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Perspective

Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development

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Abstract

Dementia is often characterized as being caused by one of several major diseases, such as Alzheimer's disease (AD), cerebrovascular disease, Lewy body disease, or a frontotemporal degeneration. Failure to acknowledge that more than one entity may be present precludes attempts to understand interactive relationships. The clinicopathological studies of dementia demonstrate that multiple pathologic processes often coexist.

How overlapping pathologic findings affect the diagnosis and treatment of clinical AD and other dementia phenotypes was the topic taken up by the Alzheimer's Association's Research Roundtable in October 2014. This review will cover the neuropathologic basis of dementia, provide clinical perspectives on multiple pathologies, and discuss therapeutics and biomarkers targeting overlapping pathologies and how these issues impact clinical trials.High prevalence of multiple pathologic findings among individuals with clinical diagnosis of AD suggests that new treatment strategies may be needed to effectively treat AD and other dementing illnesses.

Keywords: Alzheimer's disease (AD); Cerebrovascular disease; Lewy body disease; Frontotemporal degeneration; β-amyloid; Tau; α-Synuclein; TDP-43

1. Introduction

Converging research has shown the complexity of multiple pathologic substrates underlying clinical Alzheimer's disease (AD), with closely related and perhaps synergistic pathologic

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processes often involved. A better understanding of these co-pathologies (i.e., cerebrovascular disease, Lewy bodies [LBs], hippocampal sclerosis [HS] with or without TAR DNA-binding protein 43 [TDP-43] inclusions, non-AD tauopathies, neuroinflammation, etc.) could influence clinical trial strategies and outcomes and lead to novel therapeutic approaches.

2. Methods

How overlapping pathologic findings affect the diagnosis and treatment of clinical AD and other dementia phenotypes was the topic taken up by the Alzheimer's Association's Research Roundtable in October 2014. The meeting provided a forum for experts from academia, industry, funding and regulatory agencies, and payer groups to consider the implications of overlapping pathologic findings on the discovery of new drug targets, therapeutic approaches, trial designs, and the regulatory approval of new drugs. The objective of this article is to provide a summary of the topics discussed at the Research Roundtable meeting and provide a review of the latest understanding of these issues and their implications for drug development in AD.

3. Discussion

3.1. The neuropathologic basis of dementia

Although neuropathologic diagnosis is considered the gold standard for determining the etiologic cause of a dementia syndrome, this approach has limitations. Neuropathologic examination is the only technique that enables visualization of abnormal structures at a microscopic level—plaques, tangles, LBs, neuronal loss, infarcts, etc.—yet it provides only a snapshot of the brain at one point in time. Neuropathology provides limited information regarding the age of lesions, their relationship to one another over time, or their relationship to the real-time clinical characteristics of the disease. Longitudinal cohort studies with annual testing have improved clinical correlation with pathology. Indeed, observational studies such as the longitudinal Nun Study, which began in 1986 with annual examinations and by 1997 included autopsies on 146 participants, found pathologic indicators of AD even in the brains of cognitively normal individuals evaluated clinically proximate to death [1]. These studies, along with amyloid positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarkers, support the concept of preclinical disease which is now codified into the revised National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic guidelines [2–4].

After the publication of the revised diagnostic criteria, it became clear that the criteria for postmortem pathologic diagnosis of AD also required updating to reflect knowledge that has accumulated since the last consensus criteria were published in 1997 [5]. These new criteria, also proposed by an NIA-AA working group [6], aim to disentangle the clinicopathologic term "Alzheimer's disease" from the neuropathologic changes seen in the AD brain, including brain lesions that reflect comorbid conditions that are common among the elderly.

These new criteria recommended classifying "AD neuropathologic change (ADNC)" according to three different staging schemes: the distribution of amyloid β (Aβ) deposits with Thal stages [7], neurofibrillary pathology with Braak stages [8,9], and the presence and severity of neuritic plaques according to the Consortium to Establish a Registry for Alzheimer's Disease [10]. Combining results from these three variables yields an estimate of no, low, medium, or high ADNCs. Those with intermediate or high ADNC are considered to have sufficient pathology to confirm a clinical diagnosis of AD dementia during life. The working group also made recommendations regarding how to report findings for common comorbidities, including Lewy body disease (LBD), vascular brain injury (VBI), and HS, and other neuropathologic findings such as TDP-43 inclusions and argyrophilic grain disease (AGD). LBD, VBI, HS, and TDP-43 inclusions have all been shown to independently contribute to cognitive impairment [11–14], whereas the clinical significance of AGD is less well established [15].

The new NIA-AA neuropathologic criteria for AD reflect recent studies suggesting that a minority of persons with clinical diagnosis of AD have "pure AD," that is, only plaque and tangle pathology. For example, in the State of Florida Department of Elder Affairs Alzheimer's Disease Initiative (ADI) Brain Bank at Mayo Clinic in Jacksonville, which in 2014 included 1242 brains collected from memory disorders clinics across the state, fewer than half of all patients with a primary pathologic diagnosis of AD had "pure AD" neuropathology (Fig. 1) (unpublished data).

Another analysis by the Religious Orders Study (ROS) and the Rush Memory and Aging Project found that 45.8%

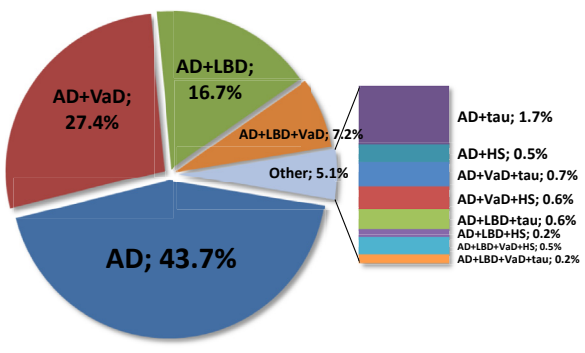

Fig. 1. Multiple pathologic findings when AD is present. A total of 1242 brains were included: all Braak stage IV or greater and Thal phase 3 or greater. Eighty-six percent of patients had a primary clinical diagnosis of dementia and 14% were diagnosed with parkinsonism. "Tau" indicates argyrophilic grain disease, an age-associated medial temporal tauopathy. Abbreviations: AD, Alzheimer's disease; VaD, vascular dementia; LBD, Lewy body disease; HS, hippocampal sclerosis.

of individuals with probable AD dementia and 19.4% of those with mild cognitive impairment (MCI) had multiple pathologies [16]. Other studies have shown that between 30% and 57% of brains with AD pathologic diagnosis have TDP-43 pathology in the medial temporal lobe [17,18] and that cases with TDP-43 pathology have greater regional brain atrophy and more severe cognitive impairment [18–20]. The most significant predictor of TDP-43 pathology in AD is HS [21]. In the Florida ADI Brain Bank, HS was detected in 20% of patients with dementia [22]. In a separate study, almost half of AD cases were shown to have LBs. LB copathology in AD is further classified based on the anatomic distribution of LBs: brainstem, limbic, or diffuse cortical. In some cases, LB copathology in AD is confined to the amygdala. Such cases are sometimes classified as the LB variant of AD [23].

The Rush study also examined the influence of overlapping pathologic processes on cognitive impairment. The majority of patients with an antemortem clinical diagnosis of AD dementia were found to have multiple pathologies at autopsy, with about half having, in addition to AD, one or more of the following: LBs, TDP-43, HS, and vascular diseases. Each pathology appears to have separate but additive effects on cognition. How these different pathologic processes interact remains unclear, although some experimental data suggest that Aβ deposition may affect tau [24,25] and α-synuclein accumulation [26].

Moreover, the distribution of neurofibrillary tangles in patients with AD does not always conform to typical Braak staging. A study that queried the brain bank database at the Mayo Clinic in Jacksonville, FL, found that of 889 AD cases studied, about a quarter fell into two "atypical" patterns: 11% had hippocampal sparing (HpSp) and 14% had limbic-predominant (LP) tangle pathology [27]. Interestingly, the HpSp subgroup experienced more rapid decline, whereas the LP subgroup showed a slower rate of decline. Those in the HpSp subgroup also tended to be younger, more often present with nonamnestic clinical syndromes, and showed shorter disease duration and less concurrent pathology.

Vascular lesions are also frequently comorbid with AD and contribute to cognitive decline. In the ADI analysis, 44% of AD cases also had vascular pathology, including 28% with small-vessel disease (lacunar infarcts, microinfarcts, or cribriform change), 12% with severe leukoencephalopathy, 10% with severe amyloid angiopathy, 2% with large-vessel infarcts, and <1% with large hematomas (personal communication, presented at Research Roundtable by Dennis Dickson). The ROS/Rush study measured different frequencies: among patients with probable AD, approximately one-third had gross infarcts, one-fourth had microinfarcts, and about one-third had moderate-to-severe cerebral amyloid angiopathy (CAA) [28]. In addition, one-third of probable AD patients had moderate-to-severe atherosclerosis and moderate-to-severe arteriolosclerosis.

3.2. Clinical perspectives on multiple pathologies

The prevalence of most neuropathologic findings increases with age. Therefore, the high rate of multiple pathologies found in neuropathologic studies, such as those described previously, may be related to the high mean age of death (mean ~90 years) of participants in most autopsy studies [14]. At the other end of the spectrum, clinical research typically involves younger patients with fewer comorbid pathologic findings, meaning that the problem is less of an issue in younger dementia patient cohorts. Researchers should consider copathologies in clinical trials, although the prevalence and impact may be lower in a younger population than the autopsy studies, composed of older populations, may suggest.

According to data collected by the National Alzheimer's Coordinating Center using the 1997 NIA-Reagan neuropathologic criteria as the gold standard [5], the sensitivity of clinical diagnosis of AD ranged from 70.9% to 87.3% and the specificity ranged from 44.3% to 70.8% [29]. Among those subjects who were misdiagnosed, the primary neuropathologic findings were tauopathies such as AGD, as well as frontotemporal lobar degeneration (FTLD), cerebrovascular disease, LBD, and HS.

FTLD comprises a family of disorders, differentiated clinically by behavioral, language (semantic or agrammatic), or parkinsonian variants (progressive supranuclear palsy and corticobasal degeneration). The neuropathologic diagnosis of FTLD is further broken down by the presence of tau, TDP-43, or the RNA-binding protein fused in sarcoma (FUS) pathology [30]. The links between clinical phenotype and pathology vary for each syndrome, and both the clinical and pathologic features overlap with AD. When evidence of both frontotemporal dementia (FTD) and AD pathologic processes coexists in a patient, both may contribute to the clinical phenotype [31].

LBD symptoms can be differentiated by fluctuating cognition, visual hallucinations, Parkinsonism, and rapid eye movement sleep behavior disorder. While most non-AD pathologic processes increase with age, LB frequency either plateaus or declines in older cohorts, further complicating diagnosis when multiple pathologies are present. Neuropathology studies have found divergent results regarding the clinical effects of concomitant LB pathology in AD. Some studies report that the combination of AD and LB pathology affects the cognitive presentation of dementia [32,33] but not the rate of cognitive decline [33]. However, one recent study failed to find clinical or neuropsychological predictors that could differentiate between AD with or without concomitant LB [34].

In AD, TDP-43 pathology is found in about 20% to 50% of AD brains, particularly in the amygdala and medial temporal lobe [18,35], and correlates with more rapid cognitive decline, even after controlling for other pathologies, particularly in the domains of episodic and working memory (Fig. 2) [20]. Moreover, TDP-43 deposition appears to progress in a stereotypic manner similar to tau, which

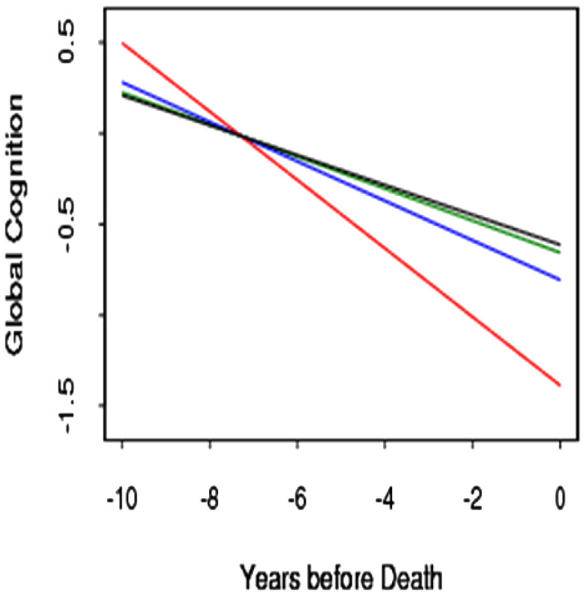

Fig. 2. Ten-year paths of global cognitive decline in 130 participants from the Religious Order Study with varying levels of TDP-43 pathology, adjusted for age at death, amyloid, tangles, and hippocampal sclerosis. Black line, no TDP-43; green line, 10th percentile; blue line, 50th percentile; and red line, 90th percentile TDP-43 [20].

gives rise to a staging scheme [18] that correlates with cognition, memory loss, and medial temporal atrophy [36].

The presence of FTLD or LBD pathology can be predicted albeit with moderate sensitivity and specificity, on clinical grounds. For cerebrovascular disease, the Hachinski Ischemic Score has been widely used to identify vascular dementia on clinical grounds but also with only moderate sensitivity and specificity for separating pure AD from AD with cerebrovascular copathology [37]. The addition of magnetic resonance imaging (MRI) allows identification of clinically unrecognized brain infarcts, microbleeds, and white matter hyperintensities of presumed vascular origin. However, MRI signs of cerebrovascular disease may not always be clinically relevant for cognition, and our understanding of the relationship between cerebral small-vessel disease burden and risk for dementia is incomplete. Furthermore, commonly available MRI (1.5 or 3.0 T) cannot detect microinfarcts, which are very common and are associated with dementia risk [38]. Therefore, MRI is a useful adjunct to increase the sensitivity for detection of cerebrovascular disease but still does not capture the full spectrum of cerebrovascular pathology. In the ROS, macroscopic infarcts, microinfarcts, and CAA were independently and additively associated with antemortem cognitive decline and/or risk for dementia, including when AD pathology was additionally present [39–41]. In clinical trials, comorbid cerebrovascular pathology could affect trial results or even obscure beneficial effects on AD if there are off-target drug effects. For example, patients with CAA appear to be at higher risk for amyloid-related imaging abnormalities in AD immunotherapy trials [42].

3.3. Therapeutics/targeting overlapping pathology

Emerging evidence suggests that AD and other neurodegenerative diseases may be driven by cell-to-cell transmission of pathologic proteins such as Aβ, tau, α-synuclein, and TDP-43 [43]. These proteins appear to become pathologic through conformational changes such as misfolding, oligomerization, fibrillization, and aggregation. These abnormal conformers then appear to serve as seeds or templates for assembly of additional protein aggregates that can be transmitted neuron to neuron [44–46]. This process could explain the spatiotemporal progression of pathology in the brain. While the mechanisms of this process are only beginning to be understood, it has nevertheless given rise to novel therapeutic approaches. For example, antibodies or small molecules may be generated that target different protein structures, either stabilizing them so they do not form fibrils or aggregates or by preventing their transmission [47,48]. Clinical trials are already in progress testing this strategy. For example, there is a phase 1 trial of an antibody against α-synuclein in patients with Parkinson's disease (PD) (NCT02095171 and NCT02157714), antitau antibodies have shown promising results in animal models of tauopathies [49], and early human studies are just getting underway.

Elucidating the mechanisms whereby abnormal conformers of key pathogenic proteins induce neurodegeneration could also reveal new treatment approaches. Toxicity from the RNA-binding protein TDP-43, for example, appears to result from both gain- and loss-of-function mechanisms, with posttranslational modifications conferring toxic properties that disrupt normal transport of mRNA to the synapse [50]. The mechanisms of TDP-43 misregulation and propagation are unknown. New animal models and a TDP-43–specific imaging agent could speed the identification of therapeutic targets and the development of new drugs.

Targeting amyloid in the vasculature presents additional complexity. In the ROS/Rush studies mentioned earlier, CAA was present in about 80% of individuals at autopsy, and the severity of CAA correlated with cognitive impairment [51]. Candidate treatment approaches to prevent deposition of Aβ in the arteries include approaches that reduce Aβ production, increase its clearance, or block its toxicity. Immunotherapy approaches to clear amyloid from the vessels could have negative consequences, such as increasing the risk of amyloid-related microbleeds as noted by imaging abnormalities [42,52].

Vascular pathology caused by atherosclerosis, arteriosclerosis, or embolism is the only common comorbid pathology of AD that is potentially treatable with current pharmacotherapies and lifestyle modification. However, although there is some evidence that blood pressure control may prevent dementia, there is not yet strong evidence for treatment of other vascular risk factors [53]. Investigators planning future trials in AD may wish to take steps to ensure that vascular risk factors are balanced between randomized

groups and to implement prospective standardized protocols to ensure similar treatment of blood pressure and other vascular risk factors in all trial patients.

Treating the comorbid pathologic processes so common in AD and related neurodegenerative diseases may ultimately require combination therapy; however, evaluating the effectiveness of combination approaches presents challenges in both drug discovery and clinical trials. For example, there currently are no accepted animal models that reflect therapeutic pathways for testing treatments or understanding multiple pathologies. As a result, combinatorial approaches may have to be advanced to human studies by demonstrating target engagement in humans.

3.4. Biomarkers and imaging

Progress in understanding nonamyloid pathologic processes and developing treatments for them requires improved biomarkers and imaging tools. Recent advances in developing radioligands for tau PET imaging, for example, may enable the differential diagnosis of the various tauopathies [54]. Although tau is molecularly heterogeneous, low in abundance, and found intracellularly, several tau radioligands are currently in development [55–57].

Novel methods for imaging vascular cognitive impairment are also emerging, including higher resolution imaging to resolve small infarcts and white matter lesions; physiologic imaging approaches such as cerebral blood flow and permeability; and diffusion tensor imaging and resting-state functional MRI to assess structural and functional connectivity [58]. However, spatial resolution limits will continue to prevent direct measurement of microinfarcts, whose mean diameter may be as small as 200 microns [59]. Functional imaging of the dopaminergic system using 123I-FP-CIT SPECT (DaTscan™, GE Healthcare, Chicago, IL, USA) may be used to identify dopaminergic deficiency in parkinsonian diseases, including LBD [60], but it remains to be determined how this technology can be used to identify concomitant LB pathology in AD patients.

Several studies have shown that the CSF biomarkers $A\beta_{1-42}$, tau, and phosphorylated tau may detect AD neuropathology and be useful in clinical practice for diagnosis and prognosis even in early disease stages [61–65]. These CSF biomarkers may also aid in differential diagnosis of AD versus other dementias and other neurologic diseases [66]. However, very few studies have examined CSF biomarkers in AD patients with well-defined copathologies, especially with neuropathologic confirmation. In a study of 142 autopsy-confirmed dementia patients (with 38 patients with AD with LBD or FTLD copathology), CSF $A\beta_{1-42}$, tau, and phosphorylated tau had robust sensitivity and specificity in AD with coincidence of other pathologies but did not differentiate between pure AD and AD with copathologies [67]. Likewise, in autopsy-characterized subjects from Alzheimer's Disease Neuroimaging Initiative, CSF $A\beta_{1-42}$, tau, and phosphorylated tau did not differ between pure AD and AD with coincident TDP-43 or LB pathology [63]. Novel CSF biomarkers are needed for in vivo identification of copathologies in AD patients. One candidate is CSF neurofilament light protein (NFL), which may indicate damage of large-diameter myelinated axons and white matter lesions [68]. Specifically, high CSF NFL levels are seen in FTD [69], especially in tau-negative FTLD [70], and in patients with small-vessel disease in the brain, including AD dementia with vascular copathology [71]. CSF NFL may also provide prognostic information because it correlates with higher mortality in patients with and without AD [71]. Another candidate biomarker is CSF α-synuclein, which is reduced in the presence of LB pathology [72,73]. Several studies have found reduced levels of CSF α-synuclein in synucleinopathies (including LBD, PD, and multiple system atrophy) compared with AD [73–76]. Hypothetically, this could inform on LB copathology in AD because LBD-like symptoms are correlated with lower CSF α-synuclein levels in AD dementia patients [77]. However, two neuropathologic studies did not find any difference in CSF α -synuclein levels between AD patients with and without LB copathology [63,75]. The use of CSF α-synuclein is complicated by several confounding factors, including increased CSF α-synuclein as response to neuronal injury [78,79] and susceptibility to analytical factors, especially blood contamination of CSF [80]. Other α-synuclein–related biomarkers, including α-synuclein oligomers, may be more specific to the presence of LB pathology [81]. Recently, CSF biomarkers of synaptic function have been developed and tested in AD [82,83], but studies on differential diagnosis and copathologies are lacking. Likewise, CSF markers of inflammation [84] and microglial function [85–87] are altered in AD and may be explored further for differential diagnosis and tested in autopsy-confirmed subjects.

3.5. Implications of multiple/variable pathologies on clinical trials

Multiple pathologic processes have substantial implications on the design of clinical trials. Because the various pathologic processes have additive effects on cognition, when enrolling a heterogeneous population, greater numbers of subjects will be needed to achieve the power necessary to see an effect from an agent targeting just one pathology (e.g., amyloid) that is related to decline. Study cohorts in which diagnostic heterogeneity is not well defined could also lead to erroneous conclusions because decline may be different among the various subgroups. Although randomization should equally allocate both measured and unmeasured accompanying pathologies between treatment arms and thus prevent confounding, the potential for off-target drug effects on accompanying pathologic processes could lead to erroneous conclusions. The alternative—screening out individuals with non-AD pathologies including cerebrovascular disease—comes with its own set of problems,

including extremely high numbers of screen failures, the potential to eliminate decliners, and the resulting lack of generalizability because so many people with these other pathologic findings also have AD. Another alternative may be clinical trials focused on people with sporadic early-onset AD, that is, onset before 65 years of age, which may reduce the likelihood of copathologies. The current trend is to intervene early in the disease process when amyloid and/or tangles may not have reached some theoretical critical threshold. However, the slope of decline is less steep, requiring even more power to see an effect. In fact, treatment in secondary prevention or primary intervention typically translates into longer treatment periods and larger patient numbers to detect the smaller absolute change on outcome measures.

Postmortem pathology studies have been invaluable in illuminating underlying disease processes, and there was a suggestion that signed intent of willingness of participants to enroll in a brain donation program should be required for participation in a clinical trial; however, this requirement could complicate recruitment and retention efforts, and it would take many years to accrue sufficient postmortem examinations, particularly in trials enrolling MCI patients. It is worth noting that this has not been an impediment to development of neuroimaging markers [88].

In the future, disease-modifying trials will need to be large, and international trials will be needed, increasing the variability across centers. Identifying people who are likely to have progressive disease will thus become even more important for early disease treatments. Although the expertise for identifying such subjects has largely been located in academic medical centers, these centers have not demonstrated the ability to enroll the large numbers of subjects needed. Better education of general neurologists and general practitioners could help rectify this problem by encouraging them to refer potential subjects for clinical trials. There are also systems-based barriers that hinder enrollment in clinical trials because detailed interviews are needed to evaluate and accurately diagnose patients. On the other hand, clinicians in current medical practice are often incentivized to see more patients in less time.

Although investigators debate the pros and cons of testing drugs in homogenous versus heterogeneous populations, they agree on the need for better imaging and fluid biomarkers for vascular disease, tau, α-synuclein, and TDP-43. In addition, even if the trial targets one pathologic process, measuring markers of other pathologies will undoubtedly lead to improved understanding of the results of interventions and prepare the field for future treatments that target multiple pathologies simultaneously.

4. Conclusions

The criteria used to classify neurodegenerative diseases are based on the assumption of unitary clinicopathologic syndromes—namely that the underlying neuropathology can be accurately predicted based on the clinical phenotype and that, as Occam's razor would postulate, a dementia syndrome in an individual patient is due to a single neuropathologic process. However, postmortem studies have revealed the real picture to be much more complex. The relationship between clinical syndrome and underlying neuropathology is probabilistic rather than deterministic: the same phenotype can be caused by different pathologies, and the same pathology can produce different phenotypes. Furthermore, a dementia syndrome is uncommonly related to a single process: Multiple pathologies seem to be the rule rather than the exception, especially in older individuals.

Multiple pathologic findings also complicate clinical trials. Although extremely common, they are mostly undetectable with current clinical, imaging, or fluid biomarker tools. New tools are needed to evaluate proteins other than amyloid and tau and to distinguish clinically relevant from "silent" cerebrovascular disease. If these tools were available and used to exclude subjects with multiple pathologic findings, the remaining cohort would likely not be representative of larger population of elderly individuals with dementia.

Roundtable participants debated the question of whether clinical phenotyping has limited promise in therapy development. They concluded that clinical phenotyping remains important and may itself be considered a biomarker, but biochemical and imaging biomarkers that can detect multiple pathologies are also needed to enable the development of better treatments. The challenge to the field is to define different etiologies according to the most definitive available biomarkers and then to assess how those biomarkers are affected by disease-modifying therapies.

In terms of therapy development, the high prevalence of multiple pathologic findings among individuals with clinical diagnosis of AD suggests that treatments for each pathologic entity may need to be developed, as well as treatments that target upstream or downstream events such as inflammation, network dysfunction, neurochemical changes, synaptic loss, and neuronal death. These treatments may then need to be used in combination to effectively treat and eventually cure AD and other dementing illnesses.

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RESEARCH IN CONTEXT

1. Systematic review: This review summarizes the presentations made at the October 2014 Research Roundtable meeting. Each presenter reviewed the literature of recent work of their specific topic area within the overall area of how overlapping pathologies affect the diagnosis and treatment of clinical Alzheimer's disease (AD) and other dementia phenotypes.
2. Interpretation: This article posits that dementia syndrome is most commonly related to multiple pathologies especially in older individuals, rather than a single process.
3. Future directions: A better understanding of the complexity of clinical phenotypes is needed. Biochemical and imaging biomarkers that can detect multiple pathologies may help enable the development of better treatments.

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