






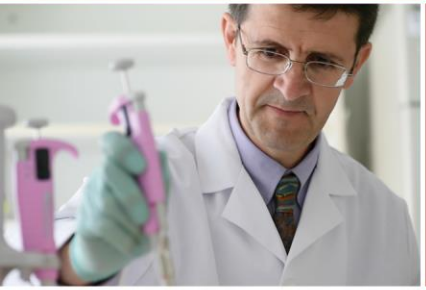


2024 Fall ADRC Meeting

October 15-17, 2024, Boston, MA

Associate Dean for Gerontology
Director, Wisconsin Alzheimer's Disease Research Center
UW School of Medicine and Public Health, Madison, WI

NIH National Institute on Aging DESIGNATED Alzheimer's Disease Research Center

Wisconsin Alzheimer's Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosure

- I have received funding from the NIA/NIH, Department of Veterans Affairs, State of Wisconsin, and UW-Madison to support my research program
- UW-Madison has received funding from pharmaceutical companies for me to serve as a site PI to conduct treatment trials involving patients with MCI and dementia
- I have no conflicts of interest for this presentation

Overarching Scientific Theme

Biomarkers of non-AD Coexisting Pathologies

- The scientific theme permeates many sessions of this 2-day meeting
- Theme aligned with the Spring ADRC meeting that focused on TDP-43

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Biomarkers of Co-existing Pathologies: Rationale as a Scientific Theme

Coexisting pathologies in people with AD dementia are common and reportedly occur in both early (EOAD) - and late-onset (LOAD) AD
Frequently reported coexisting pathologies include vascular lesions, Lewy body disease, TDP-43, Cerebral amyloid angiopathy (CAA), α synuclein, Hippocampal sclerosis, argyrophilic grain disease (AGD), aging-related tau astrogliopathy (ARTAG), etc.
Mixed brain pathologies account for most cases of dementia in community-dwelling older persons *(Schneider et al. Neurology 2007:69; 2197-2204)*
In early- and late-onset AD, at least one coexisting pathology is seen between 98-100% of patients, respectively (*Salvatore Spina et al. Brain 2021:144;2186-2198)*

Biomarkers of Coexisting Pathologies: Rationale as a Scientific Theme

Coexisting pathologies are **not "innocent bystanders",** they have a major impact on clinical phenotype, including a) severity of symptoms, b) disease progression, c) response to treatment, and d) overall mortality

Effective treatment of AD **must include** treatment of coexisting pathologies

The distribution of coexisting pathologies and their interactions among themselves and with AD proteinopathies has major impact on disease course
(Thal et al. Brain 2021:144; 700-711)

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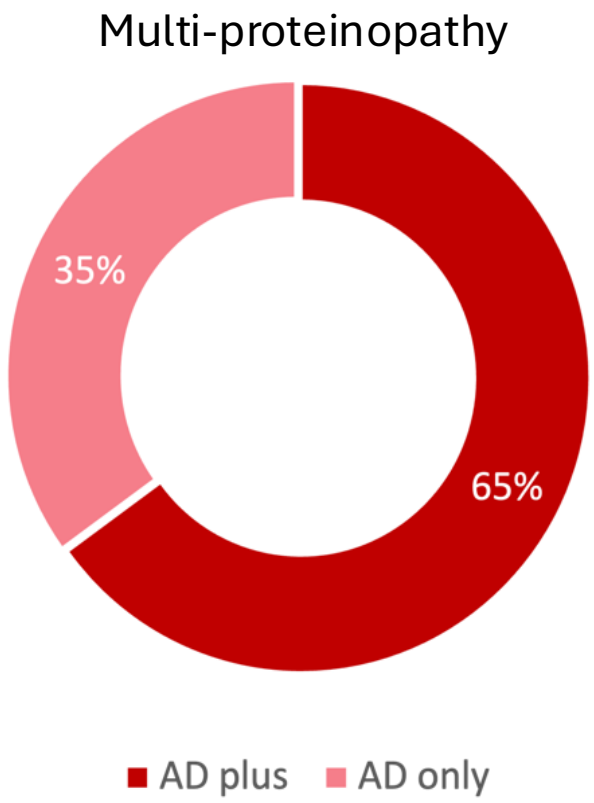
How common are mixed causes of dementia?

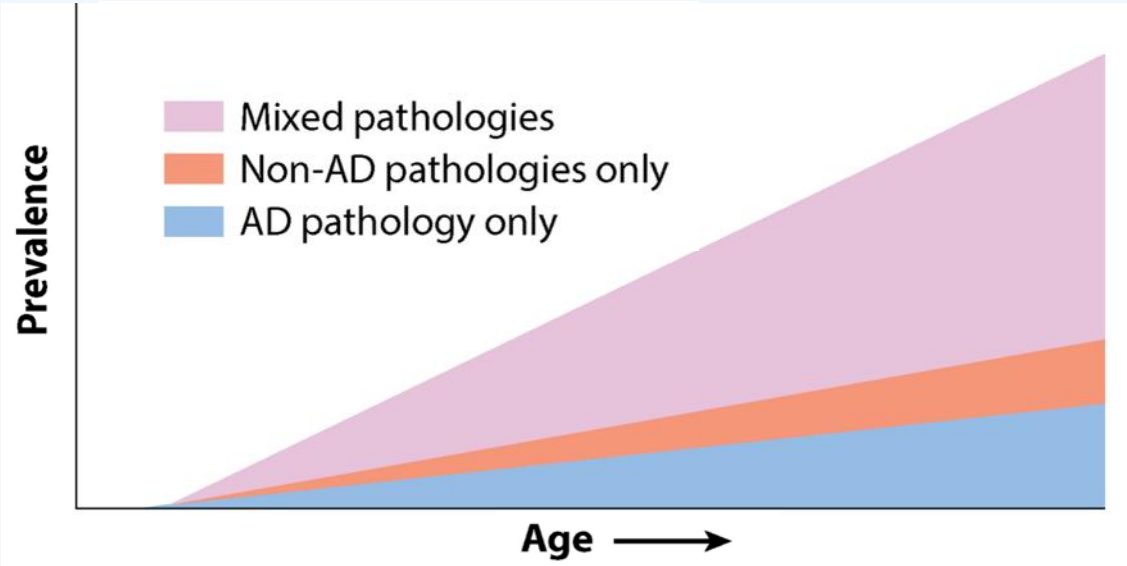


- AD only = 35%
- AD with [TDP43, or LB, or both] = 65%
- AD with Lewy Body disease = 46%
- AD with TDP43= 36%
- AD with both TDP43 and LB = 20%

Woodworth et al 2024, Acta Neuropathologica

CLARiTI Focuses on Mixed Causes of Dementia

Mixed Etiology Dementia is Common



Common co-occurring pathologies

- Cerebrovascular disease
- Lewy Body or Neuronal Synuclein Disease (NSD)
- Frontotemporal lobar degeneration (FTLD)
- LATE (TDP-43)

65% of people with autopsy proven Alzheimer's also have another proteinopathy

75% of people with proven AD also have vascular changes

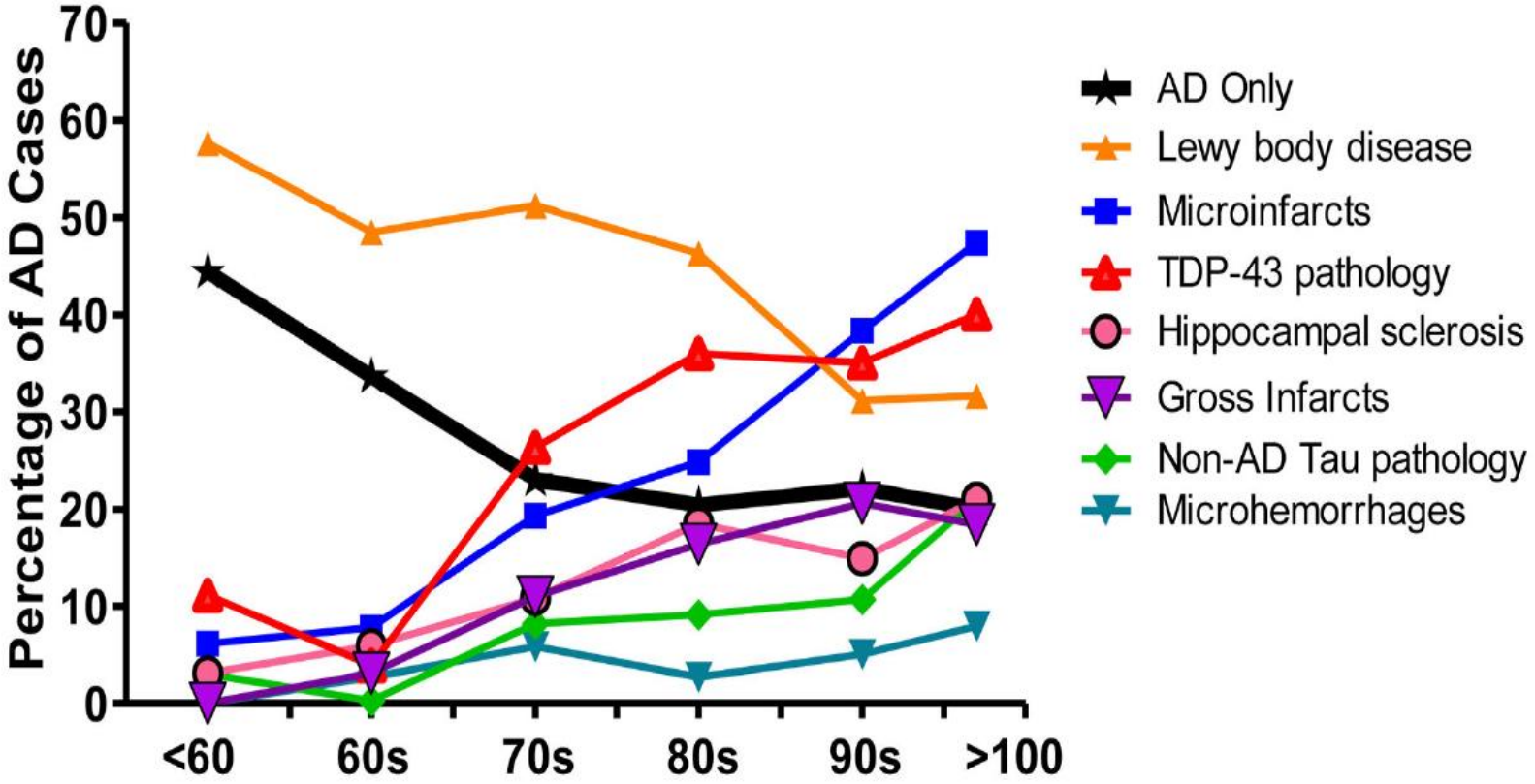
GOAL

Detect the presence of other diseases that may co-occur with Alzheimer's disease

Enroll 2000 participants from across the ADRCs in the US

Mix Pathologies Source: 2024 Alzheimer's Association Report
https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Age-Associated Prevalence of AD and Non-AD Coexisting Pathologies



Thomas Beach et al. J Alzheimer Dis. 2021, 79(1); 389-400

<u>Younger Patients (<65)</u>

- Lewy body disease

<u>Older Patients (>65)</u>

- Hippocampal sclerosis
- TDP-43
- Microinfarcts and gross infarcts
- Non-AD Tau pathology

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Biomarkers of Coexisting Pathologies: Relevant Presentations

A) SCIENTIFIC PRESENTATIONS

- **Pathology Validation of AD Biomarkers Vs. Neuropathology**
  - Speaker: Dr. Renaud La Joie, UCSF ADRC
- **Significance of Diversifying ADRC Cohorts**
  - Speaker: Dr. Rosie Curiel Cid, 1Florida ADRC
- **Advances in Biomarkers of Alpha Synuclein**
  - Speaker: Dr. Kathleen Poston, Stanford ADRC

B) PANEL DISCUSSION

Title: Understanding Mixed Pathologies: Translation to Clinical Practice

Chair: Dr. Gil Rabinovici

Panel members: Drs. Renaud Lo Joie, Rosie Curiel Cid, Kathleen Poston, Ganesh Babulal, Astrid Suchy-Dicey, Edward Lee