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Risk of Intraparenchymal Hemorrhage with MRI-Defined Leukoaraiosis and Brain Infarcts

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Abstract

Objective—To determine whether the burden of leukoaraiosis and the number of brain infarcts, defined by MRI, are prospectively and independently associated with intraparenchymal hemorrhage (IPH) incidence in a pooled population-based study.

Methods—Among 4,872 participants initially free of clinical stroke in the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS), we assessed white matter grade (range 0–9), reflecting increasing leukoaraiosis, and brain infarcts using MRI. Over a median of 13 years of follow-up, 71 incident, spontaneous IPH events occurred.

Results—After adjustment for other IPH risk factors, the hazard ratios (95% confidence intervals) across white matter grades 0–1, 2, 3, and 4–9 were 1.00, 1.68 (0.86–3.30), 3.52 (1.80–6.89), and 3.96 (1.90–8.27) (p for trend <0.0001). These hazard ratios were weakened only modestly (p for trend = 0.0003) with adjustment for MRI-defined brain infarcts. The IPH hazard ratios for 0, 1, 2, or 3 MRI-defined brain infarcts were 1.00, 1.97 (1.10–3.54), 2.00 (0.83–4.78), and 3.12 (1.31–7.43) (p for trend = 0.002), but these were substantially attenuated when adjusted for white matter grade (p for trend = 0.049).

Interpretation—Greater MRI-defined burden of leukoaraiosis is a risk factor for spontaneous IPH. Spontaneous IPH should be added to the growing list of potential poor outcomes in people with leukoaraiosis.

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Disclosures

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Introduction

Leukoaraiosis, namely changes in the white matter on brain imaging of elderly people,¹ is suspected to be a risk factor for spontaneous intraparenchymal hemorrhage (IPH). Associations between leukoaraiosis and IPH have been described since the 1980s but typically in select patients having symptomatic vascular disease and with leukoaraiosis defined by cranial computed tomography (CT).^{2–8} The question has not been addressed in populations of stroke-free people and with leukoaraiosis defined by cranial magnetic resonance imaging (MRI). Given the difficulty in treating patients with IPHs and the often-fatal outcome, a search for etiologic risk factors and clues about prevention is well justified. The Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS) are community-based prospective cohort studies in which participants have undergone cranial MRI and have been followed for the occurrence of stroke, including IPH. We hypothesized that the burden of MRI-defined leukoaraiosis and brain infarcts would be associated independently with increased risk of incident IPH. To increase the number of outcome events, we pooled data from ARIC and CHS, an approach which was possible because of the similarity of study protocols.

Methods

Study Populations and IPH Risk Factor Measures

The ARIC study cohort comprised a sample of 15,792 individuals aged 45–64 years old when recruited between 1987–1989, from four communities: Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); Washington County, Maryland; and the northwestern suburbs of Minneapolis, Minnesota.⁹ The CHS cohort comprised adults randomly sampled from Medicare eligibility files from four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania.¹⁰ CHS initially recruited 5,201 participants in 1989–1990, and added 687 African-Americans in 1992–1993. Both ARIC and CHS conducted several follow-up exams. Both studies received approval from relevant human subjects review boards, and all participants gave consent.

We could pool ARIC and CHS, because the studies assessed most IPH risk factors similarly, including cigarette smoking, blood pressure, plasma lipids and fibrinogen, and carotid intima-media thickness (IMT) and plaque. Prior work has defined several risk factors for IPH in this pooled prospective study.^{11–13} A subset of these participants also underwent a research cranial MRI.

Cranial Magnetic Resonance Imaging

In ARIC, 1,930 participants underwent cranial MRI at 2 study sites (Forsyth County, North Carolina; Jackson, Mississippi) between 1993 and 1995.¹⁴ In CHS, 3,630 participants underwent cranial MRI at all 4 study sites between 1991 and 1994.¹⁵

ARIC and CHS used identical cranial MRI scanning and image interpretation methods.^{14–16} In brief, T1- and T2- weighted magnetic resonance images were obtained. Axial images were angled to be parallel to the anterior commissure–posterior commissure line. Trained MRI readers, who were masked to participants' clinical condition, evaluated the spin-density images to estimate the overall volume of periventricular and subcortical white matter (WM) hyperintensities. These were graded on a scale from 0 (no WM signal abnormalities) to 9 (all WM involved), based on “pattern matching” of a scan to a set of reference standards from grade 1 to 8, an example of which is given in Figure 1 and which are described in detail elsewhere.^{14–16} Quality control procedures, described elsewhere,^{14,15} showed that interreader and intrareader intraclass correlation coefficients were 0.68 and 0.71,

respectively, in ARIC, and 0.76 and 0.89 in CHS. Visually-rated WM grade is strongly correlated with quantitatively estimated WM hyperintensity burden ($R^2 = 0.75$).¹⁷

As previously described,¹⁸ MRI-defined brain infarcts were defined as lesions 3 mm in size or larger with abnormal signal in a vascular distribution and no mass effect. Infarcts of the cortical gray matter, deep nuclear regions, and capsule were defined as lesions bright on spin-density and T2-weighted images compared with normal gray matter and isodense or hypodense on T1-weighted images. Infarcts in the WM were also bright on spin-density and T2-weighted images but in addition were hypointense on T1-weighted images, approximately the intensity of cerebrospinal fluid. Infarct size and location were recorded.

Incident Stroke Ascertainment

ARIC identified nonfatal and fatal hospitalized clinical strokes through yearly phone interviews, reported deaths, and surveillance, abstraction and review of relevant hospital records.¹⁹ CHS identified fatal and nonfatal hospitalized and nonhospitalized clinical strokes by semiannual phone interviews, reported deaths, and abstraction and review of relevant hospital records identified from Medicare utilization files.^{20,21}

Incident Stroke Criteria

ARIC adapted National Survey of Stroke criteria for its stroke definition.²² These criteria require stroke to have evidence of sudden or rapid onset of neurological symptoms that persist for >24 hours or lead to death and to have no other apparent cause such as trauma, tumor, infection, or anticoagulation therapy. A definite IPH met one of the following criteria: (1) CT or MRI showing intraparenchymal hematoma; (2) Demonstration at autopsy or surgery of IPH; or (3) at least one major or two minor neurological deficits; and a bloody spinal fluid on lumbar puncture; and cerebral angiography demonstrates an avascular mass effect and no evidence of aneurysm or arteriovenous malformation; and no CT or MRI. A probable IPH met criteria, other than cerebral angiography, but had a decreased level of consciousness or coma lasting 24 hours or until the participant died. In ARIC, 99% of hospitalized strokes received a CT or MRI for diagnostic purposes. In ARIC, stroke criteria were implemented as a computer algorithm, and reviewed by a physician blinded to the automated results. A second physician adjudicated disagreements between the computer and initial physician.

CHS adopted stroke criteria similar to the Systolic Hypertension in the Elderly Program (SHEP).^{20,23} Potential stroke events in CHS were referred to a Cerebrovascular Adjudication Committee, consisting of a neurologist from each site, a neuroradiologist, and a neurologist or internist representing the coordinating center. A suspected event was classified as a stroke if there was a rapid onset neurological deficit lasting >24 hours or until death. The event could not be caused by trauma, tumor, or infection, but in contrast to ARIC, an IPH while on anti-coagulation therapy did not preclude an IPH classification in CHS. Only one CHS participant with an IPH event in this analysis, however, was believed to be taking anticoagulation medication; his exclusion had little impact on results. A suspected hemorrhagic stroke was classified as an IPH if there was: (1) CT or MRI diagnostic evidence of IPH, or (2) bloody cerebrospinal fluid on lumbar puncture with a focal deficit, or (3) autopsy or surgical evidence of IPH. In CHS, 83% of stroke events (88% of IPHs) had brain imaging.

Data Analysis

The combined ARIC and CHS cohort with research cranial MRI data included 5,560 participants initially, with follow-up through December 31, 2007. For analysis, we excluded any participants who had had a clinical stroke prior to research MRI ($n=285$), were not

African-American or White ($n=19$), or were missing covariates ($n=384$), leaving 4,872 (1,627 in ARIC, 3,245 in CHS). The outcome of interest was the first definite or probable incident IPH. Participants who had clinically recognized ischemic strokes after baseline were retained in the analysis and still considered at risk for IPH.

The association of MRI WM grade (0–9) with incident IPH was analyzed with WM grades categorized into four groups (0–1, 2, 3, 4–9) as in a previous investigation.²⁴ MRI infarcts were grouped by number of infarcts (0, 1, 2, 3 or more). Age, race, and study-adjusted mean values or prevalences of risk factors were estimated within categories of WM grade or infarct number using general linear models. Hazard ratios were calculated using Cox proportional hazard models as implemented in SAS 9.2 (SAS Institute, North Carolina). Tests for trend in hazard ratios were performed by modeling medians of the WM or infarct categories as continuous variables. We adjusted for variables associated with IPH in our previous reports:^{11–13} age (continuous), race (African American, white), current cigarette smoking (yes, no), study (ARIC, CHS), systolic blood pressure (continuous), LDL-cholesterol (continuous), natural log triglycerides (continuous), fibrinogen (continuous), carotid intima-media thickness, and carotid plaque (yes, no). In the regression models, we used values of these risk factors obtained at the time of the research MRI, except for fibrinogen and carotid measures, which were from the closest measurement before the MRI. In a sensitivity analysis, we adjusted hazard ratios additionally for systolic blood pressure at inception of the ARIC or CHS cohorts; these hazard ratios (not presented) were virtually identical to the hazard ratios presented.

Results

The combined ARIC and CHS cohort initially free of stroke, who had a research cranial MRI examination and complete data ($n=4,872$), included 40% men, 25% African-Americans, and 79% 65 years or older. As shown in Table 1, more participants in the highest WM grades were from CHS than ARIC, reflecting the positive correlation of leukoaraiosis with age. The WM grade was associated with many of the other IPH risk factors and with the number of brain infarcts on MRI (Table 1).

One or more brain infarcts were present on MRI in 183 (11%) participants in ARIC and 906 (28%) in CHS. The distribution of infarct locations was: cerebro-cortical ($n=111$), cerebellar-cortical ($n=66$), deep cerebellum ($n=54$), deep cerebrum or basal ganglia ($n=839$), brain stem ($n=44$), or deep cerebral WM ($n=236$). As reported previously for CHS²⁵ and similarly in ARIC,²⁶ over 80% of the infarcts detected were lacunar. Table 2 shows relations of cardiovascular risk factors with the number of infarctions detected.

Over a median of 13 years of follow-up, 71 IPH events were identified (11 ARIC and 60 CHS). The crude incidence rate of IPH was approximately 3 times higher in CHS (17.5 per 10,000 person-years) than in ARIC (5.4 per 10,000 person-years). In Model 1, the adjusted hazard ratios for IPH were 1.00, 1.68, 3.52, and 3.96 (p for trend <0.0001) across increasing WM grades of 0–1, 2, 3, and 4–9 (Table 3). The association of WM grade with IPH was not modified by age, sex, study (ARIC, CHS), race, or systolic blood pressure (p value for multiplicative interactions all >0.20); however, statistical power to test these interactions was limited. In Model 2, additional adjustment for number of MRI infarcts attenuated the WM grade hazard ratios, but they remained quite strong (p for trend = 0.0003).

Table 4 shows that the number of subclinical brain infarcts was also strongly positively associated with IPH incidence. In Model 1, the adjusted hazard ratios of IPH were 1.00, 1.97, 2.00, and 3.12 (p for trend = 0.002) for 0, 1, 2, or 3+ infarcts on MRI. Additional

adjustment for WM grade (Model 2) attenuated these subclinical brain infarct hazard ratios for IPH (p for trend = 0.049).

The independent association of WM grade and subclinical brain infarcts with incident IPH was further demonstrated through cross-classification (Table 5). Compared to having neither dichotomized MRI finding, IPH risk was increased 2.42-fold in participants with a subclinical brain infarct and a WM grade of 0–2; 3.19-fold in those with a WM grade 3 and no subclinical brain infarct; and 4.27-fold in participants with both a WM grade 3 and a subclinical brain infarct (p interaction = 0.23).

Eight participants who had an incident IPH had an ischemic stroke also during follow-up but before the IPH. A sensitivity analysis censoring their follow-up time at the date of the ischemic stroke yielded no change in conclusions: Model 1 hazard ratios for IPH were 1.00, 1.57, 2.88, and 3.65 across increasing WM grades of 0–1, 2, 3, and 4–9, and were 1.00, 1.92, 2.28, and 2.89 for 0, 1, 2, or 3+ infarctions on MRI.

Discussion

In this pooled, community-based prospective cohort study of stroke-free participants, we found that WM grade on MRI was associated with an increased risk of subsequent spontaneous IPH. This association was strong -- with an approximately 3.5-fold increased risk for IPH in the 26% of participants who had at least mild leukoaraiosis with a WM grade of 3 or greater. The association was largely independent of the number of brain infarcts present on the MRI, a finding which itself was associated with subsequent IPH but to a lesser degree than WM grade. The combination of both WM grade being 3 or greater and infarct being present was associated with nearly 4.27-fold increased IPH risk, compared with neither MRI finding.

Based on a series of patients who underwent cranial CT as part of routine medical care, investigators proposed in 1989 an association between leukoaraiosis and IPH, likely mediated by hypertension or amyloid angiopathy.² The following year other investigators reported results of a case-control study where again all subjects were drawn from a group of patients undergoing cranial CT as a part of routine medical care.³ They found a strong association between leukoaraiosis and IPH that disappeared after controlling for a history of hypertension. They also found that leukoaraiosis was more commonly found in patients with deep than lobar hemorrhages. Among 3,017 patients with transient ischemic attacks or minor stroke randomized in a clinical trial, CT-defined leukoaraiosis was not significantly associated with subsequent risk of IPH, but only 24 of the trial participants experienced this outcome.⁴ Subsequent studies concerned the increased risk of IPH with leukoaraiosis in patients given anticoagulation for secondary stroke prevention^{5,6} or thrombolysis for acute stroke treatment.^{7,8} Only one of these studies used MRI to defined leukoaraiosis.⁷ We are not aware of prior studies that have evaluated this association in a population of stroke-free people and with leukoaraiosis defined by MRI.

We are unable to determine in the current study whether the associations could be mediated by hypertension, amyloid angiopathy, or other factors. Location of the IPH, deep suggesting hypertension and lobar suggesting amyloid angiopathy, might help to clarify mechanism but was unknown in this study. The risk of incident IPH being highest when both WM grade was 3 or higher and infarcts were present suggests that hypertension may be a more important determinant of the association than amyloid angiopathy, as proposed in prior studies.^{2,3} Although adjustment for systolic blood pressure, which was found in a prior study to be an independent risk factor for IPH in this pooled cohort,¹¹ did not eliminate the association, hypertension may still be playing a crucial role. White matter grade and brain

infarcts defined by MRI may better reflect the long-term effects of hypertension on the brain than a single measurement of systolic blood pressure around the time of the MRI. Finally, leukoaraiosis has been associated with prevalent and incident microbleeds,^{27,28} but they were not identified in this study's MRIs, which were done in the early 1990s based on protocols developed in the late 1980s. Perhaps microbleeds and leukoaraiosis share risk factors, but the true marker for incident IPH may be the microbleeds not the leukoaraiosis.

In conclusion, MRI-defined leukoaraiosis is a risk factor for spontaneous IPH in stroke-free people, even in the absence of anticoagulation. Spontaneous IPH should be added to the growing list of potential poor outcomes in people with leukoaraiosis.²⁹ Whether leukoaraiosis should influence decisions about antithrombotic therapy is an important question that cannot be addressed in this observational epidemiologic study and will be a challenge to address in future studies. A randomized trial may not be feasible, and future observational studies would require a large number of people to undergo cranial MRI to define their burden of leukoaraiosis, infarcts and microbleeds and to be followed over a prolong period for the occurrence of spontaneous IPH.

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Figure 1. Example of reference standards used to assign a white matter grade by matching a participant's overall volume of periventricular and subcortical white matter (WM) hyperintensities on spin-density images. Less than grade 1 was assigned 0 and more than 8 was assigned 9.

Table 1

Age, study, and race-adjusted participant characteristics (means or prevalences) according to white matter grade, in pooled analyses from ARIC and CHS.

Characteristic	White Matter Grade*			
	0-1	2	3	4-9
N	2,227	1,368	745	532
Age [†] (years)	67.7	71.9	74.0	76.1
Study [†] (% CHS)	52.4	72.4	83.9	86.8
Race [†] (% White)	67.8	81.1	82.1	74.8
Sex (% men)	41.5	41.2	37.1	36.7
Systolic blood pressure (mmHg)	130	132	135	138
Current smoking (% yes)	10.2	14.6	13.1	15.6
Aspirin (% using)	46.1	44.8	45.0	47.0
Triglycerides (mg/dl) [‡]	118	122	124	122
Low density lipoprotein cholesterol (mg/dl)	128	127	127	126
Fibrinogen (mg/dl)	314	320	319	323
Carotid intima-media thickness (mm)	1.03	1.05	1.07	1.12
Carotid plaque (% yes)	59.9	62.5	63.8	67.9
Infarct on brain MRI (% yes)	12.5	22.5	30.8	51.3

* p<0.001 for global difference among white matter grade categories for every risk characteristic.

[†] Crude

[‡] Geometric mean

Table 2

Age, study, and race-adjusted participant characteristics (means or prevalences) according to the number of MRI-defined brain infarcts in pooled analyses from ARIC and CHS.

Characteristic	Number of MRI-Defined Brain Infarcts [*]			
	0	1	2	3 or more
<i>N</i>	3,783	678	249	162
Age [†] (years)	69.9	73.8	74.1	74.5
Study [†] (% CHS)	61.8	82.4	83.1	86.4
Race [†] (% White)	73.8	77.9	73.9	79.0
Sex (% men)	40.1	40.9	36.4	46.1
Systolic blood pressure (mmHg)	131	134	139	136
Current smoking (% yes)	11.4	16.6	14.0	18.8
Aspirin (% using)	45.8	44.7	43.8	48.9
Triglycerides (mg/dl) [‡]	120	124	127	121
Low density lipoprotein cholesterol (mg/dl)	127	128	128	125
Fibrinogen (mg/dl)	315	323	327	319
Carotid intima-media thickness (mm)	1.04	1.11	1.11	1.12
Carotid plaque (% yes)	61.4	64.2	66.2	63.3
White matter grade 3 or greater (%)	21.0	34.5	56.6	65.9

* p<0.001 for global difference among brain infarct categories for every risk characteristic.

* Crude

[‡] Geometric mean

Table 3

Incidence rate and hazard ratio of intraparenchymal hemorrhage (IPH) according to white matter grade in pooled analyses from ARIC and CHS.

	White Matter Grade			
	0–1	2	3	4–9
<i>N</i> of subjects	2,227	1,368	745	532
<i>n</i> of subjects with IPH events	17	18	20	16
IPH incidence rate (per 10,000 person-years), age, study, and race-adjusted (95% confidence interval)	7 (4–11)	11 (7–18)	23 (14–36)	27 (16–46)
Model 1 hazard ratio* (95% confidence interval)	1.00 reference	1.68 (0.86–3.30)	3.52 (1.80–6.89)	3.96 (1.90–8.27)
<i>p</i> for trend < 0.0001				
Model 2 hazard ratio† (95% confidence interval)	1.00 reference	1.60 (0.81–3.14)	3.19 (1.61–6.28)	3.28 (1.53–7.04)
<i>p</i> for trend = 0.0003				

* Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, and carotid plaque.

† Further adjusted for MRI infarct (yes, no)

Table 4

Incidence rate and hazard ratio of intraparenchymal hemorrhage (IPH) according to the number of MRI-defined brain infarcts in pooled analyses from ARIC and CHS.

	Number of MRI-defined Brain Infarcts			
	0	1	2	3 or more
<i>N</i> of subjects	3,783	678	249	162
<i>n</i> of subjects with IPH events	43	16	6	6
IPH incidence rate (per 10,000 person-years), age, study, and race-adjusted (95% confidence interval)	10 (7–13)	19 (11–32)	20 (9–44)	31 (14–72)
Model 1 hazard ratio [*] (95% confidence interval)	1.00 reference	1.97 (1.10–3.54)	2.00 (0.83–4.78)	3.12 (1.31–7.43)
<i>p</i> for trend = 0.002				
Model 2 hazard ratio [†] (95% confidence interval)	1.00 reference	1.72 (0.95–3.11)	1.49 (0.61–3.60)	2.11 (0.87–5.14)
<i>p</i> for trend = 0.049				

^{*} Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, and carotid plaque.

[†] Further adjusted for white matter grade 3 (yes, no)

Table 5

Incidence rate and hazard ratio of intraparenchymal hemorrhage (IPH) according to the presence of MRI-defined brain infarcts and white matter grade, ARIC and CHS.

	White Matter Grade			
	0, 1 or 2		3 or more	
	MRI Infarct		MRI Infarct	
	Absent	Present	Absent	Present
<i>N</i> of subjects	3,042	553	741	536
<i>n</i> of subjects with IPH events	24	11	19	17
IPH incidence rate (per 10,000 person-years), age, study, and race-adjusted (95% confidence interval)	7 (5–10)	17 (9–31)	22 (13–35)	29 (17–48)
Model 1 hazard ratio* (95% confidence interval)	1.00 reference	2.42 (1.17–5.00)	3.19 (1.71–5.96)	4.27 (2.20–8.28)

* Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, and carotid plaque.