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Associations between micro-infarcts and other macroscopic vascular findings on neuropathologic examination in two databases

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Abstract

Clinicians may undervalue brain micro-infarcts because they are defined by neuropathology and not seen on MRI. We sought to identify what neuropathologic vascular findings -- likely to be evident on brain MRI during life -- would predict the presence of micro-infarcts. We sought associations between such findings and microinfarcts in neuropathology databases from the National Alzheimer's Coordinating Center (NACC) and the Adult Changes in Thought (ACT) study. Considering only subjects 65 years of older at death, micro-infarcts were evaluated in 6,189 from NACC and 219 from ACT. Despite different definitions being used, micro-infarcts were common in both studies (19.7% in NACC and 16.0% in ACT), and their frequency increased significantly with age. In NACC specimens, after controlling for age and sex in multivariable models, microinfarcts were strongly associated with macro-infarcts (odds ratio (OR) 4.4, 95% confidence interval (CI) 3.8, 5.0), leukoencephalopathy (OR 2.6, 95% CI 2.1, 3.3), and hemorrhages (OR 2.0, 95% CI 1.6, 2.6). Similarly in the ACT specimens, microinfarcts were strongly associated with macro-infarcts (OR 2.9, 95% CI 1.4, 6.3). These neuropathological associations suggest that people whose cranial MRI shows macro-infarcts, hemorrhages, or leukoencephalopathy are more likely also to have micro-infarcts.

Keywords

neuropathology; micro-infarcts; infarcts; hemorrhages; and leukoencephalopathy

Introduction

For clinicians, vascular disease of the brain increasingly is defined by what they see on their patients' magnetic resonance imaging (MRI), specifically acute or chronic infarcts, hemorrhages, and leukoaraiosis. Micro-infarcts are defined by neuropathology, are below the resolution of current MRI scanners, and so may be undervalued by clinicians. Neuropathologic studies suggest that micro-infarcts are linked with other findings of vascular disease and with cognitive impairment.1¯6 Key among these studies was the Honolulu-Asia Aging Study (HAAS), a longitudinal study of Japanese-American men that identified micro-infarcts as an independent predictor of dementia in 285 participants systematically evaluated at autopsies.3 Brain infarcts, hemorrhages and leukoaraiosis seen

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on MRI may simply be markers for the pathophysiologically more important, but MRI-inapparent, micro-infarcts – as suggested by two prior autopsy studies.3,6 Seeking to identify what neuropathologic findings -- likely to be evident on brain MRI during life -- would predict the presence of micro-infarcts, we investigated these associations in two neuropathology databases, one multi-centered with an emphasis on dementia and another linked to an ongoing prospective cohort study of older adults.

Methods

The National Alzheimer's Coordinating Center (NACC)

The National Institute on Aging (NIA) established the Center in 1999 to facilitate collaborative research among the 29 NIA-funded Alzheimer's Disease Centers (ADCs). The Center developed and maintains a large relational database of standardized clinical and neuropathological research data collected from each ADC, and this database provides a valuable resource for both exploratory and explanatory research.7,8 Although a standard neuropathologic protocol may be used in each ADC, it is not the same across all ADCs. The NACC requests information from each ADC on specific findings defined by the ADCs neuropathologists in a manual of operations. Personnel from the ADCs complete the neuropathology data form on each patient, answering yes-or-no questions about micro-infarcts, macro-infarcts, hemorrhages, and leukoencephalopathy. Before 2002, personnel abstracted this information from neuropathology reports completed as long ago as 1984, so information was often missing. Starting 2002 January 01, personnel prospectively completed the form based on results of the neuropathologic examination. In the NACC manual of operations, micro-infarcts are defined as, “infarcts that are detected microscopically and may not be grossly visible, or may appear to the naked eye as cortical granularity. Micro-infarcts in non-cortical areas should not be included in this category. Infarcts meeting these criteria are included regardless of the histologic age and include acute lesions as well as chronic cystic lesions.” Grossly identified macro-infarcts were divided into two groups (1 cm or less versus larger) and are also included regardless of the histologic age, including acute lesions as well as chronic cystic lesions. Hemorrhages were included regardless of size and location in the brain. Leukoencephalopathy was defined as, “multifocal or diffuse white matter pathology attributed to arteriosclerotic small vessel disease and will be associated with axonal and myelin loss in the centrum semiovale, often associated with brain infarcts. White matter rarefaction confined to the immediate periventricular region (so-called periventricular ‘capping’) should not be included.9,10” As of 2007 January, the NACC neuropathology database had information on 9,312 brains, and 8,420 were from patients who were 65 years or older at the time of their death. The presence or absence of micro-infarcts had been assessed in 6,189 brains that form the basis of these analyses.

The Adult Changes in Thought (ACT) study

This longitudinal study of aging and dementia was designed to determine the incidence of and risk factors for dementia and cognitive impairment.[6] The ACT cohort consists of a random sample of 3,700 persons 65 years or older who received all their medical care from Group Health Cooperative, a consumer-governed health maintenance organization. Participants were known not to be demented based on screening at the time of enrollment and consented to biennial follow-up. After enrollment, all participants in this study are asked for informed consent to undergo a research post-mortem neuropathologic examination in the event of their death. As of 2006 August, 1098 members of the ACT cohort had died, and 221 (20%) had come to autopsy. Compared with those who died and did not come to autopsy, those who did were significantly more likely to be older and demented but were similar with respect to sex, education, and marital status.[6] The ACT investigators counted micro-infarcts exactly as described previously in HAAS3 in bilateral sections of cerebral

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cortex from each lobe, basal ganglia, internal capsule, and thalamus. Results from this method of assessing micro-infarct burden are highly predictive of dementia in both ACT and HAAS populations.3,6 Micro-infarcts were defined as in HAAS,[3] "… a focal lesion attributed to ischemia, found only on microscopic examination, and judged to be temporally remote. In practice such lesions were identified as foci of pallor, neuronal loss, and gliosis found only on microscopic examination and unrelated to infarcts identified during the course of the gross examination." Micro-infarcts were defined as present if three or more micro-infarcts were seen in the prespecified cortical or non-cortical areas. The presence or absence of micro-infarcts had been assessed in 219 brains that form the basis of these analyses.

Analyses

Our goal was to see if grossly evident neuropathologic findings of vascular disease predicted the presence of micro-infarcts in the two neuropathology databases. To control for potentially confounding effects of age and sex, we used logistic regression with micro-infarcts as the dependent variable and various neuropathologic findings alone or in combination as the independent variables along with age and sex. The fit of models did not improve significantly with the inclusion of terms for age-squared and age-cubed. The strength and significance of the association was reflected in the odds ratio (OR) and 95% confidence interval (CI) estimated for the independent variables. Analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas). Institutional review boards approved both studies.

Results

The number of brains in which a neuropathologic finding was evaluated and the number and percent with the finding are detailed in Table 1, where the maximum denominator included patients 65 years or older at the time of death and having had micro-infarcts indicated as present or absent. In NACC, 19.7% of the 6,189 brains examined had micro-infarcts. The mean age was 81.3 years old and was significantly higher in those with micro-infarcts compared to those without (83.3 versus 80.5 years old, p-value < 0.0001). Overall, 52.2% of the patients were women, and micro-infarcts were more common in men than women (20.8 versus 18.8%, p-value = 0.04). In ACT, 16.0% of the 219 brains examined had micro-infarcts. The mean age was 85.9 years old and was significantly higher in those with micro-infarcts compared to those without (88.1 versus 85.5 years old, p-value = 0.04). Overall, 56.6% of the patients were women, and micro-infarcts tended to be slightly, but not significantly, more common in women than men (18.5 versus 12.6%, p-value = 0.24). Results from HAAS are also included in Table 1 for comparison. The mean age at death in that study was 84.9.[3] Figure 1 shows the percent with micro-infarcts in the combined NACC and ACT databases by age categories and sex.

Table 2 includes results of the multivariable models adjusted for age and sex. All associations were significant and, in NACC, were similar whether variables for the neuropathologic findings were included in models singly (model A) or as a group (model B). In NACC, associations with micro-infarcts were strongest for macro-infarcts when both small (≤ 1 centimeter) and large (> 1 centimeter) infarcts were identified. Leukoencephalopathy was more strongly related to micro-infarcts than hemorrhages.

Discussion

In two neuropathology databases, one large and multi-centered with an emphasis on dementia and the other small and single-centered with a focus on a specific population, we found that micro-infarcts were common and strongly associated with macro-infarcts, which

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would likely be visible on brain MRI done during life. These findings are consistent with those from HAAS,[3] and together suggest that in elderly populations between one in five to one in six people who die and undergo brain autopsy harbor micro-infarcts. In a recent report concerning 148 autopsied subjects of the Rush Memory and Aging Project, 35 (23.6%) had micro-infarcts, as may have been expected from Figure 1 given the average age at death in these subjects of 88 years.[11] In addition, in NACC significant, independent associations with micro-infarcts were also found for leukoencephalopathy and hemorrhages, although they were not as strong as for macro-infarcts. These results should inform clinicians and researchers that people whose cranial MRI shows macro-infarcts, hemorrhages, leukoencephalopathy, or some combination of these findings are more likely also to have micro-infarcts and that clinical manifestations of these MRI findings such as cognitive impairment may be mediated in part by the MRI-inapparent micro-infarcts.

The cause of the micro-infarcts is unknown, and we did not attempt to address questions of etiology or of clinical manifestations in this paper. Given associations seen between micro-infarcts and macro-infarcts, they likely share at least some etiologic risk factors. In a primate model, hypertension induced by surgical coarctation of the aorta resulted in micro-infarcts,[12] but they did not clearly correlate with cognitive decline seen in these animals.[13]

Heterogeneity of criteria used to define neuropathological vascular lesions has been documented.[14] In the NACC neuropathology database, a broad definition of micro-infarcts was used and may not have been applied consistently in the many centers contributing to this large database. Also NACC only considered cortical micro-infarcts, while ACT and HAAS neuropathology databases used the same definitions and considered both cortical and subcortical micro-infarcts. Despite these and other differences, the frequency of micro-infarcts was consistent across these neuropathology databases ranging from 16.0 to 19.7% and increasing with age. A bias may have existed whereby the neuropathologists' observation of macro-infarcts may have prompted a more thorough search for micro-infarcts or vice versa, although the standardized evaluation mandated in HAAS and ACT may have afforded some protection against this sort of bias. We cannot be certain that the macro-infarcts seen on the neuropathologic examination would have been seen on MRI or that infarcts seen on MRI would have been found and confirmed on the neuropathologic examination.[15] Finally we cannot be certain that these associations do not simply reflect some unique feature of those who did undergo a neuropathologic examination and would not be seen in those who did not.[16]

What is lacking from all these studies is the link between micro-infarcts identified on neuropathologic examination and vascular findings seen on MRI, which is likely more than what is identified at the neuropathology examination.[15] Few post-mortem examinations have been performed in studies with large numbers of participants undergoing MRI during life, such as Framingham Study, Rotterdam Study, and Cardiovascular Health Study. Such studies will be a challenge and may be a reason to consider post-mortem brain MRI, which likely would be a better reflection of what was seen on an MRI during life than the post-mortem neuropathologic examination. Ideally future studies would include standardized MRI and neuropsychological testing during life and standardized MRI and neuropathologic examination after death. Such studies may be needed to clarify the associations among macro-infarcts, micro-infarcts and clinical manifestations such as cognitive impairment and may provide clues as how to prevent these lesions and their associated clinical findings that so commonly affect the elderly.

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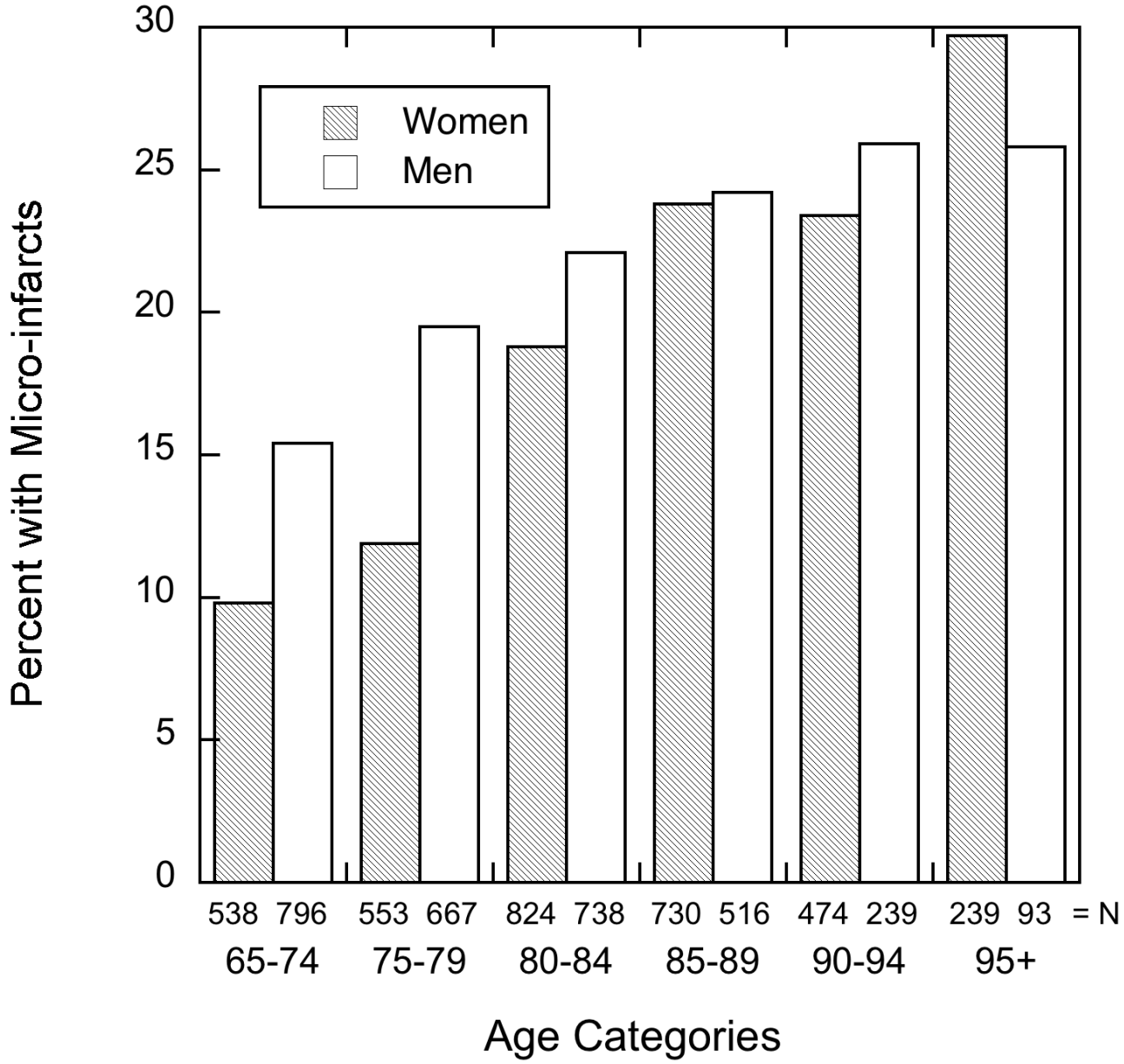

Figure 1.
Percent of patients with micro-infarcts in the combined NACC and ACT neuropathology databases by age categories and sex.

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Table 1

Micro-infarcts and other neuropathologic vascular findings in neuropathologic databases

Neuropathologic findings in each database*	**NACC**		**ACT**		**HAAS†**	
	mean age 81.3		**mean age 85.9**		**mean age 84.9**	
	Number with finding over total	**Percent**	**Number with finding over total**	**Percent**	**Number with finding over total**	**Percent**
Micro-infarcts	1,222 / 6,189	19.7	103 / 219	16.0	55 / 285	19.3
Macro-infarcts (≤ or > 1 cm)	1,535 / 5,917	25.9	67 / 206	32.5		
≤ 1 cm	742 / 5,912	12.5			129 / 285	45.3
> 1 cm	1,055 / 5,882	17.9			85 / 285	29.8
Hemorrhages	358 / 5,860	6.1				
Leukoencephalopathy	364 / 6,025	6.0				

*NACC stands for National Alzheimer's Coordinating Center; ACT, Adult Changes in Thought; and HAAS, Honolulu-Asia Aging Study. Findings are defined in the text and differed for micro-infarct between NACC and the two other studies.

†Results from the Honolulu-Asia Aging Study (HAAS) based on a previous publication.[3]

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Table 2

Multivariable models to identify vascular findings associated with micro-infarcts

Neuropathologic findings in each database*	Micro-infarct		Model A†		Model B†	
	No	Yes	Adjusted OR	95% CI	Adjusted OR	95% CI
NACC						
Macro-infarct (dichotomous)						
No	3,833	549	Reference		Reference	
Yes	918	616	4.4	3.8 to 5.0	4.1	3.6 to 4.7
Macro-infarct (multi-level)						
Only ≤ 1 cm	502	286	3.7	3.1 to 4.4		
Only > 1 cm	258	174	4.5	3.6 to 5.6		
Both ≤ 1 and > 1 cm	129	133	6.8	5.2 to 8.8		
Leukoencephalopathy						
No	4,629	1,032	Reference		Reference	
Yes	229	135	2.6	2.1 to 3.3	2.3	1.8 to 3.0
Hemorrhages						
No	4,479	1,021	Reference		Reference	
Yes	242	117	2.0	1.6 to 2.6	1.5	1.2 to 1.9
ACT						
Macro-infarcts						
No	123	16	Reference		Reference	
Yes	49	18	2.9	1.4 to 6.3		

*NACC stands for National Alzheimer's Coordinating Center, and ACT, Adult Changes in Thought.

†Odds ratios (OR) and 95% confidence intervals (CI) estimated from logistic regression with micro-infarct as the dependent variable and neuropathologic findings, age and sex as the independent variables. In Model A, only a single variable for each neuropathology finding was included in each logistic regression. In Model B, variables for macro-infarct, leukoencephalopathy, and hemorrhage were included in the same logistic regression along with age and sex. Number in the models was 5,832. The reference group always comprised those who lacked the particular finding.