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The prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study

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Abstract

Objective—Risk factors for subclinical brain infarcts (SBI) have not been well studied, especially in Hispanics and blacks who may be at higher risk for vascular disease. We examined the prevalence and determinants of SBI in a multi-ethnic community cohort.

Methods—The Northern Manhattan Study (NOMAS) includes 892 stroke-free participants who underwent brain magnetic resonance imaging (MRI). Baseline demographic and vascular risk factor data were collected. The presence of SBI was determined from the size, location, and imaging characteristics of the lesion based on FLAIR, T1 and T2, and proton density MRI sequences. We calculated the prevalence of SBI and cross-sectional associations with socio-demographic and vascular risk factors, using logistic regression to adjust for relevant covariates.

Results—Among 892 subjects (mean age 71.3 years), 158 (17.7%) had SBI (13.5% had 1 lesion, 4.3% had > 1 lesion). Of the total 216 infarcts, most were small (< 1 cm, 82.4%) and subcortical (82.9). SBI prevalence increased with age (< 65: 9.7%; 65–75: 16.4%; > 75: 26.1%), was increased among men (21.3% vs. 15.2% in women) and blacks (24.0% vs. 18.1% in whites and 15.8% in Hispanics). The presence of SBI was independently associated with older age (per year: OR 1.06, 95% CI 1.04–1.09), male sex (OR 1.79, 95% CI 1.22–2.61), and hypertension (OR 2.08, 95% CI 1.35–3.22) adjusting for age, sex, race-ethnicity, and vascular risk factors. A significant interaction ($P = 0.002$) between race and age was observed such that younger blacks had greater odds of having SBI.

Conclusions—SBI were detected in nearly 18% of subjects in a multi-ethnic community-based cohort. Age, male sex, and hypertension were independently associated with SBI. Subclinical cerebral infarcts are more prevalent than symptomatic infarcts and may increase the true public health burden of stroke.

Keywords

silent stroke; blacks; African Americans; Hispanics; lacunar infarction

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Statistical analysis: SP

Introduction

The concept of silent or, more appropriately, subclinical brain infarcts (SBI) is not new. In 1965, Fisher observed that over three-quarters of patients without a clinical history or a neurological deficit had lacunar infarcts at autopsy.¹ Three decades later, a population-based autopsy series found that nearly 13% of asymptomatic subjects had pathological evidence of SBI.² With in-vivo detection of SBI using magnetic resonance imaging (MRI), recent studies have demonstrated similar proportions.^{3, 4} In addition to understanding the pathogenesis of these infarcts, prospective studies have also shown that SBI may have value in predicting subsequent risk of stroke and vascular dementia.^{5–8}

Several community-based MRI studies have examined risk factors for subclinical brain infarction and found age and hypertension to be consistently associated with SBI.^{3, 4} Regarding race-ethnic differences, one prior study demonstrated that blacks have higher prevalence of SBI but we were unable to find studies with substantial proportions of Hispanics.⁹ We evaluated a multi-ethnic cohort of elderly, stroke-free subjects for the presence of SBI on MRI. Based on the knowledge of race-ethnic differences in clinical stroke, we hypothesized that similar differences might exist in the prevalence of SBI.

Methods

Patient selection and baseline evaluation

As previously described,^{10, 11} the Northern Manhattan Study (NOMAS) includes a prospective cohort study of stroke risk factors and outcomes with 3,298 stroke-free participants enrolled through random digit dialing and who met these eligibility criteria: 1) no prior stroke; 2) 40 years of age or older; 3) resident of Northern Manhattan for at least 3 months in a household with a telephone. The overall enrollment rate was 68%.¹⁰

Data were collected between 1993 and 2001 through interviews by trained bilingual research assistants using standardized data collection instruments, review of medical records, physical and neurological examinations by study physicians. Standardized questions about vascular risk factors were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System.¹² Hypertension was defined as a systolic blood pressure > 140 mm Hg or a diastolic blood pressure > 90 mm Hg based on the mean of 2 blood pressure measurements, self-report of a diagnosis of hypertension, or treatment with anti-hypertensive medications. Diabetes was defined as fasting blood glucose > 127 mg/dL, self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Cardiac disease was defined as a history of coronary artery disease, valvular disease, or congestive heart failure. Hypercholesterolemia was defined as fasting total cholesterol > 200 mg/dl, prior history, or lipid-lowering medication use. Race-ethnicity was based on self-identification.^{13, 14}

MRI substudy

NOMAS subjects were enrolled into the MRI substudy beginning in 2003 using the following criteria: 1) age older than 55, 2) no contraindications to MRI, and 3) signed informed consent. Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Hatch Research Center. The following sequences were performed: axial T1, axial T2, axial proton density, and fluid attenuated inversion recovery (FLAIR). Images were oriented parallel to a hypothetical line connecting the anterior and posterior commissures.

After imaging acquisition, data were transferred to the University of California at Davis for processing. All analyses were performed blind to subject identification. MRI quantification was performed with a custom-written computer program operating on a Unix, Solaris platform. Once the image was transformed into anatomic standard space, the operator returned to the

image and identified brain lobar and regional cerebrospinal fluid (CSF) measures according to previously published methods.^{15–18} Briefly, frontal lobar regions were defined as all supratemporal structures anterior to the central sulcus. Temporal lobar regions were traced from the anterior pole of the temporal lobe to the central sulcus. The parietal lobes were defined as the brain matter posterior to the central sulcus, extending to the medial transverse fissure of the striate cortex. The remaining caudal portions of the cerebral hemispheres were defined as occipital.

The presence or absence of brain infarction on MRI was determined according to previously published protocol from the size, location and imaging characteristics of the lesion.¹⁹ The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2 weighted image at three times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on the T2 weighted image was interpreted to indicate a vessel. Only lesions 3 mm or larger qualified for consideration as brain infarcts. Other necessary imaging characteristics included (1) CSF density on the subtraction image and (2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels and perivascular spaces. Scans were further interpreted for number of infarcts, their location (brain side, cortical or subcortical, and specific region), and size of infarcts (small: < 1 cm or large: > 1 cm). Two raters determined the presence of cerebral infarction on MRI (CD and MY). Previously published kappa values for agreement amongst raters has been generally good, ranging from 0.73 to 0.90.²⁰

Statistical analysis

The prevalence of subclinical infarcts in the overall cohort and stratified by age, sex, and race-ethnicity was determined. Age-adjusted prevalence was calculated using the entire prospective NOMAS cohort as the reference population. We evaluated the association between subclinical infarcts and baseline demographic (age, sex, race-ethnicity, education level) and vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, and cardiac disease) using t-tests and Chi-square tests as appropriate. We assessed the association between baseline characteristics and SBI using logistic regression (SAS software, Carey, NC). We tested for effect modification by including interaction terms in the models. A P-value < 0.05 was considered significant in all analyses. In the MRI cohort, there were no missing values for the variables listed above.

Results

Among 3,298 NOMAS subjects, 892 subjects (27.0%) underwent brain MRI between June 2003 and November 2006. Compared to NOMAS subjects who did not have MRI (N = 2406), the MRI sample was younger at baseline (64.1 vs. 71.3 years, $P < 0.001$), had a greater proportion of men (41.0% vs. 35.7%, $P = 0.006$) and Hispanics (64.0% vs. 49.7%, $P < 0.001$), and a lower proportion of diabetes (11.7% vs. 18.7%, $P = 0.001$), hypertension (67.0% vs. 75.9%, $P < 0.001$), and cardiac disease (16.3% vs. 26.7%, $P < 0.001$). Other baseline demographic and vascular risk factors of the MRI cohort are summarized in Table 1.

A total of 216 SBI were detected in 158 subjects (overall prevalence 17.7%), 120 of whom had single lesions (13.5%; Table 2). SBI were slightly more frequent on the right than left and were primarily small lesions. Though the majority of SBI was located subcortically, 17.1% involved cortical structures. The most common brain region affected was the basal ganglia (30.6%) including the lentiform, caudate, and thalamic nuclei. Other common locations included frontal lobes, the internal, external, and extreme capsules, and parietal lobes.

The figure shows the prevalence of SBI among various subgroups. The prevalence increased with advancing age (< 65 years: 9.7%; 65–75 years: 16.4%; > 75 years: 26.1%; $P < 0.001$).

Men had a greater prevalence than women (21.3% vs. 15.2%), a difference that increased with advancing age (Figure a). The prevalence of SBI was greater among hypertensives compared to non-hypertensives across all age groups, but especially in the youngest age group (Figure b). There were no significant differences in SBI prevalence by education level, smoking status, or history of diabetes, hypercholesterolemia, or cardiac disease (Table 1).

SBI were more frequent among black subjects (24.0%) compared to white (18.1%) and Hispanic subjects (15.8%). This race-ethnic difference was also exaggerated in the youngest age group (Figure c). The age-adjusted prevalence of SBI was 14.8% for Hispanics, 17.6% for whites, and 24.5% for blacks. Stratified by place of birth, the majority of Hispanics were born in Caribbean countries (N = 514, 93.1%: Dominican Republic 65.8%, Puerto Rico 13.0%, and Cuba 8.3%). Among these non-US born Hispanics, the prevalence of SBI was 14.4% compared to 29.3% among the minority who were born in the US (P = 0.022).

There were differences between race-ethnic groups by age (74.0 years for blacks vs. 67.7 for Hispanics and 74.4 for whites, P < 0.001), sex (men: 33.9% for blacks vs. 40.6% for Hispanics and 51.4% for whites, P = 0.007), history of hypertension (71.9% for blacks vs. 67.8% for Hispanics and 58.3% for whites, P = 0.031), current smoking (24.0% for blacks vs. 13.2% for Hispanics and 9.7% for whites, P < 0.001), and diabetes (9.9% for blacks, vs. 14.4% for Hispanics and 2.8% for whites, P < 0.001).

In a multivariable logistic regression model, the presence of SBI was independently associated with older age (per year: OR 1.06, 95% CI 1.04–1.09), male sex (OR 1.79, 95% CI 1.22–2.61), and history of hypertension (OR 2.08, 95% CI 1.35–3.22), adjusting for age, sex, race-ethnicity, education level, current smoking, hypertension, diabetes, hypercholesterolemia, and cardiac disease. There was no significant association by race-ethnicity (adj. OR 1.49, 95% CI 0.83–2.69 for blacks and adj. OR 1.34, 95% CI 0.75–2.37 for Hispanics compared to whites). However, we found an interaction between age and race-ethnicity (p = 0.002), such that younger blacks had a greater odds of having SBI. In further post-hoc multivariable analysis stratifying Hispanics by place of birth and adjusting for age, sex, and hypertension, US-born Hispanics had an increased odds of SBI (adj. OR 2.38, 95% CI 1.04–5.47).

Discussion

In this multi-ethnic community cohort of stroke-free individuals who underwent brain MRI, subclinical brain infarcts were found in 17.7%. Age, male sex, and hypertension were independently associated with SBI. Although no overall race-ethnic difference was seen, black subjects under age 65 years and Hispanics born in the US had disproportionately higher proportions with SBI compared to whites.

Overall, our findings corroborate those from other population-based studies and extend them to a multi-ethnic cohort. In the Rotterdam Study (subjects older than 65 years) and Cardiovascular Health Study (subjects between 60–90 years), the prevalence of SBI was even higher, approximately 25%.^{3, 4} Perhaps because of younger age (55–70 years) in the Atherosclerosis Risk In Communities Study, SBI prevalence was only 11%.⁹ Based on these studies, the overall prevalence of SBI is substantially higher than the estimated 2–3% prevalence of ischemic stroke in the US.²¹ Extrapolating the prevalence of SBI, the US population prevalence of SBI may exceed 13 million,²¹ with more than 12 million people over age 55 harboring SBI. An exploratory analysis of SBI incidence suggested that over 9 million Americans developed new subclinical infarcts in 1998 compared to only 700,000 new ischemic strokes.²² Furthermore, based on the estimated prevalence and annual risk of symptomatic stroke in those with SBI,^{5–7} more than half of all ischemic strokes in the US annually may be preceded by SBI. When applying the race- and age-specific prevalence to the US black and

Hispanic populations, one might estimate that nearly 1.5 million blacks and 750,000 Hispanics over age 55 have subclinical brain infarcts (<http://www.census.gov/compendia/statab/population>). These statistics serve to emphasize the large public health burden of ischemic cerebrovascular disease, especially in the growing elderly and minority populations.

Previous studies have shown race-ethnic differences in relation to stroke mortality and incidence,^{23, 24} as well as for other surrogate endpoints such as carotid atherosclerosis.¹³ Regarding SBI prevalence, the ARIC study found that non-white race (predominantly black) was associated with 64% increased odds of having SBI compared to whites.⁹ Although the prevalence of SBI in our study did not differ by race-ethnic group, our study suggests it may be elevated in black subjects under 65 years. Thus, blacks may have a significant burden of subclinical infarcts that begins at a younger age as compared with either whites or Hispanics.

The prevalence of subclinical infarcts has not been studied extensively in Hispanic populations, another group that may carry a higher burden of SBI. Our study did not find a greater prevalence of SBI among Hispanics compared to whites. Although the unadjusted prevalence of SBI among Hispanics compared to whites may be confounded by age differences between race-ethnic groups, age adjustment did not alter the estimates greatly. Interestingly, our data suggest that Hispanics born in the US were at increased odds of SBI compared to Caribbean-born Hispanics. We speculate that dietary or other lifestyle patterns of US-born Hispanics may be associated with increased risk of SBI. For example, prior work among the elderly in northern Manhattan has shown that Hispanics adhere more closely to the Mediterranean diet than whites or blacks.²⁵ Future studies on diet and lifestyle factors are needed to clarify this issue further.

As consistently shown in prior studies, age and history of hypertension were the strongest predictors of SBI in this sample.^{3,4,6,9,26,27} Regarding sex, the prevalence of symptomatic stroke is thought to be slightly greater in women, perhaps because they live longer than men^{21,28} while stroke incidence and mortality are higher in men.²⁹ In contrast to other studies,^{3,4,27} we found that the prevalence of SBI was increased among men compared to women, even after adjusting for age and other risk factors. Our finding raises the possibility that SBI may be occurring more frequently in men and may play a role in increasing the risk of subsequent ischemic stroke.

The clinical and prognostic implications of subclinical infarcts are emerging. Several large observational studies have shown that the presence of SBI may be an independent predictor of subsequent symptomatic stroke.⁵⁻⁷ Therefore, selective screening of intermediate- and high-risk populations with brain MRI may be a useful tool in stratifying risk of future stroke. In addition, MRI-detection of SBI may serve as a surrogate marker of vascular cognitive impairment.^{8, 30} Our data suggest that the elderly, men, hypertensives, and possibly younger blacks carry the highest burden of subclinical infarcts, making them the ideal targets for early surveillance and interventions to prevent stroke and dementia.

Strengths of this study include that it is population-based and includes a large proportion of black and Hispanic participants. The limitations include the cross-sectional design that does not allow us to draw conclusions regarding causality or permit calculation of incidence rates or relative risks. The potential for selection bias also exists since only those without contraindication to MRI (i.e. claustrophobia, obesity, pacemakers) and who could consent (non-demented) were selected. Our results may actually underestimate the true prevalence since study participants were generally younger and healthier than non-participants. Although the baseline evaluation occurred several years prior to enrollment in the MRI substudy, follow-up analysis confirmed that <0.5% developed new risk factors over time, justifying the use of responses and measurements from the time of initial NOMAS enrollment (age at MRI was

used in analyses). The reliability of MRI in the detection of SBI is also a potential limitation. Published estimates suggest it may be very good but far from perfect.²⁰ Attempts to validate subclinical infarction with pathological correlation has raised concerns about differentiating infarction from non-ischemic entities such as perivascular spaces.^{31–34} Nevertheless, MRI is currently the best modality in widespread use to detect SBI reliably and accurately.

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Figure a.

Figure b.

Figure c.

Figure.

Prevalence of subclinical brain infarcts stratified by a) age and sex; b) age and hypertension; c) age and race-ethnicity

Table 1.

Baseline characteristics of the overall MRI cohort (n=892) and comparison between those with and without SBI

	Overall (n=892)	SBI present (n=158)	SBI absent (n=734)	P value
Mean age at MRI, years (SD)	71.3 (8.2)	74.6 (8.4)	70.6 (8.0)	<0.001
Male sex, n (%)	366 (41.0)	78 (49.4)	288 (39.2)	0.021
Race-ethnicity, n (%)				0.063
White	144 (16.1)	26 (16.5)	118 (16.1)	
Black	171 (19.2)	41 (25.9)	130 (17.7)	
Hispanic	552 (61.9)	85 (53.8)	467 (63.6)	
Other	25 (2.8)	6 (3.8)	19 (2.6)	
Completed high school, n (%)	431 (48.3)	87 (55.1)	344 (46.9)	0.066
Current smoking, n (%)	131 (14.7)	27 (17.1)	104 (14.2)	0.385
Hypertension, n (%)	598 (67.0)	126 (79.7)	472 (64.3)	<0.001
Systolic blood pressure, mm Hg (SD)	140.2 (19.7)	143.7 (18.6)	139.4 (19.9)	0.013
Diastolic blood pressure, mm Hg (SD)	83.4 (10.6)	85.3 (10.8)	83.0 (10.5)	0.014
Diabetes, n (%)	104 (11.7)	22 (13.9)	82 (11.2)	0.198
Cardiac disease, n (%)	145 (16.3)	29 (18.4)	116 (15.8)	0.476
Hypercholesterolemia, n (%)	504 (56.5)	85 (53.8)	419 (57.1)	0.480

Table 2.
Characteristics of subclinical brain infarcts (n= 216)

Side, n (%)	
Left	99 (45.6)
Right	117 (54.2)
Size, n (%)	
Small (≤ 1 cm)	178 (82.4)
Large (> 1 cm)	38 (17.6)
Gross location, n (%)	
Cortical	37 (17.1)
Subcortical	179 (82.9)
Anatomic location, n (%)	
Frontal	56 (25.9)
Parietal	32 (14.8)
Temporal	4 (1.8)
Occipital	6 (2.7)
Basal ganglia	66 (30.6)
External/extreme capsule	23 (10.6)
Internal capsule	9 (4.2)
Cerebellum	18 (8.3)
Brainstem	2 (0.9)