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Sickle Cell Trait and Incident Ischemic Stroke in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background and Purpose—Numerous case reports describe stroke in individuals with sickle cell trait (SCT) in the absence of traditional risk factors for cerebrovascular disease. To date, no prospective epidemiological studies have investigated this association.

Methods—A population-based sample of African Americans (N=3,497, mean age=54, female=62%) was followed from 1987–2011 in the Atherosclerosis Risk in Communities Study (ARIC), contributing a total of 65,371 person-years. Hazard ratios and incidence rate differences for ischemic stroke were estimated, contrasting SCT to homozygous hemoglobin A (HbAA). Models were adjusted for age, sex, smoking, diabetes, hypertension, total cholesterol, atrial fibrillation, and coronary heart disease.

Results—SCT was identified in 223 (6.4%) participants. Over a median follow up of 22 years, 401 subjects experienced incident stroke (89% ischemic). Incident ischemic stroke was more frequent among those with SCT (13%) than HbAA (10%). SCT was associated with an ischemic stroke hazard ratio of 1.4 (1.0 – 2.0), and an incidence rate difference amounting to 1.9 (0.4 – 3.8) extra strokes per 1000 person-years.

Conclusion—We observed an increased risk of ischemic stroke in African Americans with SCT. Further investigation of the incidence and pathophysiology of stroke in SCT patients is warranted.

Keywords

sickle cell trait; stroke; epidemiology

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Introduction

African Americans are disproportionately burdened by cerebrovascular disease. The prevalence of stroke in African Americans 18 years or older is nearly twice that of non-Hispanic whites (4.0% vs. 2.3%)[1]. Although stroke incidence has been decreasing since the 1990s for whites, this trend has not been observed in African Americans[1]. Stroke incidence is not only higher in African Americans, it occurs at a younger age, resulting in substantial morbidity with direct and indirect costs[2]. Traditional risk factors explain much of the disparity in stroke outcomes for African Americans; however, genetics likely have a role.

Sickle cell trait (SCT), the heterozygous carrier state of sickle cell anemia, is a debated risk factor for stroke[3,4]. With a heterozygous allelic frequency of 7 – 9% in African Americans, and 0.2% in non-Hispanic whites[5], SCT is estimated to affect over 3 million Americans. The correlation between sickle cell anemia and stroke is well known[6]; however, increasing evidence suggests the heterozygous carrier state may be associated with thromboembolism[7], a potential cause of stroke. Additionally, numerous case reports describe stroke in young individuals with SCT, in the absence of traditional risk factors[8–11]. Intrigued by these findings, we conducted a prospective epidemiological investigation of SCT and ischemic stroke, by analyzing a cohort of African Americans followed in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

The ARIC study

Initiated in 1987, the ARIC study is an ongoing epidemiological cohort representing 4 U.S. areas. Along with white study participants recruited from Minneapolis, Minnesota and Washington County, Maryland, a population-based sample (N= 4,270) of African Americans aged 45–64 was recruited with written informed consent, from Jackson, Mississippi and Forsyth County, North Carolina[12]. The ARIC study encompasses 5 cohort examinations, with annual telephone surveys during interim years and ongoing surveillance of hospitalized events. Study participant retention has been excellent, with 94% of survivors participating in the annual survey in 2010. All study protocols were approved by the University of Mississippi and Wake Forest University Institutional Review Boards.

Genotyping

Genotyping was performed using functionally tested TaqMan® SNP Genotyping Assays in accordance with manufacturer protocols (Life Technologies, Grand Island, NY). Hemoglobin S was identified from biallelic variation [missense change (Glu7Val)] in the single nucleotide polymorphism rs334, using the following custom primer and probe sequences: Forward-TCAAACAGACACCATGGTGCAT, Reverse-CCCCACAGGGCAGTAACG, VIC-CTGACTCCTGAGGAGAA-MGB, 6FAM-CTGACTCCTGTGGAGAA-MGB. Hemoglobin C was identified from single nucleotide polymorphism rs33930165 [missense change (Glu7Lys)], using custom primer and probe sequences: Forward-AAACAGACACCATGGTGCATCT, Reverse-CCCCACAGGGCAGTAACG, VIC-CAGACTTCTCCTTAGGAGTC-MGB, 6FAM-

ACTTCTCCTCAGGAGTC-MGB (designed on the complement strand). For quality assurance, blind duplicate genotyping of hemoglobin S and hemoglobin C was performed in a random sample representing 5% of the total assays (kappa coefficients 0.83 and 0.93, respectively).

Ancestry and Relatedness

Ancestry was quantified using EIGENSTRAT 5.0.1 (David Reich, open source), based on genomic variation characterized by the HumanExome BeadChip v1.0 (Affymetrix, Santa Clara, CA), as previously described[13]. First degree relatives were identified by PLINK (Shaun Purcell, http://pngu.mgh.harvard.edu/purcell/plink)[14]. Relatedness pairs were broken by randomly dropping one first degree relative from each set, irrespective of SCT status or stroke outcomes.

Stroke History

History of stroke was ascertained at the study baseline by self-reported signs and symptoms. Based on the responses, a computer algorithm diagnosed stroke, and determined the vascular distribution involved[15]. The algorithm performance was previously validated, classifying prevalent stroke with a sensitivity of 87.8% and a specificity of 71.9%[16].

Incident Stroke

Incident stroke over the course of follow up was captured by hospital surveillance, as previously described[17]. Medical records from hospitalizations with diagnosis codes 430–438 and neurological deficits exceeding 24 hours were abstracted for physician review. Stroke diagnosis was verified by the discharge summary, imaging reports, neurological consults, and medical history, and categorized as either definite or probable[17]. For quality assurance, diagnoses were also determined by a computer algorithm. Any disagreements between the physician diagnosis and computer algorithm were adjudicated by a second physician reviewer. Agreement rates between the physician reviewer and computer algorithm were 78%[17]. In the majority of discordant diagnoses (65%), the physician adjudicator agreed with the physician reviewer, rather than the computer algorithm[17].

Clinical Covariates

Medical histories and clinical covariates were ascertained at the study baseline, by home interviews, health questionnaires, and clinical examinations. Age, sex, race, and current smoking were self-reported. Seated blood pressures were measured by random-zero mercury manometers. Hypertension was considered a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or antihypertensive medication use. Fasting cholesterol and glucose were assessed by ARIC central laboratories. Hypercholesterolemia was considered a total fasting cholesterol ≥ 6.2 mmol/L. Diabetes was defined by a fasting blood glucose level ≥ 7 mmol/L, non-fasting blood glucose ≥ 11.1 mmol/L, self-reported diabetes, or use of diabetic medications. Standardized, 12-lead electrocardiograms were performed, and assigned a Minnesota code[18] by the ARIC ECG Reading Center. Atrial fibrillation was identified by a Minnesota code of 8.3.1. Prevalent coronary heart disease was defined by self-report, history of myocardial infarction, coronary artery bypass graft, or percutaneous

coronary intervention; or electrocardiogram (ECG) suggestive of prior myocardial infarction.

Final study population

A total of 4,151 African Americans were genotyped for hemoglobin S and hemoglobin C. After excluding first degree relatives (N=253), those with missing or inadequate genotype calls (N=33), participants identified with hemoglobin C trait (N=88), hemoglobin C disease (N=2), hemoglobin SC disease (N=5), or sickle cell anemia (N=3), and those with missing clinical covariates (N=270), a total of 3,497 remained.

Statistical Analysis

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Categorical variables were compared by a χ^2 test and continuous variables compared by ANOVA. Categorical variables with expected cell counts < 5 were analyzed using Fisher's exact test. Stroke hazard ratios contrasting SCT to HbAA were calculated with Cox regression, adjusting for the traditional risk factors for stroke (age, sex, smoking, diabetes, hypertension, total cholesterol, atrial fibrillation, and coronary heart disease). In a separate model, the effect of genetic admixture was examined, by including 10 ancestral principal components in the adjusted Cox regression model. Proportional hazards assumptions were verified by plotting Martingale residuals, and assessing deviations of observed suprema from 1000 simulated paths by Kolmogorov-Smirnov testing[19]. No Cox models were found to violate proportional hazards. Stroke incidence rate differences (IRD) were estimated by additive Poisson regression, adjusted for demographics and the traditional risk factors for stroke. Goodness of fit was verified by the deviance to degrees of freedom ratio. No Poisson models were found to be over-dispersed.

Power calculations for stroke hazard ratios were calculated *a priori*. Based on the previously reported age-adjusted ischemic stroke incidence rates for ARIC participants aged 45–84 (6.6 / 1000 person-years for African American men, and 4.9 / 1000 person-years in African American women)[20] we estimated an age-adjusted, sex-standardized (38% men, 62% women) reference rate of 5.55 strokes / 1000 person-years. With an assumed sample size of 3,200 and SCT prevalence of 8%, we expected 80% power to detect a hazard ratio of 1.5, with significance at α=0.05 (2-sided).

Results

In the final study population (N=3,497) of African Americans, 223 (6.4%) were identified with SCT, which was similarly prevalent (7.2%) among those excluded for missing covariates or relatedness. The mean age at the study onset was 54, and 62% were female. Study participants with SCT were less often smokers, but had a higher prevalence of hypercholesterolemia. Otherwise, cerebrovascular risk factors at the study baseline did not differ by SCT classification (Table 1). History of stroke was prevalent in 70 (2%) and was similar among participants with SCT and HbAA genotypes; however, baseline neurological histories were missing for 737 (21%).

Study participants were prospectively followed a median of 22 (15 – 23) years, contributing to a total of 65,371 person-years. Over this time frame, 401 experienced a stroke. The majority of strokes, 355 (89%) were ischemic, and of these 76% were considered definite. The overall frequency of ischemic stroke (10%) was similar in those excluded for missing covariates or relatedness (9%). Among study participants with SCT, 29 (13%) experienced incident ischemic stroke, compared to 326 (10%) of those with HbAA. The mean age at incident ischemic stroke was 67 ± 7 years, and did not differ by SCT status. The crude incidence rate of ischemic stroke was 7.1 strokes per 1000 person-years in participants with SCT, compared to 5.3 strokes per 1000 person-years in individuals with HbAA (Table 2).

In multivariable regression analysis adjusted for traditional risk factors, the stroke rate among those with SCT was significantly higher than those with HbAA, resulting in approximately 2 extra strokes per 1000 person-years (IRD: 1.9, p=0.03). When risk was analyzed as a relative measure, SCT remained associated with incident ischemic stroke, but estimates were more marginal (HR: 1.4, p=0.08), as shown in Table 3. When the effect of admixture was considered by including 10 ancestral principal components in the multivariable Cox regression model, estimates were unchanged (HR: 1.4, 95% CI: 1.0 – 2.0).

Discussion

This is the first prospective, epidemiological study to examine associations between SCT and incident stroke. After adjusting for demographics and traditional cerebrovascular risk factors, we observed a greater ischemic stroke risk in African Americans with SCT, compared to those with the HbAA genotype.

Several case reports have previously described stroke in individuals with SCT[8–11]. These are remarkable in that strokes occurred in children and young adults, with no underlying traditional risk factors for cerebrovascular disease. However, in large retrospective studies, associations between SCT and hospital discharge for stroke have been conflicting. The first, conducted from 1965–1969 at North Carolina Memorial Hospital, included 227 patients with SCT and 16,701 African Americans assumed to have normal hemoglobin[21]. No differences were found in frequency of hospital discharges for stroke; however, African American controls were never confirmed to have HbAA genotypes, which may have resulted in substantial misclassification bias.

The second study, conducted in the French Caribbean colony of Guadeloupe, analyzed the prevalence of SCT in 295 hospitalizations for stroke. Interestingly, a 10-fold higher risk for hemorrhagic stroke and a 15-fold lower risk for ischemic stroke were observed in patients with SCT, compared to Guadeloupians with normal hemoglobin[22]. This study has been criticized for diagnosing stroke type by computed tomography, which may not distinguish between primary hemorrhages and hemorrhagic bleeding secondary to infarctions, causing possible under-diagnosis of ischemic stroke[3]. It is also uncertain whether the Guadeloupe population, an admixture of European, African, Indian, and Amerindian ancestries, can be generalized to African Americans.

Finally, a recently conducted analysis based on 13,964 African American adults (2,642 with SCT and 139 with sickle cell anemia) registered with the Kaiser Permanente Northern California health system reported no differences in stroke diagnoses for patients with either SCT, sickle cell anemia, or HbAA[23]. However, the mean age of the study population was only 35. In adult populations, only pregnant African American women are routinely tested for sickle hemoglobinopathies, and if positive, the fathers are tested as well[23]. Due to the young age of the study population and low number of ischemic stroke events, this analysis was inadequately designed to detect differences in stroke prevalence by hemoglobin status.

While studies examining SCT and cerebrovascular disease have been limited, many have established sickle cell anemia as a risk factor for stroke. Sickle cell anemia is characterized by hemolysis, acute chest syndrome, and pain; and is further complicated by thrombosis, microvascular occlusions, vasculopathy, and intimal hyperplasia of the cerebral arteries. In the Cooperative Study of Sickle Cell Disease, which prospectively followed 4,082 patients, 24% with sickle cell anemia experienced a first stroke by the age of 45[6]. The association between sickle cell disease and stroke is further confirmed by administrative claims data. In 35–64 year old patients with sickle cell disease, the incidence of ischemic stroke is reported to be 7.4 per 1000 person years[24], much higher than 2.7 per 1000 person years for 35–64 year old African Americans overall[25]. These estimates yield a stroke incidence rate ratio of 2.7, and an incidence rate difference of 4.7 strokes per 1000 person-years; however, it is noteworthy that the reference group of African Americans from the general population includes individuals with SCT.

Even in heterozygous carriers, hemoglobin S is associated with hypercoagulability, which may be an etiologic pathway to stroke. Under conditions of exertion, dehydration, and high altitude, SCT erythrocytes are known to sickle and polymerize[26,27]. The sickling deformation exposes phosphatidylserine on the cell membrane surface, facilitating the assembly of coagulation enzymatic complexes[28]. Laboratory assays of healthy individuals with SCT show elevated markers of coagulation (prothrombin fragment 1+2, thrombin-antithrombin complex, and d-dimer)[29], and epidemiological studies report twice the risk of pulmonary embolism and venous thrombosis[7,30]. Increased prevalence of thrombotic infarctions has also been observed by post-mortem examination. In an autopsy series of 128 SCT patients, obvious visceral infarcts were observed in 18%, but were detected in less than 1% of similarly aged African Americans without SCT[31]. The spleen was the most common site of infarction in SCT cases, followed by the kidneys, lung, –and notably– the brain[31]. However, autopsy series are based on highly selected populations, and may be subject to post-mortem artifact.

In addition to hypercoagulability, the SCT phenotype has been associated with cerebral vasculopathy and subclinical small vessel disease. In a small case-control study examining children by cerebral MRI, ectasia of the basilar artery was observed in 19%, and white matter hyperintensities in 10% of children with SCT; yet neither of these findings were noted in HbAA sibling controls[32]. Dolichoectasia, characterized by tortuous, dilated vessels causing bidirectional blood flow, stasis, and thrombus formation, has been associated with lacunar stroke in the general population[33]. White matter hyperintensities, often indicative of cerebral hypoperfusion and axon demyelination, have been correlated with cognitive

decline[34], and future stroke[35]. The presence of these lesions in children with SCT may herald future cerebrovascular events. However, to date, no large, epidemiological studies have examined associations between SCT and cerebral vasculopathy, and these results are yet to be replicated.

Despite the biological and observational evidence supporting our findings of an association between SCT and stroke, our analysis has important limitations. Observations were based on a relatively small number of stroke events in a single cohort, and warrant validation in other populations. We were also unable to consider rare hemoglobinopathies or sickle beta thalassemia; however, the likelihood of these genotypes is low. The birth prevalence of sickle beta thalassemia in African American neonates is reported to be 0.02%, while the prevalence of compound hemoglobin S with hemoglobin E, or hemoglobin S with hemoglobin D is reported to be 0.0016% each[5]. Despite this limitation, the ARIC study is well suited for the analysis of SCT and stroke, due to the large sample of older African Americans with extensive genomic characterization, who were prospectively followed for more than two decades. Phenotypic data was meticulously collected with quality assurance, and study participant retention was excellent. To ensure the best possible measurement of exposure, we based our analysis on SCT that was genotyped, rather than imputed. Our estimations of stroke risk associated with SCT yielded a hazard ratio of 1.4, with a stroke rate that was 1.9 strokes per 1000 person-years higher than those with HbAA. This seems plausible, considering the reported stroke hazard ratio associated with sickle cell disease is 2.7 in African American adults, with a stroke rate that is elevated by 4.7 strokes per 1000 person-years. It follows that the stroke risk (if any) associated with SCT would be attenuated, compared to sickle cell disease.

In conclusion, we observed a greater ischemic stroke risk in African Americans with SCT, compared to those with homozygous hemoglobin A. If our findings are confirmed by other studies, further investigation into the pathophysiology of stroke in SCT patients and potential interventions to mitigate risk would be warranted.

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Table 1

Baseline (1987–1989) demographics and clinical characteristics of African American participants in the ARIC Study

Characteristic	SCT (N=223) *Mean ± SD or No. (%)*	HbAA (N=3,274) *Mean ± SD or No. (%)*	*P-value*
Demographics			
Age (years)	53 ± 6	54 ± 6	0.7
Female	113 (63%)	1571 (62%)	0.9
Medical History			
Current smoker	56 (25%)	989 (30%)	0.1
Hypertension	121 (54%)	1,826 (56%)	0.7
Hypercholesterolemia	69 (31%)	851 (26%)	0.1
Diabetes	42 (19%)	642 (20%)	0.8
Atrial Fibrillation	0	6 (0.2%)	1.0
Coronary Heart Disease	8 (4%)	133 (4%)	0.7
Body Mass Index (kg/m^2)	30 ± 6	30 ± 6	0.4

Table 2

Crude incidence rates of ischemic stroke occurring over follow up period (1987–2011), stratified by SCT status and age at study baseline

Genotype	N	Strokes	Person-years	Crude Incidence Rate*
SCT	223	29	4,063	7.1 (5.4 – 9.5)
< 55 years	134	17	2,659	6.4 (4.5 – 9.0)
≥ 55 years	89	12	1,404	8.5 (5.3 – 13.7)
HbAA	3,274	326	61,308	5.3 (4.9 – 5.8)
< 55 years	1,892	149	38,121	3.9 (3.5 – 4.4)
≥ 55 years	1,382	177	23,188	7.6 (6.8 – 8.6)

* per 1000 person-years

Table 3

Relative and absolute risks of incident ischemic stroke associated with SCT

Model Adjustments	Hazard Ratio	Incidence Rate Difference*
Crude	1.4 (0.9 – 2.0)	1.8 (−0.1 – 2.0)
Age and sex	1.3 (0.9 – 1.9)	2.1 (0.3 – 4.2)
Age, sex, and clinical covariates†	1.4 (1.0 – 2.0)	1.9 (0.4 – 3.8)

*per 1000 person-years

†Clinical covariates = smoking, diabetes, hypertension, total cholesterol, atrial fibrillation, and coronary heart disease