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Pathologies Underlying Longitudinal Cognitive Decline in Oldest Old

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Abstract

Background: Understanding contributions of different brain pathologies to domain-specific cognitive trajectories in the oldest old is crucial to guide future intervention studies.

Methods: Two-hundred-twenty Oregon Alzheimer's Disease Center research participants who were cognitively intact at entry were followed on average for 7.3 years with annual neuropsychological testing until death (mean age 93.7 years) and autopsy. Mixed-effects models

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Dr. Nguyen is the primary author on this manuscript. She was involved in the design and conceptualization of the study, and drafted the manuscript. She has no disclosures.

Ms. Mattek was involved in the design and conceptualization of the study, drafting the manuscript and statistical analysis. She has nothing to disclose.

Dr. Woltjer contributed to data analysis and made substantive contributions in revising the manuscript for intellectual content. He has no conflicts to disclose.

Dr. Diane Howieson participated in initial design and conceptualization of the study and made substantive contributions to revising the manuscript for intellectual content. She has no conflicts of interest.

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examined the relationship between trajectories in memory, verbal fluency and Mini Mental State Exam (MMSE) and pathology (neurofibrillary tangles (NFTs), neuritic plaques (NPs), gross infarcts, hippocampal sclerosis (HS) Lewy bodies (LBs), APOE genotype, age at death and years of education. The association between the MMSE trajectory and pathological variables were examined using a Poisson model with MMSE errors as outcomes given the nonlinear distribution of MMSE scores.

Results: Memory trajectory was associated with the APOε4 allele (p=0.006). Verbal fluency trajectory was associated with gross infarcts (p=0.008). MMSE trajectory was associated with high Braak scores (p=0.03), gross infarcts (p<.0001), HS (p=0.003), moderate NPs (p=0.04) and the APOε4 allele (p=0.02).

Conclusions: The association between trajectory of decline in global cognitive scores and multiple brain pathologies highlights the importance of accounting for co-morbid pathologies in therapeutic trials aimed at one-specific pathology in the oldest old. Only the APOε4 allele showed an association with memory decline, despite accounting for AD pathology, suggesting that APOE may be involved in mechanisms beyond amyloid metabolism in its role in memory. Further studies are needed to examine the role of APOE in brain aging.

Keywords

Neuropathology; cognition

Introduction

As the number of individuals who live to 80 years old (oldest old) is rapidly increasing[1], the need for effective treatments for cognitive decline and dementia in this age group is crucial. Treatments targeting Alzheimer's disease (AD) pathology such as anti-amyloid or anti-tau antibodies are being tested and may become available in the near future. While these will likely have a major impact on individuals with pure AD it is less clear what their impact will be on the oldest old, more than half of whom have non-AD brain pathologies that can affect cognitive function [2–6] . Thus, it is crucial to understand the impact of different pathologies on rate of domain specific cognitive decline in the oldest old. Few studies have examined contributions of individual pathologies to domain-specific cognitive decline.[3–7]

In this study, our aim is to determine the contributions of different brain pathologies on domain-specific cognitive decline in a well-defined community-based cohort of oldest old individuals followed up to 20 years and who had brain autopsies upon death. We chose to focus on two cognitive outcomes: memory and verbal fluency (as a proxy for executive function and language), because these represent cognitive domains that are affected at different stages through the course of AD and other brain disease of aging, and were available in the datasets we examined. We also aim to determine whether the APOE ε4 genotype is associated with cognitive decline independent of common age-related pathologies. Only a few studies have examined its effect on domain-specific cognitive decline in the oldest old. [8–10] Our previous work suggests that the presence of the APOE ε4 allele contributes to the presence of brain atrophy and increase in white matter changes over

time in old age independent of underlying pathologies.[11,12] We wanted to determine whether this observation would hold true for cognitive decline as well.

Better understanding of the contributions of select pathologies and APOE genotype to domain specific cognitive decline will help: 1) improve selection of cognitive outcomes used in treatment trials aimed at select pathological targets, and 2) take into consideration the effects of APOE genotype on domain-specific cognitive decline in clinical research studies.

METHODS

Participants:

Participants included in this study were older adults who were followed until death as part of longitudinal aging studies at the Oregon Alzheimer's Disease Center (OADC)[13–16] and who had brain autopsy data available at the Oregon Brain Bank. Participants were derived from four studies: Klamath Exceptional Aging Project (KEAP), Oregon Brain Aging Study (OBAS), Intelligent Systems for Assessment of Aging Changes (ISAAC), and ORCATECH Life Laboratory Cohort. The OBAS, ISAAC, and ORCATECH study cohorts consist of participants recruited from the Portland, Oregon community. The KEAP study is a joint venture between the OADC in Portland and the Merle West Center of Medial Research in Klamath Falls, Oregon that recruited rural participants. These studies were approved by the Oregon Health & Science University (OHSU) institutional review board. Cohort description, recruitment and assessments are described in earlier publications. [13–16] Briefly, trained clinicians examined volunteers annually obtaining medical history, performing clinical and cognitive assessments including dementia staging, and neuropsychological test batteries that cover key domains.[17–21] From the available psychometric tests, which varied from study to study, we identified those that were consistently administered during follow up. These included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory delayed recall [19], Category Fluency: Animals [20] and MMSE.[21]

Those meeting the following criteria were included in the current study:

1. Cognitively intact at entry to the study (defined as Clinical Dementia Rating scale[18]=0)
2. Eighty years or older at the time of death in order to capture the oldest old
3. Available autopsy data
4. Annual cognitive evaluations with the last evaluation within 24 months of death.

Three-hundred-nine participants met inclusion criteria. Of these, 89 were excluded due to missing APOE genotype, missing pathology data or no follow-up evaluations. Two-hundred and twenty participants with complete data were included in our analysis. There were no differences in age, gender or education among those included vs. excluded in our analysis.

Neuropathologic methods.

Brains were examined for NFT and NP pathology and staged by Braak and CERAD systems.[22,23] Neuropathological evaluation of participants has been described previously.

[24].Brains were fixed in neutral-buffered formaldehyde solution for at least two weeks and examined grossly as well as microscopically. For microscopic evaluation, tissue samples were taken from all cortical lobes bilaterally or unilaterally, frontal lobe white matter, anterior cingulate gyrus, hippocampus, amygdala, bilateral striatum and thalamus, midbrain, pons, medulla, and cerebellum. Six-micrometer sections were routinely stained with hematoxylin-eosin, Luxol fast blue, Congo red-gallocyanin, and by the modified Bielschowsky silver impregnation method. Selected sections of hippocampus and neocortical regions were immunostained with antibody to tau (tau2, Sigma, St. Louis, MO). Clinical and pathologic diagnoses were established using current consensus criteria.[25–29] Information related to NP and NFT burdens, presence of ischemic, hemorrhagic, or vascular pathology, amyloid angiopathy, large vessel strokes, lacunes, presence of Lewy bodies (LB), hippocampal sclerosis (HS), and degree of arteriosclerosis were summarized using the National Alzheimer's Coordinating Center Neuropathology Data Form.[29]

Statistical analysis

Summary statistics were generated for total participant characteristics and pathological variables. Mixed effects models were used to examine the relationship between neuropathological characteristics and change over time in Word List Memory, Category Fluency, and MMSE using random intercept and random slopes. Independent variables of interest were interaction terms of time (i.e., age, centered at 85 years old) and (1) Braak score (divided into three groups: low- no NFTs or Braak stage 1 or 2 (reference group), moderate 3 or 4, and severe 5 or 6; (2) NP scores (divided into none/ sparse (reference group) or moderate/frequent); (3) presence or absence of gross infarcts (large vessel strokes or lacunes), (4) HS; (5) LBs and (6) APOE ε4 allele. Analyses were adjusted for age at death, education, education X time (age) interaction term, as well as pathology main effects because of their known effect on the outcomes of interest. Since MMSE did not have a normal distribution, we used a mixed effects Poisson model using errors in MMSE test scores as outcomes. Significance was set at $p \leq 0.05$. Analyses were performed using SAS software 9.4 (Cary, NC, USA).

Results

Participant Characteristics:

Mean age at death was 93.7 years (SD 4.5, Range: 80.3 – 105.2). Participants were followed for a mean of 7.3 years (SD 4.1, Range: 0.9 – 21.3). Time from last neuropsychological testing to death was on average 8.1 months (SD 5.4, Range: 0 – 24) (Table 1). Of the 220 participants cognitively intact at the time of enrollment, 156 (71%) developed cognitive impairment during follow up: eighty-three patients had mild cognitive impairment, 14 had a mixed dementia, 47 had AD, 4 had Lewy body dementia or Parkinson's disease related dementia and 8 had vascular dementia. Clinical diagnoses were made using established diagnostic criteria.[26–28]

Distribution of pathologies:

Seventy-three percent of the cohort was found to have Braak stage III or higher NFTs on autopsy. Gross infarcts were found in 44 participants (20%), HS was present in 15 (7%) and LBs were identified in 31 (14%).

Longitudinal Mixed- Effects Models presented in Table 3:

Word List Memory trajectory was associated with the APOε4 allele (p= 0.006). Category Fluency trajectory was associated with the presence of gross infarcts (p= 0.008). MMSE trajectory (measured using the Poisson model using errors in MMSE test scores as the outcome) showed an association with the presence of gross infarcts (p<.0001), HS (p=0.003), Braak NFT score 5 or 6 (p=0.03), moderate NPs (p=0.04) and the APOε4 allele (p=0.02) (Table 3).

Discussion

In this clinicopathologic study of over two hundred oldest old volunteers without cognitive impairment at baseline, whom we followed longitudinally with annual cognitive testing for up to 20 years, we found that NFT and NP burden, HS, and infarcts were associated with cognitive decline more globally, presence of gross infarcts were associated with a steeper decline in language based executive function (category fluency), while the APOε4 allele was associated with memory and global cognitive decline, even after accounting for age and pathology.

Our findings have several implications. The APOE genotype was associated with memory decline as well as global cognitive decline. Some studies support the idea that APOE exerts its risk on memory decline and AD through regulating Aβ aggregation and clearance.[30] For example, a study found that when controlling for global AD pathology the effect of the APOE ε4 allele on cognitive decline was attenuated.[31] In our study the effect of APOE was independent of NP burden or NFT stage. This discrepancy may be due to different approaches to examining and categorizing pathologies, and older age of our cohort. It is known that APOE not only increases the risk of AD but leads to an earlier age of onset. [32] Our participants were cognitively normal and on average 85 years old at the time of entry to the study and thus the influence of APOE on cognitive impairment in our study may be through other mechanisms independent of AD pathology (unlike younger old individuals), such as its role in synaptic integrity, regulation of the immune system, maintenance of vascular health.[33,34]

We found a correlation between gross infarcts and verbal fluency and global cognitive decline. The association between infarcts diagnosed during life and decline in executive function has been reported before. [35] Few studies however examined the correlation of postmortem cerebrovascular disease and clinical symptoms. One other study found an association between episodic memory and macroinfarcts, in a group of older adults who were cognitively intact at the time of death but did not find an association between micro or macroinfarcts and working memory, semantic memory, perceptual speed or visuospatial ability [3]. It is possible that these differences in observation are partially due to the location

of infarcts (which are not necessarily accounted for in either study), pathological assessment of infarcts (one versus two hemispheres), as well as the degree of cognitive impairment at death.

Last, we found that presence of infarcts, HS, high NP and NFT burden were all correlated with steeper global cognitive decline. Pathological case series suggest that HS of aging (HS-Aging) affects over 20% of those over 85 years old and the underlying pathology may be arteriolosclerosis or a proteinopathy with TAR DNA-binding protein 43 (TDP-43) pathology leading to neurodegeneration. [36] It is suggested that the clinical progression of HS follows that of a neurodegenerative disease and some studies have shown those with autopsy diagnosed HS having significant brain atrophy beyond the hippocampus. [37] This supports the hypothesis that in at least some patients HS-Aging is a more widespread brain disease, not limited to the hippocampus. Our findings of an association between HS and global decline are in accordance with this observation. Previous studies have linked HS with cognitive impairment ranging from delayed recall only to more global impairment likely reflecting the stages of the disease [36].

In our study NP and NFTs were only significantly associated with trajectory of global cognitive decline, but not trajectory of memory decline. It is possible that using semi-quantitative methods to measure these pathologies as opposed to quantitative approaches may have reduced our ability to find correlations between memory trajectory and NFTs and NPs. In our preliminary analyses (not shown here) when pathology main effects were not included in the mixed effects models, there were significant associations between higher NFT and NP burden and memory decline (data not shown), which suggests that there is some degree of association that is lost in a model either due to less power (i.e., more variables in the models) or high cross sectional correlation between pathology variables and memory score.

Our study has several limitations: focusing on a group of oldest old that came from a highly educated, mainly Caucasian volunteer cohort in relatively good health limits the generalizability of our results. Our sample size may have been too small to detect the effects of some pathologies on cognitive decline such as LBDs, which were categorized by presence rather than location due to small numbers. We did not assess TDP-43 lesion burden nor did we include other CVD lesions such as arteriolosclerosis which may modulate some of the observations between HS-Aging and cognitive decline. Last we were limited to two cognitive tests that were consistently available in the aging cohorts included for this study: CERAD Word List Delayed Recall as a single test for memory and Category Fluency as a single test representing language and executive function domains. Not having a battery of tests for each cognitive domain limits our findings to these specific tests.

Strengths of our study are that the oldest old participants were recruited from the community and documented to have normal cognition at the initiation of the study, were followed longitudinally with consistent cognitive testing, and underwent autopsy upon death, with a short interval between last assessment and death (8 months). This study group also represented urban and rural populations.

Our study adds to the mounting evidence that cognitive decline in oldest old is due to a variety of brain diseases, and targeting only one alone will likely only have partial if any impact on cognitive decline. Thus future clinical trials in AD need to consider the impact of including the oldest old and the confounding effect of pathologies that most of the time aren't adequately accounted for during life (such as HS-Aging or TDP-43 pathology). Finally, the APOE ε4 allele contributes to cognitive decline in the oldest old even after accounting for AD pathology, raising the need for future studies to better define the role of APOE in cognitive decline in the oldest old.

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Table 1.

Participant characteristics.

	Total N=220
Age at death, years	93.7 (4.5)
% Female	61%
Education, yrs	14.6 (2.7)
% with APOE ε4 allele	20%
Time from last evaluation to death (months)	8.1 (5.4)
Follow-up time, yrs	7.3 (4.1)
Baseline MMSE	28.3 (1.4)
Last MMSE	24.7 (5.1)
Baseline Word List Delayed Recall	6.1 (1.9)
Last Word List Delayed Recall	4.1 (2.8)
Baseline Animal Fluency	17.1 (4.8)
Last Animal Fluency	12.6 (5.6)

Table 2.

Number and percentage of neuropathologies

	Total N=220
Braak stage	
0/I/II	60 (27.3)
III-IV	107 (48.6)
V-VI	53 (24.1)
Neuritic plaques	
None	59 (26.8)
Sparse	78 (35.5)
Moderate	53 (24.1)
Frequent	30 (13.6)
Large vessel stroke	43 (19.6)
Lacunar stroke	44 (20.0)
Hippocampal sclerosis	15 (6.8)
Lewy bodies	31 (14.1)

Table 3.

Results of longitudinal mixed effects models for memory, verbal fluency, and Mini-Mental State Examination (MMSE) number of errors

	Word List Delayed Recall		Animal Fluency		MMSE*	
Variables	***β (SE)***	**p-value**	***β (SE)***	**p-value**	***β (SE)***	**p-value**
Time (Age centered at 85)	0.01	0.91	0.17	0.49	0.001	0.97
Braak III/IV vs 0/I/II × time	−0.01	0.82	0.09	0.42	−0.01	0.42
Braak V/VI vs 0/I/II × time	−0.07	0.26	−0.23	0.07	0.03	0.03*
Neuritic plaques (moderate /frequent vs none/sparse) × time	−0.08	0.10	−0.12	0.20	0.02	0.04*
Gross infarcts (present vs absent) × time	−0.06	0.22	−0.24	0.008*	0.05	<0.0001*
Lewy body (present vs absent) × time	0.07	0.26	−0.05	0.64	0.01	0.28
Hippocampal sclerosis (present vs absent) × time	−0.13	0.15	−0.28	0.11	0.06	0.003*
APOE ε4 allele (present vs absent) × time	−0.16	0.006*	−0.01	0.92	0.03	0.02*

Analyses were adjusted for education, education*time, pathology main effects and age at death

*Poisson model using errors in MMSE test scores as the outcomes (i.e. positive slope implies an increase in rate of errors on the MMSE and a decline in scores on the MMSE).