

The Spectrum of Brain MR Abnormalities in Sickle-Cell Disease: A Report from the Cooperative Study of Sickle Cell Disease

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PURPOSE: To define the spectrum of abnormalities in sickle-cell disease, including infarction, atrophy, and hemorrhage, that are identified by brain MR imaging. **METHODS:** All MR studies included T1, T2, and intermediate pulse sequences. Images were interpreted without knowledge of the clinical history or neurologic examination findings. Brain MR imaging was performed in 312 children with sickle-cell disease. **RESULTS:** Seventy patients (22%) had infarction/ischemia and/or atrophy. Infarction/ischemia was noted in 39 children (13%) who had no history of a stroke (the "silent" group). The prevalence rates for silent lesions were 17% for sickle-cell anemia and 3% for hemoglobin sickle-cell disease. For patients with sickle-cell anemia and a history of cerebrovascular accident, infarction/ischemia lesions typically involved both cortex and deep white matter, while silent lesions usually were confined to deep white matter. Within the age range studied, the prevalence of infarction/ischemia did not increase significantly with age, although older patients with lesions had more lesions than did younger patients with lesions. **CONCLUSIONS:** Brain MR imaging showed infarction/ischemia in the absence of a recognized cerebrovascular accident in 13% of patients. The prevalence of these lesions did not increase significantly between the ages of 6 and 14 years, suggesting that lesions are present by age 6. However, the increase in the average number of lesions per patient with age may indicate progressive brain injury.

Index terms: Brain, magnetic resonance; Children, diseases; Sickle-cell disease

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Although the management of many complications of sickle-cell disease continues to improve, neurologic complications remain a sig-

nificant problem. These complications include paralysis, seizures, and death. Cerebrovascular accident (CVA) is a leading cause of neurologic morbidity and mortality, and as many as 12% of patients will experience a stroke by age 21 years (1-3). Neurologic abnormalities also may be present in patients who do not have a clinical history of a CVA. The prevalence of clinically silent cerebral infarctions has been reported to be 11% when magnetic resonance (MR) imaging techniques are used to study the brain (4-6). Despite these findings, the spectrum of cerebral abnormalities in sickle-cell disease remains poorly defined because previous studies have been limited by small numbers of patients, many of whom have clinically expressed neurologic disease.

To characterize more accurately the spectrum of cerebral abnormalities in patients with sickle-cell disease, the Cooperative Study of Sickle Cell Disease (CSSCD) performed brain MR examinations on a cohort of children 6 years of age and older who had been followed up

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prospectively from age 6 months. This article summarizes the types and frequency of abnormalities identified in this unique patient population.

Subjects and Methods

Patient Population

All patients enrolled in the second phase of the CSSCD were recruited from the infant cohort of the initial phase of the CSSCD. The majority of the patients were identified by newborn screening programs, and all were enrolled in the cohort by age 6 months. The objectives, eligibility requirements, enrollment procedures, and data collection methods for the CSSCD have been reported (7-9). Only patients with sickle cell anemia (Hb SS) and hemoglobin sickle-cell disease (Hb SC), and heterozygotes for hemoglobin S and beta zero (Hb S β^0) or beta plus (Hb S β^+) thalassemia were enrolled in the cohort. The hemoglobin phenotype of 95% of the enrolled patients was confirmed at a central laboratory based at the Centers for Disease Control. Sickle cell-related events were recorded as they occurred, using specific definitions for events and standardized data collection forms (7).

Only patients with Hb SS and Hb SC were included in the present analyses, as there were very few infants with the sickle beta thalassemia syndromes. Patients were considered enrolled once informed consent had been given and the intake physical examination form had been received at the Statistical Coordinating Center. Informed consent was obtained from the patient's legal guardian in accordance with the requirements and guidelines of the Human Subjects Committee at the participating clinical center.

By July 1, 1993, 392 patients (91%) of the 431 Hb SS and Hb SC patients enrolled in the second phase of the CSSCD were eligible for a brain MR examination as they attained age 6 years. Three hundred twenty-five patients (83%) completed the required study. The MR images from 315 of these patients were centrally reviewed by October 1993. Two patients were excluded from all analyses because their scans were of poor quality. An additional Hb SC patient was excluded from analyses because scan findings indicated the patient had had severe perinatal asphyxia.

MR Equipment and Specifications

The MR equipment within the 15 participating clinical centers was surveyed before patients were enrolled in the study. Most centers used commercially available 1.5-T MR scanners, although a few used 0.6-T or 1.0-T scanners. Although MR equipment and software varied, criteria for an acceptable study were established by the study's three neuroradiologists. The standards included spin-echo or fast spin-echo imaging, a T1-weighted pulse sequence (short repetition time [TR], short echo time [TE]), a T2-weighted axial pulse sequence (long TR, long TE), and an

intermediate (long TR, short TE) coronal pulse sequence. Contrast agents were not used in any of the MR examinations.

MR Review Procedures

Participating institutions submitted MR studies to the Statistical Coordinating Center. Nine central reviews were conducted by the three neuroradiologists between June 1990 and October 1993. The films were interpreted without knowledge of the patient's medical history. No attempt was made to compare MR findings with transfusion history or any prescribed therapies. Specific MR findings of atrophy and infarction/ischemia were recorded on a standardized form. Scans were also examined for the presence of collateral circulation. The patency of intracerebral vessels was recorded when possible, but this was difficult to assess in all patients owing to limitations of the MR methodology. Because of these difficulties, there were no analyses undertaken related to blood vessel patency. Two neuroradiologists evaluated each MR study independently. If interpretations differed, the third neuroradiologist reviewed the scan and consensus was reached through group discussion.

Definitions

Atrophy.—Atrophy was defined as a lesser volume of brain substance than would be expected in a healthy person of similar age. It was distinguished to the degree possible by visual inspection from slight enlargement of the subarachnoid space, which was considered a normal variant. Atrophy was categorized as focal (restricted to a single anatomic region) or generalized (Fig 1).

Infarction/ischemia.—A cerebral infarction or region of focal change associated with ischemia was defined as an area of abnormally increased signal on the intermediate and T2-weighted pulse sequences. Areas of late myelination in the peritrial white matter, focal heterotopic gray matter, and unusually deep sulci were not classified as lesions of infarction/ischemia (10, 11). Anatomic locations of lesions of infarction/ischemia within the cerebrum, basal ganglia, thalamus, brain stem, and cerebellum were recorded. For each lesion within the cerebrum, the hemisphere, lobe(s), and location within the deep white matter, cortex, or both was specified. Lesions also were classified by size: small (less than 0.5 cm), medium (0.5 to 1.5 cm), and large (greater than 1.5 cm) (Fig 2).

Cerebrovascular accident (CVA).—A CVA was defined as an acute neurologic syndrome caused by occlusion of an artery or hemorrhage with resultant ischemia and neurologic symptoms and signs. CVAs included transient ischemic attack (TIA), completed infarctive stroke, and hemorrhagic stroke. TIA was defined as neurologic signs with vascular distribution that resolve within 24 hours (or 48 hours if the basilar system is involved). Strokes were classified by the investigator at the center as hemorrhagic or infarctive on the basis of available clinical and imaging data.

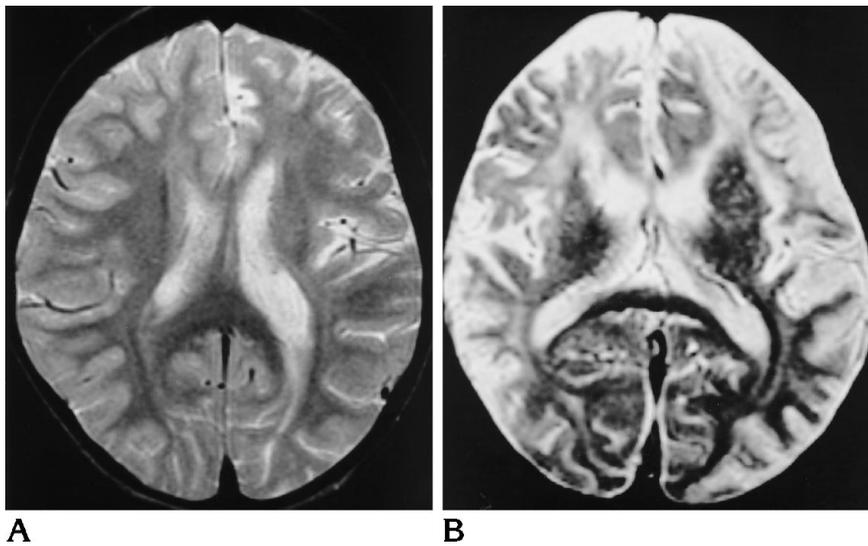


Fig 1. Representative T2-weighted axial images depicting focal (A) and general (B) atrophy, respectively.

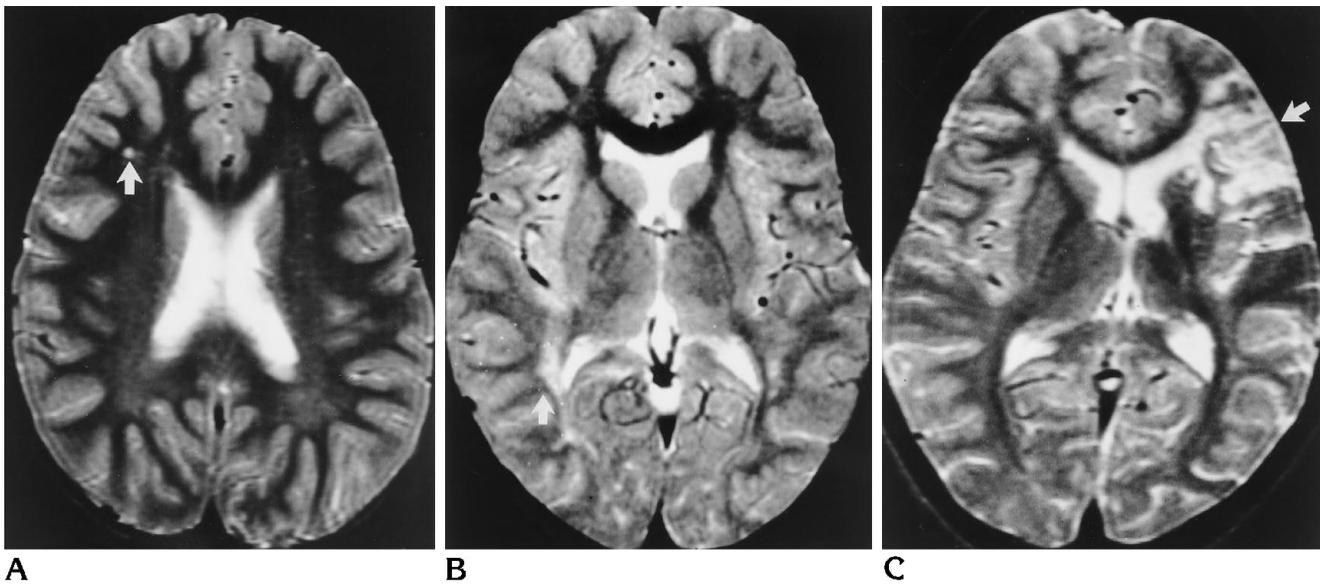


Fig 2. Representative T2-weighted axial images depicting small (A), medium (B), and large (C) areas of infarction/ischemia, respectively (arrows).

Patient Classification

Patients were divided into two groups on the basis of their MR findings and clinical history. Patients with infarction/ischemia identified at MR imaging and a CVA documented on the CSSCD database were placed in the positive CVA history group. Patients with infarction/ischemia at MR imaging and no documented CVA were placed in the negative CVA history or silent lesion group.

Statistical Methods

Fisher's Exact Test was used to compare rates of MR abnormalities by hemoglobin phenotype, sex, and history

of CVA (12). Logistic regression was used to model the relationship of infarct status to age (12). Confidence bands for predicted probabilities are based on pointwise standard errors. Poisson regression was used to model the relationship of number of infarction/ischemia lesions to age and CVA history (13). All reported *P* values are two sided.

Results

Overview of Abnormalities

The 312 participants included in the analyses ranged in age from 6 to 14 years at the time MR imaging was performed (mean age, 8.3 years;

TABLE 1: Abnormalities on brain MR by hemoglobin phenotype and history of CVA Phenotype

	Hb SS				Hb SC				Total	(%)*
	Positive	Negative	Total	(%)*	Positive	Negative	Total	(%)*		
CVA history	16	199	215	...	0	97	97	...	312	...
MR findings										
No infarction/ischemia or atrophy	0	153	153	(71)	...	89	89	(92)	242	(78)
Only atrophy	0	10	10	(5)	...	5	5	(5)	15	(5)
Only infarction/ischemia	3	29	32	(15)	...	3	3	(3)	35	(11)
Infarction/ischemia and atrophy	13	7	20	(9)	...	0	0	(0)	20	(6)
Total number with infarction/ischemia	16	36	52	(24)	...	3	3	(3)	55	(18)

* Percentage of patients within phenotype group.

SD, 1.8 years). Two hundred fifteen patients had sickle-cell anemia and 97 had Hb SC disease.

Table 1 summarizes the MR findings. There were 242 patients who had neither lesions of infarction/ischemia nor atrophy identified at the MR examination. Among these patients, however, were 2 who had other abnormalities. One of these had a right cerebellar arteriovenous malformation and the other had a contusion. There were 70 patients (22%) with lesions of infarction/ischemia, atrophy, or both. These patients included 35 (11%) with lesions of infarction/ischemia who did not have atrophy, 15 (5%) with atrophy only, and 20 (6%) with both infarction/ischemia and atrophy. One patient with Hb SS was noted to have areas of both infarction and hemorrhage.

Lesions of infarction/ischemia were identified in 55 patients (18%), including 52 with Hb SS and 3 with Hb SC. A history of CVA was documented in 16 patients, all of whom had Hb SS. Thirteen of these patients were reported to have had an occlusive stroke, 2 had documented TIAs, and 1 had a hemorrhagic stroke. Infarcts were identified in all 16 patients. The patient whose MR study showed both infarction and hemorrhage was in this group of patients. These children represented 7% of the total Hb SS study population and 31% of all Hb SS patients with infarction/ischemia lesions detected on MR images.

Silent infarction/ischemia lesions were noted in 39 children. The prevalence rates of silent lesions differed significantly between the phenotypes ($P < .001$): 17% of Hb SS patients had silent lesions compared with 3% of Hb SC patients. The overall prevalence rate of silent lesions was 13% in this patient population.

The most common areas for infarction/ischemia were the frontal and parietal lobes, regardless of hemoglobin phenotype. Among the 55 patients with 1 or more lesions, 78% had frontal lobe lesions, 51% had parietal lobe lesions, and 15% had temporal lobe lesions. Lesions within the basal ganglia or thalamus were present in 27% of the 55 patients. Lesions of infarction/ischemia in the occipital lobe ($n = 1$), cerebellum ($n = 1$), and brain stem ($n = 2$) were uncommon. All occipital lobe, basal ganglia, thalamus, cerebellum, and brain stem lesions occurred in Hb SS patients. Among the 55 patients who had lesions, 60% had them in both hemispheres, 20% had lesions in the right hemisphere only, and 20% had lesions in the left hemisphere only.

Atrophy was present in 30 (14%) of Hb SS patients and in 5 (5%) of Hb SC patients (Table 1). Twenty (67%) of the 30 Hb SS children also had lesions of infarction/ischemia; 7 patients (35%) with both abnormalities did not have a documented CVA. Atrophy was generalized in 3 of these 20 patients, focal in 15, and generalized and focal in 2, both of whom had a history of CVA.

There were 15 patients whose only brain abnormality was atrophy (Table 1). In this group, atrophy was generalized in 6 and focal in 9 patients. Focal atrophy was noted in the frontal lobes of 5 patients, in the occipital lobes of 2 patients, and in the temporal lobe and hemispheric convexity of one patient each. In the group of 15 patients, 10 children had Hb SS, of whom 6 had focal atrophy and 4 had generalized atrophy.

Three patients, two of whom had a history of CVA, had deep perforating vessel collateral circulation (moyamoya).

TABLE 2: Infarction/ischemia location(s) in 52 Hb SS patients by CVA history*

Area of MR Abnormality	History of CVA	No. of Patients†	Extent of Infarction/Ischemia		
			Cortex Only, n (%)‡	White Matter Only, n (%)‡	Cortex and White Matter, n (%)‡
Frontal lobes	Negative	27	0 (0)	24 (89)	3 (11)
	Positive	14	0 (0)	4 (29)	10 (71)§
Parietal lobes	Negative	16	0 (0)	13 (81)	3 (19)
	Positive	11	1 (9)	4 (45)	5 (45)
Temporal lobes	Negative	3	1 (33)	2 (67)	0 (0)
	Positive	5	1 (20)	3 (60)	1 (20)
Occipital lobes	Negative	0
	Positive	1	0 (0)	0 (0)	1 (100)
Basal ganglia/thalamus	Negative	4
	Positive	11
Cerebellum	Negative	1
	Positive	0
Brain stem	Negative	0
	Positive	2

* Sixteen with positive and 36 with negative CVA history.

† Total number of patients with infarcts within specified area.

‡ Number of patients with infarction/ischemia within specified lobe (percentage of patients with infarction/ischemia within specified lobe).

§ Patients with a clinical history of CVA were more likely to have cortical frontal lobe lesions than those with a negative CVA history ($P = .0002$).

|| The prevalence of lesions involving the basal ganglia or thalamus was higher in patients with a clinical history of CVA than in those with a negative history ($P < .0001$).

Relationship between History and MR Findings for Hb SS

There were 52 Hb SS patients who had infarction/ischemia lesions detected by MR imaging, including 16 with a documented CVA and 36 without a prior CVA (silent lesion group). The distribution of lesions by CVA history is shown in Table 2. The proportions of patients who had frontal, parietal, or temporal lobe lesions did not differ significantly between these two groups. There was, however, a statistically significant relationship between CVA history and prevalence of infarction/ischemia lesions in the basal ganglia or thalamus. Lesions in these areas were noted in 11 patients (69%) with a clinical history of CVA compared with only 4 (11%) in the silent lesion group ($P < .0001$).

Differences were noted in the anatomic location of infarction/ischemia injury between patients with silent lesions and those with a history of CVA. The proportion of patients with frontal lobe lesions involving both the cortex and deep white matter was higher in patients with a history of CVA than in those with silent lesions (71% versus 11%, respectively; $P = .0002$). Similarly, the percentage of patients with parietal lesions involving both the cortex and deep white matter was higher in the positive CVA history group than in the silent lesion group

(45% versus 19%, respectively), although this difference was not significant ($P = .127$).

The effect of CVA history on the number of lesions was examined and adjusted for age at the time the MR study was performed. Patients with a history of CVA had more ($P = .008$) and larger ($P = .00001$) lesions than those with no history of CVA. For patients with a history of CVA, the size of the largest lesion was more than 1.5 cm, 0.5 to 1.5 cm, and less than 0.5 cm in 75%, 25%, and 0% of patients, respectively. For patients with no history of CVA, the size of the largest lesion was more than 1.5 cm, 0.5 to 1.5 cm, and less than 0.5 cm in 11%, 61%, and 28% of the patients, respectively.

Among Hb SS patients who had areas of infarction/ischemia, however, there was no significant association between sex or hemispheric locations of lesions and CVA history. Approximately two thirds of the patients in each CVA history group had lesions in both hemispheres.

Relationship of Age to MR Abnormalities for Hb SS

Figure 3 shows the estimated probabilities of having silent infarction/ischemia and overt infarction at specific ages. Within the age group

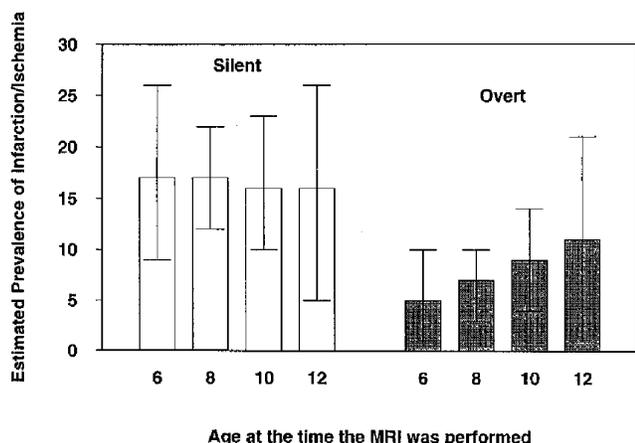


Fig 3. Estimated proportion (± 1 SE) of children of different ages who had silent and overt infarction/ischemia lesions at the time MR imaging was performed. Patients with *silent* lesions are those who had no history of a clinical CVA; patients with *overt* lesions are those who had a documented CVA event.

studied, these rates did not change significantly with age ($P = .616$).

There was a significant relationship, however, between the number of lesions and the patient's age at the time MR imaging was performed. Poisson regression analysis demonstrated that the number of lesions increased with age, regardless of the CVA history ($P = .026$).

Discussion

The term *sickle-cell disease* refers to a group of genetic disorders characterized by the production of sickle-cell hemoglobin (HbS), chronic hemolytic anemia, and ischemic tissue injury caused by altered blood flow. The more common forms of sickle-cell disease include sickle cell anemia and Hb SC disease. The alteration of blood flow results from a combination of endothelial cell injury and luminal blockage produced by sickled cells. The brains of young children with Hb SS are particularly vulnerable to ischemic injury (14). Occlusion of large and small vessels, red cell sludging, and distal field insufficiency (border-zone infarction) have been implicated in the pathogenesis of brain injury in this patient population (5, 15-18).

Historically, most imaging investigations of the central nervous system (CNS) in sickle cell patients have been done in response to obvious clinical events such as strokes, seizures, or altered levels of consciousness. The more commonly used imaging techniques include angiog-

raphy, radionuclide scanning, and computed tomography. Often these studies have shown more extensive CNS disease than anticipated from clinical signs and symptoms. More recently, MR imaging has shown brain infarcts in the absence of a clinical history of CVA (5). The limited number of patients examined to date by MR imaging makes it difficult to define either the types of CNS abnormalities or their frequency.

Our study provides information related to the types and frequency of CNS abnormalities in sickle-cell disease. All subjects were recruited before age 6 months and followed up prospectively. The members of this cohort had repeated physical examinations and laboratory assessments at regular intervals, and clinical events for each patient were documented using standard definitions and data collection forms.

Seven percent of our Hb SS population experienced a CVA before the MR examination. This frequency is similar to that reported in other large series. Our study, however, detected changes of cerebral infarction/ischemia in an additional 17% of the Hb SS population. Similar lesions in the absence of a history of CVA also were noted in 3% of the Hb SC population.

Both localized and extensive regions of infarction/ischemia were seen in this study. Localized lesions typically were confined to the deep white matter and in a distal field or border-zone distribution. Extensive lesions usually involved both the cortex and the deep white matter, following the distribution of a major artery. In Hb SS patients, the localized lesions were confined most frequently to the deep white matter of the frontal, parietal, and temporal lobes, whereas the extensive lesions involved both the deep white matter and the cortex of the frontal and parietal lobes. Cortical lesions were more common in patients with a history of CVA, suggesting that large-vessel vasculopathy is more likely to be associated with readily identifiable clinical symptoms than are small lesions occurring in border zones. Cortical lesions without subjacent white matter involvement were seen in only two patients, both of whom experienced a clinically recognized CVA before the MR study.

It is possible that the increased T2-weighted signal in some areas was not caused by infarction or ischemia. Lesions of similar appearance have been described in hemophilic children at a frequency approaching that observed in our Hb SS population (19). Focal signal abnormal-

ities also have been reported in other diseases (20–22). Other evidence, however, suggests that our findings do represent areas of infarction/ischemia. Koshy et al (23) reported diffuse gliotic scars consistent with small infarctions in the deep white matter and the cortical gray matter of brain tissue from sickle cell patients who had no history of neurologic abnormality. Evidence is also provided by a recent study involving hydrogen MR spectroscopy, which showed that increased signal on the T2-weighted image may be the result of ischemia rather than frank infarction (24).

Infarction or ischemia in border-zone areas could result from either vasoocclusion within the cerebral vessels or transient reduction in perfusion pressure. The latter might accompany a hypoxic or hypovolemic episode associated with an acute chest syndrome, aplastic or sequestration crisis, or a seizure. Extensive infarcts that occur along the distribution of the major vessels typically are caused by endothelial hyperplasia with associated vessel stenosis and occlusion, which are characteristic of cerebral vasculopathy in sickle-cell disease. The absence of a significant increase in prevalence of infarction/ischemia lesions with age suggests that lesions may begin in early childhood. In those who have these lesions, however, the observation of an increasing number of lesions with age, regardless of the clinical history of CVA, suggests that there is progressive brain injury over time.

Brain atrophy was observed commonly; it occurred in 35 patients, 20 (57%) of whom also had evidence of infarction/ischemia. In these 20 patients, atrophy was presumably related to neuronal death that accompanied an infarct. The pathogenesis of atrophy in the remaining 15 patients is less certain. The predominantly focal nature of the atrophy suggests that it also may be related to ischemic injury, but this remains to be proved.

This study did not address the management of silent lesions of cerebral infarction/ischemia. Despite significant risks, long-term transfusion therapy that suppresses the production of HbS is standard treatment for patients who experience a clinical CVA. The proper treatment of patients with lesions of infarction/ischemia in the absence of a clinical history of CVA, however, is uncertain, as there is no therapy of proved efficacy. Possible interventions include potentially toxic therapies, such as transfusions,

bone marrow transplantation, and hydroxyurea. Although it is not possible at this time to recommend specific therapy for these patients, they should be followed up closely with sequential examinations to determine whether there is progressive disease. If progression is associated with neurologic dysfunction, strong consideration should be given to placing the patient on a long-term transfusion program.

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