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Correlation of Alzheimer Disease Neuropathologic Changes With Cognitive Status: A Review of the Literature

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Abstract

Clinicopathologic correlation studies are critically important for the field of Alzheimer disease (AD) research. Studies on human subjects with autopsy confirmation entail numerous potential biases that affect both their general applicability and the validity of the correlations. Many sources of data variability can weaken the apparent correlation between cognitive status and AD neuropathologic changes. Indeed, most persons in advanced old age have significant non-AD brain lesions that may alter cognition independently of AD. Worldwide research efforts have evaluated thousands of human subjects to assess the causes of cognitive impairment in the elderly, and these studies have been interpreted in different ways. We review the literature focusing on the correlation of AD neuropathologic changes (i.e. β -amyloid plaques and neurofibrillary tangles) with cognitive impairment. We discuss the various patterns of brain changes that have been observed in elderly individuals to provide a perspective for understanding AD clinicopathologic correlation and conclude that evidence from many independent research centers strongly supports the existence of a specific disease, as defined by the presence of A β plaques and neurofibrillary tangles. Although A β plaques may play a key role in AD pathogenesis, the severity of cognitive impairment correlates best with the burden of neocortical neurofibrillary tangles.

Keywords

Aging; Alzheimer disease; Amyloid; Dementia; Epidemiology; Neuropathology; *MAPT*; Neurofibrillary tangles

INTRODUCTION

Decades of research worldwide have generated a large body of clinicopathologic correlation (CPC) scholarship related to Alzheimer disease (AD). Here we review the literature from the perspective of neuropathologists and clinicians performing research in this field. The review is designed for a broad target audience. We discuss the pathognomonic features of AD (1-3), highlight some of the challenges in CPC studies, discuss the specificity of AD neuropathologic changes, and, mindful of the controversies in this field of research, describe particular combinations of concomitant lesions that are found in human brains. We then review CPC studies that have documented observations on patients along the spectrum from intact cognition to end-stage dementia linked with AD-type neuropathologic changes. Pertinent reviews of historical background are available (4-10). Terms used in this review are defined in Table 1.

OVERVIEW OF CHALLENGES TO CPC STUDIES IN AD

There are many challenges related to the study of the neuropathologic correlates of cognitive impairment in the elderly. Sources of potential bias in AD CPC studies are summarized in Table 2; some of these are virtually impossible to avoid in the design of a research study. Autopsy is required for definitive AD diagnosis, yet autopsy rates are generally low and

autopsy inevitably confers a selection bias. Furthermore, CPC studies rarely are a random sample of the population and clinic- and hospital-based CPCs are subject to other potential biases. For example, because persons with behavioral problems are more likely to require help than those with isolated memory problems, the prevalence and types of Lewy body disease derived from a clinic are likely to be different from those from a broader community (11). Most prior studies have been performed in countries with the most advantageous socioeconomic conditions and have concentrated on middle- and upper-income whites. Thus, overall, ideal conditions have not yet been achieved for comprehensive, population-level epidemiologic study in which information from detailed, longitudinal neurocognitive assessments can be combined with that from state-of-the-art postmortem examinations. Another challenge of CPC studies is that the molecular, anatomic, and clinical changes of AD may not progress in a uniform fashion (7, 12-15). This problem may not be easily solved using statistical models because the progression of both the clinical and the pathologic disease are not necessarily parametrically distributed. The tendency to dichotomize the disease (i.e. “demented vs nondemented”) and overreliance on ordinal variables may also obscure important relationships. Variation in the elapsed time between final clinical evaluation and autopsy and competing mortality risks add more uncertainty. Studies on CPC are additionally complicated by the high prevalence and high morbidity of concurrent diseases (16, 17) (discussed in more detail below). Some researchers tend to focus on unusual or extreme cases with atypical presentations, whereas others describe the distribution of outcomes in larger and perhaps more representative samples. Both approaches can provide insights; CPC data must be reconciled or at least better understood with reference to multiple variables and potential confounders. In sum, both clinical and pathologic assessments are imperfect, variably applied, and constantly evolving. These complexities should be kept in mind as we assess the sometimes-controversial CPC literature.

A β PS AND NEUROFIBRILLARY TANGLES: THE HISTOPATHOLOGIC HALLMARKS LINKED TO AD

The neuropathologic hallmarks of AD are neurofibrillary tangles (NFTs; including pretangles) and A β Ps (including diffuse and neuritic plaques, which may also be referred to as “senile plaques” [2, 18, 19]; Fig. 1 and Table 1). Additional changes that may also occur in the brains of AD patients include amyloid angiopathy, age-related brain atrophy, synaptic pathology, white matter rarefaction, granulovacuolar degeneration, neuron loss, TDP-43 proteinopathy, and neuroinflammation (20-26), which may contribute to cognitive impairment; however, these are not considered pathognomonic features of AD (3). Therefore, we focus this review only on the defining features of AD neuropathologic changes: A β Ps and NFTs (3). Excellent reviews are available about the molecular characteristics of NFTs and A β Ps (27, 28).

Neurofibrillary tangles are not specific for AD (29-32); indeed, they are found in almost every class of brain disease and are universal (yet topographically restricted) in normal aging subjects (33). Neurofibrillary tangles are found in the brains of individuals who experienced frontotemporal lobar degeneration with tauopathy (FTLD-MAPT), focal cortical dysplasia, myotonic dystrophy, prion diseases, metabolic/storage diseases, some brain tumors, chronic traumatic encephalopathy, viral encephalitis, and other brain diseases (34-37) (Table 3). This suggests that NFTs are, at least under some conditions, a secondary response to injury. On the other hand, tau gene mutations can produce clinical dementia with NFTs; this indicates that, under some conditions, NFTs may be directly linked to the primary or at least proximal neurodegenerative changes (29, 31, 37).

Both the density and the neuroanatomic localization of NFTs are important parameters in AD neuropathology. The findings reported by Tomlinson et al (38) in 1970 have been replicated many times: “[NFTs are] found in both controls and demented [demented subjects] in the hippocampus, but elsewhere in the cortex was only severe or widespread in the demented; severe generalized neurofibrillary change in the cortex was not seen in any control; it seems possible that its occurrence always indicates dementia.” This passage underscores the key point that may be relevant to the study of tau biomarkers, that is, a modest number of medial temporal lobe NFTs are universally present in subjects older than 70 years (33), even in persons who have intact cognition. Recently, it has been reported that NFTs are also very common in certain brainstem nuclei in subjects without dementia (39-44). As such, neurofibrillary degeneration restricted to subcortical sites is often subclinical, whereas widespread neocortical NFTs are almost always associated with severe cognitive impairment in more than 1 disease state.

In contrast to NFTs, A β Ps are extracellular (45, 46) and are found in a high proportion of all elderly persons but are not universal (44, 47, 48). A particularly important subtype of A β Ps are “neuritic plaques” (NPs), as they are more likely to be associated with cognitive impairment than “diffuse plaques” (49-51). Neuritic plaques are A β Ps surrounded by degenerating axons and dendrites that often contain hyperphosphorylated tau aggregates. This subset of A β Ps is a hallmark of the current diagnostic criteria for AD, although there is no universally accepted definition of a NP. Indeed, A β Ps that lack degenerating tau-positive neurites may have dystrophic neurites that are detected using other methods, including the Bielschowsky silver method, thioflavine S, or immunohistochemistry that detects p62, ubiquitin, phosphorylated neurofilament proteins, or amyloid precursor protein (APP). Some of the variability may be due to the evolution of the NP as part of the disease process (52-54). Because non-AD tauopathies usually lack NPs, they are not an inevitable cellular response to tau pathology (Table 2).

A β Ps alone do not seem to be a sufficient substrate for advanced clinical AD dementia (ADD). However, in contrast to neurofibrillary (tau) pathology, there seems to be a strong association between AD genetics and A β plaque formation. All high-penetrance AD genetic risk alleles (i.e. *APOE* ϵ 4 allele, Down syndrome, *APP* mutations and duplications, *PSEN1* and *PSEN2* mutations) have been linked in various experimental systems with increased A β deposition and increased formation of putative toxic A β peptide species (46, 55-57). These data have strong mechanistic implications with an epidemiological scope because genetic factors confer approximately 70% of an individual’s risk for AD (58, 59).

The concordance of genetics and A β deposition is aligned with CPC studies that indicate that A β Ps may be a temporally “upstream” feature of the neocortical disease, with the caveats that brainstem and medial temporal lobe pretangles and NFTs are seen in subjects without A β deposition in all age categories (33, 39, 44). Thus, A β Ps and NFTs are the hallmark features of AD but do not develop in the human brain according to the same temporal or anatomic pattern (60, 61). These nuanced observations, which have been gathered and analyzed by many researchers, provide the bases to address some of the controversies that have existed in the field for decades.

CONTROVERSIES IN AD CPC RESEARCH

A basic goal of AD CPC research has been to assess critically whether CPC data support the hypothesis that AD neuropathologic changes (A β Ps and NFTs) correlate with clinical dementia. We note that there are publications contending that CPC data argue against a deleterious role for AD pathologic changes (i.e. that they may be an “epiphenomenon” of aging) and that the disease should not necessarily be defined by their presence (62-68). This

controversy has been ongoing for many years (38). There are 4 separate assertions that seem to have gained traction in the field, thereby resulting in uncertainty:

Assertion 1. One sometimes observes persons without dementia with advanced AD pathologic changes at autopsy.

Assertion 2. One sometimes observes persons with cognitive impairment who clinically to have AD, but who lack AD pathologic changes at autopsy.

Assertion 3. Clinical trials aimed at reducing AD pathologic changes have failed.

Assertion 4. A β P and NFTs may be neuroprotective rather than neurotoxic.

Assertions 1 and 2 are addressed directly by extensive data from AD CPC studies that support 3 points. The definition of “advanced AD pathologic changes” is critical. Some groups may consider widespread diffuse and/or NPs as advanced AD pathologic diagnosis regardless of the numbers and distributions of NFTs. It is clear, as mentioned previously, that A β P, in the absence of any other neurodegenerative disease lesions or other pathologies, are not a sufficient substrate for severe dementia and thus do not constitute “advanced AD pathologic changes.” In contrast, dense and extensive neocortical NFTs are very consistently associated with dementia and thus, according to new diagnostic criteria, these are required to constitute high burden of AD neuropathologic change (3). As for Assertion 2, it is true that dementia, even one that may be clinically similar to probable AD, may be present without AD pathologic changes; this is simply not AD, but presumably one among many other diseases that cause dementia (e.g. hippocampal sclerosis or vascular dementia). These points will be considered in the context of the AD CPC literature.

Assertion 3 relates to what clinical trials data tell us about the impact of AD pathologic changes. There have been cases in which individuals with mid- to late-stage clinical AD were administered anti-A β immunotherapy that partially cleared A β P, but this clearance did not seem to mitigate NFT formation or the inexorable disease course (69-71). There are multiple reasons why these trials may have failed, including the late timing of the therapy. Thus, conclusions drawn from these trials may be premature (72, 73). In fact, there have been hints of some beneficial effects (clinical and biochemical) linked to human anti-A β immunotherapies (74-79). As yet, there are no agents that are capable of reducing tangle density. In sum, clinical trials have not provided definitive answers as to the direct role of A β P or tangles in the cognitive impairment associated with AD pathologic diagnosis (80, 81).

Assertion 4 is that A β P and NFTs are actually neuroprotective rather than toxic. Because autopsies provide only cross-sectional data, they cannot prove mechanism. Since both tau phosphorylation and A β peptide generation are seen in “normal” brains, some contend that there are probably beneficial and adaptive aspects to these molecular processes. This is important to consider when developing therapies that seek to inhibit those pathways (62). Yet, there are strong arguments in favor of the hypotheses that the molecular processes that underlie tau and A β deposition in NFTs and A β P are indeed pathologic. Abundant evidence from many independent studies indicates that A β peptides and other plaque substances (in their various molecular forms) may be neurotoxic, both directly and through secondary responses to stress, injury, and inflammation (46, 82, 83). Both gain-of-toxic-function and loss-of-normal-function deleterious effects also have been described for phospho-tau (84-89). The toxicity of oligomeric forms of tau and A β peptides could be connected with biochemical changes that also produce NPs and NFTs; thus, the oligomeric species may be directly related to the neuropathology, although they are not exactly correlated (90-95). It must be acknowledged that a simplistic conceptualization of “plaques and tangles” does not adequately reflect the complexity of the biochemical changes in the

brains of patients with AD. Thus, peptides and higher-order aggregates derived from products of *APP* and *MAPT* genes can potentially lead to combinations of neuroprotective and toxic attributes. Here, we focus on data and analyses from particular human autopsy studies to address the specific question, “are there strong correlations between antemortem cognitive impairment and the ‘defining’ hallmarks of the disease?”

We consider it to be an important clue that most brains from elderly human subjects show abnormalities that fall somewhere along particular continua of pathologic severity (60, 96-100). These patterns of brain changes indicate specific features that can be correlated with clinical parameters, modeled to understand disease mechanisms, and targeted for therapeutics. Before addressing the “classic” AD pathologic changes and their clinical correlates, we discuss in the following section some of the less common pathologic findings in human brains, that is, the “exceptions that help test the rules.”

LESS-PREVALENT PATTERNS OF CLINICAL AND PATHOLOGIC FEATURES FOUND IN HUMAN BRAINS

“Plaque-Only” Dementia

In 1987, Terry et al (101) described what has become known as “plaque-only dementia.” There were 58 subjects with dementia and AD changes, of which 40 had 2 or more neocortical tangles per high-magnification field in frontal, temporal, and parietal lobes; 18 had no neocortical NFTs. The cases did not differ in hippocampal tangle densities and had no significant differences in brain weights, neocortical thickness, or neocortical neuron counts. Despite this, both groups were demented and did not differ significantly on the Blessed Dementia Scale. The existence of this “plaque-only” dementia category has been controversial because some subjects with pathologic findings similar to the plaque-only group described by Terry et al have dementia and some do not. The current revision of the National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of AD stipulate that subjects with moderately dense neuritic A β Ps may be regarded as having an intermediate level of AD neuropathologic change and that other potential contributors to cognitive impairment and dementia should be sought (3). Notably, prior studies necessarily included brains from persons with diseases (e.g. neocortical α -synucleinopathy or TDP-43 pathology) that were not at that time well characterized, but which can coexist with variable neocortical amyloid loads. Indeed, Hansen et al subsequently published an article titled “Plaque-only Alzheimer disease is usually the Lewy body variant, and vice versa” (102). When modern pathologic methods are used, severe cognitive impairment associated only with diffuse A β Ps in the brain at autopsy is rare and has an unknown relationship to AD. Subtle cognitive impairment may be associated with diffuse A β Ps, indicating that these lesions may play a direct role in incipient AD (54), although a direct role of diffuse A β plaques without tau pathology has not been proven. Furthermore, diffuse A β Ps may be associated with cerebral amyloid angiopathy, which could produce impairments separately (103, 104), although see Nelson et al (105). As the field moves toward identifying subtle (i.e. early) cognitive impairment, more work will be required to characterize any deleterious influence of diffuse A β Ps on cognition and clinical manifestations in cases of presumed incipient AD. On the other hand, the density of tau-positive NPs does correlate directly and statistically independently with some degree of cognitive impairment (105-107) (Fig. 2).

“Tangle-Only” or “Tangle-Predominant” Dementia and Other Non-AD Tauopathies

In most community-based autopsy series, non-AD tauopathies constitute approximately 1% of dementia cases (108-115) (but see Noda et al [116]). In autopsy series associated with dementia clinics, a higher proportion of non-AD tauopathies are seen, presumably due to

recruitment bias (111). Among well-recognized forms of tauopathies are FTLD-MAPT, progressive supranuclear palsy, corticobasal degeneration, Pick disease, argyrophilic grain disease, and “tangle-only dementia” (116-125). There are also some individuals with intact or subtly diminished cognitive abilities whose brains harbor hippocampal and/or amygdala NFTs (Braak stages III–IV) with few or no A β Ps; these represent approximately 5% of cases in some large autopsy series (41). In this condition, the NFTs comprise tau isoforms similar to those of classic AD, but these subjects do not have the same distribution of *APOE* genotypes as subjects with AD (118). It remains to be determined whether these individuals died early in the course of an idiosyncratic subtype of AD (12) or instead reflect a completely different pathogenesis.

A β Ps and NFTs But No Dementia

Confusion persists about individuals lacking documented cognitive impairment yet whose brains reveal neuropathologic findings of AD at autopsy. This is an important issue because it challenges the principle that the processes that underlie AD neuropathologic changes are the sole cause of cognitive impairment. To address this issue, longitudinal studies of participants who are enrolled while cognitively normal and followed for several decades can be used to study the sequential clinical and corresponding molecular pathologic changes in AD. Rigorous analysis requires preliminary modeling of what is expected at a population level based on what is known about the disease.

The prevalence of dementia due to AD, as judged by clinicians, doubles every half-decade after age 65; thus, approximately 30% to 40% of living 95-year-old patients receive the diagnosis of ADD (126-128). The interval between initial ADD clinical diagnosis and death is approximately 8 years (129), but A β Ps and NFTs are present well over a decade before death (130-138). New terminology has been developed to delineate stages of preclinical AD (48, 139, 140). The median life expectancy in Western countries is approximately 79 years (141). Thus, using these data, we can deduce confidently that an “average” person dying at age 79 has an approximately 15% likelihood of having been diagnosed clinically with ADD, but an approximately 30% to 40% chance of harboring significant AD neuropathologic changes (otherwise, the prevalence of ADD could not reach approximately 30%–40% by age 95). Indeed, this is precisely the observation reported by one of the largest autopsy series to date (142) and is well supported by AD biomarker studies (143-145).

The existence of persons without dementia with some AD neuropathologic changes is therefore not problematic. It is expected that many persons die with brains that exhibit AD neuropathologic change in the preclinical phase of AD; indeed, data support the modeled expectations (44, 142). One would expect a normally distributed population-based model of AD to contain individuals with early or moderate AD who are classified dichotomously (and falsely) as lacking dementia. Pathologic changes that are present before clinical manifestations are a well-accepted concept in other chronic diseases such as cancer, atherosclerosis, and others (146, 147) but are equally relevant to discussions of AD. Significantly, the severity and distribution of AD neuropathologic changes are much different (lower) in preclinical cases than in cases with clinically severe ADD (48, 108, 148-150). We are aware of no reported case of truly intact cognition despite extremely severe AD pathologic changes (i.e. widespread neocortical NFTs) measured with quantitative pathologic analysis, although many persons with intact cognition have been assessed in autopsy series (33, 42, 54, 133, 142, 148, 151-166).

Dementia Cases Lacking A β Ps, NFTs, or Other Pathologic Substrates

The literature does not indicate large numbers of patients with advanced dementia whose brains lack any pathologic changes when up-to-date neuropathologic methods have been

applied to their brains. Older studies that reported cases with dementia and no other known pathologic substrate lacked insights into more recently defined pathologies, such as those with aberrant TDP-43, valosin-containing protein, and fused in sarcoma inclusions (37, 167). Moreover, some prior methods (e.g. Bielschowsky impregnation) were less sensitive to some tauopathies than Gallyas for NFTs, Campbell-Switzer for A β Ps, and immunohistochemistry. On the basis of the discovery of these and other novel neurodegenerative disease lesions in the past 20 years, we view reports that some individuals in old age may have moderate cognitive impairment without advanced AD pathologic diagnosis as a challenge to the research community to elucidate the novel mechanisms underlying cognitive impairments in those subjects (168-173). A notable example of this is schizophrenia, which, in elderly patients, is associated with dementia, although the underlying basis of this dementia is enigmatic (174-176). Normal pressure hydrocephalus is another poorly understood cause of dementia that may lack AD pathologic changes (177, 178). Understanding these phenomena and how they may contribute to cognitive impairment in a broader population will require more thorough study of non-AD brain diseases.

AD-Related Brain Pathology in Individuals Older Than 90 Years

There have been reports of dissociation between AD neuropathologic changes and cognitive status in extreme old age, but these data merit careful analysis. The incidence of dementia increases continually up to (179-183) and above (139, 184) 90 years of age. In contrast to the increased prevalence of clinical dementia with advanced age, the prevalence of cases with high NP and high NFT pathologic diagnosis at autopsy seems to level off in the oldest old according to multiple autopsy series (154, 168-172). However, not all studies are in agreement on this point (185, 186); these “survivors” represent a small fraction of the human population with underrepresentation of *APOE* ϵ 4 allele (187). Even in extreme old age, the presence of many neocortical NFTs correlates with antemortem cognitive decline (105, 188-191). Thus, no “dissociation” exists between the AD neuropathologic change and cognitive impairment. The enigma relates to cognitively impaired individuals of advanced age whose brains lack substantial AD pathologic diagnosis at autopsy.

Cognitive impairment is associated with many diseases. Cerebrovascular disease (CVD) is the most prevalent non-AD pathologic diagnosis in the brains of the advanced aged and is directly relevant to any CPC study related to dementia. The difficulties introduced by this multifaceted and unpredictable disease category in aged individuals have been discussed previously (17, 192-204); 75% to 90% of patients older than 90 years have some degree of CVD pathologic diagnosis (189, 205-207). There is no universally applied rubric for CVD pathologic diagnosis, although the recent National Institute on Aging–Alzheimer’s Association criteria attempted to systematize neuropathologic assessment of this complex form of brain injury (3). Nevertheless, the profound impact of CVD on studies pertinent to cognition in the elderly seems to be underappreciated in dementia research (208-210).

In addition to AD and CVD, there are many widespread contributors to cognitive impairment in the elderly. Examples of these include hippocampal sclerosis (a prevalent disease that plays a strong deleterious role in extreme old age and is distinct from the disease linked to epilepsy in younger individuals [211]), α -synucleinopathies, hematomas, argyrophilic grain disease, neuropsychiatric disorders and their therapies, failure of other organ systems, diabetes, hypertension, chemotherapy, and other adverse effects of medications (157, 212-220).

Thus, in the oldest old, the prevalence of concomitant non-AD brain diseases, including CVD and hippocampal sclerosis, begins to mimic the effects of AD pathologic diagnosis (154, 221, 222). Together, these and perhaps other uncharacterized changes may weaken the

apparent association between AD pathologic diagnosis and cognitive status (189, 195, 198). An analogy can be made to heart disease: it would be difficult to study the clinicopathologic correlation between coronary atherosclerosis and cardiac function if two thirds of cases had alular dysfunction, infectious endocarditis, or severe arrhythmias. Despite all the potential pitfalls, many high-quality studies related to the correlations between cognitive status near the time of death and AD-type pathologic burden at autopsy have been performed.

CLINICOPATHOLOGIC CORRELATION IN AD

Correlation Between A β Ps and Cognitive Status

More than 40 CPC studies have assessed the correlation between A β Ps and severity of antemortem cognitive impairment (38, 98, 103, 105-108, 158, 162, 171, 185, 189, 191, 223-260). These studies vary with respect to many factors including the research cohort characteristics, anatomic areas examined, pathologic methods, A β P subcategories and counting techniques, metrics for cognition, the range and domains of cognitive decline tested, and the rigor with which concomitant pathologic findings were evaluated and factored into the study.

Although the study designs were diverse in CPC studies involving A β Ps, most studies confirm a significant correlation between antemortem cognitive impairment and neocortical A β Ps, as demonstrated by Blessed et al (254) (Fig. 3). These workers used the von Braunnmühl silver stain, which could not differentiate between diffuse and neuritic A β Ps. This, and some other earlier studies, incorporated a bias related to the inclusion of many individuals at opposite ends of the AD continuum thereby masking the poorer correlation between plaque load and dementia severity among the impaired subjects. Subsequent studies have established that the densities of NPs correlate with antemortem cognitive impairment better than the densities of diffuse A β Ps (45, 98, 106, 154, 189, 261).

It is important to note, however, that many prior studies have only considered limbic and neocortical plaques. The distribution of A β P pathology may occur throughout the entire neuraxis in advanced disease. Elderly without dementia show early stages of this hierarchical process. The progression of A β P pathology seems to begin in the neocortex with a few diffuse plaques and then sequentially progress to also include 1) the hippocampus, entorhinal cortex, cingulate cortex, and amygdala; 2) basal ganglia and diencephalon; 3) midbrain and medulla oblongata; and 4) pons and cerebellum (262). A recent study with large numbers of subjects assessed with standardized antemortem cognitive testing found that the amyloid stage that has progressed to involve the striatum is highly predictive of dementia (263). Correlations between amyloid stages (Thal phases), NFT burden, and cognitive impairment are shown in Figure 4.

A critical point supporting the importance of plaques is that widespread neocortical NFTs are virtually nonexistent without the presence of widespread A β Ps, except in the minority of cases that show a clear-cut non-AD tauopathy (e.g. progressive supranuclear palsy). Owing in part to the scarcity of neocortical NFTs in the absence of A β Ps, and the relatively modest apparent direct impact of A β Ps on cognition, it has been suggested that the pathogenetic effect of A β P-related substances may be mediated by "seeding" neurofibrillary pathology (46, 88, 189, 264, 265). The current clinical trial literature is compatible with the idea that A β P-related substances kindle a self-propagating process related to neocortical NFTs, as has been hypothesized (266-269). Regarding A β Ps in AD, an analogy can be made to the established role of high blood cholesterol in heart disease. Hypercholesterolemia promotes atherosclerosis that over time can cause myocardial infarction. Therefore, high blood cholesterol is considered a causative risk factor for heart disease, although it does not correlate with clinical heart disease in all groups (many people live with

hypercholesterolemia for years without experiencing myocardial infarction). In the same way, A β Ps may be a key pathologic factor in AD without equating with the clinical features of ADD.

Often neglected is the question of lesion turnover (i.e. A β Ps being possibly reabsorbed during life so that they would not be “counted” at autopsy), which seems to occur in some subjects (70, 270). For this reason, the number of A β Ps might plateau (or at least the rate of increase flatten out), leading to a “ceiling effect” relatively early in disease process that confounds linear correlations between plaque number and severity of cognitive change (253). A β vaccine trials also attest to the ability of the immune system to clear diffuse A β Ps (69, 70, 271), but it is not known whether toxic APP metabolites or other plaque components remain after clearance of fibrillar A β -peptides (73, 272). The active “turnover” during life could reduce the correlation between the lesion numbers observed at autopsy and clinical features of the disease.

Neuritic A β P (NP): A Pathologic Entity With Mechanistic Implications

A β Ps ringed by degenerating neurites that usually contain abundant PHF-tau, that is, NPs (Table 1), deserve special consideration. In histologic sections, NPs are characterized by nearby abnormal nerve cell processes (Fig. 1). The abnormal NP-contacting dendrites and axons contain pathologic tau fibrils identical to those seen in NFTs (244, 273), with loss of adjacent synapses (274, 275). Dystrophic axons from completely different afferent sources, expressing distinct neurotransmitters, have been shown to be present in particular NPs (276, 277), which strongly implies that toxicity is directed from the (extracellular) plaque to the radially arranged intracellular neurites. The particular toxic substance(s) within NPs still have not been completely characterized (90, 103, 278), but NPs represent a nidus in which extracellular plaque substance(s) seem to induce intracellular degenerative changes with tau pathology (18, 50, 279-281). This process may be synergistic or identical to the stimuli that could promote NFTs in human brains. Neuritic plaques seem to develop after diffuse A β Ps and NFTs (44). Using data from the National Alzheimer’s Coordinating Center with inclusion and exclusion criteria, as described previously (282), NPs and NFTs tend to coexist (Table 4); this corroborates earlier observations (283). The characteristic anatomic distribution of NPs and NFTs supports additional hypotheses in relation to their formation that are outside the scope of this review (33, 39, 284-286).

Correlation Between NFTs and Cognitive Status

Numerous CPC studies have assessed the association between NFTs and cognitive status (38, 98, 154, 158, 162, 185, 188, 189, 191, 223-232, 235-240, 244, 250-252, 258, 261, 264, 287-296). As with studies on A β Ps, those of NFTs have used diverse study designs. Regardless of methodology, the correlation between neocortical NFTs (but not necessarily allocortical or subcortical NFTs) and antemortem cognitive status is strong in studies that span the spectrum of cognitive impairment (provided there is not a strong influence by other diseases that can cause cognitive impairment). Results from the University of Kentucky Alzheimer’s Disease Center (189) corroborate previous findings (Fig. 2). Duyckaerts et al (287) and Sabbagh et al (252) independently arrived at the conclusion that the density of NFTs in selected cerebral cortical fields significantly ($p < 0.01$) correlated with Blessed or Mini-Mental State Examination scores (297). Likewise, Dickson et al (251) described a strong correlation between cortical NFT counts or phospho-tau ELISA measurements and Blessed Information, Concentration, and Memory test scores. Similar results were obtained by Bennett et al (264) who found a strong correlation between global cognitive status and densities of neocortical tau-positive tangles.

On the basis of the review of an enormous sample of cross-sectional autopsy data, the pattern of NFT development across the clinical spectrum of disease has been integrated in Braak neuropathologic staging (60, 298, 299). Neurofibrillary pathology is observed in the human brain long before A β plaques develop (39, 44, 300). At 40 years, all individuals studied by Braak and Del Tredici (39) and Braak et al (44) exhibited at least initial neurofibrillary pathology in the brainstem (Fig. 5). The relationship between the near-universal tau pathology seen in the locus coeruleus of middle-aged individuals and AD is not known. As AD progresses, the NFTs become numerous in locus coeruleus which may suggest the same pathogenetic process is becoming more severe (301).

In more advanced disease, the neuroanatomic distribution of NFTs correlates both with the location at which neurons die (302-305) and with the cognitive domains affected in patients with ADD. For example, early AD symptoms tend to relate to memory, when the anatomic substrates of memory in the medial temporal lobe are selectively affected by NFTs (Braak stages III–V). The cognitive domains affected in mid- and late-stage ADD expand to include areas of executive function, visuospatial capacities, and speech. These manifestations occur in synchrony with the development of NFTs in the neocortical areas responsible for those functions (Braak stages V–VI). Braak staging provides a useful ordinal system for describing the topographical distribution of pretangles and NFTs in human brain. Nevertheless, Braak staging also masks the fact that marked variability in pathologic lesion density across cases exists within a given Braak stage (7, 12) and that not all AD cases fall within the same spatial continuum with regard to brain NFT distributions (12, 15, 151).

A key question in this regard is whether a heavy neocortical NFT load is present in individuals with intact cognition. In a review of 11 different studies comprising 555 subjects without dementia, a total of 12 brains were assessed as Braak stage V (2.2%); 3 were assessed as Braak stage VI (0.5%) (142). However, not all Braak stage VI brains were the same; there was significant variation in NFT burden in these cases (142, 151). In the Braak stage VI cases studied where neocortical NFTs were most abundant, cognitive impairment was found on testing (151). It is important to emphasize that, among thousands of cases from dozens of CPC studies worldwide, there never has been a report of a thoroughly documented individual with truly “end-stage” neocortical NFT pathology who lacked antemortem cognitive impairment proximal to death (142, 151). Even the single case report “outlier,” a Braak neuropathologic stage VI case without full-blown dementia, had some degree of cognitive impairment within expectations for late preclinical AD (306).

As with A β Ps, NFTs are quantified with certainty only at autopsy. Therefore, it is necessary to know whether some NFTs are removed (or reabsorbed) from the brain before death. Some, but not all, studies have indicated that more neurons disappear in brains of demented subjects than can be explained directly by the number of NFTs and “ghost tangles” observed at autopsy (285, 304, 307-310) (but see [305]). Thus, some evidence exists for NFT “turnover,” neuronal shrinkage, and/or non-NFT cell death mechanism(s).

Overview of Specific Large Autopsy Series

A subset of the CPC studies is highlighted in Table 5. These studies were chosen because they represent large autopsy series with detailed clinical and pathologic assessments. The inclusion criteria for Table 5 were as follows: number of patients more than 40, neuropathologic assessments that included study of both NFTs and A β Ps in the cerebral neocortex (not just the hippocampus), subjects with a broad range of pathologic severities, and nondichotomous correlation with cognitive status (i.e. not demented vs nondemented). These inclusion criteria do not minimize the contributions of studies with smaller sample sizes, for example, the important CPC study by Arriagada et al (293) that assessed 10 patients. Nonetheless, a detailed description of all smaller autopsy series would comprise

many dozens of additional studies along with a commentary regarding each of their specific attributes. It should also be mentioned that some of the important autopsy series of AD CPC are excluded from this list because they only assessed A β Ps and not NFTs, assessed only the hippocampus, or viewed cognitive status as a dichotomous variable. Studies not shown in Table 5 include the seminal articles of Blessed et al (254), Roth et al (255), and Tomlinson et al (38, 256), which found a correlation between dementia severity and amyloid plaques counted in cerebral cortex (with the caveat described previously), and previous studies that had also helped to establish the connection between A β Ps, NFTs, and antemortem cognitive impairment (311-320).

Diversely designed studies from at least 18 different research centers have produced high-quality data with some common conclusions, notably that the density of neocortical NFTs is the pathologic feature that best correlates with antemortem cognitive status (Table 5). The correlation is less strong for neuritic A β Ps, and less still for diffuse A β Ps. Hippocampal pathology is nearly universal in AD cases, yet AD neuropathologic changes in hippocampus do not correlate as well as neocortical pathology with cognitive status at any stage of the disease due to floor and ceiling effects. Finally, it is critically important to take into account concomitant pathologies that contribute substantial “noise” to the system.

There are increasingly detailed and insightful assessments of both clinical and neuropathologic parameters, combined with more optimal subject recruitment, improved testing for new disease entities, and well-powered sample sizes. All of these factors help us to perform more valid analyses and generate consistent data. The overwhelming conclusion from many academic centers around the world is that AD neuropathologic changes, especially in the advanced stages of the disease (i.e. with abundant neocortical diffuse and neuritic A β Ps and NFTs), correlate with the severity of antemortem cognitive impairment.

EVOLVING CONCEPTS AND UNANSWERED QUESTIONS

The field of AD research has made progress with respect to in vivo diagnostic methods to track the progression of AD and to identify patients who may benefit from candidate therapies. For the most part, these methods, which include neuroimaging, cerebrospinal fluid, and blood markers, are beyond the scope of the current review. Nonetheless, the strong focus on neuroimaging and biomarkers has raised important issues about the basic concept and definition of AD. There may be a future method that does not involve brain autopsy and that is optimized for diagnosing specifically the devastating illness that we refer to as AD. However, until such a method becomes available, neuropathologic examination remains the criterion standard for disease definition. Because cognitive impairment in aging may be attributed to many different conditions other than AD, current biomarkers for AD are limited to predicting which patients may become cognitively impaired with neocortical A β Ps and NFTs, rather than just predicting cognitive impairment alone. For example, hippocampal atrophy is visualized on magnetic resonance imaging in both AD and hippocampal sclerosis patients and is therefore not a distinct AD biomarker. This is an important consideration because up to 20% of individuals in advanced age are affected by hippocampal sclerosis that correlates with cognitive impairment independently of AD pathologic diagnosis (105, 211, 321-323). A patient lacking AD pathologic diagnosis at autopsy, despite “biomarker positivity,” is not an AD case and suggests the biomarker has imperfect specificity. Conversely, AD pathologic diagnosis at autopsy in a biomarker-negative case implies imperfect sensitivity. Moreover, it is important to remember that AD is often mixed with other pathologies in the aging brain; thus, the finding of a positive biomarker for AD will not eliminate the need for autopsy studies. Indeed, there are still also no recognized biomarker-based criterion standards for a large number of other neurodegenerative tauopathies, synucleinopathies, and vascular brain changes.

There are limitations to CPC studies and significant questions remain unanswered at this time. Pathologic assessments cannot prove molecular mechanisms; instead, they identify and describe deviations from what is recognized as “normal.” We try to understand these changes by using an array of immunohistochemical and experimental methods. Although the density of neocortical NFTs and neuritic AβPs on autopsy correlate with the severity of cognitive dysfunction, and the observed results align with a plausible hypothesis, this does not prove that these pathologic hallmarks are proximate to the ultimate neurotoxic species. Moreover, we still seek answers to the following critical questions: What biochemical changes are upstream of the formation of NFTs and AβPs? What exactly is the role of pretangles in the pathologic process? What processes occur in parallel with “classic” neuropathologic lesions? And, why are some cell populations differentially vulnerable?

SUMMARY AND CONCLUSIONS

Summary points are presented in Table 6. Neuropathology of aging-related brain disease must take into account diverse medical, technical, biochemical, and anatomic considerations. Concomitant pathologies are very common in aging brains. These diseases and many other factors collectively are formidable obstacles to aligning pathology and cognition along strictly linear scales. Although copathologies (CVD, hippocampal sclerosis, synucleinopathies, etc.) contribute to cognitive impairment, the universal observation of a strong independent correlation between plaques and tangles with dementia severity (despite the “background noise”) means that AD neuropathologic changes are likely significant. An extensive literature on CPC correlations related to AD dementia, a body of research-based on work performed around the world with many thousands of patients, indicates a sequence that may begin with specific genetic and environmental factors that increase risk of widespread AβPs. Neuritic plaques combine extracellular Aβ deposition and intracellular neurofibrillary (tau protein) pathology. Cross-sectional data indicate that pretangles and NFTs develop first in the brainstem and medial temporal lobe structures. Among patients with measurable clinical disease and lacking comorbidities, the extent of cognitive impairment parallels the severity of neocortical NFT pathology. In sum, there is a complex but predictable correlation between AD pathologic hallmarks and cognitive impairment.

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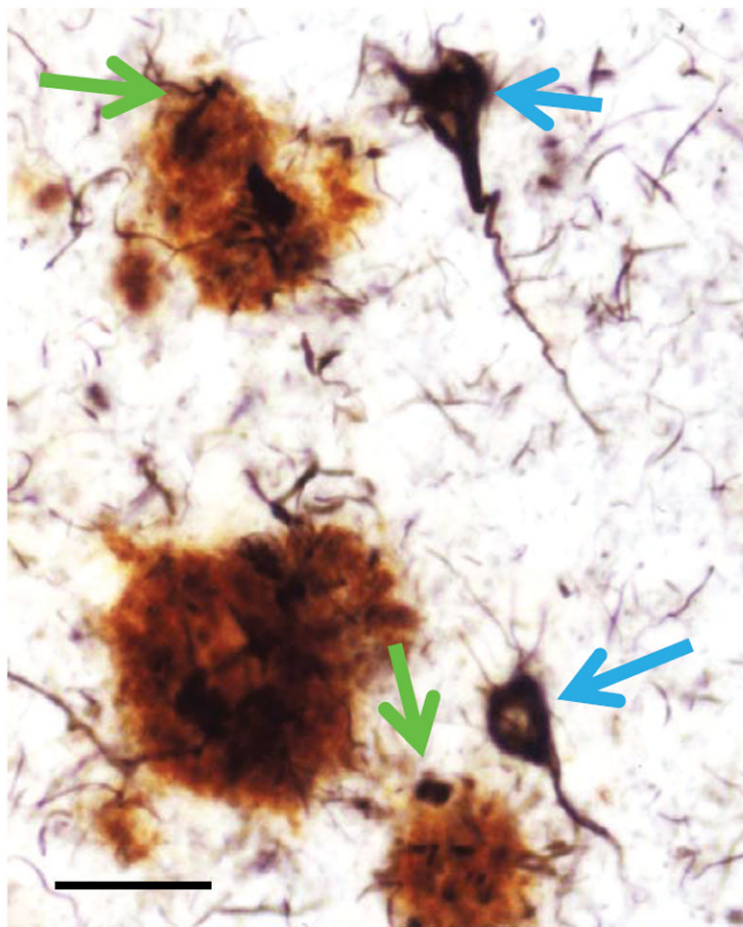
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Immunohistochemistry: A β (brown) and Tau (black)

FIGURE 1.

Photomicrograph of a section from the cerebral neocortex of an Alzheimer disease brain stained using double-label immunohistochemistry for β -amyloid (A β , reddish brown) and microtubule-associated protein tau (black). A β plaques (A β Ps; blue arrows) are roughly spherical and extracellular, whereas neurofibrillary tangles (NFTs; green arrows) develop within neurons. Note that some of the dystrophic neurites in the A β Ps contain aberrant tau protein pathology (black), which is biochemically identical to that seen in intracellular NFTs. These A β Ps have been described to be “neuritic plaques.” Scale bar = 50 μ m.

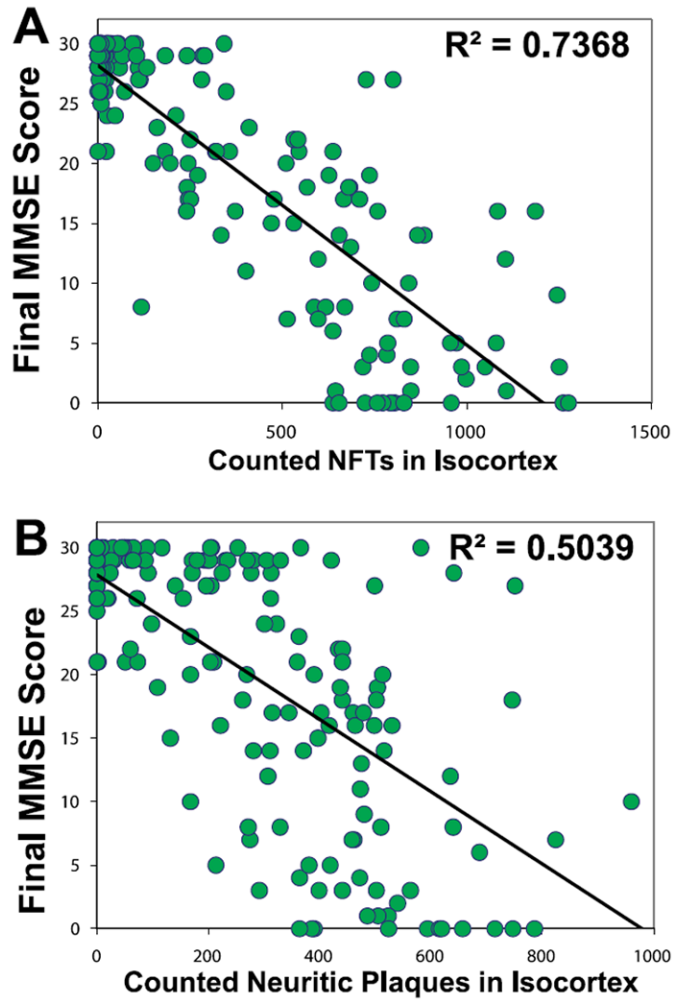


FIGURE 2.

(**A, B**) Correlations between antemortem cognitive status (final Mini-Mental State Examination [MMSE] scores), counted neocortical neurofibrillary tangles (NFTs; **A**), and neuritic β -amyloid plaques (NPs; **B**) for 178 patients lacking concomitant neuropathologic findings (189). Each circle represents data from a single individual. Neurofibrillary tangles and NPs were counted and summed from 4 different portions of cerebral neocortex: Brodmann areas 21/22, 18/19, 9, and 35, as described (189). Data are reprinted with permission from the *Journal of Neuropathology and Experimental Neurology* (2007;66:1136–46). Copyright 2007, American Association of Neuropathologists. The correlation between final MMSE scores and neocortical NFT counts is stronger than that between MMSE scores and NP counts.

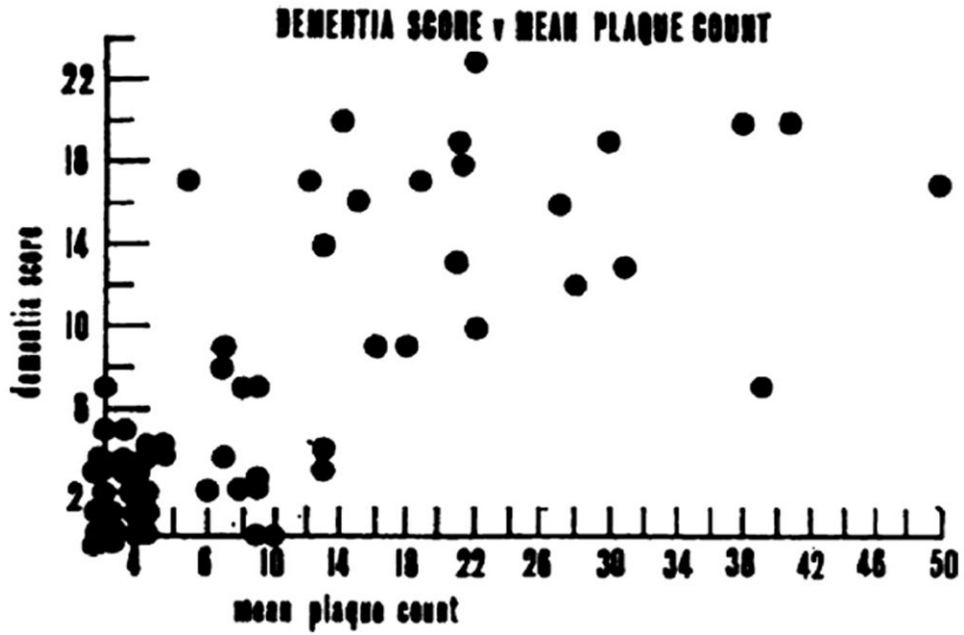


FIGURE 3. Correlations between antemortem cognitive status (“dementia scores”) and counted amyloid plaques from the 1968 article by Blessed et al (254). Dementia scores were derived from “psychological tests of orientation, remote memory, recent memory, and concentration.” Amyloid plaques were visualized using the von Braunmühl silver stain. Each circle represents data from a single individual. There is reasonable correlation between the dementia scores and the number of plaques, although this work antedated the era of neocortical synucleinopathy, TDP-43, and other factors now known to both clinicians and neuropathologists. This figure was reproduced with permission from *The British Journal of Psychiatry* (1968;114:797–811). Copyright 1968, The Royal College of Psychiatrists.

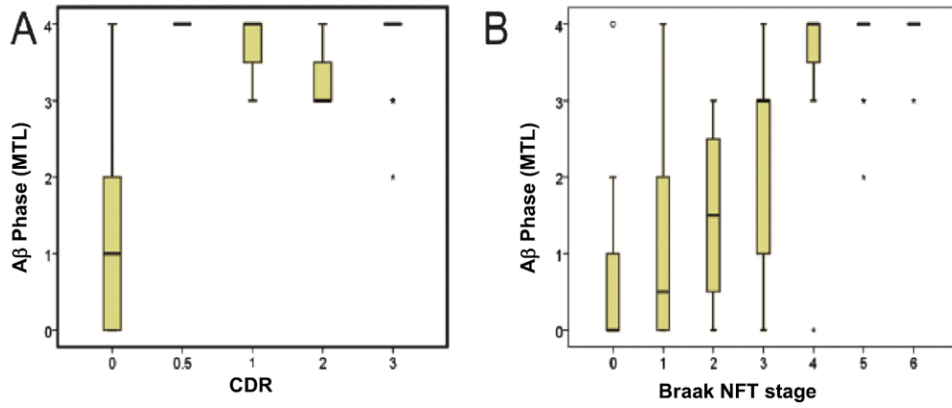


FIGURE 4. β -Amyloid (A β) phase showing the relationship between cognition, as represented by the retrospectively determined clinical dementia rating scale (CDR) score, and the phase of A β deposition determined in the medial temporal lobe (MTL) in 202 cases (103, 262). Non-Alzheimer disease (AD) dementia cases were excluded from this analysis. **(A)** Almost all demented cases exhibited end phases of the expansion of A β deposition without major differences; cases without dementia had early-phase A β pathology (partial correlation controlled for age and sex for all cases: $r = 0.582$, $p < 0.001$; only for AD cases: $r = 0.086$, $p = 0.605$). **(B)** Relationship between Braak neurofibrillary tangle (NFT) stage and A β phase in 201 AD and control cases. With increasing Braak ? NFT stage, the distribution of A β plaque deposition expanded to end-phase A β deposition reached with Braak NFT stage IV (partial correlation controlled for age and sex for all cases: $r = 0.621$, $p < 0.001$; only for AD cases: $r = 0.07$, $p = 0.671$).

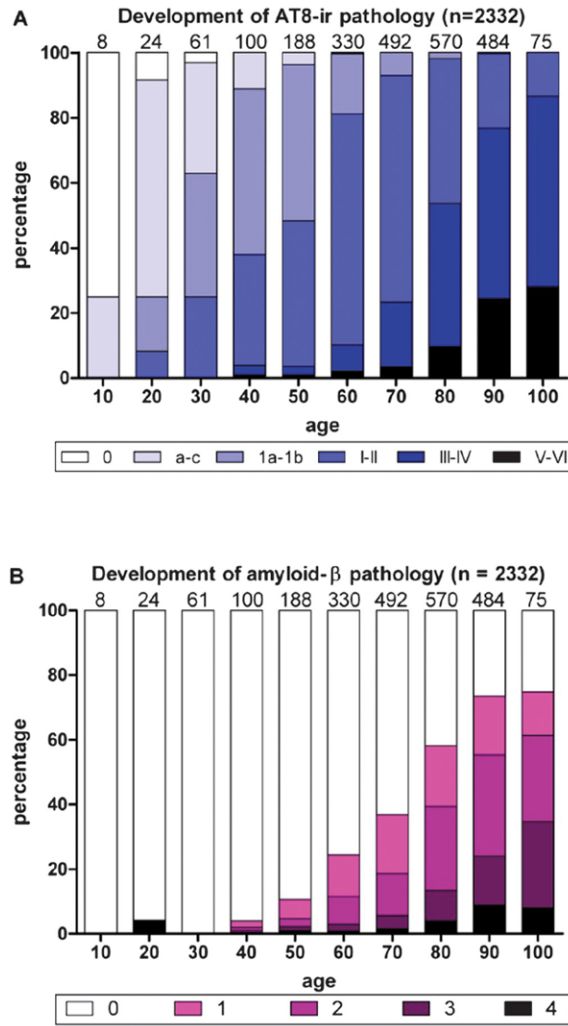


FIGURE 5. Development of phospho-tau (AT8)-immunoreactivity (ir) versus β -amyloid ($A\beta$) pathologic findings. **(A)** White columns indicate the relative frequency of 2,332 nonselected autopsy cases devoid of any abnormal intraneuronal tau deposits. Columns in shades of blue indicate the relative frequency of cases with all types of intraneuronal lesions (Braak NFT stages). **(B)** Development of extracellular $A\beta$ deposits. Purple areas within the columns indicate subgroups of cases showing plaque-like $A\beta$ -amyloid deposits in temporal neocortex (Phase 1, light purple), allocortex and neocortical association areas (Phases 2 and 3, middle purple and dark purple), or in virtually all cerebral cortical regions (Phase 4, black). Note the relatively late appearance of $A\beta$ plaques in comparison to subcortical neurofibrillary tangles. This figure is reproduced with permission from the *Journal of Neuropathology and Experimental Neurology* (2011;70:960–99) (44). Copyright 2011, American Association of Neuropathologists.

TABLE 1

Definition of Terms

Pathologic terms:

Neurofibrillary pathology: Neurofibrillary pathology comprises aberrant, partly insoluble, protease-resistant, hyperphosphorylated tau aggregates; by electron microscopy, some have a paired helical filament appearance inside various cellular compartments or extracellular after death of the parent cell.

Neurofibrillary tangles (NFTs) and pretangles: The term NFT describes neurofibrillary pathology found in cell bodies. A pretangle is contains abnormal hyperphosphorylated tau in nonfibrillar (partially soluble) and nonargyrophilic form. Some pretangles are capable of developing into NFTs.

Amyloid plaques that contain the A β peptide (A β Ps): A β Ps are extracellular, often roughly spherical structures containing A β peptide and other material. A β Ps in histological preparations may be detected using Congo red, silver stains, and thioflavin-like molecules. Diffuse A β Ps may be visualized using silver stains and anti-A β immunostains.

Neuritic A β plaques (NPs): NPs are A β Ps that are invested by swollen, degenerating neurites and glial cell processes. The swollen neurites may contain filamentous tau protein aggregates identical structurally to the inclusions within the NFT. The density of NPs is graded according to the Consortium to Establish A Registry for Alzheimer's Disease (CERAD) criteria (51). By definition, diffuse plaques lack dystrophic tau-immunoreactive neurites.

Braak stages: Braak stages (60) refer to the hypothetically predictable progression of NFT-type pathologic features in the brain during the course of Alzheimer disease (AD). In early stages (I–III), the pathologic finding is mostly isolated to the medial temporal lobe structures; later stages (IV–VI) progressively affect the neocortex.

Anatomic terms:

Medial temporal lobe structures (MTLs): MTLs comprise amygdala and allocortical structures including the entorhinal cortex, and the cornu ammonis (CA) fields and subiculum of the hippocampus. MTLs play an important role in consolidating short-term memory. Hippocampal pathology is ubiquitous in AD patients but is not relevant for clinicopathologic correlation due to strong “floor-and-ceiling” effects.

Isocortex or neocortex: “Neocortex” refers to the areas of cerebral cortex outside allocortical areas. Neocortical areas subserve high order functions including aspects of judgment and executive function. The distinction between MTL areas and neocortical areas is important in comprehending the predictable, but nonlinear, progression of pathology in AD.

TABLE 2

Sources of Potential Bias for Clinicopathologic Correlation Studies of Alzheimer Disease

Patient Characteristics	Clinical Workup	Study Design	Disease Heterogeneity	Pathologic Workup
>Baseline “cognitive reserve” and education-linked factors	>Quantification of “cognition”: nonparametric cognitive changes	>Recruitment, inclusion, and exclusion criteria	>Different genetic risk factors at play	>Evaluation and quantification of other pathologies
>Varied access to high-quality health care (diagnostics and therapeutics)	>Quantification of non-AD changes such as cerebrovascular disease	>Cross-sectional vs longitudinal assessments	>Some “atypical” forms of disease	>Focus on complete brain or mainly hippocampus
>Non-AD structural brain comorbidities (cerebrovascular, neurotrauma, etc)	>Cognitive assessment instruments used	>Focus on rare cases or attempting to understand “epidemiological” perspective	>Unknown effects of environmental factors	>Multiple methods to detect A β Ps and NFTs
>Emotional and mood disorders	>Individual clinician “thresholds”	>Bias in terms of autopsy rates	>Overlap and interplay between different diseases	>Skew toward end-stage disease at autopsy
>Systemic diseases that affect cognition (metabolic, hormonal, neoplastic, etc.)	>Variation among clinician practices	>Age of individuals in cohort at death	>Specificity of clinical, biomarker, and pathologic features	>Individual pathologist “thresholds”?
>Environmental and behavioral (substance abuse)	>Evolution in assessment methodology over time	>Definitions: “case” and “control” and other terms		>Variation among pathologist practices
>Cohort effects	>Use of biomarkers	>Interval between final clinic evaluation and death		>Accentuation nonhallmark lesions (acetylcholine, synapses)
	>Use of semiquantitative or ordinal variables	>Biostatistical methodology		>Quantitative or ordinal variables

A β P, amyloid β -containing plaque; AD, Alzheimer disease; CPC, clinicopathologic correlations; NFT, neurofibrillary tangle.

TABLE 3
 Alzheimer Disease Y-Linked Pathologic Features and Their Presence in Conditions That Have Pathologic Overlap With Alzheimer Disease

Clinical Condition	Neuropathologic Observation							References
	Diffuse A β Ps	A β Ps With Tau Neurites	Hippocampal NFTs	Neocortical NFTs	Hippocampal NFTs	Neocortical NFTs	References	
Alzheimer disease	+++	+++	+++	+++	+++	+++	This review	
“Oldest old” without dementia	±	--	+--	+	+	+	(172, 324, 325)	
Tangle-only dementia			+++	+	+	+	(116, 326)	
Dementia with Lewy bodies	+--	--	+	+	+	+	(327, 328)	
Chronic traumatic encephalopathy	+--	±	+--	+	+	+	(329-331)	
Niemann-Pick Type C	±	±	+	+	+	+	(332, 333)	
Guamanian amyotrophic lateral sclerosis parkinsonism/dementia syndrome	++	--	++	++	++	++	(334-338)	
Tauopathies: PSP, CBD, Pick disease, FTLD-MAPT	--	--	++	++	++	++	(37, 339, 340)	

A β P, neuritic and diffuse amyloid plaques containing A β peptide; FTLD-MAPT, frontotemporal lobar degeneration with mutation in *MAPT*; CBD, corticobasal degeneration; NFT, neurofibrillary tangle; PSP, progressive supranuclear palsy.

--, no disease-specific pathologic feature; ±, scattered or inconsistent pathologic features; +, low level of pathologic features; ++, moderate level of pathologic features; +++, high level of pathologic features.

TABLE 4

Distribution of Cases According to Braak Stages and Neuritic Amyloid Plaque Densities

	Neuritic Aβ Plaque Density			
	None	Sparse	Moderate	Frequent
Braak staging (NFTs)				
0	52	14	10	3
I	79	24	31	7
II	68	59	48	17
III	48	59	108	64
IV	22	41	160	158
V	0	25	134	553
VI	3	14	72	1,035

Data are from the National Alzheimer's Coordinating Center (n = 2,903 included, as described previously [282]) to show distribution of cases according to Braak stages (0 to VI) of neurofibrillary tangles (NFTs) (60) and neuritic amyloid (A β) plaque densities, graded according to Consortium to Establish A Registry for Alzheimer's Disease criteria (51).

TABLE 5

Large Clinicopathologic Studies of Alzheimer Disease

Study Institution	References*	Year	N	Avg Int	Methodological Considerations†	Main Finding(s) Correlating AD Pathology to CI
Harvard Medical School	(261)	1991	56	NR	C-S, QP	NFT > total amyloid plaques correlate with dementia severity
Oxford Project to Investigate Memory and Aging	(296, 341)	1995	86	NR	L, BP	NFTs > NPs > total amyloid plaques correlate with dementia severity
Mount Sinai ADRC	(291, 342, 343)	1995	70	NR	C-S, QP, cognitive status based on chart review	NFTs >> AβPs correlate strongly with CI
Albert Einstein	(154, 155, 251)	1995	45	11.7	L, QP	NFTs > AβPs correlate strongly with CI
Vienna Longitudinal Study on Dementia	(98)	1996	122	6.8	L, QP	NFTs > AβPs correlate strongly with cognitive status
Washington University ADRC	(225, 344)	1998	199	NR	L, QP	Correlation to CI: NFTs > “cored senile plaques” > total senile plaques
Nun Study	(109, 151, 288)	1999	495	9.6	L, CC, QP, only (female) nuns	NFTs correlate best with CI; all cases above threshold demented
Cambridge, UK Group	(345)	2000	48	<12	L, BP	NFTs ~ NPs > total amyloid plaques correlate with global “clinical severity” of AD
Mayo Clinic ADC	(346)	2002	67	0.7	L, BP	Significant correlation between Braak stage and CI
Rush University	(190, 264, 347, 348)	2004	652	8.2	L, CC, QP	NFTs > NPS correlate with CI
University of California, San Diego, ADRC	(106)	2004	131	8.5	L, QP	NFTs correlate best with late AD CI, but NPs correlate better in early disease
Honolulu-Asia Aging Study	(349)	2005	333	16.0	L, CC, QP, only males	NFTs and NPs far more dense in subjects with than those without dementia Caveat: many concomitant pathologies
Adult Changes in Thought	(108, 350)	2007	211	<24	L, BP, CC	NFTS (Braak stage) correlates with CI much stronger than AβPs
University of Kentucky ADC	(105, 189)	2007	334	13.1	L, QP	NFTs correlate best with cognitive status; all cases above threshold demented
Combined ADC project	(54)	2009	97	0.7	Various, QP, Subjects without dementia only	Presence of diffuse amyloid plaques correlates with subtle CI
Banner-Sun Health Research Institute	(252, 351) (258)	2010	150	12.5	L, QP, BP	NFTs > AβPs correlate strongly with CI
Baltimore Longitudinal Study on Aging	(161, 188)	2010	209	8.8	L, BP	NFTs in neocortex the key correlate of CI across the aging spectrum including past 90 y
90+ Study	(191)	2011	108	5	L, QP, BP	Neocortical NFTs and hippocampal sclerosis key CI correlates in aged group

* References refer to the most relevant articles. See text for inclusion and exclusion criteria.

⁷Methodological considerations: A β P, neuritic and diffuse amyloid plaques containing A β peptide; AD, Alzheimer disease; ADC, Alzheimer Disease Center; ADRC, Alzheimer Disease Research Center; Avg Int, average documented interval between death and autopsy in months; BP, pathology assessed using Braak stages (60); CC, community-based cohort; C-S, cross-sectional; CI, cognitive impairment; L, longitudinal; N, number of subjects in most relevant and recent article; NFT, neurofibrillary tangle; NP, neuritic plaque; NR, not recorded; QP, quantitative pathology (lesion counts).

TABLE 6

Summary Points

-
- There are 2 separate, important subtypes of AD neuropathologic changes, i.e., neuritic and diffuse amyloid plaques containing A β peptide, and NFTs (including pretangles), which develop in different patterns in AD brains
 - Evidence from CPC studies strongly support the existence of a specific, prevalent disease defined by the presence of clinical dementia, neuritic A β plaques, and NFTs in the neocortex
 - It is extraordinarily rare for a case with widespread, dense AD-type neocortical lesions to lack documented antemortem cognitive decline
 - With some notable exceptions (e.g. elderly schizophrenia patients, substance abusers, systemic disease), no significant subset of patients with severe age-associated cognitive decline exists that lacks any pathologic substrate when modern methods (i.e. immunohistochemistry) are used in the neuropathologic examination
 - It is best that AD not be regarded as a hippocampal disease because the disease process does not exert its full impact without extension into the neocortex, where correlation is stronger between clinical and pathological observations
 - There are prevalent (more than two thirds of patients) comorbidities, including cerebrovascular diseases, synucleinopathies, tauopathies, frontotemporal lobar degeneration, and TDP-43-related diseases, in the brains of aged persons that inevitably skew correlations between neuropathologic findings and cognition
 - CPC studies, like biomarker studies of living patients, must consider the long prodromal phase of AD during which AD pathology is accumulating but is not yet clinically manifest as overt cognitive impairment
-

AD, Alzheimer disease; CPC, clinicopathologic correlation; NFT, neurofibrillary tangle.