Silent infarct is a risk factor for infarct recurrence in adults with sickle cell anemia

Lori C. Jordan, MD, PhD, Adetola A. Kassim, MD, Manus J. Donahue, PhD, Meher R. Juttukonda, PhD, Sumit Pruthi, MD, Larry T. Davis, MD, Mark Rodeghier, PhD, Chelsea A. Lee, BS, Niraj J. Patel, MPH, and Michael R. DeBaun, MD, MPH

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Correspondence

Dr. Jordan
lori.jordan@vanderbilt.edu

Abstract

Objective

Because of the high prevalence of silent cerebral infarcts (SCIs) in adults with sickle cell anemia (SCA) and lack of information to guide treatment strategies, we evaluated the risk of recurrent SCIs and overt stroke in adults with SCA with preexisting SCI.

Methods

This observational study included adults with SCA (HbSS or S β^0 thalassemia) aged 18 to 40 years. Participants received 3-tesla brain MRI and a detailed neurologic examination. Time-to-event analysis assessed those with or without baseline SCI and with new or progressive infarcts. The incidence rate of new events was compared by log-rank test. Univariable Cox regression assessed the association of SCI with infarct progression.

Results

Among adults with SCA with 2 MRIs and at least 6 months between MRIs ($n = 54$, mean interval = 2.5 years), 43% had SCI at baseline. Of participants with baseline SCI, 30% had new or progressive SCI over 2.5 years compared to 6% with no SCI at baseline; no participant had an overt stroke. New SCIs at follow-up were present in 12.9 per 100 patient-years with existing SCI compared with 2.4 per 100 patient-years without prior SCI (log-rank test, $p = 0.021$). No statistically significant differences were seen among those with or without baseline SCI in use of hydroxyurea therapy, hydroxyurea dose, or other stroke risk factors. The presence of SCI was associated with increased hazard of a new or progressive infarct (hazard ratio 5.27, 95% confidence interval 1.09–25.51, $p = 0.039$).

Conclusions

Silent infarcts in adults with SCA are common and are a significant risk factor for future silent infarcts.

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From the Department of Pediatrics, Division of Pediatric Neurology (L.C.J., C.A.L., N.J.P.), Vanderbilt-Meharry Sickle Cell Center for Excellence (A.A.K., M.R.D.), Departments of Radiology and Radiological Sciences (M.J.D., M.R.J.), Neurology (M.J.D.), and Psychiatry (M.J.D.), and Department of Radiology, Divisions of Pediatric Radiology and Neuroradiology (S.P.), and Department of Radiology, Division of Neuroradiology (L.T.D.), Vanderbilt University Medical Center, Nashville; Department of Physics and Astronomy (M.J.D.), Vanderbilt University, Nashville, TN; and Rodeghier Consultants (M.R.), Chicago, IL.

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Glossary

CI = confidence interval; MCV = mean cell volume; SCA = sickle cell anemia; SCI = silent cerebral infarct; TCD = transcranial Doppler.

Silent cerebral infarcts (SCIs) are the most common permanent neurologic injury in children and adults with sickle cell anemia (SCA), occurring in 39% and 50% of individuals with SCA by age 18 and 30 years, respectively.^{1,2} SCI prevalence increases from childhood to adulthood. In children with SCA, SCIs are associated with a mean 5 full-scale IQ point decrement, poor academic performance, and future overt strokes.^{3,4} For adults with SCA and SCIs, cognitive morbidity and influence on socioeconomic status have not been extensively studied. Given the high prevalence of SCIs in SCA, coupled with evidence that SCI is a risk factor for future silent and overt strokes in children with SCA,⁵ we prospectively tested the hypothesis that adults with SCA and SCIs have a significantly higher risk of SCI or overt stroke recurrence relative to adults with SCA without SCI or overt stroke.

Methods

Adults with SCA (referred to here as either HbSS or HbS β^0 thalassemia phenotypes), aged 18 to 40 years, were enrolled in a longitudinal observational study from September 2014 to September 2017 with focus on developing novel imaging methods capable of predicting SCI and infarct risk. Each participant received 3-tesla (Philips Healthcare, Best, The Netherlands) MRI of the brain, magnetic resonance angiography of head and neck without contrast, and a neurologic examination by the study neurologist. Two board-certified neuroradiologists independently recorded neuroimaging findings including presence of existing cerebral infarcts (lesion at least 3 mm in 1 dimension and visible in 2 planes on T2-weighted fluid-attenuated inversion recovery images) and intracerebral hemorrhage according to prior established MRI criteria.⁵ They documented new infarcts and progression of previously identified infarcts that increased by 3 mm along any linear dimension on MRI.⁵ Disagreements were resolved by consensus. If detailed neurologic examination was normal or an abnormality on neurologic examination could not be explained based on location of the infarct-like lesion, infarcts were judged to be silent.⁵ Exclusions were prior stroke, regular blood transfusions, or not having 2 MRIs at least 6 months apart. Data analysis was performed using SPSS version 24.0 (IBM, Armonk, NY). Participant characteristics were described by mean and SD for continuous measures and by number and percent for categorical measures. A 2-sided p value ≤ 0.05 was considered statistically significant. Time-to-event analysis with a log-rank test assessed those with or without SCI at baseline for a new or progressive infarct. The small sample size and low fraction of events of 17% (9 in 54 patients) precluded multivariable Cox regression with all covariates; instead, we used univariable Cox regression with clinically relevant covariates to assess their association with progression.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all participants; the study was approved by the Vanderbilt University institutional review board.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

The study population included 80 adults with HbSS (89%) or HbS β^0 thalassemia (11%) out of 107 individuals with either phenotype, aged 18 to 40 years, followed in the adult sickle cell disease clinic at Vanderbilt University Medical Center (figure 1). Of these 80 participants, 100% had a study MRI and 72 (90%) had a baseline screening clinical MRI as part of

Figure 1 Study flowchart

Flowchart shows number of adults with sickle cell anemia included and excluded in the study. SCD = sickle cell disease.

standard care (one screening MRI recommended for all adults with SCA) prior to study participation; 69 (86%) had a minimum time of 6 months between MRIs, and 15 (19%) were excluded because of preexisting overt strokes. Fifty-four (68%) participants were analyzed: mean age = 26.9 years, 100% black, 31 (57%) with no SCI at baseline, and 23 (43%) with SCI at baseline.

With a mean interval of 2.5 years between MRIs, 30% (7/23) with SCI at baseline had new or progressive SCI compared to 6% (2/31) with no SCI at baseline. No overt strokes occurred during the follow-up period of 137 patient-years, consistent with the overt stroke risk of 1 per 100 person-years in this age range.⁶ At the time of the initial and follow-up MRI, 80% (43/54) were receiving hydroxyurea therapy. Kaplan-Meier curves show the time-to-event data in those with and without SCI at baseline (figure 2). In the subgroup that progressed, 78% (7/9) were treated with hydroxyurea with a mean dose of 22.0 mg/kg/d; however, only 4 of 7 were judged adherent to therapy with an increase in the mean cell volume (MCV) from baseline to last MCV of 10.0 fL or more. One was non-adherent and 2 were equivocal with increase in MCV of 5 to 9.9 fL. No statistically significant differences were seen based on intracranial or extracranial artery stenosis, hydroxyurea dose, baseline laboratory measures, or stroke risk factors among those with or without SCI at baseline (table).

In this cohort of young adults with SCA, new SCIs were present in 12.9 per 100 patient-years in those with existing SCI compared with 2.4 per 100 patient-years in those without prior SCI or overt stroke (log-rank test, $p = 0.021$). Using univariable Cox regression analysis, baseline SCI was associated with increased hazard of a new or progressive infarct (hazard ratio 5.27, 95% confidence interval [CI] 1.092–25.51, $p = 0.039$). Use of hydroxyurea therapy throughout the follow-up period was not protective (hazard ratio 0.27, 95%

Table Demographic features and stroke risk factors of study participants with sickle cell anemia ($n = 54$)

Measure	No silent infarct at baseline ($n = 31$) ^a	Silent infarct at baseline ($n = 23$) ^a	p Value ^b
Age at baseline MRI, y	26.9 (6.1)	27.0 (5.9)	0.960
Male sex	16 (51.6)	12 (52.2)	0.967
Black race	31 (100)	23 (100)	1.00
Phenotype, HbSS	28 (90.3)	21 (91.3)	1.00 ^c
Follow-up time, y	2.7 (2.0)	2.4 (1.4)	0.510
New infarct or progression of existing infarct	2 (6.5)	7 (30.4)	0.028 ^d
Intracranial stenosis >50% ($n = 53$)	0 (0.0)	1 (4.5)	0.415 ^d
Extracranial stenosis >50% ($n = 53$)	0 (0.0)	2 (8.7)	0.184 ^d
Hydroxyurea therapy	27 (87.1)	15 (65.2)	0.096
Hydroxyurea dose, mg/kg/d ($n = 42$)	22.3 (6.4)	22.4 (6.4)	0.953
Chronic blood transfusions	3 (9.7)	5 (21.7)	0.264 ^d
Hemoglobin, g/dL	9.3 (1.2)	8.7 (1.6)	0.158
White blood cell count, $10^9/L$	10.7 (4.4)	11.4 (4.9)	0.575
Absolute neutrophil count, $10^6/L$	5.4 (2.7)	5.6 (3.4)	0.853
Reticulocyte count	0.32 (0.15)	0.35 (0.16)	0.459
Systolic blood pressure, mm Hg	114.5 (13.2)	117.1 (14.3)	0.485
Body mass index, kg/m ²	23.4 (3.3)	22.8 (3.9)	0.548
Diabetes mellitus ^c	0 (0.0)	1 (4.3)	0.426 ^d
Coronary artery disease ^c	0 (0.0)	0 (0.0)	NA
High cholesterol ^c	0 (0.0)	0 (0.0)	NA
Nephropathy ^e	1 (3.2)	2 (8.7)	0.569 ^d
Smoking currently	3 (9.7)	4 (17.4)	0.443 ^d

Abbreviation: HbSS = hemoglobin SS; NA = not applicable.

^a Data represent count (%) for categorical variables and mean (SD) for continuous variables, unless otherwise noted.

^b Chi-square test for categorical variables and t test for continuous variables, unless otherwise noted.

^c Self-reported by study participant and/or documented medical records.

^d Fisher exact test.

^e Defined as serum creatinine of 2 mg/dL or 1.5 times the baseline creatinine or an estimated glomerular filtration rate of <60 mL/min/1.73 m² body surface area persistent over at least 3 months based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.

Figure 2 Kaplan-Meier curve depicting time to new SCI in adults with sickle cell anemia

A total of 54 participants had a minimum time of 6 months between MRIs; in this group of adults, 43% ($n = 23$) had SCI at baseline, and 57% ($n = 31$) had no SCI at baseline. Individuals with overt stroke were excluded. + = Censored. SCI = silent cerebral infarct.

CI 0.06–1.25, $p = 0.095$). Risk factors for SCI and strokes in children with SCA and in the general population (table), in particular baseline systolic blood pressure and baseline hemoglobin levels, were not associated with new or progressive SCI, with hazard ratio of 1.02 (95% CI 0.98–1.07, $p = 0.32$)

and 1.14 (95% CI 0.70–1.85, $p = 0.59$), respectively, with no missing data.

Discussion

Silent infarcts increase in prevalence with age with no evidence of a plateau through 30 years of age.² In this prospective cohort study, we report both the incidence and risk factors for SCI among adults with SCA, which have been poorly characterized previously. Using baseline and follow-up MRI of the brain, we demonstrated that preexisting SCI is a significant risk factor for cerebral infarct recurrence.

A retrospective Italian sickle cell disease cohort study evaluated the effect of hydroxyurea on morbidity and mortality.⁹ Investigators also found that SCI was a risk factor for recurrent SCI with a median follow-up duration of 7 years and mean hydroxyurea dose of 16 mg/kg/d. This study population is not generalizable to the SCA population in the United States because of phenotypic heterogeneity: <50% of their cohort vs >90% of our cohort had HbSS. Furthermore, this prior study utilized imaging reports rather than central neuroradiologist review of MRIs to determine presence and progression of SCI.

Unlike children with SCA in whom abnormal transcranial Doppler (TCD) velocity is a predictor of first stroke,⁷ abnormal TCD velocities are uncommon in adults,⁷ and TCD measurements have not been demonstrated to have clinical utility for predicting stroke risk in adults with SCA.⁸ Based on our findings and those of others,⁹ the presence of SCI is a predictor of future infarct recurrence in adults with SCA, similar to children with SCA. However, the rate of new cerebral injury in our study, 12.9 events per 100 patient-years, is significantly higher than the rate of new SCI in untreated children with existing SCI, at 4.8 events per 100 patient-years.⁵ Hydroxyurea is one of only 2 approved therapies for SCA and has not been studied for stroke prevention in adults; our sample size and study design preclude a statement about the effectiveness of hydroxyurea therapy to prevent SCI recurrence. Our data demonstrate that treatments are needed to prevent progressive infarcts in this population. In summary,

similar to children with SCA and SCIs, adults with SCA are at significant risk of new or progressive infarcts. Novel neuroimaging strategies may identify the subgroup of adults with SCIs at highest risk of infarct recurrence to facilitate stroke prevention trials.¹⁰

Author contributions

S.P. and L.T.D. reviewed the neuroimaging. M.R. analyzed results and made the table and figure. M.R.J. and M.J.D. acquired the imaging data. N.J.P. and C.A.L. recruited study participants and entered the data. L.C.J., M.J.D., A.A.K., and M.R.D. designed the research and wrote the paper. All authors reviewed and critically revised the manuscript.

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Disclosure

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References

1. Bernaudin F, Verlhac S, Arnaud C, et al. Chronic and acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. *Blood* 2015;125:1653–1661.
2. Kassim AA, Pruthi S, Day M, et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia. *Blood* 2016;127:2038–2040.
3. King AA, Strouse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. *Am J Hematol* 2014;89:162–167.
4. Miller ST, Macklin EA, Pegelow CH, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the cooperative study of sickle cell disease. *J Pediatr* 2001;139:385–390.
5. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med* 2014;371:699–710.
6. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998;91:288–294.
7. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.
8. Valadi N, Silva GS, Bowman LS, et al. Transcranial Doppler ultrasonography in adults with sickle cell disease. *Neurology* 2006;67:572–574.
9. Rigano P, De Franceschi L, Sainati L, et al. Real-life experience with hydroxyurea in sickle cell disease: a multicenter study in a cohort of patients with heterogeneous descent. *Blood Cells Mol Dis* 2018;69:82–89.
10. Jordan LC, Gindville MC, Scott AO, et al. Non-invasive imaging of oxygen extraction fraction in adults with sickle cell anaemia. *Brain* 2016;139:738–750.