Original Research *Feature article*

Progression of central nervous system disease from pediatric to young adulthood in sickle cell anemia

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Impact statement

Central nervous system (CNS) disease in individuals with sickle cell anemia (SCA) can be devastating but its progression from pediatric years into adulthood has not been well characterized. In young adults with SCA exposed to long-term disease-modifying therapies, an abnormal brain MRI or MRA during childhood represents a risk factor for later progression of CNS disease in young adulthood. Early identification of CNS damage should prompt consideration for institution of effective therapies.

Abstract

Silent cerebral infarcts and arteriopathy are common and progressive in individuals with sickle cell anemia. However, most data describing brain lesions in sickle cell anemia are cross-sectional or derive from pediatric cohorts with short follow-up. We investigated the progression of silent cerebral infarct and cerebral vessel stenosis on brain MRI and MRA, respectively, by describing the incidence of new or worsening lesions over a period of up to 25 years among young adults with sickle cell anemia and explored risk factors for progression. Forty-four adults with sickle cell anemia (HbSS or HbSβ^0thalassemia), exposed to chronic transfusions ($n = 12$) or hydroxyurea ($n = 32$), median age 19.2 years (range 18.0–31.5), received a screening brain MRI/MRA and their results were compared with a clinical exam performed during childhood and adolescence. We used exact log-rank test to compare MRI and MRA progression among any two groups. The hazard ratio (HR) and 95% confidence interval (CI) were calculated from Cox regression analyses. Progression of MRI and MRA occurred in 12 (27%) and 4 (9%) young adults, respectively, relative to their pediatric exams. MRI progression risk was high among participants with abnormal pediatric exams (HR: 11.6, 95% CI: 2.5–54.7) and conditional or abnormal transcranial Doppler ultrasound velocities (HR: 3.9, 95% CI: 1.0–15.1). Among individuals treated with hydroxyurea, high fetal hemoglobin measured in childhood was associated with lower hazard of MRI progression (HR: 0.86, 95% CI: 0.76–0.98). MRA progression occurred more frequently among those with prior stroke (HR: 8.6, 95% CI: 1.2–64), abnormal pediatric exam ($P = 0.00084$), and elevated transcranial Doppler ultrasound velocities ($P = 0.004$). Brain MRI/MRA imaging in pediatrics can identify high-risk patients for CNS disease progression in young adulthood, prompting consideration for early aggressive treatments.

Keywords: Stroke, sickle cell anemia, disease-modifying therapy, vasculopathy, silent cerebral infarct, young adult

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Introduction

Central nervous system (CNS) damage is common among individuals with sickle cell anemia (SCA) and brings substantial morbidity. Silent cerebral infarct (SCI), defined as an abnormality of at least 3 mm on magnetic resonance imaging (MRI) of the brain, with a normal neurologic exam or an abnormality on neurologic exam that does not correlate with the location of the MRI lesion,[1] is prevalent in children and adults with SCA and leads to neurocognitive decline and overt stroke.[2,3] Vasculopathy seen on brain magnetic resonance angiography (MRA) is also common in individuals with SCA and is associated with SCI[4,5] and future strokes.[6]

SCI progresses over time with additional lesions in patients with or without previous overt strokes.[7–12] Progression of SCI is observed both in the pediatric and adult SCA populations; however, most data regarding the longitudinal development of brain parenchymal or vascular lesions are derived from pediatric cohorts with relatively short prospective follow-up.[7,11] Additionally, pediatric cohort studies have not spanned the period of transition between pediatric and adult care, when overall disease severity and end-organ damage become more evident.[13,14] Our group previously showed that presence of SCI on brain MRI in infancy is associated with greater progression of brain lesions (SCI, overt stroke, stenosis) in adolescence.[2] We are now expanding our findings to describe and test the long-term progression of SCI and vasculopathy in young adults with SCA by comparing their brain MRI and MRA images in early adult years (ages 18.0 to 32.0 years) with those performed during childhood years (<18 years). We tested the hypothesis that young adults with SCA whose pediatric or adolescent brain MRI or MRA was abnormal would experience more frequent CNS disease progression, involving SCI and arteriopathy, compared to young adults with normal pediatric brain imaging studies.

Materials and methods

Patient selection

Young adults with SCA (HbSS or HbSβ^0-thalassemia) who participated in the IRB-approved Sickle Cell Clinical and Intervention Program (SCCRIP)[15] were included in the prospective SCCRIP sub-study that investigated the progression of brain lesions (SCI and cerebral arteriopathy) on brain MRI and MRA imaging studies. Eligible SCCRIP sub-study participants were young adults with SCA between the ages of 18.0 and 32.0 years who had undergone a brain MRI and MRA during pediatrics (ages 0 to 11.9 years) or adolescence (12.0 to 17.9 years) for a clinical indication. All participants or legally authorized representatives signed informed consent to participate in SCCRIP. Exclusion criteria included contraindication to MR studies as an adult participant, a prior cerebral revascularization procedure, or prior hematopoietic stem cell transplantation (HSCT). Prior history of transcranial Doppler ultrasound (TCD) velocities performed during childhood, treatment history with disease-modifying therapies (hydroxyurea and chronic transfusions), prior history of overt stroke or transient ischemic attack (TIA), and laboratory tests were obtained from the SCCRIP database and supplemented by chart review. Hematologic laboratory indices, including hemoglobin (Hb), mean corpuscular volume (MCV), fetal hemoglobin (HbF), sickle hemoglobin level (HbS), white blood cell count (WBC), and absolute reticulocyte count (ARC) were collected within 30 days from the imaging studies.

Brain imaging

All imaging exams were centrally reviewed by an experienced neuroradiologist who was blinded to the participants medical and treatment history. Pediatric and adolescent MRIs and MRAs were performed for clinical indications (e.g. elevated TCD velocity or a neurologic concern), while young adult MRI/MRAs were performed as part of the SCCRIP sub-study. MRI/MRA studies were performed on 1.5 T or 3 T scanners. The imaging protocols varied because of the long duration of time between studies but were consistently performed in the same pediatric or adult facility and all the studies included axial T2- and T1-weighted images. Relatively, recent studies included axial fluid-attenuated inversion recovery (FLAIR) images, while some of the older studies only had proton-density images. Axial diffusion-weighted imaging was also used to assess acuity of infarctions. Axial MRA images were acquired with 3D time-of-flight technique. The MRA images were reformatted in multiple planes and maximum intensity projection images were also generated. The severity of stenosis or occlusion of the arteries of the circle of Willis was assessed using a vasculopathy grading scoring system.[16] Most exams did not include neck vessels, and these were not reviewed.

Childhood MRI imaging studies were considered abnormal if SCI or overt strokes were present. SCIs were defined as the presence of a focal T2-weighted or FLAIR hyperintensity on brain MRI of $\geq$3 mm, consistent with the silent infarct transfusion (SIT) trial definition.[17] Progression of MRI findings was defined by the presence of new SCI lesions, not seen on prior brain imaging, or new overt strokes. Evolution of old infarcts to encephalomalacia was not considered as MRI progression; the neuroradiologist made the determination after careful review, if an area of change was due to encephalomalacia versus new infarct. Overt stroke was defined as a clinical neurologic deficit, lasting more than 24 h, with a new infarct on MRI. TIA was defined as neurologic symptoms lasting less than 24 h with no change on MRI.[17] Cerebral vasculopathy was graded from 0 to 6, based on amount of vessel stenosis (mild, moderate, severe, and complete obstruction) along with the number of vessels affected.[16] Abnormal MRA was defined as a vasculopathy grading score of $\geq$1. Progression of MRA cerebral vessel stenosis was defined as any increase in the vasculopathy grading score, which equated to worsening or new stenosis.

Statistical analysis

The count and percentage of participants with abnormal MRI/MRA were calculated for three time points based on

age range: pediatrics (0–12.9 years), adolescence (13.0–17.9 years), and young adulthood (18.0–32.0 years). The generalized linear mixed effect model (GLMM) with a Gaussian link function was used to assess the trend of the laboratory variables across the time point. The GLMM with a binomial link function was used to associate age with the binary outcome of abnormal MRI/MRA and to associate laboratory variables with the binary outcome of normal or abnormal MRI/MRA after adjusting for age. There were 12 MRI missing pediatric or adolescent data time points ($12/(44\times3)=9\%$) on 12 participants and 20 MRA missing data points ($20/(44\times3)=15\%$) on 17 participants, respectively. We used a forward-backward multiple-imputation algorithm to impute the missing data only for the GLMM analyses. We then combined pediatric and adolescent MRI/MRA exams and defined baseline MRI/MRA as normal if both pediatric and adolescent MRI/MRA were normal, or abnormal if otherwise. The MRI/MRA disease progression free survival (PFS) was estimated using the Kaplan–Meier method. MRI/MRA PFS was defined as the time from the baseline MRI/MRA exam until MRI/MRA progression, censoring those without disease progression at last (i.e. young adult) MRI/MRA exams. The MRI/MRA PFS was compared between the two groups (normal versus abnormal baseline exam) using exact log rank tests. The hazard ratio (HR) and 95% confidence interval (CI) were calculated from Cox regression analyses. The proportional hazard assumption was checked in all analyses. With a total of 12 and 4 participants who progressed on MRI and MRA, respectively, we included only one laboratory variable in the Cox model analysis. Univariate cox regression analysis was also used to associate laboratory tests with progression of brain MRI. We did not associate the laboratory tests with progression of MRA due to the small number of MRA progression events ($n=4$). All *P*-values were two-sided and were considered significant if less than 0.05. Statistical analyses were performed with R version 4.0.2.

Results

Participant characteristics

Forty-four young adults had MRI and/or MRA exams during childhood (pediatrics and/or adolescence) and underwent a prospective young adult exam. All but three participants had HbSS, all were African American, and their median age at the time of their pediatric, adolescent, and adult MRI/MRA exams were 4.5 years (range 0.7 to 11.9 years), 13.9 years (range 12.1 to 17.9 years), and 19.1 years (range 18.0 to 31.5 years), respectively (Table 1). A total of 256 MRI and 236 MRA studies were centrally reviewed among these 44 participants. All 44 young adults received disease-modifying therapy prior to their adult MRI and MRA studies, for a median hydroxyurea exposure duration of 10.3 years (range 0.2 to 22.5 years) or chronic transfusion exposure duration of 9.2 years (range 2.5 to 14.4 years). Median hydroxyurea dose at the time of adult MRI and MRA studies was 23.3 mg/kg/day. Indications for hydroxyurea therapy were recurrent vaso-occlusive events ($n=30$), overt stroke ($n=1$), and abnormal TCD ($n=1$). Indications for chronic transfusion therapy included abnormal TCD velocities ($n=6$), overt stroke

Table 1. Participant characteristics according to treatment group exposure.

	All ($n=44$)	Hydroxyurea therapy ($n=32$)	Chronic Transfusions ($n=12$)
Sex (male), *n*	21	16	5
Race (African American), *n*	44	32	12
Sickle genotype			
HbSS, *n*	41	29	12
HbS/β^0-thalassemia, *n*	3	3	0
Median duration of treatment exposure (years) (range)	10.1 (0.2–22.5)	10.3 (0.2 to 22.5)	9.2 (2.5 to 14.4)
Brain imaging			
MRI			
Median (range) age pediatric MRI (years)	4.5 (0.7–11.9)	4.2 (0.7–11.9)	6.3 (1.4–11.6)
Median (range) age adolescent MRI (years)	13.9 (12.1–17.9)	13.9 (12.3–17.9)	13.7 (12.1–16.6)
Median (range) age adult MRI (years)	19.2 (18.0–31.5)	19.5 (18.1–31.5)	18.6 (18.0–30.5)
Abnormal pediatric MRI, *n* (%)[a]	19 (43.2%)	10 (31.3%)	9 (75%)
MRI worsened from pediatric to adulthood, *n* (%)	12 (27.3%)	7 (21.9%)	5 (41.7%)
Mean (SD) time to progression MRI (years)	7.6 (4.1)	8.8 (4.7)	5.9 (2.6)
MRA			
Median (range) age pediatric MRA (years)	4.5 (0.7–11.9)	4.2 (0.7–11.9)	6.3 (1.4–11.8)
Median (range) age adolescent MRA (years)	13.9 (12.1–17.4)	13.9 (12.3–17.4)	13.7 (12.1–16.6)
Median (range) age adult MRA (years)	19.0 (18.0–30.5)	19.3 (18.1–28.1)	18.3 (18.0–30.5)
Abnormal pediatric MRA, *n* (%)[a]	10 (22.7%)	4 (12.5%)	6 (50%)
MRA worsened from pediatric to adulthood, *n* (%)	4 (9.1%)	0 (0%)	4 (33.3%)
Mean (SD) time to progression (years)	6.8 (6.0)	9.3 (1.0)	6.8 (6.0)
Pediatric transcranial Doppler (TCD) ultrasound category[b]			
Abnormal TCD, *n* (%)	10 (22.7%)	3 (9.4%)	7 (58.3%)
Conditional TCD, *n* (%)	7 (15.9%)	6 (18.8%)	1 (8.3%)
Normal TCD, *n* (%)	21 (47.7%)	20 (62.5%)	1 (8.3%)

SD: standard deviation; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.
[a]Pediatric evaluations occurred before age 18.
[b]Categorization based on highest TCD value documented; 7 pts did not have TCD performed during pediatric years.

($n=4$), recurrent acute chest syndrome ($n=1$), and chronic kidney disease ($n=1$). Increases in MCV and decreases in HbS were observed after initiation of hydroxyurea and chronic transfusion therapy, respectively. HbF was increased after initiation of hydroxyurea but not statistically significant when adult values were compared with adolescent and pediatric ones (Supplemental Table 1). The total follow-up time for the cohort was 680 person-years.

MRI progression

The number (proportion) of participants with abnormal MRI increased from 15 (37.5%) in pediatric exams to 19 (50%) in adolescent exams and to 21 (47.7%) in adult exams (estimate = 1.6, standard error (se)=1.0, $P=0.11$, based on imputed data). As a sensitivity analysis, for three patients with abnormal adolescent and younger adulthood MRI data who were missing pediatric MRI data, if we imputed them as normal pediatric MRIs, age was significantly associated with higher proportion of abnormal MRI (estimate= 2.8, se = 1.3, $P=0.035$). There were no statistically significant associations between hematologic laboratory indices (before or after initiating disease-modifying therapies) and abnormal brain MRI after adjusting for age.

Nineteen participants (43%) had abnormal MRI exams at baseline. The median follow-up time from baseline to young adult MRI imaging study was 15.1 years (range 2.3 to 25.3 years). Relative to the baseline timepoint, progression of MRI occurred in 12 (27%) young adults (Figure 1(a)), representing an incidence of 1.76 events/100 patient-years. Participants with abnormal baseline MRI had greater cumulative incidence of MRI progression than those with normal baseline MRI (HR: 11.6, 95% CI: 2.5–54.7, $P=0.00017$, Figure 1(a)). MRI progression occurred among seven young adults treated with hydroxyurea and five treated with transfusions (two of whom with history of prior stroke in pediatrics). MRI progression occurred more frequently among 17 participants with conditional or abnormal TCD velocities (HR: 3.8, 95% CI: 1.0–15.1, $P=0.035$) but not among six participants with prior stroke ($P=0.24$). High HbF at the adolescent timepoint was associated with lower risk of young adult MRI progression among participants continuously treated with hydroxyurea (HR: 0.84, 95% CI: 0.71–1.00, $P=0.046$). No other statistically significant associations between baseline or young adulthood hematologic laboratory indices were found with progression of brain MRI.

MRA progression

The number (proportion) of participants with abnormal MRA increased from 6 (15.8%) in pediatric exams to 10 (26.3%) in adolescent exams and 9 (25.7%) in adult exams (estimate = 4.5, se = 1.8, $P=0.013$, based on imputed data). There were no statistically significant associations between hematologic laboratory indices (before or after initiating disease-modifying therapies) with abnormal brain MRA after adjusting for age.

Ten participants (22.7%) had abnormal MRA exams at baseline. The median follow-up time from baseline to young adult MRA imaging study was 13.9 years (range 0.4 to 25.1 years). Relative to the baseline timepoint, progression of MRA occurred in 4 (9.1%) young adults (all with abnormal baseline MRA exams), representing an incidence of 0.59 events/100 patient-years. Participants with abnormal baseline MRA had larger cumulative incidence of MRA progression than those with normal baseline exam (HR: not estimable (NE) due to absence of progression among patients with normal baseline MRA, $P=0.00084$, Figure 1 (b)). MRA progression occurred more frequently among those with prior stroke (HR: 8.6, 95% CI: 1.2–64, $P=0.02$) and among those with conditional or abnormal TCD velocities (HR: NE, $P=0.004$). Additionally, of the 17 patients with either conditional or abnormal TCD velocities, 6 (35%) had an abnormal MRA at some point during their lives.

New neurologic events

Five patients had an overt stroke as a child, all presented with stroke symptoms prior to starting therapy and were started on chronic transfusion at the time of stroke. One was changed to hydroxyurea therapy as per the SWiTCH protocol,[18] and later refused to restart transfusions after results were published recommending transfusions as

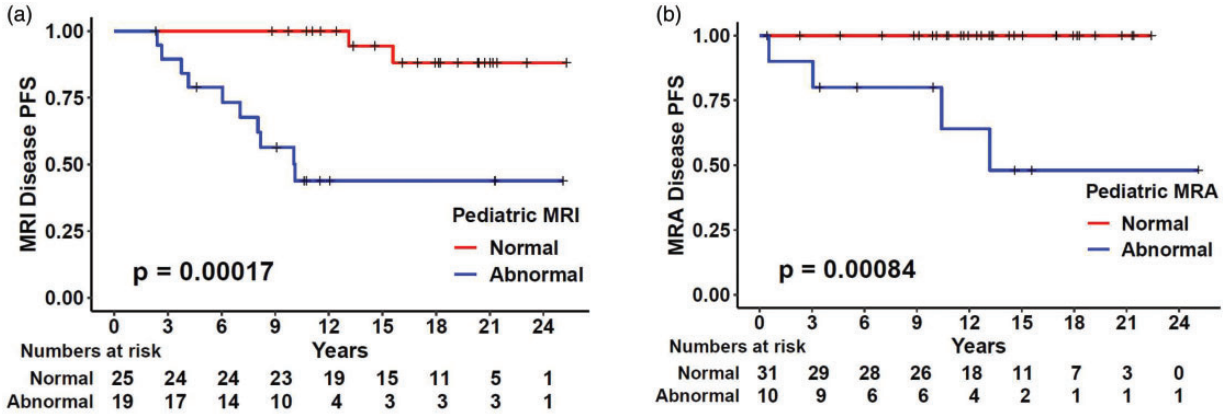

Figure 1. CNS disease progression according to baseline status. The risk of MRI (a) and MRA (b) disease progression is significantly higher among those with baseline abnormal exams. PFS: progression free survival. *P*-values were calculated using exact log rank test. (A color version of this figure is available in the online journal.)

preferred treatment for secondary stroke prevention. During the interval period from baseline to young adult imaging dates, one patient had an additional overt stroke while treated with transfusions and four had TIA events, while on hydroxyurea or transfusion therapy for an incidence of 1.47 events/100 patient-years. The combined incidence of SCI, TIA, and strokes was 3.23 events/100 patient-years.

Discussion

In a population of young adults with SCA-treated hydroxyurea or chronic transfusions since childhood, we observed up to 27% progression of cerebral brain lesions (arteriopathy or SCI) in comparison with their imaging studies in childhood. An abnormal brain MRI or MRA imaging study or TCD velocity elevation (conditional or abnormal velocities) in pediatrics or adolescence increased the risk of cerebral disease progression on both MRI and MRA. In this cohort exposed to long-term disease-modifying therapy, prior stroke increased the risk of progressive arteriopathy, but not SCI.

Consistent with prior findings, we observed that a history of stroke[19] and abnormal/conditional TCD velocities[20] predict future brain disease progression. We also found that an abnormal brain imaging study in pediatrics or adolescence increases the risk of further progression of brain lesions. Collectively, our results continue to highlight the importance of modifying treatment in response to stroke, the utilization of regular TCD screenings to detect patients at risk for CNS disease, and regular brain imaging to detect progression after stroke or when SCI is detected. The American Society of Hematology evidence-based guidelines have recently recommended screening of school age children with SCA with brain MRI/MRA, and our findings support this recommendation, by demonstrating a higher CNS disease progression risk when an initial study during childhood is abnormal.[21]

Our study follows patients with SCA from childhood to young adulthood, giving important insight into progression of neurological changes. Prior studies examining changes in cerebral lesions followed patients for shorter intervals. Close-monitoring into young adulthood is particularly important given the notable difficulties SCA patients face when transitioning from pediatric to adult care.[22,23]

Although SCI and arteriopathy progression occurred from pediatric to young adulthood years, and in contrast with pooled cross-sectional data analyses,[3] their incidence seemed to have attenuated starting in adolescence (Figure 1). Disease-modifying therapies (hydroxyurea and transfusions) may reduce the incidence of SCI.[11,17,24] In fact, in our cohort, a higher baseline HbF decreased the likelihood of new SCIs, a finding corroborated by higher risk of SCIs in adults with lower HbF levels.[25] Our study was not designed to evaluate the long-term efficacy of hydroxyurea or chronic transfusions in prevention of brain lesion progression, however, and the lack of an untreated control group precludes any definitive conclusion. But our findings provide preliminary data regarding the incidence of new brain lesions as children with SCA emerge into adulthood while receiving disease-modifying therapies. Further investigation of the long-term neuroprotective effects of disease-modifying therapies in the young adult population is needed.

Progression of SCI and other neurological events differed in some aspects from prior studies examining patients treated with hydroxyurea[11] or chronic monthly transfusion.[17] In the SIT trial,[17] the infarct progression rate was 2.0 per 100 patient-years after being followed for an average of three years. In contrast, the hydroxyurea study of long-term effects (HUSTLE; NCT00305175)[11] followed patients treated with hydroxyurea and observed an SCI progression rate of 0.49 SCI per 100 person-years over a six-year time period. In the present study, we observed SCI progression at a rate of 1.76 per 100 patient-years over a median of 15 years. The slightly greater progression rate in the SIT trial is likely accounted for by selection criteria, as all SIT participants had SCI at baseline. The reduced progression rate observed in the HUSTLE study, compared to current findings, may be due in part to the older age of our cohort and the removal of two participants from that study due to worsening TCD values. Interruptions of care are relatively common in the transition from pediatric to adult care.[26,27] Possibly, challenges related to adolescence and continuity of care may also have contributed to this increased risk of progressive CNS disease.

Among our sample, 23% displayed an abnormal MRA in childhood and 9% of patients demonstrated progression of vasculopathy at follow-up. These findings differ from those of Hulbert *et al*.[9] that assessed progression of vasculopathy among SCD patients with a prior history of stroke requiring chronic blood transfusions. They observed a 38% progression in vasculopathy over three years compared to the 9% we observed. These differences are likely due, in part, to the baseline characteristics of each sample, with the Hulbert sample having much greater baseline vasculopathy than we observed (63% versus 23%) and all participants had a prior history of stroke.

Strengths of our study included the long-term longitudinal follow-up of a relative homogeneous sample of patients with SCA from pediatric into young adulthood and the blind central adjudication of brain lesions. Limitations of our study include the small number of participants and lack of an untreated control group. Additionally, the potential for selection for greater severity exists, given that pediatric exams were done for clinical indications (neurologic symptoms) and were not performed as screening exams, possibly selecting our population for a more severe phenotype. Except for HbF, we did not observe any associations between hematologic indices (including Hb) and brain disease progression on MRI, in contrast to prior studies. This difference is potentially because hematologic labs were done during exposure to disease-modifying therapies, the long interval between pre-treatment values and when the brain images were done, and the small sample size of the analysis, limiting our power to detect an association. Furthermore, because of our long follow-up period, lab values captured near neuroimaging evaluations may not fully reflect fluctuations in labs over the duration of the patient's course. The trajectory

of laboratory results, including sudden declines in Hb concentration during acute events, may better reflect the patient's course and associated brain complications, but they were not available for all participants. We did not examine neurocognitive function at the time of the imaging study, which could have been informative in demonstrating functional decline associated with brain disease progression. We were unable to examine all possible risk factors for brain disease progression, notably, we did not evaluate Hb oxygen saturation, episodes of severe anemia, or blood pressure due to our limited sample size precluding multiple and meaningful comparisons. Because our study spanned over 25 years, the quality of MRI/MRA imaging changed over time, potentially altering our ability to detect brain lesions with changes in technology in the early pediatric years.

In conclusion, in a cohort of young adults exposed to long-term disease-modifying therapies, brain disease progression continued for most patients with SCA when lesions were present since childhood. Our results suggest a possible role of disease-modifying therapies, when used since childhood, in palliating the progression of CNS disease, but not completely stopping it. In children with SCA, the presence of SCI and vessel stenoses in childhood should prompt close follow-up with repeat imaging, assessment, and treatment of other conditions such as sleep disorders[28] and systemic hypertension,[29] and consideration of alternative treatments (including curative treatments, such as hematopoietic stem cell transplantation) given the evidence that brain lesions are progressive. Early screening for childhood brain lesions with continued follow-up into adulthood will be important to further elucidate brain disease progression, while investigating the long-term protective role of therapies given in pediatrics, and how cumulative risk factors (e.g., hypertension, hypoxemia) increase this risk. Correlation with neurocognitive data could help to demonstrate the functional implications of brain disease progression in SCA.

AUTHORS' CONTRIBUTIONS

GC, JSH: study concept, data collection, data interpretation, manuscript writing and editing. SNH: central imaging review. JN, RD, WCW, WH, LJ, JHE, KIA, CLO, and AAK: data interpretation and manuscript editing. JD and GK: statistical analysis, data interpretation and manuscript editing.

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DECLARATION OF CONFLICTING INTERESTS

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ETHICAL APPROVAL

This work was approved by the St. Jude Children's Research Hospital Institutional Review board with written consent from participants.

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SUPPLEMENTAL MATERIAL

Supplementary material for this article is available online.

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