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Dementia From Alzheimer Disease and Mixed Pathologies in the Oldest Old

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To the Editor: The oldest old (≥90 years of age) are the fastest growing segment of the US population and account for half of all persons with dementia. Alzheimer disease (AD) is the most common pathology underlying dementia in the old (ages 65-89 years). Recent community-based autopsy studies[1,2] suggest the relationship between AD pathology and expression of dementia is attenuated in the oldest old.[3] Studies may be complicated by the common coexistence of AD plus infarct and/or Lewy body (LB) pathology (mixed pathologies).[4] Few data exist on mixed pathologies and dementia in the oldest old.[5] We examined the relationship of AD and mixed pathologies to dementia in the oldest old compared with the old. We tested the hypothesis that the clinical expression of AD and mixed pathologies differs across age groups.

Methods

We included 804 persons from the Religious Orders Study (n=456) and Rush Memory and Aging Project (n=348), ongoing longitudinal clinical-pathological studies of aging started in 1994 and 1997, respectively.[4] Both were convenience samples of community-dwelling older adults with high follow-up (>90%) and autopsy (87%) rates. All autopsied participants with complete data as of June 2, 2011 (93.7% of 858 autopsied) were included. Both studies were approved by the Rush University Medical Center institutional review board and all participants provided written consent.

Dementia was diagnosed using standard criteria (Table 1; last assessment: mean 7.1 months before death). Neuropathologic diagnoses were blinded to age and clinical diagnosis, using standard criteria (Table 1). Mixed pathologies included at least 2 of the following: a pathological diagnotisis of AD, infarct (macroscopic or microscopic), or neocorcal LB

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Study concept and design: James, Bennett, Schneider.
Acquisition of data: Bennett, Schneider.
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(identified on α-synuclein immunostaining) pathology. We report prevalence ratios from log-binomial regression models controlling for sex and education with interaction terms for pathology by age group. Analyses were performed using SAS version 9.2 (SAS Institute Inc). Testing was 2-sided with statistical significance threshold of α=.05.

Results

The oldest old (n=301; mean age=94.3 years) were more likely to be demented and to have pathological diagnoses of AD or infarct than the old (n=503; mean age=83.8 years) (Table 1). A pathological diagnosis of AD was associated with a higher prevalence of dementia in the old and the oldest old; however, the association was attenuated in the oldest old (model 1 in Table 2). In a model including pathological diagnoses of AD, infarct, and LB, all 3 pathologies were associated with dementia in the old and the oldest old, but only AD showed an interaction with age (model 2 inTable 2). Mixed but not single pathologies were more common in the oldest old, specifically AD plus infarct (Table 1). In both age groups, a pathological diagnosis of AD plus infarct and/or LB (mixed AD pathology) was associated with a higher prevalence ratio for dementia than a diagnosis of AD alone; however, the association of mixed AD pathologies with dementia was attenuated in the oldest old (model 3 inTable 2).

Comment

We found that a pathological diagnosis of AD was more common in the oldest old and strongly related to dementia. The increase in AD pathology in the oldest old was primarily in the form of mixed AD and infarct pathology, which was related to a higher probability of dementia than AD pathology alone. Thus, the proportional effect of AD pathology is high in the oldest old. Nonetheless, the relationship between a pathological diagnosis of AD and dementia was significantly attenuated in the oldest old compared with the old even after accounting for known mixed pathologies, suggesting additional factors in the pathogenesis of dementia in the oldest old.

Limitations include data from a volunteer cohort agreeable to autopsy and few minorities, which may limit generalizability. These data suggest that research on dementia in the oldest old should focus on AD, mixed pathologies, and exploration of additional factors in the pathogenesis of dementia in the oldest old.

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Table 1

Clinical and Pathological Characteristics at or Proximate to Death for Persons Younger Than 90 Years of Age at Death Compared With Persons Aged 90 Years or Older

Characteristic	Total (N = 804)	Age 65-89 (n = 503)	Age ≥90 (n = 301)	*P* Value[a]
Age at death, mean (SD), y	87.7 (6.7)	83.8 (4.8)	94.3 (3.3)	<.001
Sex, No. (%)				
Male	296 (36.8)	213 (42.3)	83 (27.6)	
Female	508 (63.2)	290 (57.7)	218 (72.4)	<.001
Education, mean (SD), y	16.5 (3.7)	16.7 (3.8)	16.2 (3.4)	.05
MMSE score, mean (SD) (range: 1-30)	21.9 (8.8)	23.5 (8.1)	19.2 (9.3)	<.001
Dementia, No. (%)[b]	304 (37.8)	143 (28.4)	161 (53.5)	<.001
Pathological type, No. (%)				
Any diagnosis[c]	599 (74.5)	351 (69.8)	248 (82.4)	<.001
AD[d]	493 (61.3)	279 (55.5)	214 (71.1)	<.001
LB (neocortical)	78 (9.7)	46 (9.2)	32 (10.6)	.49
Infarct[e]	272 (33.8)	147 (29.2)	125 (41.5)	<.001
Single pathologies	374 (46.5)	238 (47.3)	136 (45.2)	.56
AD (no infarct or LB)	271 (33.7)	167 (33.2)	104 (34.6)	.70
LB (no AD or infarct)	15 (1.9)	12 (2.4)	3 (1.0)	.16
Infarct (no AD or LB)	88 (11.0)	59 (11.7)	29 (9.6)	.36
Mixed pathologies	225 (28.0)	113 (22.5)	112 (37.2)	<.001
AD plus LB	41 (5.1)	25 (5.0)	16 (5.3)	.83
AD plus infarct	162 (20.2)	79 (15.7)	83 (27.6)	<.001
LB plus infarct	3 (0.4)	1 (0.2)	2 (0.7)	.29
AD plus LB plus infarct	19 (2.4)	8 (1.6)	11 (3.7)	.06

Abbreviations: AD, Alzheimer disease; LB, Lewy body; MMSE, Mini-Mental State Examination.

[a] Calculated from χ^2 tests or *t* test.

[b] Diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders criteria (McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer Disease. *Neurology*.

1984;34[7]:939-944). Of participants with dementia, 18 (12.6%) aged 65 to 89 years and 21 (13.0%) aged 90 years or older had no pathological diagnosis of Alzheimer disease; 9 (6.3%) aged 65 to 89 and 9 (5.6%) aged 90 years or older had none of the pathological diagnoses examined (Alzheimer disease, LB, or infarct pathology).

[c] Includes diagnosis of AD, LB, or infarct pathology.

[d] A modified Bielschowsky silver stain was used to visualize neuritic plaques and neurofibrillary tangles in the frontal, temporal, parietal, entorhinal, and hippocampal cortices. Neuropathologic diagnoses were made by a board-certified neuropathologist blinded to age and clinical diagnosis. The neuropathologic diagnosis of AD was made using the National Institutes of Aging-Reagan criteria (intermediate or high likelihood) without adjustment for age or clinical diagnosis (National Institute on Aging; Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer disease. *Neurobiol Aging*. 1997;18[4 suppl]:S1-S2).

[e] Included all confirmed chronic macroscopic infarcts and chronic cortical microscopic infarcts.

Table 2

Prevalence of Clinical Dementia Associated With Alzheimer Disease Pathology Alone and Mixed Pathologies

Pathological Diagnosis	Prevalence of Dementia	Prevalence Ratio (95% CI)	
		Alone[a]	Interaction[b]
Model 1[c]			
No AD			
Age 65-89 y	0.08	1 [Reference]	
Age ≥90 y	0.24	2.99 (1.67-5.33)	
AD			
Age 65-89 y	0.45	5.57 (3.51,8.84)	
Age ≥90 y	0.66	8.08 (5.13-12.74)	0.49 (0.27-0.89)
Model 2[d]			
No AD, infarct, or LB			
Age 65-89 y	0.07	1 [Reference]	
Age ≥90 y	0.23	3.11 (1.72-5.60)	
AD			
Age 65-89 y	0.39	5.23 (3.29-8.32)	
Age ≥90 y	0.59	7.95 (4.94-12.77)	0.49 (0.27-0.90)
LB			
Age 65-89 y	0.12	1.67 (1.29-2.16)	
Age ≥90 y	0.31	4.12 (2.22-7.65)	0.80 (0.57-1.12)
Infarct			
Age 65-89 y	0.10	1.28 (1.01-1.63)	
Age ≥90 y	0.27	3.60 (1.99-6.52)	0.91 (0.67-1.23)
Model 3[e]			
No AD			
Age 65-89 y	0.08	1 [Reference]	
Age ≥90 y	0.24	2.99 (1.67-5.33)	
AD			
Age 65-89 y	0.37	4.47 (2.75-7.27)	
Age ≥90 y	0.58	7.12 (2.98-17.00)	0.53 (0.28-1.01)

AD, infarct, or LB

Pathological Diagnosis	Prevalence of Dementia	Prevalence Ratio (95% CI)	
		Alone[a]	Interaction[b]
Age 65-89 y	0.59	7.22 (4.51-11.55)	
Age ≥90 y	0.73	8.98 (3.79-21.26)	0.42 (0.23-0.77)

Abbreviations: AD, Alzheimer disease; LB, Lewy body.

[a] Results are from log-binomial regression models and are adjusted for sex and education.

[b] Calculated as pathology type × age of 90 years or older. A value below 1 indicates the increase in prevalence for that pathology type is attenuated in the oldest old (age ≥90 years).

[c] Includes terms for age (≥90 years), AD pathology, and interactions of age (≥90 years) with AD.

[d] Everything in footnote[c] plus LB pathology, infarct pathology, and the interactions of age (≥90 years) with AD, LB, and infarct pathologies.

[e] Includes terms for age (≥90 years), AD pathology only, mixed AD pathologies (AD plus infarct, AD plus LB, or AD plus infarct plus LB), and the interactions of age (≥90 years) with AD only and age (≥90 years) with mixed AD pathologies.