Emerging Concepts in Alzheimer's Disease

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Abstract

Alzheimer's disease/senile dementia of the Alzheimer type (AD/SDAT) is the most common neuropathologic substrate of dementia. It is characterized by synapse loss (predominantly within neocortex) as well as deposition of certain distinctive lesions (the result of protein misfolding) throughout the brain. The latter include senile plaques, composed mainly of an amyloid (Aβ) core and a neuritic component; neurofibrillary tangles, composed predominantly of hyperphosphorylated tau; and cerebral amyloid angiopathy, a microangiopathy affecting both cerebral cortical capillaries and arterioles and resulting from Aβ deposition within their walls or (in the case of capillaries) immediately adjacent brain parenchyma. In this article, I discuss the hypothesized role these lesions play in causing cerebral dysfunction, as well as CSF and neuroimaging biomarkers (for dementia) that are especially relevant as immunotherapeutic approaches are being developed to remove Aβ from the brain parenchyma. In addition, I address the role of neuropathology in characterizing the sequelae of new AD/SDAT therapies and helping to validate CSF and neuroimaging biomarkers of disease. Comorbidity of AD/SDAT and various types of cerebrovascular disease is a major theme in dementia research, especially as cognitive impairment develops in the oldest old, who are especially vulnerable to ischemic and hemorrhagic brain lesions.

INTRODUCTION

AD: Alzheimer's disease

SDAT: senile dementia of Alzheimer type

Aβ: amyloid β

MRI: magnetic resonance imaging

PET: positron emission tomography

Dementia is a clinically defined entity or syndrome; though it has many causes, the most common etiology of dementia is Alzheimer's disease (1–5). Alzheimer's disease/senile dementia of the Alzheimer type (AD/SDAT) is the most common neurodegenerative disease worldwide; it afflicts over 5 million Americans, and given that aging is the major risk factor for developing it, absent a cure or definitive prevention strategy its incidence will continue to increase in the coming years as medical advances lead to increasing life span (6). One estimate based on US Census Bureau data is that, between 2000 and 2020, the number of individuals living to 100 years or more will increase by over 200% and the number of individuals surviving to 90–95 years will double (7). From an epidemiologic perspective, the Baltimore Longitudinal Study of Aging (1985–1998) found that the incidence rates of AD increased with age from an estimated 0.08% per year in the 60–65-year age group to an annual estimated incidence of 6.48% in the ≥85-year age group (8). This study furthermore estimated that the doubling time of incidence rates was approximately 4.4 years, with a similar time interval for conversion from mild cognitive impairment (MCI) to AD.

Autopsy of a subject with this clinical diagnosis is used to confirm the clinical assessment and to assess any comorbidities that may have contributed to cognitive impairment (2, 5, 9, 10). The neuropathologic diagnosis of AD in a given subject is made by evaluating the location, distribution, and abundance of characteristic brain lesions. Attempts to standardize the neuropathologic diagnosis of AD and comorbidities have evolved rapidly beginning in the 1980s and continuing to the present (see below). Neurodegenerative diseases are traditionally considered as disorders in which progressive loss of neurons and synapses occurs in distinct anatomical loci, resulting in different phenotypes. A defining biochemical theme in the study of most neurodegenerative disorders is that of protein misfolding, the molecular nature of which is explored in depth (and from various perspectives) in a recent book (11). In this review I discuss the practical aspects of gross, microscopic, and immunohistochemical features of AD/SDAT; how the neuropathologist optimally approaches evaluation of an autopsy or biopsy brain specimen from a clinically affected individual; and how selected biochemical, molecular, and genetic findings—of which there has been an explosion in recent years—inform and often refine the clinicopathologic evaluation of brains originating from cognitively impaired individuals or from those lacking neurologic impairment.

Sensitive neuroimaging techniques are emerging and being refined that are capable of both quantifying AD-associated cerebral atrophy and detecting amyloid β (Aβ) peptide, phosphorylated tau (phospho-tau), or other β-pleated sheet proteins in the brain while patients are alive, even when completely asymptomatic or at early stages of neurodegeneration (12–15; see also the discussion of biomarkers below). Yet detailed autopsy—or (less commonly) biopsy neuropathologic examination of the brain—continues to be considered the gold standard for the diagnosis of AD and non-AD dementias (1, 2, 5, 16). Careful clinicopathologic correlation, that is, attempting to explain complex neurologic symptoms in an often end-stage central nervous system (CNS) by autopsy examination of the brain, was a central pillar of dementia research through the 1970s. At the end of the 1970s, structural imaging emerged and began to provide valuable information about the CNS in vivo, though CT scanning was most valuable for assessing mass lesions in the brain but was less effective at detecting cortical atrophy. Magnetic resonance imaging (MRI) and positron emission tomography (PET), the latter performed with highly specialized ligands, have provided valuable information in the study of neurodegenerative disorders (see below). It bears reemphasis that the starting material for important biochemical and molecular studies that have linked abnormally folded proteins to neurodegeneration was rapidly harvested (autopsy) brain tissue, the neuropathologic features of which were subsequently often correlated with the relevant neurochemical data (1, 4, 17, 18).

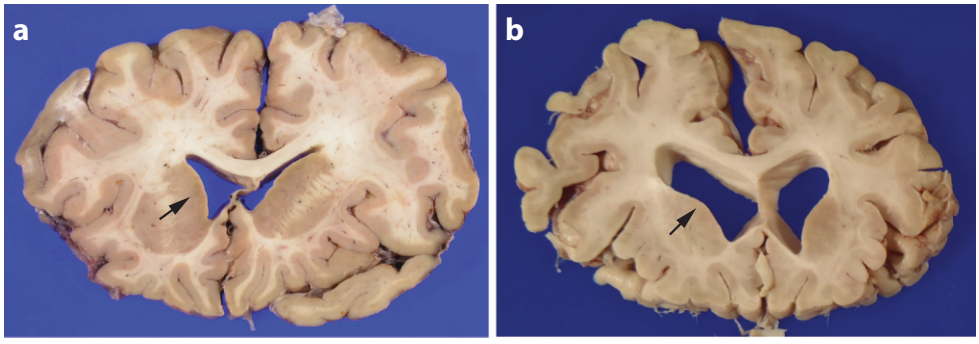

Figure 1

Coronal slices of (fixed) brain from two different patients, one without dementia (panel *a*) and one with (panel *b*); slices are at comparable coronal levels (near the head of the caudate nucleus). Arrows indicate a relatively normal lateral ventricle in the control case (panel *a*) versus a markedly enlarged lateral ventricle in the Alzheimer's disease subject (panel *b*). Cortical thinning is less prominent.

The main neuropathologic feature of the AD brain on gross inspection is cortical atrophy, which is usually diffuse and fairly symmetrical throughout the cerebral hemispheres rather than being accentuated in certain lobes or on one side of the brain [as in the case of some frontotemporal lobar degenerations (FTLDs)] (1, 2, 5, 19–21). Fresh brain weight is usually below the normal range for an adult (1,200–1,400 g), though not necessarily so—it may be entirely normal and even, rarely, above the upper range of normal (2, 5, 22). When the fixed brain is sliced, the cortical atrophy (manifest as thinning of the cortical ribbon) is usually accompanied by enlargement of the ventricular system, or hydrocephalus ex vacuo, and sometimes by shrinkage, atrophy, and/or pallor of the subcortical white matter (**Figure 1**). Precise etiology of the white matter change is not known—it may in part represent downstream (anterograde, Wallerian) degeneration secondary to cortical atrophy with neuron loss or may be the manifestation of the leukoencephalopathy that is an integral component of AD/SDAT (23). If the brain of a demented patient shows hydrocephalus out of proportion to the degree of cerebral cortical atrophy, the possible diagnosis of normal pressure hydrocephalus must be considered, though microscopic lesions of AD should still be sought in such a brain. Most experienced neuropathologists (myself included) are impressed by the variability in brain weights, cerebral cortical atrophy, and hydrocephalus ex vacuo among individuals who eventually have the diagnosis of AD confirmed by light microscopy (22).

ALZHEIMER'S DISEASE: MICROSCOPIC LESIONS

As Nelson et al. have emphasized (7, 24), AD/SDAT is defined by the presence of three elements—one clinical and the other two neuropathologic:

1. clinical dementia (cognitive impairment, with a memory component, that impacts daily living skills);
2. substantial numbers of neurofibrillary tangles (NFTs) within neocortex; and
3. significant numbers of senile (neuritic) plaques within the brain.

(The issue of whether AD can be diagnosed in the brain of someone who has not experienced significant well-documented neurocognitive abnormalities is addressed below.) The microscopic lesions that are known to accumulate in the CNS (mainly cerebral cortex, but often also deep central gray matter, cerebellum, and brainstem) of individuals with AD can, when prominent and numerous, be identified on routine sections of the brain; however, they are much more easily demonstrated

NFT: neurofibrillary tangle

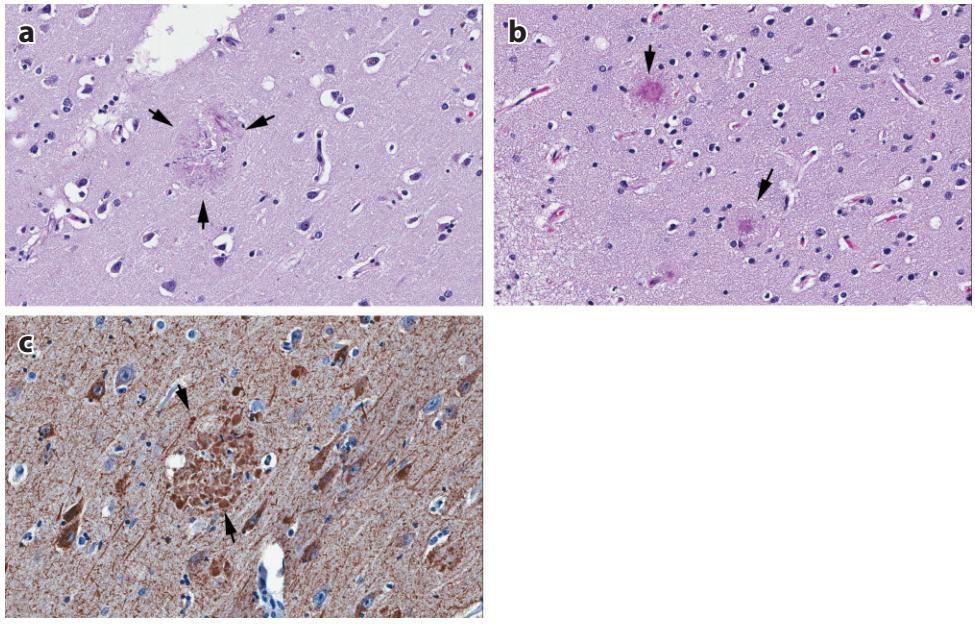

Figure 2

Senile plaques (SPs). (*a*, *b*) Hematoxylin and eosin (H&E)-stained sections show a neuritic SP without a prominent amyloid core (panel *a*, *arrows*) and two SPs with prominent amyloid cores (panel *b*, *arrows*). (*c*) Section immunostained with phospho-tau shows an SP with a prominent tau-immunoreactive neuritic component (*arrows*). Note tau-immunoreactive neurofibrillary tangles (or pretangles) in the surrounding cortex.

by the use of special stains, especially silver impregnation techniques (modified Bielschowsky, Bodian, Campbell–Switzer, and Gallyas techniques) (1, 2, 5, 9, 25–27) and immunohistochemical methods incorporating primary antibodies to proteins deposited within afflicted brain. Though many of the older silver stains have an intrinsic elegance, they are sometimes capricious and result in annoying tissue section artifacts that tend to limit their usefulness.

SENILE PLAQUES

Neuritic senile plaques (SPs) appear, on routine hematoxylin & eosin (H&E)-stained sections, as an irregularity or coarsening of the neuropil (the neuritic component of the SP) centered on the core of the SP, an amorphous eosinophilic globule of amyloid (**Figure 2**). Masters et al. (28) showed that SP cores are composed of Aβ. The dynamic relationship between the amyloid core of a mature SP and its neuritic corona (both seen on silver stains) has been debated for years, but such mature neuritic SPs are thought to be more reflective of cortical brain injury than are the more diffuse SPs lacking a neuritic component (1, 2). Diffuse SPs (seen using silver stains or Aβ immunohistochemistry) are a common finding in the brains of elderly cognitively normal subjects (7, 24). Outstanding reviews on the hypothesized cellular and molecular pathogenesis of SPs are available (e.g., 29). The precise role of astrocytes and microglia in SP genesis [through the generation of Aβ from amyloid precursor protein (APP)] or Aβ clearance is controversial. Although neuritic SPs have a neuronal component, insofar as the neurites encircling the amyloid core represent processes emerging from (presumably) damaged nerve cell bodies, they are located within the neuropil. Although SPs are often found in elderly individuals without AD, their density among

SP: senile plaque

APP: amyloid precursor protein

such subjects is far less than that in patients with AD (30); most neuropathologists have, however, encountered autopsy brains from cognitively intact elderly individuals that contain abundant neuritic SPs. Anecdotal reports have described all neuropathologic features of AD in cognitively normal elderly—indeed, even in rare individuals who had been examined neurologically shortly before death and judged to be cognitively intact (7, 31). Dense core SPs may be identified with Thioflavin S stains (32). One study has shown that SPs vary in size among both AD patients and normal elderly individuals; larger size distributions correlated with an earlier age of disease onset. SPs did not, however, appear to increase significantly in size over the clinical course of the disease (32). Thal et al. (33) have proposed five neuroanatomical phases in the deposition of Aβ within the CNS: deposition in the neocortex, allocortex, diencephalic-striatal-basal forebrain, brainstem, and cerebellum, with the final stage representing the most advanced Aβ pathology.

NEUROFIBRILLARY TANGLES

NFTs are dense intraneuronal cytoplasmic basophilic aggregates of filaments that include, on ultrastructural examination, characteristic paired helical filaments (PHFs; also described as bifilar helices) (1, 2, 5, 34). PHFs were first identified by Kidd (35) in brain biopsies; the filaments have a diameter of 10–15 nm and a periodicity of 160 nm. NFTs are almost invariably accompanied by neuropil threads in the adjacent brain parenchyma—these threads are interpreted as constituting the processes of NFT-bearing neurons (36, 37). Tangles tend to accommodate to the shape and morphology of a given neuron; when present in the pyramidal cell layer of the hippocampus, they appear as elongated parallel skeins of fibrillar intracytoplasmic basophilic material, but when seen in globose or oval neurons, they take on a more disorganized or globular configuration. A provocative study of more than 2,330 autopsy brains over an age range of 1–100 years (27) concluded that abnormal intraneuronal tau deposits may occur as early as the second or third decade of life (at least within the transentorhinal cortex) and that brainstem tau deposition (e.g., in the locus ceruleus) may even antedate transentorhinal changes.

NFTs (**Figure 3**) occur in the CNS of patients with many non-AD neurodegenerative conditions, including subacute sclerosing panencephalitis, postencephalitic parkinsonism, dementia pugilistica, and the parkinsonian–amyotrophic lateral sclerosis–dementia complex of Guam (38). NFT-like neuronal cytoplasmic lesions are commonly encountered within the dysmorphic and enlarged neuronal cell bodies of infants and children with epilepsy-causing cortical dysplasia or

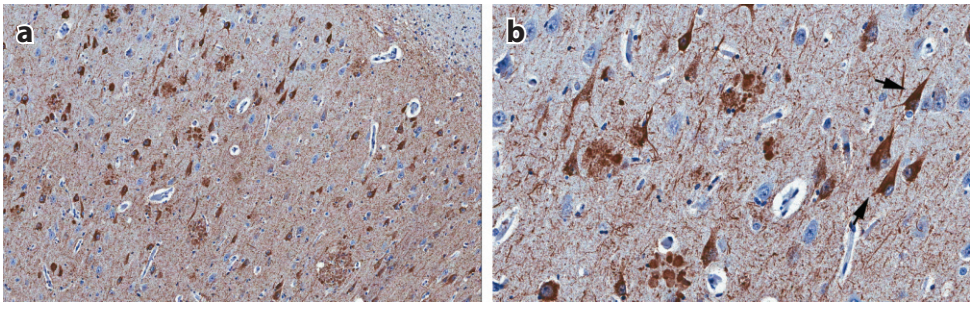

Figure 3

Neurofibrillary tangles (NFTs). Sections were immunostained with primary antibody to phospho-tau and visualized at low (panel *a*) and high (panel *b*) magnification. Note that most neurons in the field show tau immunoreactivity. Arrows in panel *b* highlight immunoreactive neurons with classic flame-shaped NFT morphology. Threadlike immunoreactivity (panel *b*) represents neuropil threads.

cortical tubers of tuberous sclerosis complex (39). The NFTs in this pediatric population show disorganized clumps of neurofilaments and neurotubules adjacent to cytoplasmic debris (40). The interesting question of how phospho-tau may mediate synaptic dysfunction has been addressed by several laboratories. Tai et al. (41) have shown that in AD, tau becomes hyperphosphorylated and misfolded at both presynaptic and postsynaptic nerve terminals; furthermore, accumulation of hyperphosphorylated tau oligomers (at human synaptic terminals) is associated with increased levels of ubiquitinated substrates and proteasome components, suggesting dysfunction of the ubiquitin-proteasome system (41).

CAA: cerebral amyloid angiopathy

SMC: smooth muscle cell

CEREBRAL AMYLOID ANGIOPATHY

An often underappreciated or overlooked lesion of AD is cerebral amyloid angiopathy (CAA), sometimes described as congophilic angiopathy (42–45). CAA was the microscopic AD lesion from which Glenner & Wong (46) isolated the protein we now know as Aβ. CAA is less prominently featured (than SPs and NFTs) when considering AD neuropathologic lesions in part because it is variable in severity among AD patients, though when sought diligently it is identified in an estimated 85–95% of AD brains (42, 43). CAA results from a process whereby the media of parenchymal arterioles, normally composed of smooth muscle cells (SMCs), undergoes progressive loss of these SMCs and simultaneous accumulation of an eosinophilic hyaline material that has the staining properties of amyloid, that is, positivity for thioflavin S or T and congophilia, with the characteristic yellow-green birefringence (of the congophilic material) when a brain section is viewed under polarized light (34, 47). By ultrastructural examination, the amyloid has a fibrillar appearance but not the PHF morphology of NFTs. The fibrils are 7–10 nm in diameter and may be identified in close proximity to SMC debris within arteriolar media (34). It is unclear whether the amyloid fibrils are toxic to SMCs; however, tissue culture experiments suggest that mutant Aβ peptides are selectively injurious to cerebral microvessel-derived SMCs (48). Hypoxia and reoxygenation of cultured brain microvessel-derived SMCs are known to mediate APP production in these cells (49). CAA may also involve cortical parenchymal capillaries and venules; at least a subset of SPs in the neocortex may be intimately associated with capillary walls and may originate from these vessels (1, 50, 51). It has been suggested that in AD, capillary Aβ should be distinguished from pericapillary amyloid, the former being strongly associated with the ApoE ε4 isoform as a risk factor. Pericapillary Aβ may represent initial Aβ accumulation along the glia limitans, which is integral to perivascular drainage of ApoE and Aβ; by contrast, capillary CAA could be explained by a limited transendothelial clearance of ApoE ε4–Aβ complexes (52). A shift in microglial Aβ binding in AD is associated with severe CAA (53).

When CAA is noted in the subarachnoid space, the amyloid deposits are usually adventitial rather than medial in the walls of larger affected arteries and have a chunky or multifocal appearance, suggesting they may have resulted from aggregates of Aβ in the CSF that came to lodge in arterial adventitia. CAA almost never involves the subcortical white matter, basal ganglia, brainstem, or spinal cord, but (in severe and especially familial autosomal dominant cases of AD) may involve the cerebellar molecular layer and meninges (see below) (42, 44, 47). The pathogenesis of CAA is incompletely understood and highly complex. It probably involves overproduction of Aβ (from APP) in or near the vessel wall, together with abnormal and/or impaired clearance of Aβ, probably along perivascular adventitial pathways of brain microvessels (54). Transgenic animals can be engineered to develop varying degrees of CAA, ranging from minimal to extremely severe (55).

CAA (**Figure 4**) is a significant cause of spontaneous nontraumatic intracerebral hemorrhage within the brains of elderly individuals—including many who do not manifest a dementing illness

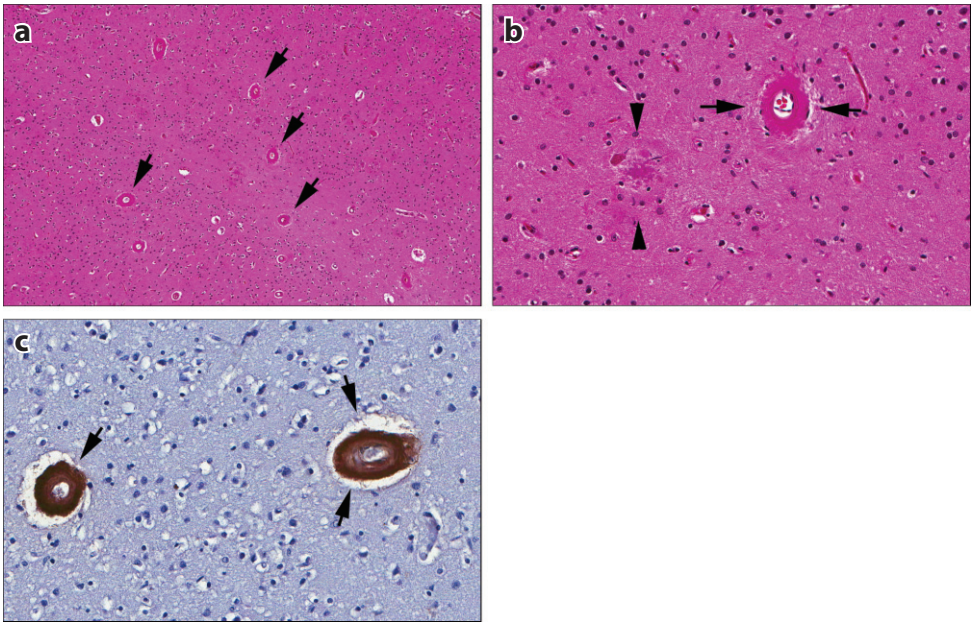

Figure 4

Cerebral amyloid angiopathy (CAA; also known as congophilic angiopathy). (*a*,*b*) Micrographs from hematoxylin and eosin (H&E)-stained sections. Panel *a* shows numerous arterioles affected by CAA (*arrows*). Panel *b* shows a magnified view of an arteriole (*arrows*) in which the media (normally composed of smooth muscle cells) has been replaced by eosinophilic, slightly refractile material, with resultant thickening of the arteriolar wall. Arrowheads indicate a nearby senile plaque. (*c*) Section immunostained with anti-Aβ shows two arterioles with thickened walls (*arrows*), in which media is strongly immunoreactive for Aβ. Note the negligible parenchymal Aβ immunoreactivity.

or cognitive impairment at the time of their stroke; a subset of such individuals have predominantly severe CAA (with a small burden of NFTs and SPs) as their neuropathologic finding (42, 44, 47). Intraparenchymal hematomas that result from CAA are usually lobar. In some patients, multiple hematomas caused by CAA occur over months or years, with progressive neurologic decline. These substantial, invariably symptomatic, and sometimes fatal hemorrhages occur in a relatively small proportion of those with AD and CAA. CAA-related microbleeds [brain microbleeds (BMBs) detectable on high-resolution MRI scans] are now accepted as a reliable biomarker for the presence of CAA (56). The large numbers of BMBs noted by MRI are rarely, however, seen in autopsy brain specimens—a disconnect that is often the subject of spirited debate at meetings involving neuropathologists and neuroradiologists. Severe CAA has also been associated with the occurrence of cerebral microinfarcts, lesions that may worsen cognitive impairment in a patient afflicted by AD or may by themselves produce progressive neuropsychological impairment (57, 58). Some of the microfoci of encephalomalacia identified as microinfarcts at necropsy may actually be the residua of BMBs in which the blood has been resorbed. Rarely, severe CAA is associated with a prominent and rapidly progressive angiitis, sometimes described as Aβ-related angiitis (ABRA), which may have a significant granulomatous component (59). We have encountered a case in which an elderly woman presented with fatal cerebral edema, found at autopsy to be caused by ABRA (**Figure 5**). Is there otherwise a distinctive CAA phenotype? Arvanitakis et al. (60) have suggested that severe CAA is associated with impaired performance in perceptual speed tasks.

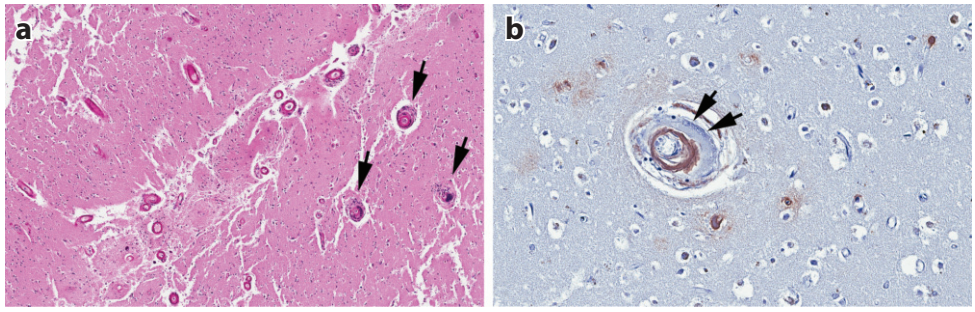

Figure 5

Aβ-related angiitis. Sections are from autopsy brain of a woman who had experienced rapidly progressive, fatal cerebral edema. (*a*) Low-magnification micrograph from a hematoxylin and eosin (H&E)-stained section shows numerous arterioles involved by cerebral amyloid angiopathy, many with surrounding inflammatory cells (*arrows*), including multinucleated giant cells. (*b*) Micrograph from a section immunostained with Aβ, showing prominent medial immunoreactivity; arrows indicate a large multinucleated (foreign body) giant cell encircling the Aβ.

OTHER LESIONS

Granulovacuolar degeneration (GVD, of Simchowicz) describes an abnormality in which the neuronal cytoplasm of hippocampal pyramidal cells is replaced by vacuoles containing small basophilic granules; these may represent an abnormality of neuronal autophagy. Hippocampi showing prominent GVD (**Figure 6**) also often show eosinophilic hyaline rodlike structures—rodlike bodies of Hirano—in the neuropil. GVD and Hirano bodies have been the subject of limited study and are thought to contribute minimally to AD pathogenesis and progression. Nevertheless, neurons showing GVD and Hirano bodies are a frequent finding in AD hippocampi. Ball (61, 62) has characterized the topographic distribution of both GVD and NFT neuronal change along the anteroposterior length of the hippocampus as well as within pyramidal cell layer subfields. Spongy change and reactive gliosis of varying severity are often noted in the superficial cortex (layers I–II) of AD brain; their etiology and significance are not known, but these changes need to be distinguished from the pancortical spongy change characteristic of transmissible spongiform encephalopathies (1, 2, 5).

One of the most important findings in AD brain is loss of synapses and synaptic proteins; this loss can be demonstrated biochemically or by immunohistochemistry using quantitative

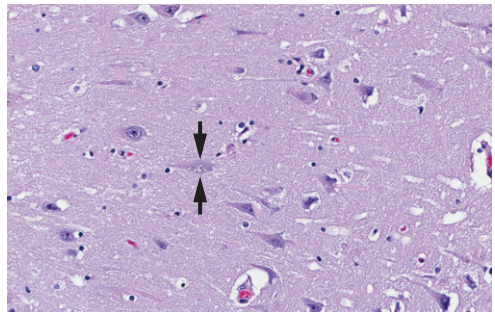

Figure 6

Granulovacuolar degeneration (*arrows*) in a hippocampal pyramidal neuron from an Alzheimer's disease patient: hematoxylin and eosin (H&E)-stained section.

immunohistochemistry or a Western blot or ELISA assay (63). It was first shown dramatically in affected cortex when brain sections were immunostained with antibodies against synaptophysin (64). Quantification and subsequent interpretation of the immunohistochemical signal in such cases must be done by meticulous comparison to brain from a cognitively normal control, because the loss of synaptophysin protein may be subtle on a naked-eye inspection of the tissue section. When synaptic proteins (synaptophysin, synaptotagmin, and rab3a) were compared (by Western blot) among subjects with early- and late-onset AD and vascular dementia, the most profound loss of all synaptic proteins was noted in the early-onset AD subjects; vascular dementia brains showed minimal abnormalities (65). Soluble oligomers of Aβ protein impair synaptic plasticity and behavior, studied (respectively) by assessing long-term potentiation in hippocampal slice and rat experiments (66–68). An inverse relationship has also been noted between APP production (in transgenic mice) and evidence of synaptic plasticity (69, 70).

AD patients (and thus their brains) may also show evidence of comorbidity, not surprising given the many age-related diseases (e.g., cerebrovascular disease, neoplasms, infections) that may impact the aging brain (71). Coexistent Parkinson's disease changes and evidence of infarcts or hemorrhage have been seen, respectively, in as many as one-fifth and one-fourth of AD brains (72). The role of cerebrovascular disease (CVD) in contributing to cognitive impairment is described in greater detail below (73, 74).

IMMUNOHISTOCHEMICAL FEATURES

Aβ protein is the major constituent of SPs (especially their cores) and CAA. The amyloid (cascade) hypothesis (more recently reworked as the amyloid oligomer hypothesis) remains a widely accepted concept of AD pathogenesis; it asserts that Aβ protein deposition within the CNS is the primary cause of AD and an early critical event that promotes downstream features of the disease, such as NFT formation and synaptic injury and loss, leading to progressive dementia (1, 75, 76). It is not firmly established, however, whether aggregated fibrillar Aβ or soluble oligomers of the protein impair normal brain physiology. The immunohistochemical study of AD amyloid brain lesions became feasible soon after the partial peptide sequence of Aβ was first published (1, 2, 46); antibodies to synthetic peptides representing portions of the molecule were rapidly developed (77, 78). Numerous commercially available antibodies to Aβ (various amino acid lengths), tau, ubiquitin, α-synuclein (to detect Lewy bodies) and TDP-43 are currently available to facilitate accurate immunohistochemical characterization of a given autopsy brain specimen originating from a patient with dementia. SPs are more prominently immunoreactive for the Aβ peptide spanning amino acids 1 to 42 ($A\beta_{1-42}$), whereas CAA is more effectively immunolabeled with antibodies to $A\beta_{1-40}$ (**Figures 4**, **7**, and **8**). Diffuse SPs are effectively shown by anti-Aβ antibodies, as are the amyloid cores of mature SPs. Brain specimens with abundant SPs also often show subpial accumulations of Aβ-immunoreactive material. The neuritic halos or coronas of mature SPs, NFTs, and neuropil threads are prominently immunolabeled with antibodies to phospho-tau and less prominently with anti-Aβ (**Figures 7** and **8**). In cases of severe CAA, gamma trace may also be found in affected vessel walls, and a heavily infiltrated arteriole may be surrounded by tau-immunoreactive neuritis or a halo of perivascular Aβ immunoreactivity (78).

STAGING ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGE

All AD lesions described above may be encountered in the CNS of cognitively normal elderly individuals. It is therefore useful to quantify (or semiquantify) these abnormalities and assess their topographic distribution. Correlations between lesion load, severity of neuropathologic findings,

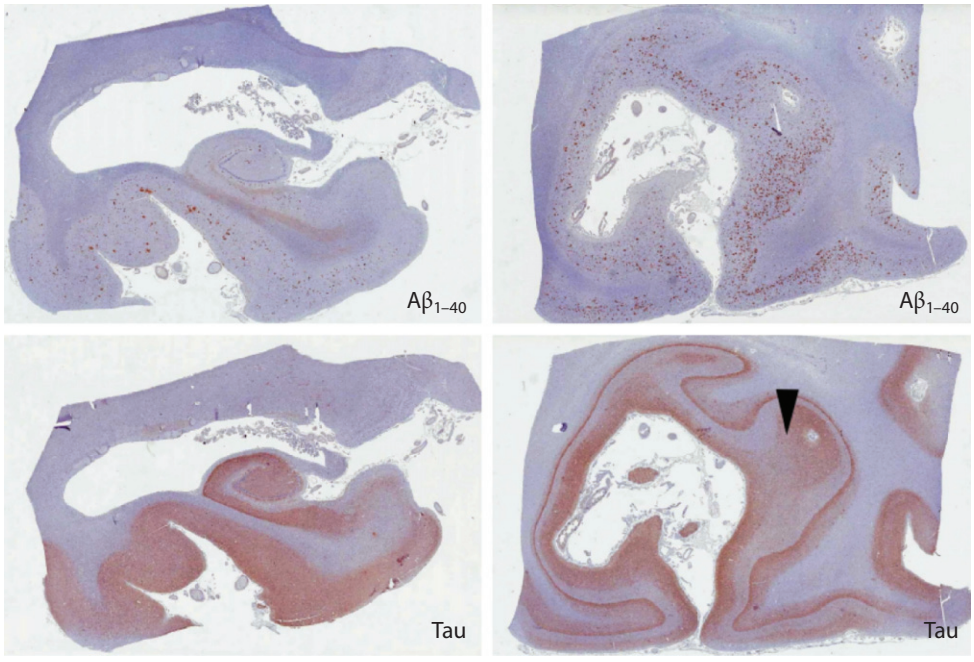

Figure 7

Whole-mount parallel sections of hippocampus (*left panels*) and neocortex (*right panels*) immunostained with primary antibodies as indicated in each panel. Note dense accumulations of Aβ (*top panels*, especially in neocortex) and phospho-tau (*bottom panels*), with sparing of subcortical white matter.

and antemortem neuropsychological testing in a given patient are important, to the extent they are feasible. The neuropathologist usually examines the brain of an end-stage subject, yet that individual may have experienced her/his maximal neurologic deficit months or years prior to death (1, 79). Correlations between neuropathologic autopsy findings and neuroimaging or neuropsychology are likewise problematic because the patient may not have been well enough to be tested for many months or years before passing. Rarely, biopsies are carried out on AD subjects—for example, incidental sampling of the brain during therapeutic insertion of a ventricular catheter. Small studies have used biopsy and autopsy data from the same patient to describe the progression of AD lesions over years (80). These studies have proven that there are significant AD lesions in the brain of an individual who is at a cognitively early stage of clinical symptoms.

Attempts have been made, since the 1980s, to standardize neuropathologic diagnostic criteria for AD/SDAT. A consensus conference in the 1980s resulted in the widely used Khachaturian criteria for the neuropathologic diagnosis of AD—criteria that utilized nonimmunohistochemical approaches for evaluation of the brain (81). These were modified and updated by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (9, 72), a highly productive group effort to simplify AD diagnosis with easy-to-use templates and diagrams. The Braak criteria for AD severity (25, 26) assume a progression of neuropathologic abnormalities (predominantly NFT and neuropil thread accumulation) from the transentorhinal cortex (stages I and II) to the hippocampus (III and IV), finally with widespread involvement of the neocortex (stages V and VI).

The National Institute on Aging (NIA)–Reagan Institute criteria for the neuropathologic diagnosis of AD came into widespread use in the late 1990s and have been tested and operationalized

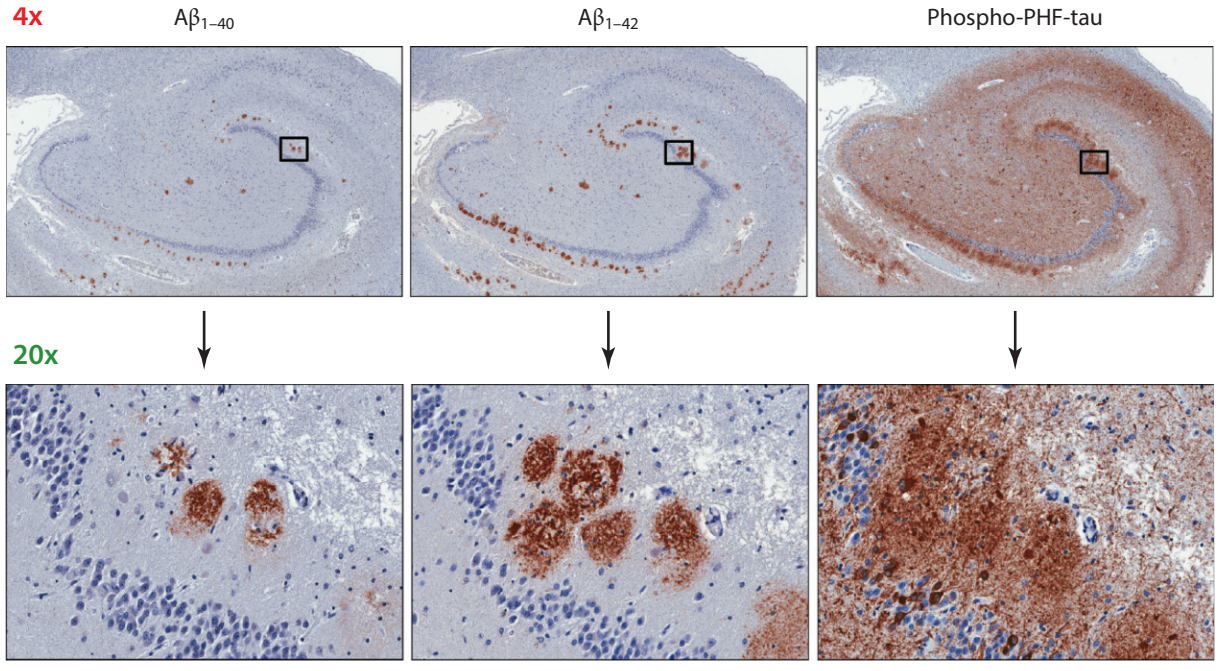

Figure 8

Sections of hippocampus immunostained with three different primary antibodies: $A\beta_{1-40}$, $A\beta_{1-42}$, and phospho–paired helical filament–tau (phospho-PHF-tau). Boxes in each of the upper three panels indicate the region magnified in the corresponding lower panel. Note prominent senile plaques (demonstrated most effectively with anti-$A\beta_{1-42}$); tau immunostaining highlights immunoreactive neurons in the granule cell layer.

(82). These criteria assign a high, intermediate, or low likelihood that a given individual's dementia was due to AD neuropathologic features. One such study found a good correlation between a high NIA-Reagan probability likelihood of AD and clinical dementia but further ascertained that the older Khachaturian and CERAD criteria correlated fairly well with those of NIA-Reagan (82). Occasional cases arise—especially among the oldest old—in which advanced AD neuropathologic changes were clearly present in the brain of a subject who was known to be cognitively intact until shortly before death (31), though such rare cases may be outliers. Quantification of AD neuropathologic change is increasingly facilitated by the ability to digitize immunostained glass slides, retain the images as a permanent electronic record of a given autopsy, and use these digital images as a starting point for further quantitative morphometric analysis. A novel antibody capture assay has recently been developed for immunostained paraffin sections, facilitating quantitative antigen assays in such tissue sections (83).

In recent years, new guidelines for the neuropathologic assessment of AD have been developed (84, 85). These have built on the Braak, NIA-Reagan, and CERAD approaches and recognize that the neuropathologic changes of AD may occur in the apparent absence of cognitive impairment. They are based upon an assessment of three spheres of neuropathologic change, including (*a*) the extent of Aβ deposition [using the scoring system of Thal et al. (33)], (*b*) staging of NFT burden (collapsing the six Braak stages into a more simplified three), and (*c*) assessing density of neuritic SPs, as was initially proposed by CERAD. Furthermore, these NIA–Alzheimer's Association guidelines provide more detailed and specific approaches to evaluating comorbid conditions such as Lewy body disease, vascular brain injury, and hippocampal sclerosis. The final AD score

is thus formulated so as to allow the tissue evaluator to state that a given case does not show AD pathologic change or that it has a low, intermediate, or high likelihood of AD. This system, while recently developed and published, is currently being evaluated for interobserver and intercenter reproducibility.

MILD COGNITIVE IMPAIRMENT

MCI emerged as a concept and nosologic entity in the mid- to late 1990s. It describes subclinical complaints of memory dysfunction (usually in elderly subjects). Deficits in some cognitive tests have been noted in MCI subjects, but normal intellectual function is generally preserved (86). Affected individuals have a high probability of evolving towards AD/SDAT. MCI subjects are considered a potentially important group to study in terms of early intervention, that is, at a time prior to irreversible brain changes, when their cognitive deficit is relatively mild and might be stabilized or improved. Neuropathologic studies on such patients are infrequent, because (unlike end-stage AD subjects) they are not medically unwell and prone to life-threatening events. However, when autopsies have been performed on individuals with amnestic MCI (aMCI), the neuropathologic findings suggest a transitional state of evolving AD. Braak stage III and IV AD neuropathologic change was most commonly encountered, but two (of fifteen) patients in one study had neocortical pathologic abnormalities (Braak stage V). Over half of the patients who came to necropsy had evidence of significant CVD, including hippocampal injury that was often interpreted as ischemic in origin, that is, hippocampal sclerosis (87, 88). The concept of aMCI has been present for a sufficiently long time that many affected patients have progressed to dementia. Neuropathologic studies of these subjects show that approximately two-thirds had AD changes at necropsy, and the remainder showed heterogeneous neuropathologic abnormalities that explained their cognitive decline, including FTLDs, hippocampal sclerosis, and nonspecific tauopathy (89). Data from the Religious Orders Study show that among over 130 individuals with MCI who underwent autopsy, 54.5% had pathologically confirmed AD and 19.4% had mixed pathologies, usually including ischemic infarcts or Lewy bodies (90). As in the Mayo Clinic study (87), therefore, CVD was a common accompaniment of AD—indeed, macroscopic brain infarcts (in the absence of pathologically confirmed AD) accounted for 13.3% of aMCI cases and 18.6% of nonamnestic MCI cases.

FAMILIAL ALZHEIMER'S DISEASE

AD is infrequently inherited as an autosomal dominant trait, the result of mutations in one of three genes: the amyloid precursor protein (*APP*) gene on chromosome 21, presenilin 1 (*PSEN1*) on chromosome 14, and presenilin 2 (*PSEN2*) on chromosome 1. *PSEN1* mutations are the most common, whereas *PSEN2* mutations are very rare (1, 2). Disease onset is variable but often occurs at an early age (in the third or fourth decade of life). Down syndrome (DS, trisomy 21) subjects will invariably develop AD neuropathologic change if they survive to the fourth or fifth decade. (Note that the ApoE ε4 isoform is a genetic risk factor for developing AD, but is not in itself a disease-determining abnormality.) Autosomal dominant variants of AD are of obvious interest to investigators; a subject with an *APP*, *PSEN1*, or *PSEN2* mutation will invariably develop the disease; thus, neuropsychological and neuroimaging features of reliable disease progression, as well as other putative CSF biomarkers, can be studied in an afflicted individual, even at an early age. Such subjects are also of great interest in examining prevention and treatment strategies that target early stages of the disease. *APP* mutations are found in and adjacent to the short Aβ-coding domain of the gene, flanking the β- and γ-secretase sites at which Aβ is cleaved from APP (91).

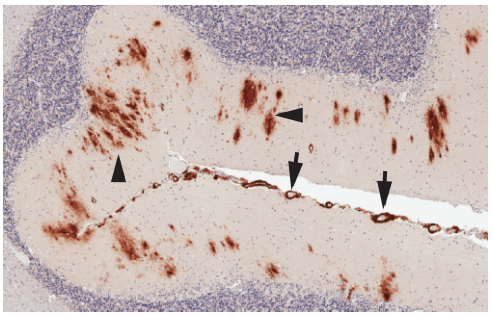

Figure 9

Section of cerebellum from a familial (autosomal dominant) Alzheimer's disease subject with a *PSEN1* mutation. Note prominently Aβ-immunoreactive deposits throughout the molecular layer (*arrowheads*). Arrows indicate prominent cerebral amyloid angiopathy affecting many leptomeningeal arterioles.

Although most *APP* mutations cause AD, an Icelandic group has discovered a coding mutation in this gene (A673T) that protects against AD cognitive decline—apparently as the result of an approximately 40% reduction in the formation of amyloidogenic peptides (92). Autopsy data on this unique cohort of protected subjects have not been published. All *APP* and *PSEN* mutations are thought to mediate their effects through their impact on Aβ processing from APP (93). Of interest, *APP* mutations in any of three adjacent codons—692, 693, and 694—result in a phenotype dominated by severe CAA; in the hereditary Dutch form of CAA, the neuropathologic features are almost exclusively vascular, including numerous infarcts and hemorrhages throughout the brain in the presence of some SPs but in the absence of significant tau pathology (47, 56). Quite severe CAA may also be encountered in the brains of *PSEN1* mutation carriers when the mutation is beyond codon 200 (unlike in *APP*, *PSEN1* mutations are found throughout the gene, which encodes a multi-membrane-spanning protein). We have found rather prominent Aβ deposition in the cerebella of some familial AD patients, in the form of both SPs and CAA (**Figure 9**).

There is increasing interest in genes that may modify expression of the AD phenotype, analogous to the effect of ApoE ε4. Many of these have been discovered using the powerful technology of genome-wide association studies (for review, see 94). These include complement component (3b/4b) receptor 1 (*CR1*), on chromosome 1q32; bridging integrator 1 (*BIN1*), on chromosome 2q14; phosphatidylinositol-binding clathrin assembly protein (*PICALM*), on chromosome 11q14; membrane-spanning 4-domains, subfamily A, members 6A and 4E (*MS4A6A* and *MS4A4E*), on chromosome 11q12.1; ATP-binding cassette, subfamily A, member 7 (*ABCA7*), on chromosome 19p13.3; and clusterin (*CLU*), on chromosome 8p21-p12. Examining the neuropathologic effects (if any) of these genes (and polymorphisms and amino acid changes within them) will be a challenge to neuropathologists. As Holton et al. (94) have stated, "Measuring changes in damage induced expression in tissue with changing cell populations and developing rigorous algorithms to interpret such data is problematic." One of the most interesting observations has been that variants in triggering receptor expressed on myeloid cells 2 (*TREM2*) result in susceptibility to late-onset AD (95, 96, 97). Though the significance of this association remains the subject of debate, it suggests a plausible mechanism of disease pathogenesis: TREM2 is an innate immune receptor expressed on the membranes of some myeloid cells (including tissue macrophages and brain microglia). TREM2 on microglia may be critical to the clearance of neural debris of the lesioned CNS (95)—though the specific research questions to be addressed will need to be more clearly focused, given that the ligand of the lesioned neural tissue recognized by TREM2 is as yet unknown.

CLINICOPATHOLOGIC CORRELATION IN DEMENTED SUBJECTS

Clinicopathologic analysis of subjects with dementia was, until the refinement of structural and metabolic antemortem brain imaging, the definitive way to link structural brain lesions with neurobehavioral and neurologic brain abnormalities. Despite their seminal contributions to understanding neurodegenerative diseases, autopsy studies are frequently criticized for their shortcomings. They often focus on studying highly selected patients who are not necessarily representative of a given population (1, 2, 5). They examine tissue at the end stage of a disease process that began years—possibly decades—prior to the affected subject's demise; therefore, causal or precipitating events that are of etiologic importance in AD/SDAT may be difficult or impossible to decipher. As one recent multicenter study has affirmed (24), "Studies on human subjects with autopsy confirmation entail numerous potential biases that affect both their general applicability and the validity of the [clinicopathologic] correlations." However, its well-argued conclusion was that AD is indeed a specific disease entity, one defined by the presence within brain of Aβ SPs and tau-immunoreactive NFTs. It further concluded that although Aβ SPs may play a key role in disease pathogenesis, cognitive decline and impairment correlate best with the burden of neocortical NFTs.

A recent theme of autopsy studies of dementing disorders has been the high frequency of non-AD comorbidity. In a large Austrian autopsy study and review of the literature (98), AD was the most frequent neuropathologic diagnosis (in >40% of subjects), but AD together with significant CVD was found in approximately 25% of subjects. Pure vascular dementia was identified in 10% of subjects and AD along with diffuse Lewy body disease in a similar percentage (these are described as mixed dementias). Cerebrovascular pathology was subclassified into four degrees of severity, depending upon the frequency and extent of lacunes, cystic infarcts and microinfarcts or hemorrhages, CAA, and hippocampal injury. The brains of nonagenarians appear to be impacted less by AD than by other comorbid conditions, especially sequelae of CVD (7, 24). Neuropathologic study of 108 decedents in the 90+ Study (based in Southern California) found that in 66 subjects with clinical AD-type dementia, quantitative immunohistochemistry showed a strong correlation between cognitive impairment and "area of cortex occupied" by Aβ and tau immunoreactivity; Braak stage also correlated with dementia, whereas semiquantitative SP scores did not. The 5.6% estimated area of cortex showing Aβ immunoreactivity in those without dementia nearly doubled, to 10.7%, for demented subjects (99). Comparable figures for tau immunoreactivity within hippocampus were 4.6% (nondemented) and 7.2% (demented). Hippocampal sclerosis was noted in 42% of subjects, and this correlated strongly with neuronal TDP-43 immunoreactivity.

Findings from the Adult Changes of Thought study (Seattle) as well as the Religious Orders Study and the Memory and Aging Project (Rush University, Chicago) highlight the etiologic complexity of dementing syndromes in older populations (100). Cerebral microinfarcts appear to be an especially important neuropathologic correlate of cognitive decline or dementia resulting from vascular brain injury in population-based studies. Review of autopsy data from the UCLA Alzheimer Center neuropathology database shows an age-related increase in the frequency of cerebral microinfarcts, ranging from less than 5% of brains examined from those ≤60 years of age to over 35% in those >90 years of age. Schneider et al. (101, 102) have observed that community-based subjects carrying the clinical diagnosis of AD had less severe AD neuropathologic change and more ischemic brain injury than clinic-based patients seen at the Rush Alzheimer Center. Clinic-based subjects had a higher frequency of diffuse Lewy body disease and atypical pathologies than did community-based individuals. The issue of whether and how CVD causes or contributes significantly to vascular cognitive impairment (a pre–vascular dementia condition analogous to MCI as pre-AD) has been addressed in the proceedings of a multidisciplinary workshop (103).

Table 1 Biomarkers of potential value in supporting the clinical diagnosis of Alzheimer's disease/senile dementia of Alzheimer type

Method	Measures
Thorough neurologic and neuropsychological examination of the subject	Emphasize mental status, memory storage and retrieval, focal signs
Neuroimaging (structural, magnetic resonance imaging)	Ventricular enlargement (ventriculomegaly) Thinning of the cortical ribbon Hippocampal atrophy/enlargement of the temporal horn of the lateral ventricle Brian microbleeds (for cerebral amyloid angiopathy)
Neuroimaging (metabolic)	Pittsburgh compound B (PiB), labeled with ^{18}F or ^{11}C: florbetapir or amyvid [^{18}F]Fluoroethyl-methyl-amino-2-naphthyl-ethylidene malononitrile (FDDNP) [^{18}F]Fluoro-dexoyglucose positron emission tomography Tau markers
Cerebrospinal fluid testing	Amyloid beta 1–42 Total tau and phospho-tau 14-3-3 protein (to rule out spongiform encephalopathy)
Blood testing	Apolipoprotein E isoforms (polymerase chain reaction–based assay) Neuron-specific enolase, S100B (as a measure of brain injury)

BIOMARKERS OF ALZHEIMER'S DISEASE/SENILE DEMENTIA OF THE ALZHEIMER TYPE AND OTHER DEMENTIAS

Biomarkers of various human disorders (especially neurodegenerative diseases) have become a major theme of twenty-first century biomedical research. Biomarkers serve as proxies or surrogates for specific pathophysiological disease processes (104, 105). Identifying quantifiable markers of disease—whether by neuroimaging, CSF, or blood markers—has the potential (*a*) to allow for early identification of possibly presymptomatic subjects at risk for developing AD and (*b*) to provide measures by which disease severity and progression may be evaluated; thus, such biomarkers may be invaluable in providing endpoints (or objective milestones) for clinical therapeutic trials. Careful and detailed physical examination of a human patient thus in itself represents a type of biomarker. **Table 1** summarizes the major biomarkers of importance in individuals suspected of having AD or another neurodegenerative disease. A role for the neuropathologist is to provide validation of biomarkers by providing feedback on putative structural (autopsy) brain changes that a given biomarker is thought to measure or reflect (1, 6). Of the large numbers of AD and MCI subjects who have had structural and/or metabolic brain imaging, for example, only a small percentage have had confirmatory neuropathologic brain examination, frequently with a considerable interval between the radiographic study and necropsy.

As the Alliance for Aging Research AD Biomarkers Work Group has stated, there are five important and established AD biomarkers: findings from three modes of neuroimaging [amyloid PET, fluorodeoxyglucose (FDG)-PET, and structural MRI] (**Figure 10**) and levels of two CSF proteins [Aβ and tau, including total tau (t-tau) and phospho-tau (p-tau)]. MRI images can be evaluated using visual assessment, quantitative region of interest–based techniques, automated and semiautomated methods, and quantitative voxel-based methodology (104). Studies suggest that the cortical degeneration in AD is the reverse of the normal developmental sequence within brain, a process described as retrogenesis (6). Both cross-sectional and longitudinal study approaches have been used with all neuroimaging techniques. Global atrophy can be quantified using the technique of boundary shift integral or tensor-based morphometry. Correlative MRI-neuropathologic studies show that quantitative measures of brain volume loss correlate well with

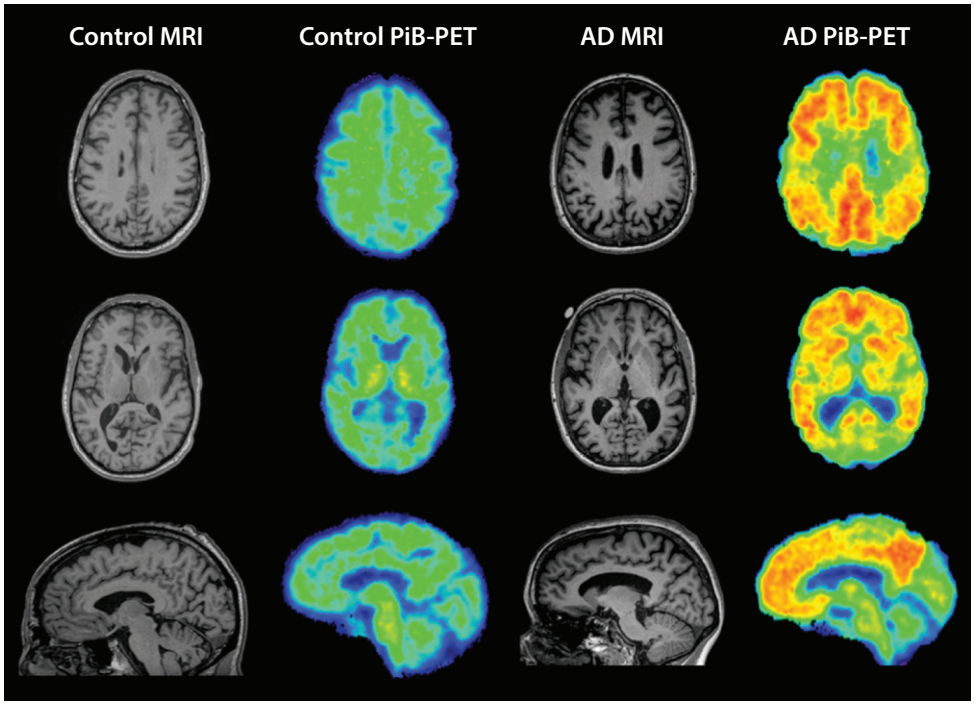

Figure 10

Structural (MRI) and amyloid PET imaging of axial slices of brain from a control subject (*two columns at left*) and an Alzheimer's disease (AD) subject (*two columns at right*). Note the prominent Pittsburgh compound B (PiB) signal in the AD brain (*far right column*). Images courtesy of William Jagust, University of California, Berkeley.

pathologic measures of the severity of neurodegeneration. Regionally accentuated atrophy (e.g., affecting the mesial temporal lobe) is especially characteristic of AD (105). Volumetric MRI scans (emphasizing region-specific atrophy) are also useful in distinguishing AD from frontotemporal dementia (106, 107). Ventricular volume increases over time may also be a marker for AD and vascular brain injury in elderly individuals (108).

Brain Aβ can be imaged in vivo using Pittsburgh compound B (PiB) labeled with ^{11}C ([^{11}C]PiB) or ^{18}F ([^{18}F]PiB) (109). PET scanning using fluorodeoxyglucose (FDG-PET) provides a measure of brain glucose utilization and thus of cortical metabolism. Of interest, whereas structural (MRI) imaging has emphasized mesial temporal (e.g., hippocampal) atrophy (see above), FDG-PET scanning shows hypometabolism in the lateral temporoparietal and medial parietal cortex, including the precuneus and posterior cingulate gyrus (3, 105). It is now possible to study a living brain using all of these modalities and to integrate or coregister the resultant data and correlate them with CSF markers (110–114). Much of this work has been accomplished through the Alzheimer Disease Neuroimaging Initiative (ADNI), a multicenter, multidisciplinary investigation charged with studying large numbers of subjects with early AD or MCI and comparing them with normal controls (110). PiB scanning has been performed on cognitively normal elderly subjects, who were also assessed for evidence of gray matter atrophy (115). Reading of PiB scans often dichotomizes subjects as being PiB^+ or PiB^-. Older subjects showed age-related gray matter atrophy throughout the CNS, regardless of Aβ deposition. Among PiB^+ subjects, amyloid burden was associated with gray matter atrophy within frontal, parietal, and temporal cortices. Neuropathologic examination of a PiB^+

PiB: Pittsburgh compound B

and a PiB$^-$ case (postmortem examination 10 and 17 months postimaging) showed that Aβ amyloid pathology within brain may be associated with undetectable or low levels of [^{11}C]PiB retention (116, 117). A considerably larger study of [^{18}F]PiB (florbetapir), correlating antemortem imaging with autopsy findings, showed the sensitivity and specificity of florbetapir to be 92% and 100%, respectively, among subjects who had been scanned within 2 years prior to death and 96% and 100%, respectively, among those who had autopsy within 1 year (118). In autopsy brain tissue, PiB appears to bind to SPs immunoreactive for either $A\beta_{1-42}$ or $A\beta_{1-40}$ and to microvascular amyloid. Progressive hippocampal atrophy can be evaluated by measuring changes in hippocampal volume over time (119). Antemortem imaging of CNS phospho-tau appears to be more difficult, though some studies suggest it can be done using [^{18}F]fluoroethyl-methyl-amino-2-naphthyl-ethylidene malononitrile (FDDNP); studies using this ligand have been performed in subjects with MCI (13).

Within the CSF, levels of t-tau, p-tau, and β-protein (usually $A\beta_{1-42}$) can be measured, though longitudinal study of these peptides may be challenging because (potentially unpleasant) serial lumbar punctures are required (104, 120, 121). A clinician attempting to differentiate a patient with FTLD from one with AD/SDAT can do so using the CSF t-tau:Aβ ratio; Aβ levels decrease with AD/SDAT progression, whereas t-tau levels tend to increase. These levels and ratios may also be helpful in predicting which MCI subjects will progress to AD. There appears to be an inverse correlation between CSF $A\beta_{1-42}$ levels and SP pathologic change (at autopsy), suggesting sequestration of this peptide into extracellular SPs (120). Measures of premorbid cognitive reserve (level of education, occupation, premorbid IQ) may also be reflected in the CSF levels of these peptides (119). CSF Aβ and amyloid PET measurements of peptide were shown to be consistent, with a small but significant number of discordant subjects, in a large ADNI study (122). A major challenge in future studies of CSF biomarkers will be identifying reliable markers of FTLD subtypes, as well as AD cases with significant comorbidity (e.g., cerebral microinfarcts) that are currently suboptimally identified on neuroimaging studies.

Analysis of blood samples is less likely to be informative in providing biological insights into AD/SDAT, though it may be of some limited value. In a clinical setting, blood tests are valuable in providing important information in a given patient on metabolic disease that may mimic a neurodegenerative disorder. ApoE genotype is easily assessed using a polymerase chain reaction–based assay on a blood sample. One study has concluded that low plasma $A\beta_{1-42}$:$A\beta_{1-40}$ ratios may be associated with increased imminent risk of developing MCI and AD/SDAT (123). Other studies suggest some clinical or prognostic value in measuring blood levels of oxysterols, isoprostane, and plasma signaling proteins (124, 125). Plasma Aβ levels appear not to reflect brain Aβ levels as measured at necropsy by immunohistochemistry or biochemical assays (126).

EFFECTS OF TREATMENT ON ALZHEIMER'S DISEASE NEUROPATHOLOGIC FINDINGS

Neuropathologic studies are likely to be crucial in documenting how and why (yet to be developed) treatments for AD/SDAT work or fail to work. AD is currently neither treatable nor preventable. Cholinesterase inhibitors or memantine provides temporary symptomatic improvement in some patients (75). In the late 1990s and early 2000s, based upon success in clearing brain Aβ from transgenic mice using an amyloid vaccine, a clinical vaccine trial was initiated in humans. Unfortunately, 5–6% of immunized subjects developed a rapidly fatal meningoencephalitis. Autopsy studies on a few of these subjects showed remarkable findings. There was evidence of Aβ clearance from cerebral cortex, though NFT and neuritic changes remained, as did CAA (127). The meningoencephalitis appeared to be mediated by T lymphocytes. Aβ immunoreactivity was associated

with (possibly activated) microglia, and the subcortical white matter showed extensive infiltration by macrophages. A second case report (128) described similar findings in an immunized subject and commented on the presence within cerebral cortex of dense SPs surrounded by microglia and multinucleated giant cells. T lymphocytes present within brain included predominantly $CD8^+$, $CD4^+$, $CD3^+$, and $CD5^+$ cells; B cells and cytotoxic T cells were absent. Multiple cortical BMBs (usually a marker for severe CAA) were observed. These fascinating initial case reports presented data on a very limited number and subset of patients and made inferences of dynamic events pertinent to Aβ clearance that could not be compared with appropriate controls or prior tissue examination, as no patients had undergone brain biopsies. Much larger numbers of subjects have now been studied.

There has been subsequent detailed clinical, neuroimaging, and neuropathologic analysis of many vaccine-treated subjects, and observations in these individuals have been compared with those in nonvaccinated controls (129). Though the *n* of subjects in these studies has been comparatively small, several intriguing observations have emerged. Mean Aβ load was lower in the immunized group than in age-matched untreated controls. The degree of SP removal varied with mean antibody response attained. Dementia did not improve in treated subjects, nor did overall survival. Aβ clearance has been documented in other studies (130), as has diminution of neuritic change in SPs, though NFTs, neuropil threads, and CAA persisted. No evidence for a beneficial effect on synapses and no morphologic evidence of synaptic integrity were found (131).

Boche et al. (131, 132) and Weller et al. (54) have hypothesized that SP Aβ is solubilized by antibodies generated during immunization and that the peptide then drains along perivascular pathways in the CNS, detectable (by immunohistochemistry) as severe CAA. When immunized subjects were compared with controls, the former had 14 times as many Aβ-containing blood vessels within cortex and 7 times as many within the leptomeninges; the parenchymal CAA was severe, involving the full thickness of many arteriolar walls. Significantly more $A\beta_{1-40}$ was seen in the immunized cases, which also showed a higher density of BMBs and microvascular lesions. An intriguing observation was that two of the longest survivors (4 and 5 years after initial immunization) had virtually complete absence of SPs and CAA within their brains. Autopsy studies on the effect of a given treatment are limited by the fact that the treated brain is examined at only one point in time, as the authors of these papers acknowledge—this and the small number of specimens available for analysis limit detailed biochemical study (133). However, imaging of brains using amyloid PET (e.g., with PiB) will likely allow for dynamic observations of Aβ deposition and clearance over time—amyloid PET imaging can be carried out over several time points—but autopsy examination of the brain will remain crucial. Comparisons of treated versus untreated subjects (rigorously matched for age, disease duration, etc.) will always be valuable. Recently, a detailed analysis of inflammatory components within autopsy brain of Aβ immunized versus nonimmunized subjects has been undertaken (134). Quantitative analysis was undertaken of various microglial and inflammatory markers, including CD68, macrophage scavenger receptor A, CD64, CD32, Iba-1+, C1q, the T cell marker CD3, and IgG. Levels of CD68, macrophage scavenger receptor A, CD64, and CD32 were significantly lower in immunized than nonimmunized subjects, though there was no significant difference in Iba-1+ load, numbers of Iba-1+-positive cells, IgG load, or numbers of T cells. In this study, there was evidence of substantial reduction of $A\beta_{1-42}$ load (by over 80%) and phospho-tau (by 40%), though the tau decrease appeared to impact mainly neuronal processes rather than NFTs. This paper provides substantial evidence for the importance of microglial function or activation (as a function of vaccination) in phospho-tau accumulation or clearance within the brain (see also the comments on TREM2 above).

Recent high-profile reports have presented largely negative results of AD immunotherapy using humanized anti-Aβ antibodies, bapineuzumab and solanezumab (76, 135, 136). Clinical and

neuropsychological outcomes did not improve in treated patients, despite significant improvements in CSF phospho-tau levels in ApoE ε4 carriers. Decreased rate of Aβ accumulation within brain was seen (on PiB PET scans) in ApoE ε4 carriers. A significant complication of both humanized antibodies was cerebral edema or hemorrhage, possibly mediated by the impact of the immunotherapy on CAA (see the discussion above). Bapineuzumab significantly alters Aβ composition, according to neuropathologic and biochemical analysis of a small number of specimens (133). It has also been shown to neutralize the detrimental effects of Aβ oligomers on synaptic plasticity in an animal model (137).

The search for an effective candidate AD therapy continues. The use of Aβ-degrading enzymes (e.g., neprilysin, cathepsin B) has been suggested as one treatment strategy (138). However, an approach to preventing the extensive tau pathologic change that characterizes AD brain will also need to be developed, and indeed may be a key to definitively improving cognitive function.

CEREBROVASCULAR DISEASE AND ALZHEIMER'S DISEASE/SENILE DEMENTIA OF THE ALZHEIMER TYPE

Just as the aging human brain is at increased risk, with every decade, for the development of AD/SDAT, so is it prone to manifest the consequences of CVD. In considering CVD as a cause of cognitive impairment, there are several important themes: (*a*) pure CVD (with minimal AD brain changes) as a cause of cognitive impairment (ischemic vascular dementia or IVD) (74, 139–142); (*b*) comorbidity between AD and CVD in a given brain (sometimes described as mixed dementia), leading to more severe impairment than would result from AD changes alone (73, 143–147); (*c*) the hypothesis that cerebral atherosclerosis itself is a major risk factor for AD/SDAT; and (*d*) blood-brain barrier dysfunction as a key contributing factor to AD pathogenesis and progression. I emphasize above that a microvascular lesion commonly found in the brains of aged individuals (and more severe in those with AD/SDAT), CAA, is associated with brain parenchymal abnormalities including large hematomas, BMBs, and microinfarcts (42, 58, 148). Brains of the elderly and those with AD also show a significant degree of arteriolosclerosis, sometimes described as lipohyalinosis, and these microangiopathies may synergistically contribute to AD progression (149, 150). In large autopsy series, with the inherent bias of such investigations, relatively pure IVD accounts for 7–10% of cases, genuinely mixed findings (significant CVD and AD neuropathologic changes) for 3–5% of cases, and AD with a minor CVD component for 20–40% of cases; estimates vary widely depending upon the center reporting them (98, 146). Neuropathologic substrates of IVD include cystic infarcts, usually in the territories of large arteries or their branches, lacunar infarcts (grossly visible in the autopsy brain or on neuroimaging) smaller than 1.0 cm in greatest dimension, and microinfarcts (not visible grossly or on neuroimaging but seen in histologic sections of the brain; see the discussion above) (74, 149–152). Cystic infarcts in certain regions are especially likely to cause memory storage and retrieval deficits as well as cognitive impairment; these regions include the hippocampi and angular gyrus. Ischemic changes within hippocampi (resembling hippocampal sclerosis that causes temporal lobe epilepsy)—especially common in the oldest old—are an important substrate for neurobehavioral changes that may resemble AD/SDAT, with prominent deficits in memory storage and retrieval (153–156). Because most neuropathologic examinations of the brain entail sampling a relatively restricted region of the hippocampus, neuropathologic change within it (including linear scars and small infarcts) is almost certainly underestimated and only becomes apparent when serial blocks of this structure are carefully examined, sometimes using morphometric techniques (157). Though it was at one time suggested that AD/SDAT is a hippocampal dementia, the prevailing view is now that neocortical lesions are a necessary substrate of cognitive decline (158).

Abnormalities of cerebral microcirculation (i.e., the neurovascular unit, which includes the capillary and arteriolar endothelium and surrounding pericytes, SMCs, and astrocytes) have been suggested as key elements in AD/SDAT pathogenesis (159–161). The role of the perivascular spaces (surrounding brain parenchymal vessels) in clearing brain parenchymal Aβ is discussed above, including with reference to the consequences of Aβ vaccination. Aβ transport through the blood-brain barrier endothelium is mediated by two main receptors, the low-density lipoprotein receptor–related protein (LRP1) and the receptor for advanced glycation end products (RAGE) (159, 160). Subtle abnormalities of the blood-brain barrier suggestive of leakiness have been demonstrated by ultrastructural studies (162). Whether large artery atherosclerosis (e.g., affecting branches of the circle of Willis) contributes directly to AD/SDAT pathogenesis has been the subject of lively and as yet unresolved debate. Most of the studies supporting or questioning such an association have been based upon autopsy data (163–167). The Baltimore Longitudinal Study of Aging, for example, concluded that atherosclerosis is an important and independent risk factor for dementia, but one unrelated to AD/SDAT pathologic change (167). Data from our longitudinal California-wide study of vascular factors important in brain aging suggest a similar conclusion (168). We have also found an interesting association of cerebral atherosclerosis with brain cystic infarcts (well known previously) and CNS microinfarcts (169). Others, however, report a compelling association between circle of Willis atherosclerosis and SPs and NFTs within the brain (163). One problem with such investigations is that large cervical arteries—atherosclerosis within which significantly impacts brain parenchyma, arguably more prominently than circle of Willis atheroma—are almost never examined in autopsies.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

This article has intentionally focused on selected clinicopathologic aspects of AD/SDAT, while avoiding others. The contributions of transgenic animal models to understanding AD pathogenesis have been immense but are beyond the scope of this review (55, 170). The amyloid (cascade) hypothesis has been the foundation upon which much modern AD research is based—yet strategies that appear to be effective in removing this protein from the brain have led to negligible clinical improvement in treated subjects and to only modest decreases in phospho-tau abnormalities within treated brains (see the section Effects of Treatment on Alzheimer's Disease Neuropathologic Findings, above). Several excellent recent reviews have discussed practical and theoretical frameworks for considering AD/SDAT in the context of brain aging and important genetic abnormalities that influence this process (171). Jagust (3, 105) has stressed the neuroanatomical heterogeneity of brain aging, including varying degrees of dysfunction in its different regions—for example, the medial temporal lobe memory system and a frontostriatal executive system. Huang & Mucke (172) emphasized that AD probably has multiple causes with complex interactions, thus concluding that investigative and drug discovery and development efforts should be diversified to realistically address the multifactorial nature of the disease; monotherapy is extremely unlikely to work. The emphasis of much research is on expanding from the level of synapses, where (as discussed above) AD produces significant abnormalities, to the level of neural networks (4). Skeptics of the amyloid (cascade) hypothesis abound and provide interesting, sometimes controversial points of view.

Ball et al. (173) have proposed a role for viral (herpes simplex) infection in intracerebral propagation of AD pathologic change. It has also been hypothesized that Aβ may seed and self-propagate by a mechanism analogous to that seen in prion diseases; indeed, transsynaptic spread of tau and α-synuclein may be an important mechanism that explains stereotypical patterns of lesion spread within the brain (174). Stohr et al. (175) have demonstrated the ability of Aβ aggregates to self-propagate and spread throughout the brains of transgenic mice after intracerebral inoculation;

they were able to show this propagation using either purified Aβ aggregates derived from brain tissue or aggregates composed of synthetic Aβ. They have taken the bold (but possibly justified) step of referring to Aβ as Aβ prions (175). Hamaguchi et al. (176) have shown that the presence of Aβ seeds, and not the age of the host animal being tested, is crucial to the initiation of Aβ aggregation within the CNS and leads to spread of the protein throughout the brain. Transsynaptic progression of Aβ-induced neuronal dysfunction has been demonstrated within the entorhinal-hippocampal network (177). Analogous phenomena have been suggested or demonstrated for tau within both human and mouse brains. Braak & Del Tredici (178) have made the provocative observation that tau abnormalities may be seen in the brains of individuals younger than 20 years of age—for example, in the pontine locus ceruleus (which projects to cortex)—supporting the idea of neuron-to-neuron propagation of abnormal cytoskeletal protein. Injection of brain extract from mutant P301S tau–expressing mice into the brains of transgenic wild-type tau–expressing animals induced assembly of wild-type human tau into filaments and the spread of pathologic lesions from the injection site(s) to nearby brain regions (179). Conversely, Perry and colleagues (180, 181) have repeatedly suggested that the microscopic lesions associated with AD are a suboptimal, even poor, therapeutic target, and that AD pathology is indicative of an active host response or environmental adaptation to pathophysiologic mechanisms such as oxidative stress within the CNS.

The full neuropathologic characterization of evolving and unforeseen types of neurodegenerative disease will provide stimulating full employment for neuropathologists in the decades to come (182–186). They will be charged not only with characterizing abnormal shadows and signals detected by neuroradiologists, but also with providing feedback to clinicians on how well therapies aimed at clearing abnormal proteins from the brain have worked (or failed to work). Finally, will removing abnormal brain proteins that accumulate in neurodegenerative diseases lead to clinical improvement in patients? This will be the crucible in which novel therapeutic strategies will need to be tested; neuropathologic evidence will be crucial to interpreting the results of new and innovative therapies.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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