Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease

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Children with sickle cell anemia (HbSS) are at high risk for neurologically overt cerebral infarcts associated with stroke and neurologically silent cerebral infarcts correlated with neuropsychometric deficit. We used complete magnetic resonance imaging (MRI) histories from 266 HbSS children, aged 6 through 19 years, who were enrolled in the Cooperative Study of Sickle Cell Disease (CSSCD) to examine silent infarct prevalence, localization, recurrence, and progression. We report a baseline prevalence of 21.8%, marginally higher than previously reported due to improved imaging technologies. Although we observed no overall sex difference in prevalence, most lesions in girls occurred before age 6, whereas boys remained at risk until age 10. Silent infarcts were significantly smaller and less likely to be found in the frontal or parietal cortex than were infarcts associated with stroke. Children with silent infarct had an increased incidence of new stroke (1.03/100 patient-years) and new or more extensive silent infarct (7.06/100 patient-years) relative to stroke incidence among all children in our cohort (0.54/100 patient-years). Both events were substantially less frequent than the risk of stroke recurrence among children not provided chronic transfusion therapy. Although chronic transfusion is known to decrease occurrence of new silent infarcts and strokes in children with elevated cerebral arterial blood flow velocity, further study is required to determine its risk-benefit ratio in children with silent infarct and normal velocities. Until safe and effective preventive strategies against infarct recurrence are discovered, MRI studies are best reserved for children with neurologic symptoms, neuropsychometric deficits, or elevated cerebral artery velocities. (Blood. 2002;99: 3014-3018)

Introduction

Cerebral infarction is a frequent complication of sickle cell disease. For children with sickle cell anemia (HbSS) under age 20 years, the prevalence of stroke is 11%.[1] In addition, children with HbSS have been shown to have "silent infarcts," abnormal magnetic resonance imaging (MRI) without neurologic deficit.[2,3] Preliminary analysis indicated that the prevalence of such lesions between the ages of 6 and 16 years was 17%.[4]

The relationship between silent infarcts and stroke is uncertain. In fact, the designation of silent infarcts as silent has been questioned because those affected have minor, but measurable, neuropsychologic abnormalities.[5-7] Because children with HbSS who have had one stroke are known to be at high risk for subsequent events,[8-10] there has been concern that children with silent lesions also may be at increased risk for recurrence.[11] Should that be the case, subsequent lesions might occur in a location and be of sufficient size to cause neurologic deficits, fulfilling the usual definition for stroke.

We report data that extend our understanding of the prevalence of silent infarct in children with sickle cell disease using the complete Cooperative Study of Sickle Cell Disease (CSSCD) newborn cohort and newer technologies where available. In addition, we report the imaging findings for those HbSS children who had repeat MRIs done at 2-year intervals over a 10-year period. These data allow analysis of the risk of developing initial silent infarcts in children with previously normal MRI results and the risk of developing new or more extensive lesions in children previously identified with silent infarcts.

Patients, materials, and methods

Patient population

The CSSCD study design has been reported previously.[12-14] From 1978 through 1988, infants with HbSS, HbSC, HbS-β^+, and HbS-β^0 were enrolled in phase I. Consent and assent were obtained in accordance with the requirements and guidelines of the human subjects committees at participating clinical centers. Children were followed prospectively and monitored for clinical events and certain laboratory parameters during phase I. Brain MRI began in phase II of the study for all children older than 6 years. Phase III continued those observations on the pediatric cohort at 2-year intervals for a total of 10 years. The study was completed in 1998.

The 415 children had at least one acceptable, study-mandated MRI. Only scheduled, study-mandated MRI studies were included in our

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analyses. MRI studies performed in response to acute clinical events were excluded to avoid bias toward reporting those events. Fewer than 2% of scheduled MRI studies were considered unacceptable, virtually all due to motion defects. The number of acceptable, scheduled MRI studies separated by children's hemoglobin phenotypes are shown in Table 1. There was no difference in the sex distribution of children at the baseline or at any subsequent examination (Table 1). Because many children were older than 6 when this study began, the mean age for the first MRI study and during follow-up MRI studies was 8.3 years and 12.1 years, respectively (Table 1). Follow-up examinations were obtained at approximately 2-year intervals (Table 1).

Neurologic events

As in a previous report from the CSSCD,[1] stroke was defined as an acute neurologic syndrome secondary to occlusion of an artery or hemorrhage with resultant ischemia and neurologic symptoms and signs that lasted longer than 24 hours; for this report transient ischemic attack (TIA) was not considered to be a stroke.

Brain MRI images

The original brain MRI films were sent to the Data Coordinating Center for reading by study radiologists (R.Z., J.B., F.M.), 2 of whom read each study without knowledge of the children's medical history. The presence, location, and size of lesions were noted. Films were submitted to the third radiologist when there was disagreement in the initial readings and a consensus reading was made following discussion.

During the 10-year course of the study, technical changes in MRI provided higher resolution images. Each MRI was compared to the previous study allowing a retrospective determination of the accuracy of earlier readings. The original interpretation of normal or abnormal was changed if necessary to reflect the later and more accurate reading. Only 47 (6.2%) of 755 MRI studies with follow-up were updated (36 lesions not previously recognized were identified, 11 lesions previously recognized were dismissed as artifacts). Although not perfect, we feel that this reflects our best estimate of how the earlier MRI studies would have been interpreted using current technologies.

Statistical methods

Sex and age dependence of silent infarct prevalence was estimated by logistic regression. The location of lesions was compared between children with and without a history of stroke by exact Mantel-Haenszel tests with stratification based on the number of brain regions with lesions evident in each study. The involvement of the cortex and white matter within each lobe was compared between children with and without a history of stroke by the Fisher exact test. Distributions of lesion size were compared between children with and without a history of stroke by an exact Cochran-Armitage trend test. Incidence and recurrence rates of new or more extensive silent infarcts were estimated by parametric survival analysis assuming constant hazard and accounting for interval censoring of MRI results. The relative odds of developing new or more extensive silent infarcts was estimated with respect to the child's prior MRI status using generalized estimating equations and controlling for sex and age at baseline. Stroke incidence rates were estimated by parametric survival analysis assuming constant hazard. Except where otherwise noted, MRI and stroke history status of children was treated as time dependent, updating each child's status at the time of the first observed silent lesion or stroke.

Table 1. Summary statistics of children's characteristics and MRI follow-up

	Baseline MRI studies	Follow-up MRI studies
Hemoglobin phenotype		
HbSS	266	229
HbSC	120	103
HbS-β^+	20	14
HbS-β^0	9	7
Total	415	353
Male, %	52.5	53.0
Age (y, mean ± SD)	8.33 ± 1.90	12.09 ± 2.57
	(range, 6.0-16.2)	(range, 7.2-19.8)
Number of MRI studies/child	1	2.12
(mean)		(range, 1-5)
Interval between MRI studies		2.31 ± 0.76
(y, mean ± SD)		

Table 2. MRI classification of baseline studies by hemoglobin phenotype

	Hemoglobin phenotype				
Group	HbSS	HbSC	HbS-β^+	HbS-β^0	Total
Normal	190	113	17	7	327
Silent infarct	58	7	3	2	70
Prior stroke	18	0	0	0	18
Total	266	120	20	9	415

Results

Including all hemoglobin phenotypes, 88 (21.2%) of 415 children studied had a lesion on their baseline MRI. Clinical strokes, excluding TIAs, were documented in 18 (4.3%), whereas 70 (16.9%) had silent infarcts. The number of children affected at baseline varied by phenotype (Table 2). Of 266 HbSS children, silent infarcts were found in 58 (21.8%) and strokes in 18 (6.8%) at baseline, rates that are significantly higher than the prevalence of silent infarcts and stroke found in HbSC children, 5.8% and 0%, respectively ($P < .001$ and $P < .002$). Although silent infarcts were noted in HbSC children and those heterozygous for both HbS and β-thalassemia, there were not enough of these children for meaningful statistical analysis. Subsequent analyses in this paper are limited to HbSS children.

There was no significant difference by sex in the proportion of HbSS children between 6 and 16 years of age who were found to have lesions (odds ratio = 1.02, $P = .75$). However, there was a significant difference between boys and girls in the relationship between lesion prevalence and age at the time of baseline MRI (Table 3, $P = .014$). Among boys, prevalence of silent infarcts increased significantly with age, perhaps with a plateau above 10 years of age (odds ratio = 1.24 for a 1-year age increment, 95% CI, 1.01-1.54, $P = .04$). Among girls, prevalence of silent infarcts did not change significantly with age (odds ratio = 0.82, 95% CI, 0.63-1.06, $P = .13$), suggesting that few girls with normal MRI studies girls suffered silent infarcts between 6 and 16 years of age.

There was considerable scatter in the location of lesions observed in baseline MRI studies (Table 4). Among children with silent infarcts, the majority had lesions involving the frontal lobe (81%), followed by the parietal lobe (45%), the basal ganglia or thalamus (16%), and the temporal lobe (9%). Very few lesions were located in the occipital lobe or cerebellum. As reported previously,[4]

Table 3. Silent infarct prevalence at baseline among HbSS children by sex and age group

Group	6 to 7 y	7 to 8 y	8 to 10 y	Older than 10 y	Total
Female					
Normal (%)	71	81	76	87	79
Silent infarct (%)	29	19	24	13	21
Total (n)	31	31	25	31	118
Male					
Normal (%)	90	75	58	65	75
Silent infarct (%)	10	25	42	35	25
Total (n)	42	36	26	26	130

Table 4. Locations of brain lesions at baseline for HbSS children with silent infarcts compared to those with a history of stroke

Location	Silent infarct (n = 58)	Prior stroke (n = 18)	Odds ratio*
Frontal lobe	81.0%	94.4%	1.27
Cortex	17.0	82.4	0.05†
White matter	100	100	Indet
Parietal lobe	44.8	77.8	4.56
Cortex	34.6	85.7	0.09‡
White matter	100	100	Indet
Temporal lobe	8.6	33.3	1.34
Cortex	20.0	50.0	0.25
White matter	80.0	83.3	0.80
Occipital lobe	1.7	11.1	1.26
Cortex	100	100	Indet
White matter	100	50.0	Inf
Basal ganglia and thalamus	15.5	66.7	0.25§
Capsular/corona	3.4	5.6	Inf
Cerebellum	5.2	0.0	Inf
Cortex	20.7	77.8	0.25
White matter	89.7	94.4	2.18

Many children had more than one lesion. Many lesions involved more than one area. For each lobe, lesions are further characterized as involving the cortex or white matter.

Indet indicates the odds ratio is indeterminate because both odds are zero or infinity; Inf, infinite odds ratio.

*Odds ratios are listed for the odds of a lesion in the specified location among children with silent infarcts relative to the odds of a lesion in that location among children with a history of stroke.

†$P < .001$.

‡$P < .01$.

§Indicates $.05 < P < .10$.

children with a history of stroke were more likely than those with silent infarcts to have lesions involving the basal ganglia or thalamus even after controlling for the greater extent of lesions associated with a history of stroke (common odds ratio = 0.25, $P = .059$). Cortical involvement was demonstrated in 77.8% of children who had stroke compared to 20.7% of those with silent infarcts. Cortical involvement was significantly more likely among children with frontal or parietal lesions associated with stroke than among those with no history of stroke ($P < .001$ and $P = .003$ for frontal and parietal lesions, respectively).

At baseline, all children with a history of stroke had lesions at least 0.5 cm in diameter. Only 64% of children with silent infarct had lesions this large (Table 5). Size distribution differed significantly between children with silent infarcts and those with a history of stroke ($P < .0001$).

There were 229 HbSS children who had follow-up MRIs. In this group, 160 had normal baseline MRIs, 53 had silent infarcts, and 16 had suffered neurologic abnormalities typical of stroke before their baseline MRIs (all of which contained evidence of cerebral infarcts). Children with silent infarcts at baseline were significantly more likely to demonstrate new or progressive neurologically silent lesions compared to those whose baseline MRIs were normal. Only 4 of 160 (2.5%) children with normal baseline MRIs developed silent infarcts on follow-up MRI examination compared to 13 of 53 (24.5%) who had baseline silent infarct. Incidence rates of new or more extensive silent infarcts based on children's previous MRI studies were 1.01 (95% CI, 0.4-2.7) and 7.06 (95% CI, 4.2-11.8) per 100 patient-years respectively, for children with normal MRI or silent infarcts (odds ratio = 13.0; $P < .001$). Two of the 13 children with progressive neurologically silent lesions demonstrated worsening on 2 follow-up MRIs. Two of the 16 (12.5%) children who had clinical strokes prior to their baseline MRI demonstrated new or progressive silent lesions.

The incidence of stroke also was higher among children with silent infarcts compared to those with normal MRI (1.03 versus 0/100 patient-years, respectively) and lower relative to those with a history of stroke (3.6/100 patient-years). All but 2 of the 21 children with stroke in this study were on chronic transfusion regimes following their initial stroke, but data regarding the specifics of transfusion therapy were not collected. Estimates of stroke incidence rates following baseline MRI studies are limited by the fact that the majority of strokes (18 of 24) occurred before initiation of MRI studies. In addition, 3 strokes occurred after the children's final scheduled MRI, 2 in those with silent infarcts and 1 in a child with a normal MRI. These were not included in our analyses because observation for silent infarcts ended at the time of each child's final MRI.

Discussion

In a previous report, the prevalence of silent infarcts in HbSS was 36 of 215 (17%) at a mean age of 8.3 ± 1.8 years.[4] The rate obtained by inclusion of children studied for the first time in this phase was 58 of 266 (21.8%), which was not significantly different from that previously obtained. The discrepant results were due in part to latter studies being performed with improved imaging technology, including changes in pulse sequences, which allowed higher spatial and contrast resolution and improved discrimination of lesions, addition of new pulse sequences, and the increased availability of high field-strength scanners. These improvements allowed the identification of lesions in children whose earlier studies were initially read as normal.

Our data demonstrate that compared to children with HbSS, those with HbSC have a significantly lower risk for silent infarct and stroke (Table 2). Further, they suggest that there may be a sex-dependent difference in the age at which silent infarcts first occur. The prevalence of silent infarcts was higher among older boys but not older girls (Table 3), suggesting that most silent infarcts occurred in girls before age 6, whereas boys were still susceptible to sustaining first lesions up to age 10. By contrast, no sex-related differences were reported in the prevalence of stroke at any age.[1]

The prevalence of silent infarct in children with 2 transcranial Doppler ultrasonography (TCD) time averaged maximum mean velocities more than 200 cm/s in the Stroke Prevention Trial in Sickle Cell Disease (STOP) was 38%. Approximately 10% of all children with sickle cell anemia have elevated TCD velocity.[15] Therefore, in an unselected population, 3.8% (= 38% × 10%) would be expected to have both abnormalities. Conversely, in a cross-sectional analysis, approximately 83% (= 1−3.8%/21.8%) of all children with silent infarcts would be expected to have a normal TCD velocity. This hypothesis is supported by analysis of children from the 5 centers participating in both STOP and CSSCD.[16] Of the 78 children studied by both modalities, TCD velocities over 200 cm/s were found in 10 (12.8%) and silent

Table 5. Lesion size classified by children's history of stroke

Group	Lesion size		
	Less than 0.5 cm	0.5 to 1.5 cm	Greater than 1.5 cm
Silent infarct (%)	21 (36.2)	28 (48.3)	9 (15.5)
Prior stroke (%)	0 (0.0)	3 (16.7)	15 (83.3)

infarcts in 17 (21.8%). Of the 17 who had silent infarcts, 11 (64.7%) had velocities that were normal (<170 cm/s). Because TCD velocity does not decrease substantially over time,[17] it is likely that the pathogenesis of most silent infarcts differs from the large vessel abnormalities that are associated with elevated TCD velocity and the majority of strokes.

The locations of the lesions at baseline were compared in children who had a history of stroke and those who had silent infarct (Table 4). As in previous reports, infarctions were found primarily in the anterior part of the brain. The probability that a given lobe would contain a lesion did not differ significantly between children with silent infarcts and those with a history of stroke when the analysis was controlled for the difference in number of locations with lesions. Children with silent infarcts were significantly less likely than were children with a history of stroke to have lesions in the frontal or parietal cortex ($P < .01$). Moreover, silent lesions were significantly smaller than lesions associated with stroke ($P < .0001$, Table 5).

With a majority of children studied on a longitudinal basis, these data allowed us to estimate the frequency with which new lesions occurred over time and the relative risk for the development of new or more extensive silent lesions or stroke. For children with HbSS whose baseline studies were normal, 4 of 160 (2.5%) developed new silent lesions, whereas none sustained a stroke during a mean follow-up period of 4.8 years. Conversely, 13 of 53 (24.5%) of those with silent lesions at baseline developed new or more extensive silent lesions and 3 (5.7%) suffered stroke during a mean follow-up period of 5.2 years. The risk for stroke or development of new or more extensive silent lesions in children with silent infarcts was significantly higher than among children with normal MRIs. Maximum size, total extent, and location of silent lesions did not affect the probability of children developing new or more extensive silent lesions.

Compelling evidence is beginning to mount indicating that silent infarct lesions have important clinical consequences. First, these lesions are associated with impaired function on standardized psychometric tests.[5,6] Second, Miller et al[18] have recently shown that there is a significant risk of classical strokes in the CSSCD patients with silent infarcts and no history of clinical stroke and that a silent infarct on MRI is the strongest independent predictor of stroke among various clinical and laboratory parameters examined. Finally, our data illustrate that silent infarct lesions are not static but can progress over time, occurring in multiple locations and capable of further impairing neurologic function.

In summary, there exist both similarities and differences in the occurrence of silent infarcts and strokes. Both cause brain dysfunction,[6] albeit of different type and degree. Although the stroke rate differs between those who do or do not have silent lesions by age 6 years, the increased risk (1.03/100 patient-years) does not approach that reported following stroke which, using data provided prior to the widespread use of transfusion for prevention, can be calculated to be 25.6/100 patient-years.[8,9] More recent data suggest the risk for recurrence for children receiving chronic transfusion is 4.2/100 patient-years.[19]

Preliminary analysis of the data from the STOP study shows that transfusion prevents the occurrence of new strokes or silent infarcts in those with elevated arterial blood flow velocity and silent infarcts.[20] It is not clear whether similar protection would be provided for children with silent infarct and normal TCD velocity. In view of that uncertainty and a silent infarct recurrence risk of 7.1/100 patient-years, a rate roughly comparable to that found for stroke when patients are chronically transfused, provision of chronic transfusion therapy for children with silent infarcts should be approached with caution. With the significant risks associated with transfusion therapy, additional clinical investigations should be undertaken to compare the value of chronic transfusion relative to standard care and to determine whether hydroxyurea might provide protection[21] before considering use of transfusion therapy for children who have silent infarcts. The combination of the association of cognitive deficits with silent infarcts in addition to the modest increased risk for stroke provide a reasonable justification for the development of such trials.

Until the safety and efficacy of the above-mentioned or other interventions are tested to determine if new silent infarcts or strokes can be prevented, it is difficult to support routine MRI studies in HbSS children who are neurologically normal. However, if normal images are obtained in girls over age 6 or boys over age 10, these data suggest that normal results preclude the need to obtain subsequent routine studies.

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Appendix

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