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AD brain pathology: Vascular origins? Results from the HAAS Autopsy Study

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Abstract

An increasing number of studies suggest a vascular contribution to Alzheimer's disease [AD]. One major question these findings raise is whether vascular disease enhances the formation of AD-like lesions, or whether vascular disease just adds to clinical severity. We examined this question in a fully characterized autopsy sample based on the Honolulu Asia Aging Study. We found that AD markers of neurodegeneration [amyloid plaques, cerebral amyloid angiopathy and neurofibrillary tangles] were no more prevalent in those with neuropathologically defined vascular lesions compared to those without lesions. Our study suggests the burden of vascular and AD type lesions are independent of each other, and are consistent with an additive effect of the two types of lesions on cognitive impairment.

Introduction

Recent studies suggest that in an important sub-group of Alzheimer disease [AD] cases, vascular pathology that may contribute to the dementia [1]. Compared to those with only AD pathology, those with both vascular lesions and markers of AD pathology, often present with a more severe form of dementia [6]. Further, vascular dementia and AD share risk factors, such as hypertension and diabetes [4]. There is also a growing body of evidence of biologic interaction within the neurovascular unit [3]. Based on these data, the question arises as to whether or not there is an interaction between vascular factors and neuronal factors such that, compared to those with no neuropathologic evidence of vascular disease, those with such lesions have significantly more than expected markers of AD, including neuritic plaques [NP], neurofibrillary tangles [NFT], and cerebral amyloid angiography (CAA).

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Conflict of interest statement:

None of the authors have any conflict of interest to report that is relative to this manuscript.

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Methods

This question was examined in a large community based autopsy sample of Japanese American men who participated in the Honolulu Asia Aging Study [HAAS 1991 – ongoing]. The HAAS, and this sub-study, have been extensively described previously [6]. This current report is based on 439 men autopsied between April 1992 and October 2001. Permission to be included in the autopsy study was obtained from the next of kin. The Institutional Review Board of the Kuakini Hospital approved the study.

Evaluation of the neuropathologic material has been described previously [6]. Briefly, a neuropathologist identified gross lesions from coronal sections of cerebral hemispheres, and transverse sections of brainstem and cerebellum. Lacunar infarcts were defined as circumscribed, cystic, cavitary lesions that were <1 centimeter in maximum dimension; infarcts >1 centimeter were classified as large infarcts. In a microscopic exam, micro infarcts were evaluated bilaterally in the four cortical lobes, basal ganglia, hippocampus, thalamus, brainstem and cerebellum. They were defined as focal ischemic areas with reduced number of neurons, pale appearance and noticeable gliosis. All acute (<10 days) CV lesions were excluded. A modified Bielschowsky method was used to count neocortical NP and NFT in five fields in each of the four neocortical regions. There was no upper limit to the number of NFT counted; NP counts were truncated at 17/mm². Cerebral amyloid angiopathy was quantified by A β immunohistochemistry of parenchymal blood vessels; for the analysis CAA was classified as absent (all vessels non-reactive) or present.

For the analysis, we created mutually exclusive groups of vascular pathology: No lesions (reference group), only microinfarcts, only lacunae, both lacunae and microinfarcts, only infarcts or infarcts plus one other lesion (combined to increase sample size), and all three lesions. Multiple regression analysis was used to estimate the risk for neuropathology, controlling for age at death and whether the subject carried the Apolipoprotein E ϵ 4 allele. Regression models for plaque and tangle pathology were based on a poisson distribution, and those for CAA were based on a binomial distribution. We examined the association of NP and NPT to vascular lesions in any location, and to lesions in the neocortex only. For these latter analyses we collapsed the vascular pathology groups to increase sample size.

Results

The average age at death was 85.2 (5.1) years, 35% of the decedents were diabetic, 16.8% carried the apolipoprotein E ϵ 4 allele, 11.6% had a history of stroke, and 29% were demented ante mortem. There is very high prevalence of AD pathology in this cohort (99%, due primarily to the high prevalence of NFT); some type of vascular lesion was present in 78% of the sample. Both plaques and vascular lesions were present in 50.6%. Overall there was no statistical association of vascular lesions and AD lesions. There were no sub-groups of vascular lesions in any location where the risk for more AD lesions was significantly increased (Table 1). Results were similar when the analysis was restricted to neocortical NP, NFT and vascular lesions (Table 2).

Conclusion

In autopsy specimens of very old men identified in a community-based study, the prevalence of vascular lesions was high, as was the prevalence of co-morbid neuropathologic markers of AD and vascular lesions. Our study suggests the burden of vascular and AD type lesions are independent of each other, and are consistent with an additive effect of the two types of lesions on cognitive impairment. However, these findings do not reflect the possible interaction that takes place on a very local level. New possibilities to image cerebral amyloid

deposits will permit longitudinal study of this question [7]. Further additional micro-analytic studies, such as those reporting co-localization of microbleeds, NFT and NP [2] are needed.

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References

1. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet*. 2004; 363:1139–46. [PubMed: 15064035]
2. Hardy J, Cullen K. Amyloid at the blood vessel wall. *Nature Medicine*. 2006; 12:756–7.
3. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci*. 2004; 5:347–60. [PubMed: 15100718]
4. Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev*. 2002; 1:61–77. [PubMed: 12039449]
5. Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, Nelson J, Hardman J, Masaki K, Vogt MR, Launer L, White LR. AD lesions and infarcts in demented and non-demented Japanese-American men. *Ann Neurol*. 2005; 57:98–103. [PubMed: 15562458]
6. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study *JAMA*. 1997; 277:813–7.
7. Wang Y, Klunk WE, Debnath ML, Huang GF, Holt DP, Shao L, Mathis CA. Development of a PET/SPECT agent for amyloid imaging in Alzheimer's disease. *J Mol Neurosci*. 2004; 24:55–62. [PubMed: 15314250]

Table 1
Common Alzheimer's disease pathology by vascular pathology group: The HAAS Autopsy Study

Vascular lesion group		No lesions	Lacunae Only	Microinfarcts Only	Infarct or Infarct + 1 Lesion Only	Lacunae and Microinfarcts	All lesions
N		97	33	99	46	85	79
Senile plaques							
Median		4.34 (0.0,16.88)	3.57 (0.0,9.09)	5.84 (0.0,16.88)	7.71 (0.0,16.88)	5.19 (0.0,16.88)	2.60 (0.0,15.22)
OR [95% CI]		1.0	0.79 (0.51–1.24)	0.9 (0.66–1.22)	1.21 (0.85–1.71)	0.93 (0.68–1.27)	0.75 (0.53–0.1.05)
Neocortical neuritic plaques							
Median		0.65 (0.0,5.84)	0.32 (0.0,3.90)	0.97 (0.0,4.22)	1.73 (0.0,7.79)	0.32 (0.0,3.90)	0 (0.0–3.91)
OR [95% CI]		1.0	0.91 (0.48–1.72)	0.69 (0.43–1.12)	1.35 (0.8–2.22)	0.66 (0.40–1.10)	0.60 (0.35–1.04)
Hippocampal neuritic plaques							
Median		0 (0.0,2.44)	0 (0.0,6.38)	0 (0.0,2.27)	0.64 (0.0,2.83)	0 (0.0,2.39)	0.32 (0.0,1.95)
OR [95% CI]		1.0	1.46 (0.75–2.82)	0.98 (0.57–1.69)	1.70 (0.95–3.06)	1.03 (0.59–1.81)	0.88 (0.48–1.60)
CAA							
% with CAA		61.9	48.5	65.7	71.7	65.9	57.0
OR [95% CI]		1.0	0.45 (0.17–1.14)	1.03 (0.53–2.0)	1.16 (0.51–2.66)	0.91 (0.45–1.82)	0.69 (0.35–1.37)
Neocortical tangles							
Median		1.71 (0.0,6.36)	0.91 (0.0,5.41)	1.35 (0.0,5.41)	2.40 (0.91,6.76)	1.35 (0.0,4.05)	1.35 (0.0,3.64)
OR [95% CI]		1.0	0.75 (0.33–1.71)	0.89 (0.51–1.53)	1.08 (0.57–2.07)	0.57 (0.29 – 1.08)	0.58 (0.30–1.13)
Hippocampal tangles							
Median		14.19 (5.41,35.81)	17.89 (4.21,41.89)	10.81 (4.05,31.08)	18.85 (7.27,50.68)	20.9 (4.21,43.24)	17.56 (6.76,37.84)
OR [95% CI]		1.0	0.97 (0.58–1.63)	0.81 (0.55–1.17)	1.23 (0.81–1.88)	1.10 (0.77–1.58)	1.10 (0.76–1.59)

Table 2
Common Alzheimer's disease pathology by vascular pathology group: Neocortex The HAAS Autopsy Study

Vascular lesion group				
	No lesions	Only microinfarcts or only lacunae, or only both	Infarct + other path	All Lesion Types
N	97	98	98	27
Senile plaques				
Median [25 th , 75 th]	4.35 [0, 16.88]	8.73 [0, 16.88]	3.70 [0, 16.88]	4.22 [0, 16.88]
OR [95% CI]	1.0	1.08 (0.80–1.45)	0.94 (0.69–1.28)	0.93 (0.58–1.49)
Neocortical neuritic plaques				
Median [25 th , 75 th]	0.65 [0, 5.84]	1.79 [0, 5.52]	0.22 [0, 4.87]	1.30 [0, 5.84]
OR [95% CI]	1.0	0.87 (0.54–1.38)	0.94 (0.59–1.49)	0.76 (0.36–1.63)
Neocortical tangles				
Median [25 th , 75 th]	1.71 [0, 6.36]	2.26 [0.91, 6.76]	1.35 [0, 4.21]	1.35 [0, 4.05]
OR [95% CI]	1.0	0.95 (0.55–1.63)	0.82 (0.47–1.44)	0.71 (0.28–1.79)

Neocortical subset n = 320. All models adjusted for age at death and Apolipoprotein E ε4 allelic frequency.