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Amyloid load in nondemented brains correlates with APOE e4☆

Richard J. Caselli[a,*], Douglas Walker[b], Lucia Sue[b], Marwan Sabbagh[c], Thomas Beach[b]

[a] Mayo Clinic Arizona, Department of Neurology, 13400 East Shea Blvd, Scottsdale, AZ 85259, United States
[b] Sun Health Research Institute, Civin Laboratory for Neuropathology, United States
[c] Sun Health Research Institute, Cleo Roberts Clinical Research Center, United States

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ABSTRACT

179 cognitively healthy adults enrolled in the Sun Health Brain Donation program between 7/91 and 12/07 were at least 60 years old and nondemented at the time of death (21 had developed mild cognitive impairment [MCI]). Amyloid plaque density, congophilic amyloid angiopathy (CAA), and neurofibrillary tangle (NFT) density scores were based on CERAD criteria and compared in apolipoprotein E (APOE) e4 carriers ($n=42$) and noncarriers (NC) ($n=137$). Mean age (83.4 ± .6), gender (45% women), interval between death and brain harvest (3.1 ± 2.4 h), and brain weight (1200 ± 119 g) did not differ between e4 carriers ($n=42$) and NC. Total plaque density was higher in e4 carriers than NC (6.8 ± 4.9 vs. 4.3 ± 4.4, $p=.002$), and this was true in each of 5 subregions examined. Total CAA ($p=.002$) and all subregion CAA burden was also higher in e4 carriers. Total neuritic plaque density (1.2 ± 1.0 vs. 1.0 ± 1.0, $p=.18$) and total NFT density (3.9 ± 2.4 vs. 3.6 ± 2.3, $p=.50$) did not differ between e4 carriers and NC, nor in any subregion. Eliminating the 21 with MCI did not alter these results. Nondemented APOE e4 carriers over age 60 have a higher burden of total parenchymal and vascular amyloid neuropathology than NC, but no difference in neuritic plaque and NFT pathology.

Neuropathological studies of normal aging and Alzheimer's disease (AD) have shown overlap between the two. Neurofibrillary tangle (NFT) formation begins in the entorhinal cortex, is nearly universal over age 65 years, and is generally considered part of normal aging [4,6,22,24,29]. Extension of NFTs into neocortical regions, however, is never considered part of normal aging and only occurs to a significant extent in those who develop AD or another tauopathy [4,6,22,24,29]. Amyloid deposition, in contrast, begins in neocortical regions [4,6,22,24,29], and while it is a hallmark feature of AD at least 40% of individuals dying after age 65 years without signs of dementia have neocortical amyloid plaques at autopsy suggesting it may be a part of normal or "pathological" aging [4,24].

Apolipoprotein E (APOE) e4 carriers are at increased risk for AD [9,28]. Imaging studies of presymptomatic e4 carriers have shown reduced cerebral glucose metabolism [30,26], increased cerebral amyloid deposition [27] and enhanced cortical atrophy [8] along with accelerated memory decline [7]. Though much milder, these changes qualitatively resemble those seen in patients with AD suggesting they may represent a very early stage that precedes the symptomatic expression of mild cognitive impairment (MCI). Total amyloid burden in patients with AD is higher in apolipoprotein E (APOE) e4 carriers than noncarriers (NC) [11], as well as in some nondemented individuals with and without a variety of other neurological disorders [13]. A recent study of a large Finnish cohort found that APOE e4 carriers without dementia at the time of death also had higher amyloid (but not NFT) burdens than noncarriers [18]. If confirmed in another large cohort, such findings further support the existence of an extended presymptomatic stage of AD that may represent a therapeutic opportunity for preventing symptomatic cognitive loss. We therefore sought to replicate these findings in a large U.S. based cohort.

Participants were residents of Maricopa County, Arizona aged 65 years or older at the time of death who were prospectively enrolled in the Sun Health Research Institute (SHRI) Brain Donation Program as normal controls [2], expired between July 1991 and December 2007 without clinical evidence of dementia, and came to autopsy. Since its inception in 1987, more than 2500 donors (about 2% of the current combined populations of the surrounding retirement communities) have been enrolled. Of these, 1042 donors have expired and their brains have been collected and stored, while there are 1061 living donors. The population studied primarily resides in the retirement communities of northwest Phoenix. Donors volunteered specifically for the program and were highly motivated, with an annual drop-out rate of only 1.8%. Recruitment was primarily through word-of-mouth, through interactions of the population with physicians and nursing staff belonging to the Sun Health provider network, and through public speaking events and tours of the Institute given by Institute staff to community groups and the

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* Corresponding author. Tel.: +1 480 301 6574; fax: +1 480 301 8451.
E-mail address: Caselli.Richard@Mayo.edu (R.J. Caselli).

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Table 1
Prevalence of any Alzheimer lesions by age decile.

Age	*N*	% with amyloid (total plaques)	% with CAA	% with limbic NFTs
60–69	11	54.5	28.6	9.1
70–79	43	58.1	53.3	30.2
80–89	86	73.3	48.8	54.7
90+	39	76.9	41.7	82.1

general public. Eligibility criteria required that the subjects be free of hazardous infectious diseases, must consent to annual clinical assessments at SHRI, and provide at least 2 years of the applicant's private medical records that are reviewed by Brain Donation Program staff prior to acceptance.

Through 2000, mental status was determined by requisitioning medical records from primary care physicians, neurologists, psychologists and psychiatrists, and through telephone interviews with family members and caregivers, both at the time of enrollment and in the immediate postmortem period. Since January 2001, standardized clinical assessments at entry were added and included a minimental status examination (MMSE [12]) and neuropsychological battery. A postmortem Clinical Dementia Rating (CDR) Scale [20] was also completed in 39. At the time of their death, none had been diagnosed with AD, but 21 developed mild cognitive impairment (MCI) that reflected subjective memory concerns, but all remained functionally unimpaired, and none were institutionalized.

Standardized representative blocks from the following regions of interest (ROI) were examined using hematoxylin and eosin, thioflavine S, modified Campbell-Switzer, and modified Gallyas stains: middle frontal gyrus, middle temporal gyrus parietal lobe, temporal lobe (including amygdala, hippocampus and entorhinal cortex), and occipital lobe (association and primary visual cortex). Amyloid pathology in each ROI was quantified using the CERAD neuropathology templates to generate density scores for senile plaques (total and neuritic-cored), NFTs and congophilic amyloid angiopathy (CAA) based on a 4-point numerical conversion (0 for none, 1 for sparse, 2 for moderate, and 3 for severe) [19]. Braak staging was also used to describe the geographic spread of NFT pathology [5]. APOE genotype was determined using a DNA polymerase based assay [14]. Global cerebral scores for the above microscopic lesion densities were calculated based on the sums of the regional scores from frontal, temporal, parietal, entorhinal, and hippocampal regions. Total CAA burden was calculated based on frontal, temporal, parietal, and occipital regions.

All provided their written informed consent that was in compliance with the Sun Health Research Institute Institutional Review Board.

Comparisons between the two groups (APOE e4 carriers and noncarriers) were made using unpaired *t*-tests for continuous data, and chi-square for categorical data, all two-tailed.

Of 179 included were the following APOE genotypes: e4/4 $n=2$, e3/4 $n=38$, e2/4 $n=2$, e3/3 $n=105$, e2/3 $n=28$, e2/2 $n=2$. Mean age ($83.4 \pm .6$, $p=.18$), gender (45% women), MMSE score (28.3 ± 1.7), interval between final MMSE and death (21.9 ± 18.3 months), and postmortem interval (PMI; the interval between death and brain harvest) (3.1 ± 2.4 h) did not differ between e4 carriers ($n=42$) and noncarriers ($n=137$). MCI patients ($n=21$) were older (89.2 years vs. 82.6 years, $p=.0002$) with slightly lower MMSE scores (26.6 vs. 28.6, $p<.0001$), but gender, APOE distribution (23% e4 carriers), and PMI did not differ between the normal and MCI subgroups.

Brain weight did not differ between e4 carriers and noncarriers (1200 ± 119 g, $p=.36$). Total amyloid plaques, CAA, and limbic (Braak stage III and IV) NFT burden increased with age (Table 1), but this reached significance only for NFT burden ($p<.0001$, chi square), and there were no significant age interactions with APOE for any of these lesions.

The neuropathology results for the cohort overall are summarized in Table 2. Total plaque density was higher in e4 carriers than NC (6.8 ± 4.9 vs. 4.3 ± 4.4, $p=.002$), and this was true in each of 5 subregions examined: frontal ($p=.004$), temporal ($p=.01$), parietal ($p=.008$), hippocampal ($p=.0007$), and entorhinal ($p=.005$). Total CAA ($p=.002$) and all subregional CAA burden was higher in e4 carriers including frontal ($p=.002$), temporal ($p=.05$), parietal ($p=.001$) and occipital ($p=.005$). In contrast, total neuritic plaque density did not differ between e4 carriers and NC (1.2 ± 1.0 vs. 1.0 ± 1.0, $p=.18$). Total NFT density did not differ between e4 carriers and NC (3.9 ± 2.4 vs. 3.6 ± 2.3, $p=.50$), nor in any subregion. Excluding the 21 individuals with MCI did not change the results.

Comparing the 21 MCI patients with the remaining 158 normal controls (Table 3) showed no difference in any form of amyloid lesion (total, neuritic, or CAA), but Braak scores for NFT density were higher in MCI patients in hippocampus (2.2 vs. 1.3, $p<.0001$), entorhinal (2.3 vs. 1.6, $p=.003$), and temporal (0.73 vs. 0.36, $p=.009$) cortex as well as in total (5.4 vs. 3.4, $p=.0002$).

Our findings in an Arizona-based cohort show that amyloid lesions, particularly total plaques and CAA are present in greater amounts in the brains of nondemented APOE e4 carriers than noncarriers while neuritic and cored plaques as well as neurofibrillary tangles are not. Our findings replicate those of Kok et al. in a Finnish cohort [18]. Given the strong association between APOE e4 and AD susceptibility, our data and that of Kok et al. are consistent with the possibility that amyloid pathology may represent an early stage of AD pathogenesis even in the absence of cognitive symptoms. The NFT pathology we observed, in contrast to the amyloid pathology, appeared to be age-driven as has been previously reported [4–6,24] and unassociated with APOE e4 carrier status.

Bennett and co-workers recently showed that the association of APOE e4 with AD was strengthened by the inclusion of neuropathologically defined AD in the absence of clinical dementia. Among persons without AD, the APOE e4 genotype explained 17% of the variance in pathology; in those with AD, 18%, and the associ-

Table 2
Neuropathology results (total).

	e4+	e4−	*p*
N	42	137	
Age	82.0 (8.6)	83.8 (7.5)	.18
Gender (% women)	50%	43%	.48
Amyloid plaque burden			
Total	6.8 (4.9)	4.3 (4.4)	.002
Frontal	1.5 (1.1)	1.0 (1.0)	.004
Temporal	1.5 (1.1)	1.1 (1.1)	.01
Parietal	1.6 (1.0)	1.0 (1.1)	.008
Entorhinal cortex	1.3 (1.0)	.8 (1.0)	.005
Hippocampus	.9 (.8)	.4 (.7)	.0007
Neuritic burden (total)	1.2 (1.0)	1.0 (1.0)	.18
NFT burden			
Total	3.9 (2.4)	3.6 (2.3)	.5
Frontal	.06 (.2)	.09 (.2)	.49
Temporal	.4 (.6)	.4 (.6)	.77
Parietal	.2 (.4)	.09 (.3)	.25
Entorhinal cortex	1.8 (.9)	1.7 (.9)	.27
Hippocampus	1.4 (1.0)	1.3 (.9)	.55
CAA burden			
Total	3.3 (3.6)	1.5 (2.8)	.002
Frontal	.8 (1.1)	.3 (.7)	.002
Temporal	.6 (.7)	.3 (.7)	.05
Parietal	.8 (1.0)	.3 (.7)	.001
Occipital	1.1 (1.2)	.6 (1.0)	.005

Table 3
Neuropathology results: normal cognition vs. mild cognitive impairment.

	Normal			MCI			Normal vs. MCI
	e4+	e4−	*p*	e4+	e4−	*p*	*p*
N	35	123		7	14		
Age	80.2 (7.8)	83.3 (7.5)	.03	90.9 (6.6)	88.4 (6.4)	.41	.0002
% Women	49%	57%	.44	57%	57%	>.99	>.99
Amyloid plaque burden							
Total	6.3 (4.9)	4.3 (4.5)	.02	9.2 (4.2)	4.4 (4.5)	.028	.25
Frontal	1.4 (1.1)	1.0 (1.0)	.04	2.3 (1.1)	1.0 (1.1)	.025	.18
Temporal	1.4 (1.1)	1.0 (1.0)	.05	2.0 (.9)	1.2 (1.2)	.11	.2
Parietal	1.5 (1.2)	1.0 (1.1)	.05	2.2 (1.0)	1.1 (1.1)	.039	.2
Entorhinal cortex	1.2 (1.1)	.8 (.9)	.02	1.5 (.8)	.8 (1.1)	.12	.63
Hippocampus	.8 (.8)	.4 (.7)	.009	1.2 (1.0)	.3 (.7)	.021	.56
Neuritic burden (total)	1.2 (1.0)	1.0 (1.0)	.26	1.4 (1.0)	1.1 (1.2)	.58	.33
NFT burden							
Total	3.7 (2.3)	3.4 (2.2)	.47	4.9 (2.6)	5.7 (1.8)	.45	.0002
Frontal	.03 (.1)	.09 (.2)	.15	.2 (.4)	.05 (.1)	.16	.57
Temporal	.3 (.6)	.4 (.6)	.81	.6 (.6)	.8 (.9)	.53	.009
Parietal	.1 (.4)	.1 (.3)	.78	.4 (.6)	.07 (.2)	.048	.28
Entorhinal cortex	1.8 (.9)	1.6 (.9)	.14	1.9 (1.0)	2.4 (.7)	.17	.003
Hippocampus	1.4 (1.0)	1.2 (.8)	.43	1.8 (.9)	2.3 (.8)	.21	<.0001
CAA burden							
Total	3.3 (3.5)	1.4 (2.7)	.001	3.0 (4.2)	2.5 (3.6)	.77	.29
Frontal	.8 (1.0)	.3 (.7)	.003	.9 (1.2)	.5 (.9)	.41	.46
Temporal	.5 (.8)	.3 (.7)	.04	.6 (.8)	.5 (1.0)	.94	.21
Parietal	.8 (1.0)	.3 (.6)	.0009	.7 (1.3)	.5 (.9)	.72	.25
Occipital	1.2 (1.2)	.5 (.9)	.002	.9 (1.2)	.9 (1.1)	.9	.43

ation was more robust for amyloid plaques than NFTs [3]. Our data are consistent with Bennett et al.'s suggestion that asymptomatic AD-like pathology may in fact be AD itself. Aging APOE e4 carriers experience accelerated memory loss compared to noncarriers [7], have imaging changes that resemble AD [8,26,27,30], and now have been shown to have increased AD-like neuropathology all suggesting the existence of a pre-MCI stage of AD that clinically resembles normal aging. The duration of this stage, and the frequency with which it progresses to symptomatic MCI and dementia remains unknown, but its age of onset can be as early as the mid to late 1950s [7].

Our data show that total, but not neuritic plaque densities are influenced by APOE genotype, implying that diffuse plaques are driving this association. We observed amyloid deposition throughout all neocortical regions, consistent with previous neuropathological studies [4,6,22,24,29]. Recent amyloid ligand imaging studies in younger, genetically at-risk individuals have showed a greater preponderance of amyloid deposition in the frontal cortices during preclinical and early clinical stages of AD [10,17,24,27], as well as an absence of amyloid deposition in APOE e2 carriers [23]. Although we found neither a frontal predominance, nor an absence of pathology in e2 carriers, neuropathological studies including ours, generally reflect an older population than preclinical imaging studies. This may be one reason for these discrepancies, but further study is needed to resolve the important question of the comparability of neuropathology and amyloid ligand imaging.

A limitation of our study, as with that of Kok et al. [18] is the nonstandardized antemortem clinical assessment of some of its participants. Enrollment into the Brain Donation Program required participants to be competent to engage in such a study with supporting evidence from at least 2 years of medical records as well as normal functional and independent living status. Further, the number of participants whose clinical cognitive status had changed between entry and death was small. Separating out those with MCI did not change the results of our study, and the neuropathological findings in both normal and MCI subgroups appeared highly consistent with previous reports.

NFT severity has been shown to correlate more strongly with dementia severity than amyloid pathology [1,15,21], but amyloid pathology appears to correlate with genetic risk at the presymptomatic stage. Taken together, this suggests that amyloid is the earlier step and may peak during an early clinical stage such as MCI, whereas tau-based pathology is a subsequent step that better characterizes actual degenerative progression [31]. An important implication of the pre-MCI state that appears to be prevalent among APOE e4 carriers is that APOE genotype together with age may be sufficient to warrant empiric therapy aimed at preventing disease progression and symptom onset. One could argue whether this would constitute primary or secondary prevention, but it would provide an opportunity to test neuroprotective agents that have failed in previous clinical trials that might be more efficacious if started at an earlier stage of disease. More specifically, asymptomatic APOE e4 carriers between ages 50 and 60 years might be considered for clinical trials aimed at preventing disease progression [7]. Imaging endophenotypes of AD such as PIB-PET, FDG-PET, and MRI hippocampal volumes and cerebrospinal fluid biomarkers could serve as potential short term outcome measures (in the absence of symptoms) [8,16,25–27].

In summary, we have confirmed in an independent cohort that nondemented APOE e4 carriers have a greater burden of total cerebral amyloid pathology compared to NC supporting the possibility that, even in the absence of clinical impairment, neocortical and vascular amyloid represent an early step in AD pathogenesis. The frequency of progression to clinically symptomatic dementia from this stage remains to be determined.

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