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The current consensus criteria for the neuropathologic diagnosis of Alzheimer’s disease (AD), the National Institute on Aging/Reagan Institute of the Alzheimer Association Consensus Recommendations for the Postmortem Diagnosis of Alzheimer’s Disease or NIA-Reagan Criteria,[1] were published in 1997 (hereafter “1997 Criteria”). Knowledge of AD and the tools used for clinical investigation have advanced substantially since then and have prompted this update for the neuropathologic assessment of AD.
Revised Neuropathologic criteria for Alzheimer’s disease

The criteria proposed here for the neuropathologic assessment of AD differ from the 1997 Criteria in several respects.

The 1997 Criteria require a history of dementia, insofar as they were designed to help address the question of whether AD was the underlying cause of the patient’s dementia. From the clinical perspective, the concept of AD has evolved to include patients with milder symptoms,[2] including the proposition that there is a preclinical phase of the illness.[3] Moreover, data have emerged demonstrating that at least some individuals who, to all reports were cognitively intact during life, are found at autopsy to have a relatively high level of AD neuropathologic change.[4, 5] Indeed, substantial evidence now exists to show that the pathophysiologic processes of AD are present in brain well in advance of subjective or objective deficits.[3] There is consensus to disentangle the clinicopathologic term "Alzheimer disease" from AD neuropathologic change. The former refers to clinical signs and symptoms of cognitive and behavioral changes that are typical for patients who have substantial AD neuropathologic change and is the focus of recent NIA-AA sponsored consensus reports on three defined stages in a clinical continuum that include preclinical,[3] mild cognitive impairment,[2] and dementia.[6] The latter refers to the presence and extent of neuropathologic changes of AD observed at autopsy regardless of the clinical setting.

The current criteria provide guidance on clinicopathologic correlations to pathologists reporting autopsy findings based on the literature and analysis of the National Alzheimer Coordinating Center (NACC) database. They emphasize the importance of assessing non-AD brain lesions in recognition of commonly co-morbid conditions in cognitively impaired elderly. Indeed, pathologic findings for all potentially contributing diseases need to be
recorded and then integrated with clinical findings in the neuropathology report for each person.

AD Neuropathologic Change

There are several characteristic neuropathologic changes of AD, of which neurofibrillary tangles (NFT) and senile plaques are considered essential for the neuropathologic diagnosis of AD (Text Box 1). NFT can be visualized with a variety of histochemical stains or with immunohistochemistry directed against tau or phospho-tau epitopes. NFT commonly are observed in limbic regions early in the disease but, depending on disease stage, also involve other brain regions, including association cortex and some subcortical nuclei.[7] The 1997 Criteria utilized a staging scheme for NFT described by Braak and Braak,[8] which proposes six stages that can be reduced to four with improved inter-rater reliability:[9] no NFT, stages I/II with NFT predominantly in entorhinal cortex and closely related areas, stages III/IV with NFT more abundant in hippocampus and amygdala while extending slightly into association cortex, and stages V/VI with NFT widely distributed throughout the neocortex* and ultimately involving primary motor and sensory areas. Neuropil threads and dystrophic neurites, lesions often associated with NFT, likely represent dendrites and axons of NFT-containing soma that can be used to further elaborate disease,[10] but are not part of NFT staging.

*Neocortex refers to the evolutionarily most recent portion of the cerebral cortex that is characterized by nerve cells arranged in six layers, and is synonymous with “isocortex” and “neopallium”.

Senile plaques, the other major component of AD neuropathologic change, are extracellular deposits of the amyloid (A) β peptide but their nomenclature and morphologic features are complex. Aβ deposits can be at the center of a cluster of dystrophic neurites that
frequently, but not always, have phospho-tau immunoreactivity; these are neuritic plaques. Aβ deposits are morphologically diverse and also include non-neuritic structures called diffuse plaques, cored plaques, amyloid lakes and subpial bands. The situation is further complicated because different types of plaques tend to develop in different brain regions, and even though all genetic causes of AD have Aβ deposits, they do not invariably have many neuritic plaques.[11] Further, Aβ peptides are diverse proteins with heterogeneous lengths, amino- and carboxy-termini and assembly states that span from small oligomers and protofibrils to fibrils with the physicalchemical properties of amyloid.[12]

Among these different forms of Aβ plaques, neuritic plaques have been considered to be most closely associated with neuronal injury. Indeed, neuritic plaques are defined by dystrophic neurites within or around deposits of Aβ, and are characterized by greater local synapse loss and glial activation. The 1997 Criteria adopted a previously developed Consortium to Establish a Registry for AD (CERAD) neuritic plaque scoring system, which ranks the amount of neuritic plaques identified histochemically in several regions of neocortex.[13] Several alternative protocols for assessing plaque accumulation have been proposed, including that of Thal, et al., that proposes phases of Aβ distribution in brain,[14] and a hybrid that uses CERAD scoring of Aβ deposits identified by immunohistochemistry.[15] Which, or which combination, of these protocols optimally represents this facet of AD neuropathologic change is not clear.

Other features of AD neuropathologic change are less straightforward to assess by conventional histopathologic methods or are considered less closely related to neural system damage than NFT and plaques. These include, synapse loss, neuron loss, atrophy, gliosis, and other neuronal lesions like TDP-43 immunoreactive inclusions, granulovacuolar degeneration, and actin immunoreactive Hirano bodies, as well as congophilic amyloid angiopathy (CAA). In addition, soluble forms of both Aβ and tau have been implicated in AD pathogenesis, but
would not be apparent by morphological techniques.[12] It is important to recognize that the recommended use of NFT, parenchymal Aβ deposits, and neuritic plaques as the tractable histopathologic lesions of AD neuropathologic change in the current criteria does not preclude the possibility that other processes or lesions may contribute critically to the pathophysiology of AD.

NFT and senile plaques do, however, correlate with the presence of the clinical symptoms of AD. For example, the national Alzheimer Coordinating Center (NACC) has collected data on individuals who have come to autopsy and who had been clinically evaluated in a standardized fashion in one of the approximately 30 AD Centers located throughout the United States. While there are limitations to these data, including the potential biases introduced by varied cohort selection criteria, and the fact that it is not a population-based sample, this nonetheless represents one of the largest clinicopathologic correlations yet assembled; as of the end of 2010, data from over 1200 autopsies has been collected. We analyzed these data to provide a general guide to pathologists for the clinical correlations of various levels of AD neuropathologic change.

The sample was narrowed by several criteria: subjects were excluded if the primary neuropathologic diagnosis was a dementia other than AD, if they had not had a formal clinical evaluation within 2 years of death (mean duration between clinical evaluation and death = 288 days), or if there was a medical condition felt to be a major contributor to cognitive or behavioral impairments. The remaining 562 individuals were then analyzed in terms of Braak NFT stage, CERAD neuritic plaque score, and the clinical Dementia Rating Scale sum of boxes score (Table 1). Of these individuals, 95 were reported as being cognitively normal (CDR sum of boxes 0), 52 had very mild symptoms of cognitive impairment (CDR sum of boxes 0.5 to 3.0), and 415 had dementia; of the patients with dementia, 63 were mild (CDR sum of boxes 3.5 to 6.0), 108 were moderate (CDR sum of boxes 6.5 to 12), and 244 were
severe (CDR sum of boxes > 12). Although the number of individuals in some cells is relatively modest, the overall pattern supports the 1997 Criteria. For individuals with Braak NFT stage V or VI and frequent CERAD neuritic plaque score, 91% were had moderate or severe dementia. Similarly, there was an intermediate probability of cognitive impairment in individuals with an intermediate level of AD neuropathologic change. For example, just over half the individuals with Braak NFT stage III or IV and intermediate CERAD neuritic plaque score had a diagnosis of at least mild dementia. Finally, although most individuals who were cognitively normal clustered in the cells with no or low levels of AD neuropathologic change, rare individuals appeared to be able to withstand at least some AD neuropathologic change and remain cognitively intact. Similarly, individuals who had very little AD neuropathologic change and no other detected lesions were generally normal clinically, but an occasional case was reported with dementia despite no obvious neuropathologic explanation.

Other diseases that commonly co-exist with AD neuropathologic change

While AD is the most common cause of dementia and can exist in a “pure” form, it commonly co-exists with pathologic changes of other diseases that also can contribute to cognitive impairment. The most common co-morbidities are Lewy body disease (LBD), vascular brain injury (VBI), and hippocampal sclerosis (HS), although these also may occur in “pure” forms without co-existing AD neuropathologic change or as neuropathologic features in other diseases. For a given amount of AD neuropathologic change, cognitive symptoms tend to be worse in the presence of co-morbidities such as LBD or VBI.[16] However, it is difficult to judge the extent to which each disease process observed at autopsy may have contributed to a given patient’s clinical course. Nevertheless, it is critical to document the type and extent of co-morbidity in brains of individuals with AD
neuropathologic change.

**Lewy Body Disease**

LBD is a subset of diseases that shares the feature of abnormal accumulation of α-synuclein in regions of brain (Text Box 2). Indeed, Lewy bodies (LB) are immunoreactive for α-synuclein and IHC is used for their identification. LBD includes not only LB but also α-synuclein-immunoreactive neurites (so called “Lewy neurites”) and diffuse cellular immunoreactivity; these features can be useful even in the absence of classical LB.

LB are frequent in the setting of moderate to severe levels of AD neuropathologic change,[17, 18] including some early-onset familial AD cases with APP or PSEN1 mutations.[19, 20] LB are considered to be independent in some circumstances, since not all cases with LB or related changes have AD neuropathologic change; however, there appears to be a relationship between AD neuropathologic change and LBD because in most series, subjects with dementia who have the most neocortical LBs also have concomitant AD neuropathologic change.[21]

In the clinical setting of cognitive impairment, pure LBD with no or low level of AD neuropathologic change is relatively rare and most often seen in younger individuals, including those with mutations in the gene for α-synuclein. LBD also is characteristic of patients with Parkinson’s disease, with or without cognitive impairment or dementia, and may also be observed in some older individuals without clinical history of motor or cognitive deficits; these cases potentially represent preclinical disease.[22]

Following the previous consensus paper on LBD,[23] we recommend that LBD be classified as No LB, Brainstem-Predominant, Limbic (Transitional), Neocortical (Diffuse), or
Amygdala-Predominant, understanding that in the clinical context of cognitive impairment and dementia, LBD may not follow the proposed caudal-rostral progression of accumulation as reported in the setting of Parkinson’s disease.[24] While the olfactory bulb can be involved early in LBD,[25-27] we have not included its sampling in the proposed classification scheme for practical reasons.

Cerebrovascular Disease and Vascular Brain Injury

CVD and VBI, which describes parenchymal damage from CVD as well as systemic dysfunction like prolonged hypotension or hypoxia,[28] increase exponentially with age beyond the 7th decade of life, similar to AD (Text Box 3). Not surprisingly, evidence of CVD and VBI commonly is encountered in the brains of those who die with AD neuropathologic change.[28-30] The current ability to estimate the relative contributions of AD or VBI to cognitive impairment in a given individual is limited.[31-34]

The major types of CVD that cause VBI are atherosclerosis, arteriolosclerosis (sometimes described as lipohyalinosis) and CAA.[35-38] The presence of CAA, in particular, further interweaves AD and VBI, since Aβ-positive CAA often occurs together with the other neuropathologic changes of AD.[39-41] There are many less common forms of CVD including various forms of vasculitis, CAA from non- Aβ amyloidoses, and inherited diseases that affect vessel integrity, some of which are associated with the development of cognitive impairment in the absence of AD, e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

VBI usually is characterized as infarcts or hemorrhages. Infarcts often are classified by size: territorial infarcts (larger than 1 cm in greatest dimension) in the region supplied by a large basal artery), lacunar infarcts (smaller than 1 cm in greatest dimension but grossly
visible) and microinfarcts (not grossly visible but seen only on microscopic sections).[35, 38, 42] The last appear to have various etiologies, including emboli, arteriosclerosis, and CAA.[43] Other forms of ischemic injury occur, such as diffuse white matter injury; however, these are more difficult to judge objectively than infarcts.

Hemorrhages in the brain also are usually classified as grossly visible hemorrhages or microhemorrhages, and both are strongly associated with CAA and arteriolosclerosis. It may be impossible to distinguish microinfarcts from remote microhemorrhages, and for this reason, these lesions have been called microvascular lesions (MVL).

**Hippocampal sclerosis**

Our understanding of HS and its relationship to AD, frontotemporal lobar degeneration (FTLD, vide infra), and VBI is evolving rapidly (Text Box 4). HS is defined by pyramidal cell loss and gliosis in CA1 and subiculum of the hippocampal formation that is out of proportion to AD-type pathology in the same structures.[44] HS and TDP-43 immunoreactive inclusions are found in 30% or more of cases with AD neuropathologic change,[45, 46] and TDP-43 immunoreactive inclusions are present in as many as 90% of cases of HS.[45, 47, 48] Large autopsy series have shown that HS is correlated with impaired cognition although this relationship is complex and variable.[16, 49] HS in the context of VBI or epilepsy may lack aberrant TDP-43 inclusions.[49, 50]

**Other Diseases in the Differential Diagnosis of Dementia**

AD neuropathologic change should be assessed in all cases of dementia. There are many other neurodegenerative disorders that can cause dementia in addition to those
discussed so far, and any may be co-morbid with AD neuropathologic change, especially in the elderly. Although providing specific protocols for the diagnosis of all possible co-morbidities is beyond the scope of this paper, we highlight two important examples: “tauopathies” and CJD.

The neuropathologic evaluation of FTLD and its subtypes is the subject of another recent consensus conference. For FTLD-TDP and FTLD-FUS, IHC for ubiquitin, alphainternexin, TDP-43 and FUS can assist.[51-53] For FTLD-tau, a careful determination of the morphologic changes and distribution of the abnormal tau and neuron loss are important in the differential diagnosis. IHC for 3R and 4R tau may be useful in some cases, while biochemical characterization of tau abnormalities, e.g., Western blot, remains a research adjunct to neuropathologic diagnosis.[51-53] For some tauopathies, such as tangle-predominant senile dementia (TPSD), chronic traumatic encephalopathy (CTE), dementia pugilistica (DP), or diffuse neurofibrillary tangles with calcification (DNTC), the distribution and density of tangles and the paucity of neocortical plaques must be carefully observed, since TPSD, CTE, DP, and DNTC tangles, like AD-type NFT, also contain both 3R and 4R tau.[51-56] At this point, making the diagnosis of either concomitant FTLD-UPS or FTLD-ni (DLDH) in cases with AD may not be possible.

A note of caution is warranted concerning Braak NFT staging in non-AD tauopathies since neuronal lesions in some these diseases may be undetectable by some histochemical staining methods useful for AD neuropathologic change. Indeed, some cases of FTLD-tau may be Braak NFT stage “None” despite widespread abnormal tau in the neocortex or hippocampus detected by IHC or biochemical methods.

Finally, not only can the neuropathologic changes of prion disease be co-morbid with
AD, but some forms of prion disease can present neuropathologic changes that overlap with AD and need to be distinguished with special stains.[57]

**Recommendation on Biomarkers**

We recommend that genetic risk and biomarkers (chemical and neuroimaging) be used in research settings to complement neuropathologic data for the postmortem diagnosis of AD. We emphasize, however, that no single finding or combination of findings from these modalities currently is known to define better the disease state than neuropathologic examination. We recognize that this is a rapidly advancing field of investigation and that in the future some combination of genetic testing and biomarkers may be used as surrogates for neuropathologic changes or functional decline.

**Comments and Areas for Further Research**

There is broad agreement in numerous clinicopathologic studies that the extent of NFT correlates with severity of dementia, while the extent of senile plaques is less closely tied to the degree of cognitive impairment, perhaps in part due to the heterogeneity of senile plaques, the range of methods for their detection, and varying schemes for their classification. In agreement with the 1997 Criteria, any AD neuropathologic change is viewed as evidence of disease, and is abnormal. Nonetheless, there are multiple aspects of the neuropathologic evaluation of AD, and of their relationship to cognitive changes, that may require refinement, both methodologically and conceptually. We highlight here issues that would benefit from additional study, recognizing that each "consensus" conference both addresses issues as well as raises questions.
A major point of discussion among committee members was the relative value of evaluating all three parameters (A, B, C) of AD neuropathologic change. Since the relative independent value of these three parameters is not currently known, we suggest collecting data on all three parameters and evaluating their independent value in future analyses.

Both quantitative and qualitative aspects of AD neuropathologic change have significance, but current diagnostic methods are not robustly quantitative and/or not systematically qualitative. Evaluating the degree of Aβ and phospho-tau accumulation may rely on estimates of the burden of the lesions in a given region or on a qualitative assessment of their distribution throughout the brain. For example, the widely employed Braak NFT staging protocol evaluates NFT distribution rather than density. Methods for Aβ deposition are less standardized. For example, Thal phases of anatomical distribution of amyloid deposits, CERAD ranking of neuritic plaque density, and image analysis based evaluation of amyloid load are three methods in common use to estimate this facet of AD. Biochemical assays provide a fourth approach that has the advantage of also discriminating soluble forms and specific peptides. It was the opinion of this committee that it is not yet clear if one of these methods is superior to any other. Indeed, this point engendered much discussion, highlighting the need for additional data. Important issues to address when comparing different methods that attempt to assess lesion burden include brain regions investigated, volume of tissue examined, differing sensitivity and specificity among tests, standardization across laboratories and groups of neuropathologists, and ultimately correlation with function.

The idea that Aβ deposition, abnormal tau accumulation, and neuritic plaques reflect the molecular pathology of AD is an oversimplification. The view that they are but a byproduct of a hidden mechanism cannot be ruled out from current data; for example, oligomeric Aβ and nonfibrillar tau have been considered key players in the cascade of lesions. New ways of evaluating additional molecular species and of determining their relation to the...
clinical and neuropathologic data need to be developed. Moreover, neuropathologists should continue to pursue the study of the molecular content of the microscopic changes by established methods and new approaches in both experimental animals and in human brain.

In addition to the autosomal dominant PSEN1, PSEN2 and APP gene mutations or APOE ε4 allele, which clearly have a major impact on degree of both plaques and CAA in AD, numerous other genetic variations and environmental risk factors have recently been described; the extent to which these impact the neuropathologic changes of AD remains largely unknown.

As new treatments are being evaluated, interpretation of neuropathologic assessments may need to be adapted to the changes that therapeutics may induce.

The three parameters of AD neuropathologic change need to be investigated in relationship to clinical outcomes and laboratory testing, including biofluid biomarkers and neuroimaging.

Current consensus pathologic criteria for dementia with LB (DLB) utilize the 1997 Criteria for AD and a method for assessing the severity and distribution of LB (i.e., brainstem-predominant, limbic, and diffuse neocortical types),[23] and refinements have been proposed. The revisions in criteria proposed here for the neuropathologic assessment of AD need to be assessed with respect to their impact on DLB classification using established well-characterized cohorts. Ischemic injury to gray and white matter is much more complex than formation of infarcts, hemorrhages, or MVL; however, current pathologists’ tools are limited in assessing this type of damage and need to be expanded.

Summary
The goals of the consensus Committee were to update the 1997 Criteria so as to broaden the criteria to include all individuals, regardless of clinical history of cognitive impairments (which had been required in 1997), emphasizing the nature of the continuum of neuropathologic changes that underlie AD and ultimately are associated with dementia. The Committee goals also included a renewed emphasis on the common role of co-morbid diseases in the neuropathologic evaluation, to define better the role of neuropathologic changes of AD in individuals with intermediate levels of pathologic changes, and to consider the role of new genetic and biomarker data in the neuropathologic evaluation of AD changes. A consensus was reached that criteria should be data based, focused primarily on neuropathologic rather than clinical criteria, and to the extent possible reflect current molecular understanding of disease mechanisms. The Committee recommends an ABC staging protocol for the neuropathologic changes of AD, based on three morphologic characteristics of the disease. A change in nomenclature to allow reporting of AD neuropathologic changes in individuals regardless of cognitive status is recommended. Finally, several issues that require further investigation are highlighted to guide further clinicopathologic studies.

Text Box 1. AD Neuropathologic Change

**Method.** Recommended brain regions for evaluation are in **Table 2.** Preferred method for Aβ plaques is IHC for Aβ, and for NFT is IHC for tau or phospho-tau (other acceptable methods are Thioflavin S or sensitive silver histochemical stains). Preferred method for neurotic plaques is Thioflavin S or modified Bielschowsky as recommended by the CERAD protocol.[13]
Note that IHC probes for neuritic processes within senile plaques, such as amyloid precursor protein, ubiquitin, neurofilament or phospho-tau, will identify specific, and partially overlapping, subtypes of dystrophic neurites; the significance of these specific subtypes of neuritic plaques has not been established.

**Classification.** AD Neuropathologic change should be ranked along three parameters (Table 3) to obtain an “ABC score”:

A. Aβ plaques (modified from Thal, et al.[14]):

A0: no Aβ or amyloid plaques

A1: neocortical Aβ or amyloid plaques in sections of frontal, temporal, or parietal lobes

A2: plus hippocampal Aβ or amyloid plaques

A3: plus neostriatal Aβ or amyloid plaques. Consider determining all five Thal phases and record these results.

B. NFT (modified from Braak and Braak[8])

B0: no NFT

B1: Braak stage I or II

B2: Braak stage III or IV

B3: Braak stage V or VI
C. Neuritic plaques (modified from CERAD[13])

C0: no NP
C1: CERAD score sparse
C2: CERAD score moderate
C3: CERAD score frequent

Note that while CAA is not considered in these rankings it should be reported (e.g., the Vonsattel, et al., staging system for CAA [58]).

**Reporting.** For all cases, regardless of clinical history, reporting should follow the format of these examples:

“Alzheimer Disease Neuropathologic Changes: A1, B0, C0” or

“Alzheimer Disease Neuropathologic Changes: A3, B3, C3”

The ABC scores are transformed into one of four tiered summary descriptors of the level of AD neuropathologic change according to **Table 3**.

It is important to recognize that pathologic evaluation can be applied to specimens from surgery as well as autopsy; however, regional evaluation will be limited in biopsy specimens. Nevertheless, involvement of the neocortex by NFT indicates B3, while involvement of cerebral cortex by Aβ deposits indicates A1 or possibly a higher score. In
Clinicopathologic correlations should follow these guidelines.

For individuals without cognitive impairment at the time tissue was obtained, it is possible that AD neuropathologic change may predate onset of symptoms by years.[3]

For individuals with cognitive impairment at the time tissue was obtained, “Intermediate” or “High” level (Table 3) of AD neuropathologic change should be considered adequate explanation of cognitive impairment or dementia. When “Low” level of AD neuropathologic change is observed in the setting of cognitive impairment it is likely that other diseases are present. In all cases with cognitive impairment, regardless of the extent of AD neuropathologic change, it is essential to determine the presence or absence as well as extent of other disease(s) that might have contributed to the clinical deficits.

For cases with incomplete clinical history, large clinicopathologic studies indicate that higher levels of AD neuropathologic change typically are correlated with greater likelihood of cognitive impairment. The National Alzheimer Coordinating Center (NACC) experience is outlined in Table 1. These data may help guide interpretation of results from autopsies with insufficient clinical history.

Text Box 2. LBD

Method. Recommended brain regions for evaluation are in Table 2. IHC for α-synuclein is strongly preferred.[59-61] LB may be detected in neurons of medulla, pons and midbrain with
H&E-stained sections; however greater sensitivity can be achieved with IHC, and related abnormalities in α-synuclein will be unapparent by H&E.

**Classification** (modified from McKeith, et al.[23])

- No LBD

- Brainstem-predominant: LB in medulla, pons, or midbrain

- Limbic (Transitional): LB in cingulate or entorhinal cortices usually with brainstem involvement

- Neocortical (Diffuse): LB in frontal, temporal or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala

- Amygdala-Predominant: LB in amygdala with paucity of LB elsewhere

**Reporting.** Reporting should follow the format of these examples:

“Lewy Body Disease, Limbic” or

“Lewy Body Disease, Amygdala-Predominant”

Again, it is important to recognize that these classifications can be applied to specimens from surgery as well as autopsy with the same limitations discussed for AD neuropathologic change.
Clinicopathologic correlations should follow these guidelines.

For individuals without cognitive impairment at the time tissue was obtained, we stress that, although much less common than AD, large autopsies series have observed LBD in individuals without apparent cognitive or motor deficit.[62-64] This may represent preclinical LBD;[65-68] however, proof awaits methods of in vivo testing and longitudinal studies.

For individuals with cognitive impairment at the time tissue was obtained, we recommend that Neocortical LBD be considered adequate explanation of cognitive impairment or dementia; this does not preclude contribution from other diseases. Brainstem-Predominant or Limbic LBD in the setting of cognitive impairment should stimulate consideration of other pathologic processes. Amygdala-Predominant LBD typically occurs in the context of AD neuropathologic change.[18]

For cases with incomplete clinical history, we note that large clinicopathologic studies indicate that “Neocortical” LBD is correlated with greater likelihood of cognitive impairment.[25, 69]

Text Box 3. CVD and VBI

Method. CVD in large vessels should be evaluated by macroscopic examination. Macroscopic examination also will reveal infarcts and hemorrhages. Screening sections for MVL as potential contributors to cognitive impairment are listed in Table 2. IHC, such as for GFAP, may increase sensitivity for detection of MVL; however, this has not been rigorously demonstrated.
Classification. The extent of different types of CVD should be reported according to a standardized approach.[70] All infarcts and hemorrhages observed macroscopically should be documented and include location, size, and age. The location, age, and number of MVL in standard screening sections should be recorded.

Reporting. Reporting should follow the format of these examples:

“Cerebrovascular disease:

Atherosclerosis, non-occlusive, affecting basilar artery, left internal carotid artery and middle cerebral artery”

“Arteriolosclerosis, widespread involvement of hemispheric white matter”

“Vascular brain injury:

Infarct in the territory of the left middle cerebral artery, remote, measuring 3 x 3 x 2 cm”

“Lacunar infarct, right anterior caudate, remote, measuring 0.5 x 0.3 x 0.2 cm”

“Microvascular lesions: 2 remote lesions detected on standard sections (right middle frontal gyrus and right inferior parietal lobule)”

Evaluation of CVD and VBI can be applied to specimens from surgery as well as autopsy.
Clinicopathologic correlations for grossly visible infarcts or hemorrhages should follow classic neuropathologic approaches. Clinical correlations for MVL have been investigated in a few large cohorts. Although there are some differences in approach, the following guidelines have emerged: one MVL identified in standard sections of brain like those proposed in Table 2 is of unclear relationship to cognitive function, while multiple MVL are associated with increased likelihood of cognitive impairment or dementia.

Text Box 4. HS

Method and Classification. Recommended regions for evaluation are in Table 2. HS should be evaluated by H&E-stained sections as described above. If HS is present, further evaluation is indicated, including TDP-43 IHC. If negative for TDP-43 and associated with other evidence to suggest FTLD, consider IHC for ubiquitin or FUS.

Reporting. HS should be reported as present or absent with description of results from IHC.

Clinicopathologic correlations are complicated because HS can occur in several different diseases and may derive from multiple mechanisms. Indeed, HS observed in the setting of VBI, epilepsy, or FTLD have different clinical implications. Relatively isolated HS may occur in up to 30% of very old individuals, and in this context it is associated with TDP-43 immunoreactive inclusions and with cognitive impairment, which may be domain specific.[16, 49]
Table 1. Frequency (proportion and confidence interval) of each CDR sum of boxes score for each Braak NFT stage and CERAD neuritic plaque score combination from the National Alzheimer Coordinating Center Data Set, 2005-2010.

<table>
<thead>
<tr>
<th>Braak stage</th>
<th>Neuritic plaques</th>
<th>CDR Sum of Boxes score</th>
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</thead>
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<tr>
<td></td>
<td>0.0</td>
<td>0.5-3.0</td>
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<tr>
<td>0</td>
<td>None/sparse</td>
<td>6 (.600)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1 (.100)</td>
</tr>
<tr>
<td></td>
<td>Frequent</td>
<td>0 (.000)</td>
</tr>
<tr>
<td>I/II</td>
<td>None/sparse</td>
<td>30 (.612)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>15 (.600)</td>
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<tr>
<td></td>
<td>Frequent</td>
<td>5 (.714)</td>
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<tr>
<td>III/IV</td>
<td>None/sparse</td>
<td>16 (.390)</td>
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<td></td>
<td>Moderate</td>
<td>11 (.208)</td>
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<tr>
<td></td>
<td>Frequent</td>
<td>7 (.715)</td>
</tr>
<tr>
<td>V/VI</td>
<td>None/sparse</td>
<td>1 (.111)</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>1 (.024)</td>
</tr>
<tr>
<td></td>
<td>Frequent</td>
<td>2 (.007)</td>
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<tr>
<td>Column total</td>
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<td>95</td>
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</table>
Table 2. Minimum recommended brain regions to be sampled and regional evaluation.

Each brain region should receive a hematoxylin and eosin (H&E) stain. H&E-stained sections for screening in the evaluation for MVL and HS are designated. Regions for immunohistochemical evaluation of AD neuropathologic change and LBD are listed. Other lesions should be sampled as appropriate.

<table>
<thead>
<tr>
<th>Region</th>
<th>AD</th>
<th></th>
<th></th>
<th>LBD</th>
<th>MVL &amp; HS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
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<tr>
<td>Medulla including DMV</td>
<td></td>
<td></td>
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<tr>
<td>Pons including LC</td>
<td></td>
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<tr>
<td>Midbrain including SN</td>
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<tr>
<td>Cerebellar cortex and dentate n.</td>
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<td></td>
<td></td>
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<tr>
<td>Thalamus and subthalamic n.1</td>
<td></td>
<td></td>
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<tr>
<td>Basal ganglia at level of AC with basal nucleus of Meynert1</td>
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<tr>
<td>Hippocampus and EC1</td>
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<tr>
<td>Cingulate, anterior</td>
<td></td>
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<tr>
<td>Amygdala</td>
<td></td>
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<tr>
<td>Middle frontal gyrus1</td>
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<tr>
<td>Superior &amp; middle temporal gyr1</td>
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<tr>
<td>Inferior parietal lobule1</td>
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<tr>
<td>Occipital cortex1</td>
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</tr>
</tbody>
</table>

1 Consider taking bilateral sections if both cerebral hemispheres are available

2 Screen leptomeningeal and parenchymal vessels for CAA

3 Screen for LB with H&E in brainstem and IHC in amygdala. If positive, then expand IHC for LB in brainstem, limbic, and neocortical regions.

Abbreviations: DMV=dorsal motor nucleus of the vagus, LC=locus ceruleus, SN=substantia nigra, AC=anterior commissure, EC=entorhinal cortex
Table 3. Level of AD Neuropathologic Change

<table>
<thead>
<tr>
<th>A AE deposits (Thal Phases)(^7)</th>
<th>C Neuritic Plaque Score (CERAD)(^3)</th>
<th>B NFT Stage (Braak)(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFT stage should be determined by the method of Braak and Braak.[8] Note that Braak staging should be attempted in all cases regardless of the presence of coexisting diseases.</td>
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<tr>
<td>1. 2. or 3</td>
<td>0 (none)</td>
<td>1 (I/II)</td>
</tr>
<tr>
<td>1. 2. or 3</td>
<td>1 (sparse)</td>
<td>Low</td>
</tr>
<tr>
<td>1. 2. or 3</td>
<td>2 or 3 (moderate or)</td>
<td>Low(^6)</td>
</tr>
</tbody>
</table>

2. Aβ deposits should be determined by the method of Thal, et al.[14]

3. Neuritic plaque score should be determined by the method of CERAD.[13]

4. Medial temporal lobe NFT in the absence of significant Aβ or neuritic plaque accumulation. This occurs in older people and may be seen in individuals without cognitive impairment, mild impairment, or those with cognitive impairment from causes other than AD. Consider other diseases when clinically indicated.[71]

5. Widespread NFT with some Aβ accumulation but limited neuritic plaques. These two categories are relatively infrequent and other diseases, particularly a tauopathy, should be considered. Such cases may not fit easily into a specific Braak stage, which is intended for categorization of AD-type NFT. AD neuropathologic change should be categorized as “Low” for Thal phases 1 and 2 and “Intermediate” for Thal phase 3.
6. Moderate or Frequent NPs with low Braak stage. Consider contribution of co-morbidities like 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.

References

TEXT REQUIRES ADDITIONAL REFERENCES


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clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons


in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity


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assessments of Alzheimer disease-related lesions: a study of the BrainNet Europe Consortium. J


Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles


Brains with medial temporal lobe neurofibrillary tangles but no neuritic amyloid plaques are a diagnostic dilemma