology. Overall, about 20% to 30% of FTD has a genetic cause, most commonly related to *GRN*, *MAPT,* and *C9orf72*.[38] Probably the best-known pathology of FTLD is that of Pick disease. Pick bodies are composed of abnormally phosphorylated tau protein, but unlike in AD, they are straight rather than paired helical filaments. They form circular basophilic round intracytoplasmic inclusions in the frontal and temporal cortical neurons. In addition to Pick bodies, cortical regions also contain distended neurons called Pick cells (ballooned neurons). In older literature, the name *Pick disease* was often the nomenclature for all types of FTLD.

SUBCLINICAL PATHOLOGIES AND COGNITIVE RESILIENCE

Most dementia-related pathologies, whether they be neurodegenerative or vascular, accumulate over time. Epidemiologic studies have been pivotal to our understanding of aging, neuropathology, and dementia. Depending on age and other cohort characteristics, about one-third of older individuals have a pathologic diagnosis of intermediate or high AD neuropathologic changes in their seventh decade of life despite having normal cognition proximate to death. These research findings have been confirmed with molecular PET studies that can image amyloid pathology in vivo. Thus, the brain is able to tolerate some level of pathology before clinical symptoms ensue. This cognitive resilience varies across individuals and may be related to genetics, pathology, or environment. Probably one of the biggest tipping points for the resilient brain is the accumulation of additional pathologies. This is best recognized in individuals with subclinical AD pathology who have a clinical stroke, but it can also occur as other subclinical neurodegenerative and/or vascular pathologies accumulate with age. Many other person-specific factors are important in cognitive resilience and include, but are not limited to, years of education, physical activity, cognitive activity, social activity, diet, and mood or anxiety disorders. Genetic factors, including polymorphisms related to immune function, cellular stress, and lipid metabolism, are also likely to play an important role in cognitive resilience.

NEURONAL NEUROFIBRILLARY TANGLES IN OTHER DISORDERS AND AGING

Neuronal neurofibrillary tangle pathology is not unique to AD and FTLD. It has also been commonly described in normal aging and is the central proteinopathy in chronic traumatic encephalopathy (CTE, discussed below), PSP, and CBD. PSP and CBD are sometimes categorized with the FTLD-tau diseases. Other brain diseases with neuronal neurofibrillary tangles include postencephalitic parkinsonism, pellagra, and Niemann-Pick disease type C.[39]

PRIMARY AGE-RELATED TAUOPATHY

Neuronal neurofibrillary tangles are nearly ubiquitous in the aging brain, specifically in the entorhinal and hippocampal cortices. The presence of tangles in the mesial temporal lobe in aging is referred to as *primary age-related tauopathy* (PART).[40] The tangles in PART are morphologically indistinguishable from the tangles observed in AD, containing both 3-repeat and 4-repeat tau and accumulating in the mesial temporal lobe, a location affected early in AD. However, much evidence suggests that PART and AD are separate processes, including differing genetic risk factors for

PART and AD and the lack of elevated soluble amyloid in PART. PART may be related to mild memory changes in aging but is only rarely related to dementia.

TRAUMATIC BRAIN INJURY AND CHRONIC TRAUMATIC ENCEPHALOPATHY

Traumatic brain injury is a risk factor for AD and other neurodegenerative disease dementia; however, the data are conflicting and the pathologic mechanism(s) is not always clear, especially when the trauma is mild. In a 2016 community-based study, people with a history of mild traumatic brain injury with loss of consciousness had an increased risk of parkinsonism and Lewy bodies.[41] Other studies have shown an association with other neurodegenerative pathologies, including AD, but this research is still ongoing.

CTE describes the specific pathology of the brain condition associated with multiple repetitive concussive and/or subconcussive hits to the head. AD-like changes to the brain were initially described in professional boxers, and the syndrome was called *punchdrunk syndrome*. Recently the literature on CTE has focused on the professional sports of American football, hockey, and soccer. The neuronal neurofibrillary tangles in CTE show a specific perivascular pattern, especially in the depths of the cortical sulci of the frontal cortex. In addition to an accumulation of perivascular neuronal neurofibrillary tangles, CTE also shows a progressive accumulation of tangles more diffusely throughout the brain, including the hippocampus and brainstem. Supportive pathologic features of CTE include perivascular glial tau, subpial tau in the depths of the sulci, and a patchy distribution of pathology. Many individuals with CTE pathology also have mixed pathologies, especially AD, Lewy body, and TDP-43 pathology, and vascular disease, specifically arteriolosclerosis. Years of playing sports are related to the tangles and other proteinopathies, whereas the vascular pathology appears to have risk factors not directly related to years of playing sports.[42] All of the pathologies contribute to the cognitive impairment that may be seen in former athletes. Aging, AD, and CTE all have neuronal neurofibrillary tangles composed of 3-repeat and 4-repeat tau, but the microstructure of the tangles in CTE appears to be distinct from those in AD. Using cryoelectron microscopy, investigators found a different conformation of the β-helix region, creating a hydrophobic cavity that encloses an additional density not connected to tau. These hydrophobic regions and additional densities are absent in AD tangles.[43]

PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL DEGENERATION

Neuronal neurofibrillary tangles are a central pathology in both PSP and CBD, both atypical parkinsonian disorders. In both diseases, cognitive impairment may be the presenting or predominant feature. The neuronal neurofibrillary tangles are prominent in the substantia nigra in both PSP and CBD. In PSP, other subcortical regions, such as the globus pallidus, subthalamic nucleus, and basis pontis, are heavily involved. In CBD, neuronal loss, degeneration involving the perirolandic cortex (especially the postcentral gyrus), and characteristic achromatic or ballooned neurons are seen. This pathology results in the characteristic cortical sensory loss. Unlike in AD and PART, only 4-repeat tau comprises the tangles of these diseases. Although typically considered atypical parkinsonian disorders, cognitive impairment is common in these disorders and may occur early in the diseases or even be a presenting feature.

KEY POINTS

- Cognitive resilience varies across individuals and may be related to genetics, pathology, or environment. Many other person-specific factors are important in cognitive resilience, including years of education, physical activity, cognitive activity, social activity, diet, and mood or anxiety disorders. Genetic factors are also likely to play an important role in cognitive resilience.
- Neuronal neurofibrillary tangle pathology is not unique to AD and FTLD. It has also been described commonly in aging and is the central proteinopathy in chronic traumatic encephalopathy, progressive supranuclear palsy, and corticobasal degeneration.
- Neuronal neurofibrillary tangles are nearly ubiquitous in the aging brain, specifically in the entorhinal and hippocampal cortices. The presence of tangles in the mesial temporal lobe in aging is referred to as *primary age-related tauopathy* (PART).
- Chronic traumatic encephalopathy describes the specific pathology of the brain condition associated with multiple repetitive concussive and/or subconcussive hits to the head.
- The neuronal neurofibrillary tangles in chronic traumatic encephalopathy show a specific perivascular pattern, especially in the depths of the cortical sulci of the frontal cortex.

AGING-RELATED TAU ASTROGLIOPATHY

It has been long recognized that tangles can accumulate not only in neurons but also within glia cells in individuals with tauopathies. Although the astrocytic plaques of CBD and the tufted astrocytes of PSP are well described, recent in-depth pathologic studies show that astrocytic tangles are especially prominent in aging and AD. This astroglial pathology, known as *aging-related tau astrogliopathy* (ARTAG), is also a common astrocytic pathology in older adults and those with AD.[12] ARTAG has two tangle types, thorn-shaped astrocytes and granular fuzzy astrocytes, and may be located in the gray matter and/or white matter in multiple locations. The glial tau has a propensity also for subpial and perivascular regions of the cortex. ARTAG in the gray matter may be related to cognitive impairment in aging and AD,[44] but the clinical significance of the pathology continues to be investigated.

OTHER LESS COMMON DEMENTIA-RELATED PATHOLOGIES

Numerous other less common dementia-related pathologies exist across different age groups and under differing neurologic disease subtypes. Several examples are described below. Creutzfeldt-Jakob disease (CJD), although rare, is unique in that it may be infectious, hereditary, or sporadic. Huntington disease, historically a pathologically diagnosed entity, now can be detected using genetic testing. Finally, Wernicke-Korsakoff syndrome is an important and probably underrecognized syndrome with a unique pathologic footprint.

Creutzfeldt-Jakob Disease

CJD is a very rare rapidly progressive dementia caused by prion proteins. CJD is a unique disease as it may be infectious, genetic, or sporadic. The infectious agent responsible for CJD and other spongiform encephalopathies is the prion protein, and these infections have no viral particles. Prion proteins are able to self-propagate from neuron to neuron, and some cases are transmitted via iatrogenic means, such as dural or corneal transplants. CJD causes transmural spongiform changes with severe neuronal loss and gliosis throughout the cortex. Ingestion of infected cow meat from the spongiform encephalopathy mad cow disease causes an atypical form of CJD known as *variant CJD*. Genetic forms of spongiform encephalopathy also exist, including fatal familial insomnia and familial CJD. CJD is associated with conformational changes in the human prion protein, and more than 40 mutations in the human prion protein have been recognized to cause clinical disease.[45]

Huntington Disease

Huntington disease is a rare dominantly inherited neurodegenerative disease caused by mutations, specifically CAG (polyglutamine) expansion repeats, within the huntingtin gene (*HTT*) on chromosome 4. The size of the expansion is associated with the severity of the disease and accelerated age of onset. The brain shows prominent atrophy of the caudate and putamen, with lesser atrophy of the cerebral cortex. Striatal pathology can be graded on a scale from 0 to 4[46] and is related to loss of medium spiny neurons and gliosis. Cortical neuronal loss is most prominent in the frontal cortex. Similar to other neurodegenerative diseases, Huntington disease is characterized by inclusion bodies formed from huntingtin protein misfolding (aggregated mHTT) and aggregation of the abnormal protein.

In Huntington disease, the inclusions are intranuclear and formed by the mutant huntingtin protein.

Wernicke-Korsakoff Syndrome

Wernicke encephalopathy and Korsakoff syndrome, together known as Wernicke-Korsakoff syndrome, are diseases related to thiamine deficiency. Often described in association with alcohol use disorder, Wernicke-Korsakoff syndrome is also observed in other causes of malnutrition and in liver disease. In the acute phase, Wernicke encephalopathy is marked by mental status changes, ophthalmoplegia, and ataxia, whereas the chronic phase of Korsakoff syndrome results in a dementia that includes memory loss and confabulations. The most prominent acute pathology of Wernicke-Korsakoff syndrome involves bilateral mammillary body destruction, with destruction of neuropil, hemorrhagic lesions, and preservation of neurons. In chronic disease, particularly Korsakoff syndrome, involvement of the bilateral medial thalamic nuclei is seen and diencephalic periventricular damage is prominent.[47]

CONCLUSION

AD, Lewy body disease, LATE, and vascular pathologies are the most common underlying pathologies in age-related dementias. AD is composed of Aβ plaques and paired helical filament tau neuronal neurofibrillary tangles. α-Synuclein is the main component of Lewy bodies and is the *sine qua non* of both DLB and PD dementia. LATE describes a late-onset amnestic dementia that is typified by limbic-predominant TDP-43 inclusions. Vascular pathologies in aging are common and include vessel pathology and tissue injury, both of which contribute to cognitive impairment. Most clinical diagnoses of AD dementia have mixed pathologies, especially AD with Lewy body disease, TDP-43, or vascular pathologies. Recognition of other common age-related pathologies, including PART and ARTAG, is increasing. Their role in dementia, however, is not clear. Many older people have significant AD and other pathologies despite intact cognition; this is consistent with cognitive or neural reserve. FTDs are less common causes of dementia, and the main FTD pathologies include FTLD-tau and FTLD-TDP. Less common neuropathologic causes of dementia include CTE, PSP, CBD, CJD, and Wernicke-Korsakoff syndrome.

KEY POINTS

- **Neuronal neurofibrillary tangles are a central pathology in both progressive supranuclear palsy and corticobasal degeneration, both atypical parkinsonian disorders.**
- **Aging-related tau astrogliopathy is a common astrocytic pathology in older adults and those with AD.**
- **Creutzfeldt-Jakob disease is a very rare rapidly progressive dementia caused by prion proteins. It is a unique disease as it may be infectious, genetic, or sporadic.**
- **Huntington disease is a rare dominantly inherited neurodegenerative disease caused by mutations, specifically CAG (polyglutamine) expansion repeats, within the huntingtin gene (*HTT*) on chromosome 4.**
- **Wernicke encephalopathy and Korsakoff syndrome, together known as Wernicke-Korsakoff syndrome, are related to thiamine deficiency. Often described in association with alcohol use disorder, Wernicke-Korsakoff syndrome is also observed in other causes of malnutrition and in liver disease.**
- **AD, Lewy body disease, LATE, and vascular pathologies are the most common underlying pathologies in age-related dementias.**

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