Session Identifier: B.3
Session Theme: Biomarkers and Brain Health
Thursday, June 16, 2016
1:30 p.m. – 3:00 p.m.

Relationship between Frailty and Biomarkers of Alzheimer's disease: A Scoping Review

Lindsay M K Wallace, Dalhousie University; Dr. Olga Theou, Dalhousie University; Dr. Kenneth Rockwood, Dalhousie University; Dr. Melissa Andrew, Dalhousie University

Background & Purpose: Mechanisms of development and progression of Alzheimer's disease (AD) are poorly understood, hindering progress in treatment options. The purpose of this scoping review is to investigate the association between frailty and biomarkers of AD in order to better understand its pathophysiological trajectory. Methods: Pubmed, Embase, and PsycInfo were searched using the following medical subject headings and their synonyms: 'frail elderly; AND 'alzheimer disease'; AND 'neuropathology'. Searches using synonymous text words were also carried out. Selection was limited to original articles involving humans, published in English up to November 2015. All studies including measures of frailty and any biomarkers of AD (including: amyloid-beta 42 or tau cerebrospinal fluid measurements, PiB PET amyloid imaging, FDG PET imaging, structural MRI showing selective atrophy; McKhann et al., 2011, *Alzheimers Dement*) were included. Two independent reviewers completed a two-step screening process (title and abstract, full-text) to avoid bias and all disagreements in screening were resolved by consensus. Results: Our search identified 368 references for inclusion, 285 articles were excluded during screening of titles and abstracts (142 were not original articles, 12 did not have human subjects, 45 did not measure frailty, and 86 did not measure biomarkers). Full-text screening was completed on the 83 remaining articles. Seven articles were not written in English, 39 were excluded because they were not original research, one because it did not have human subjects, 13 did not measure frailty, and 12 did not measure AD-related biomarkers. This left 8 articles included in the study for data extraction. Data on study population characteristics, number of participants, design (cross sectional vs. longitudinal), length of follow-up (where applicable), type of frailty measure, type of biomarker(s), outcome measures and results were extracted and categorized accordingly. This scoping review sheds light on the complex relationship between biomarkers of AD and frailty and identifies gaps in our knowledge to direct future research.

Frailty, Neuropathology, and Dementia Disease Expression

Dr. Kenneth Rockwood, Dalhousie University; Judith Godin, Nova Scotia Health Authority; Dr. Melissa Andrew, Dalhousie University; Dr. Joshua Armstrong, Dalhousie University

Although a number of studies have linked frailty with cognitive impairment, fewer studies have examined these constructs together in relation to brain health. With the understanding that there is an inexact correlation between neuropathological lesions and cognitive function in late-life, examining autopsy data through the lens of frailty may provide novel insights. Here, we examine the National Alzheimer's Coordinating Center (NACC) database to evaluate the variance in clinical outcomes explained by frailty, after accounting for neuropathology. METHODS Health assessment data from the last visit prior to death was linked to

neuropathology information collected at autopsy in the NACC. An accumulation of health deficits frailty index (FI) was developed using 30 assessment variables. Hierarchical multiple regression models were developed to evaluate the separate impact of control variables (age, sex, education), neuropathology, and frailty on clinical outcome measures. RESULTS After accounting for the control variables, seven neuropathological markers accounted for a significant amount of variation in both the Mini-Mental State Exam (MMSE; R2 change = 0.24) and Clinical Dementia rating (CDR; R2 change = 0.21) scores. When the FI was added to these models, the FI accounted for a significant amount of additional variation in both the MMSE (R2 change = 0.07) and CDR (R2 change = 0.14) scores. DISCUSSION Inclusion of frailty reduced the explanatory power of neuropathology on clinical outcomes. Additional analyses using the NACC may provide further insights into the relationships between frailty, aging, neuropathology, and cognition in older adults.

Development of PET Probes for Alzheimer's Disease

Dr. Sultan Darvesh, Dalhousie University; Dr. Ian Pottie, Mount Saint Vincent University; Dr. Terrone L. Rosenberry, Mayo Clinic; Earl Martin, Mount Saint Vincent University

Background: Alzheimer's disease (AD) is a common neurodegenerative disorder. Definitive diagnosis of AD requires post mortem neuropathology analysis. Observation shows cholinesterases associate with Alzheimer neuropathology and can distinguish AD characteristics from those in normal aging. Hypothesis: Positron emission tomography (PET) scanning probes targeting cholinesterases can effect definitive diagnosis of AD during life. Theoretical framework: Substituted 2,2,2-trifluoro-1-phenyl-1-ethanones have been shown to strongly bind to cholinesterases. Radioactive 18F-, incorporated into such compounds, could provide PET images of brain cholinesterase activity indicative of AD. Methods: This work describes development of "cold" (19F) techniques to simulate eventual radioactive 18F incorporation into substituted 2-chloro-2,2-difluoro-1-phenyl-1-ethanones. Specifically, all derivatives were produced using a Weinreb amide synthetic strategy. Synthesized products underwent biochemical investigations to test affinity towards cholinesterases. All chlorodifluoro precursors were tested for incorporation of "cold" nucleophilic fluoride (19F-) to produce corresponding trifluoro compoundsResults: Substituted 2-chloro-2,2-difluoro and 2,2,2-trifluoro-1-phenyl-1-ethanones were produced in 50-80% yields. All compounds showed affinity towards cholinesterases. To simulate production of radioligands, fluoride (19F-) incorporated into chlorodifluoro precursors produced trifluoro compounds in acceptable yields. Structures were validated spectroscopically. Conclusions: Weinreb amide strategies produces substituted 1-phenyl-1-ethanones in good yields. These structures have sufficient cholinesterase affinity to hold promise as PET imaging agents for AD diagnosis. Educational significance: New synthetic strategies have generated substituted 2-chloro-2,2-difluoro-1-phenyl-1-ethanones as precursors for PET radio imaging agents for AD that are amendable to incorporation of radioactive fluorine. Practice implications: Early, non-invasive diagnosis of AD promises timely interventions and the ability to test more effective therapeutic approaches to the disease.