ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2016) 1-9

Alzheimer's & Dementia

Perspective

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

Gil D. Rabinovici[a], Maria C. Carrillo[b], Mark Forman[c], Susan DeSanti[d], David S. Miller[e], Nicholas Kozauer[f], Ronald C. Petersen[g], Christopher Randolph[h,i], David S. Knopman[g], Eric E. Smith[j], Maria Isaac[k], Niklas Mattsson[l,m], Lisa J. Bain[n], James A. Hendrix[b,*], John R. Sims[o]

[a]*Memory & Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA*
[b]*Alzheimer's Association, Chicago IL, USA*
[c]*Merck, Kenilworth, NJ, USA*
[d]*Piramal Pharma, Inc., Boston, MA, USA*
[e]*Bracket Global, Wayne, PA, USA*
[f]*Quintiles, Rockville, MD, USA*
[g]*Department of Neurology, Mayo Clinic and Foundation, Rochester, MN, USA*
[h]*MedAvante, Hamilton, NJ, USA*
[i]*Department of Neurology, Loyola University Medical Center, Maywood, IL, USA*
[j]*Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada*
[k]*European Medicines Agency (EMA), London, UK*
[l]*Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden*
[m]*Department of Neurology, Skåne University Hospital, Lund, Sweden*
[n]*Independent Science Writer, Elverson, PA, USA*
[o]*Eli Lilly & Co., Indianapolis, IN, USA*

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

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the official position of the European Medicines Agency or any of its Committees or Working Parties.

*Corresponding author. Tel.: ■■■; Fax: ■■■.
E-mail address: jhendrix@alz.org

http://dx.doi.org/10.1016/j.trci.2016.09.002

pathologic processes often involved. A better understanding of these copathologies (i.e., cerebrovascular disease, Lewy bodies [LBs], hippocampal sclerosis [HS] with or without 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%

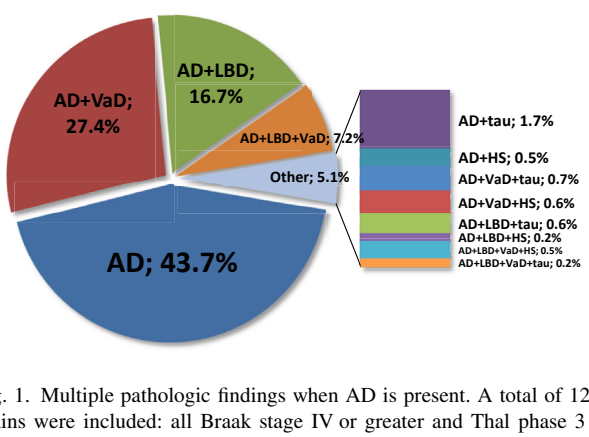

Fig. 1. Multiple pathologic findings when AD is present. A total of 1242 brains were included: all Braak stage IV or greater and Thal phase 3 or greater. Eighty-six percent of patients had a primary clinical diagnosis of dementia and 14% were diagnosed with parkinsonism. "Tau" indicates argyrophilic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