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Sickle Cell Trait and Risk of Ischemic Stroke in Young Adults

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Abstract

Background and Purpose: Approximately 8% of African-Americans have sickle cell trait (SCT) and there are conflicting reports from recent cohort studies on the association of SCT with ischemic stroke (IS). Most prior studies focused on older populations, with few data available in young adults.

Methods: A population-based case-control study of early-onset IS was conducted in the Baltimore-Washington region between 1992–2007. From this study, 342 African-American IS cases, ages 15–49, and 333 controls without IS were used to examine the association between SCT and IS. Each participant's SCT status was established by genotyping and imputation. For analysis, χ^2 tests and logistic regression models were performed with adjustment for potential confounding variables.

Results: Participants with SCT (n=55) did not differ from those without SCT (n=620) in prevalence of hypertension, previous myocardial infarction, diabetes mellitus, and current smoking status. Stroke cases had increased prevalence in these risk factors compared to controls. We did not find an association between SCT and early-onset IS in our overall population (odds ratio=0.9 [95% CI: 0.5–1.7]) or stratified by sex in males (odds ratio=1.26 [95% CI: 0.56–2.80] and females (odds ratio=0.67 [95% CI: 0.28–1.69]).

Conclusion: Our data did not find evidence of increased risk of early-onset stroke with SCT.

Keywords

sickle cell trait; stroke; young adult

Subject terms:

Ischemic stroke; Risk factors; Epidemiology; Genetics

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INTRODUCTION

Sickle cell disease, due to homozygous hemoglobin S gene, is a well-documented genetic risk factor for ischemic stroke (IS) in children and young adults. In contrast to sickle cell disease, sickle cell trait (SCT) occurs in patients heterozygous for the mutated hemoglobin gene and has historically been considered a benign carrier state. However, some[1], but not all[2], recent prospective studies have found an association between SCT and IS. These studies focused on older populations, and there is limited data on the association between SCT and early-onset IS among young adults, which is particularly important because this is the age range in which African-Americans have the highest excess stroke risk compared to their non-Hispanic white counterparts[3]. We address this evidence gap by examining the association between SCT and IS in a large population-based case-control study of stroke in young adults.

METHODS

Genetics of Early-Onset Stroke Study

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Genetics of Early-Onset Stroke Study is a population-based case-control study of early-onset IS in the bi-racial population of the Baltimore-Washington region. Details of the study design and case adjudication have been previously described[4]. For this report, we included only African-American participants, specifically 342 cases and 333 controls, identified by genetic ancestry[5]. Cases 15 to 49 years old with a first IS were identified between 1992–2007 by hospital discharge in the Baltimore-Washington region and by direct referral. Using the TOAST system, each IS was categorized into etiologic subtypes[6]. A single case with known hemoglobin SS was excluded from genotyping. Controls without a history of IS were identified by random digit dialing and frequency matched to cases by age category, ethnicity, and area of residence. A standardized interview was used to obtain information about stroke risk factors, including age, history of hypertension, diabetes mellitus, myocardial infarction, and current smoking[7].

The study was approved by the University of Maryland at Baltimore Institutional Review Board and all participants gave written informed consent.

Genotyping

SCT is defined by the presence of one copy of the Glu7Val mutation at rs334 on chromosome 11 in the *HBB* gene (OMIM 141900). Participants were genotyped with Illumina platform; rs334 was imputed using 1000 genomes with an imputation quality score of 0.80 (Supplementary Methods, https://www.ahajournals.org/journal/str).

Statistical Analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC). We compared the prevalence of SCT and other characteristics between cases and controls using t-tests for continuous variables and Cochran-Mantel-Haenszel chi-square tests for categorical variables. We calculated the overall, sex-stratified, and stroke subtype-specific odds ratios

(OR) for SCT using logistic regression models controlling for age, hypertension, myocardial infarction, diabetes mellitus, and current smoking. Two-tailed probability values <0.05 were considered statistically significant. Given our 9.1% rate of SCT among controls and alpha-0.05, our study had 80% power to detect an OR of 1.93.

RESULTS

Table 1 shows the demographic and clinical characteristics of participants by SCT status and history of IS. Participants with SCT (HbAS; n = 55) and wildtype hemoglobin (HbAA) genotype (n = 620) did not differ significantly in age, sex, or prevalence of hypertension, myocardial infarction, diabetes mellitus, or current smoking. Only 34.6% of participants with SCT were aware they had SCT, while 1.9% of participants without SCT believed they had SCT. Cases (n = 342) and controls (n = 333) did not differ in sex, self-reported SCT, or prevalence of SCT through genotyping. Cases had a higher mean age than controls ($p<0.0001$) and an increased prevalence of hypertension ($p<0.0001$), myocardial infarction ($p=0.0004$), diabetes mellitus ($p<0.0001$), and current smoking ($p=0.006$), compared to controls.

The overall OR for SCT, adjusted for age, hypertension, myocardial infarction, diabetes mellitus, and current smoking was 0.92 (0.51–1.66). The adjusted OR for SCT was 1.26 (95% CI: 0.56–2.80) in males and 0.67 (95% CI: 0.28–1.69) in females. Table 2 depicts the stroke subtype-specific ORs and p-values. There was no significant association between SCT and any IS subtype.

DISCUSSION

Our study did not find evidence of an association between SCT and all IS. Because many gene-stroke associations are subtype-specific[8], we provided subtype-specific analyses for hypothesis generation. The strongest association in our study was with the large artery atherosclerosis subtype, which will require further support from other studies.

A previous study of 2,642 participants with SCT and 11,183 participants with HbAA (overall mean age 36 years) from Kaiser-Permanente Northern California found no difference in stroke prevalence (relative risk=0.98 [95% CI: 0.85–1.13]) among those with SCT[9]. However, many participants were not tested for SCT, and since only 34.6% of our participants with SCT were aware they had SCT, there were likely participants with SCT who were misclassified as HbAA in the Kaiser-Permanente study. This bias would tend to decrease the relative risk for SCT. Our study differs from the Kaiser-Permanente study because we determined the SCT status of all participants through imputation, included only recently diagnosed strokes rather than prevalent cases, and drew cases from an economically diverse population versus a single health maintenance organization.

Available evidence in predominantly older adults is conflicting (Supplementary Table, https://www.ahajournals.org/journal/str). A report from the Atherosclerosis Risk in Communities (ARIC) using direct genotyping of 223 African-Americans with SCT and 3274 African-Americans with HbAA found an association between SCT and IS (HR=1.4 [95% CI: 1.0–2.0])[1]. However, a subsequent meta-analysis of Reasons for Geographic and

Racial Differences in Stroke (REGARDS), Jackson Heart Study (JHS), Multi-Ethnic Study of Atherosclerosis (MESA), and Women's Health Initiative (WHI), failed to find an association (HR=0.80 [95% CI: 0.47–1.35])[2]. Participants from REGARDS were directly genotyped, while genotypes of participants from JHS, MESA, and WHI were imputed. A later study from the ARIC cohort suggested that SCT and chronic kidney disease act synergistically to increase the risk of IS[10]. No subtype-specific analyses were performed in either study.

Our study has several limitations. Our findings suggest against a strong association (OR>1.9) between SCT and IS in young adults but is not adequately powered to detect a weaker association. We did not adjust for all potential confounding variables, including body mass index, hyperlipidemia, and alcohol consumption. SCT status was imputed rather than directly genotyped. Nevertheless, our findings are consistent with the Kaiser Permanente study of young adults but extend these findings to a socially and economically diverse population. While our study did not find a statistically significant association between SCT and any IS subtype, subsequent higher-powered studies may uncover a subtype-specific association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

SCT	sickle cell trait
IS	ischemic stroke
OR	odds ratio
ARIC	Atherosclerosis Risk in Communities
REGARDS	Reasons for Geographic and Racial Differences in Stroke
JHS	Jackson Heart Study
MESA	Multi-Ethnic Study of Atherosclerosis
WHI	Women's Health Initiative

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Table 1.

Demographic and Clinical Characteristics of Participants

	By sickle cell trait status:			By history of ischemic stroke:		
Characteristic	**SCT (n=55)**	**HbAA (n=620)**	**p-value***	**Case (n=342)**	**Control (n=333)**	**p-value***
Sickle Cell Trait, n (%)	--	--	--	25 (7.3%)	30 (9.1%)	0.42
Mean Age (SD)	39.4 (8.0)	41.0 (6.8)	0.1	41.9 (6.9)	39.9 (6.8)	0.0001
Male Sex, n (%)	31 (56.4%)	340 (54.8%)	0.83	188 (55.0%)	183 (55.0%)	0.997
Hypertension, n (%)	20 (36.4%)	262 (42.3%)	0.4	197 (57.6%)	85 (25.5%)	<0.0001
Diabetes Mellitus, n (%)	7 (12.7%)	101 (16.3%)	0.49	79 (23.1%)	29 (8.7%)	<0.0001
Current Smoker, n (%)	19 (34.6%)	264 (42.6%)	0.25	161 (47.1%)	122 (36.6%)	0.006
Myocardial Infarction, n (%)	0 (0%)	23 (3.7%)	0.15	20 (5.9%)	3 (0.9%)	0.0004

* p-values by chi-square

Table 2.

Stroke Subtype-Specific Odds Ratios

Subtype	SCT (n=25)	HbAA (n=317)	p-value	OR (95% CI)
Cardioembolic	6 (24.0%)	65 (20.5%)	0.97	1.02 (0.39–2.71)
Large artery atherosclerosis	3 (12.0%)	18 (5.7%)	0.29	2.05 (0.54–7.84)
Small vessel occlusion	5 (20.0%)	69 (21.8%)	0.85	1.11 (0.36–3.48)
Other determined	0 (0%)	22 (6.9%)	0.96	--
Other undetermined	11 (44.0%)	143 (45.1%)	0.997	1.00 (0.47–2.13)