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MR and CT Investigation of Cerebrovascular Disease in Sickle Cell Patients

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Stroke is a common complication of sickle cell disease. Using MR and CT, we studied 10 patients with sickle cell disease and a history of stroke and compared these findings with those of 10 sickle cell patients without stroke. The purpose was to determine if MR could visualize the large vessel vasculopathy previously seen on angiography and to estimate the incidence of asymptomatic abnormalities in the nonstroke group. MR consistently demonstrated the major intracranial arteries and showed three cases with occlusion and three with stenosis of either the internal carotid or middle cerebral arteries. Infarctions were better delineated on MR but were also seen on CT. Seven cases with and two without stroke had high-signal white matter lesions on MR. Further research using cranial MR to develop noninvasive means of identifying sickle cell patients at risk for stroke is warranted.

Cerebrovascular complications have been reported in 5–17% [1–5] of patients with sickle cell disease (hemoglobin SS). The risk for cerebral infarction is highest in children less than 15 years old, while older children and adults primarily experience intracranial hemorrhage. The cause of stroke in this population is not clear. The initial concept of infarction resulting from small-vessel occlusion due to sickling, as observed in bone and spleen [6], has not been supported by recent data.

While there is pathologic evidence that small-vessel occlusion does occur in brain [1, 7], the clinical presentation of hemiplegia and the cranial CT reports have been more consistent with large-vessel or major branch occlusions. In addition, the stroke cases that have been studied angiographically show a surprisingly high incidence of an occlusive vasculopathy affecting the major intracranial arteries of the anterior circulation, in many cases bilaterally [8–12]. Limited pathologic data indicate that these lesions are areas of noninflammatory endothelial hyperplasia [11, 13]. The incidence of moyamoya associated with this vasculopathy is as high as 30% in some series [8, 14].

Recent studies have reported neuroradiologic findings in cases with major neurologic symptoms, usually hemiplegia [2–5, 8, 12]. The frequency and distribution of cerebrovascular lesions in sickle cell disease patients with less dramatic or with no neurologic symptomatology has not been studied. High resolution MR imaging may provide a means to detect cerebrovascular abnormalities noninvasively. Accordingly, a pilot study was conducted in patients with and without a history of stroke (1) to determine if MR could visualize the major intracranial vessels and demonstrate occlusive vasculopathy, and (2) to estimate, using MR and CT, the frequency and anatomic distribution of relatively asymptomatic lesions in these patients.

Materials and Methods

Twenty subjects with hemoglobin SS documented by hemoglobin electrophoresis were recruited from the pediatric hematology or the pediatric and adult sickle cell clinics of the

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TABLE 1: **Findings in Patients with History of Stroke**

Case No.	Age	Age at Stroke	Neuro Exam	CT	MR	Comments
1	20	13, 15	Left hemiparesis	Infarction, right frontal (1975)	Bilateral ICA occlusion; right frontoparietal and left frontal infarction; moyamoya?	Angiography (1975): bilateral ICA occlusions distal to ophthalmic; moyamoya
2	14	5	Left hemiparesis	Infarction, right watershed distribution	Stenosis, distal right ICA; right watershed infarction	Angiography (1976): stenosis, right ICA from 3 cm above bifurcation
3	12	9, 10	Right hemiparesis	Massive infarction, left frontoparietal	Apparent left ICA occlusion; left frontoparietal infarction	Cortical calcification on CT not shown on MR
4	11	9	Left hemiparesis	Infarction, right frontoparietal	Apparent right MCA occlusion; right frontoparietal infarction	
5	18	3	Left hemiplegia	Infarction, right frontoparietal	Stenosis, right ICA terminal portion; right frontoparietal infarction	
6	11	6	Normal	Infarction, right occipital	Right anterior occipital infarction	
7	4	3	Normal	Infarction, left parietal, occipital, and caudate; left lateral ventricle dilation	Left parietooccipital and caudate infarction; left lateral ventricle dilation	Initial right hemiparesis resolved over 3 months
8	16	11	Left hemiparesis	Infarction, right frontal	Right frontal infarction	
9	29	28	Left hemiparesis	Intraventricular hemorrhage (1984); infarction, right frontoparietal (1985)	Right frontoparietal infarction; left frontal focal atrophy	Angiography refused
10	17	17	Normal	SAH, right sylvian fissure	Normal	Angiography normal

Note.—ICA = internal carotid artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage.

Medical College of Georgia. Seventeen of these have been followed for more than 2 years. Based on available records and history, and prior to neurologic examinations and MR, subjects were assigned to either the stroke or nonstroke group. Ten subjects with a prior diagnosis of stroke and 10 with no known history of stroke made up each study group. All subjects received a screening neurologic examination at the time of MR. For the purpose of this study, a "normal" neurologic status implies the absence of focal deficits on bedside neurologic examination; formal neuropsychological testing was not performed, although simple tests for visuospatial deficits and dysphasia were included. All but three subjects were studied as outpatients; none were in vaso-occlusive crisis at the time of study. The stroke group comprised seven males and three females, mean age 15 years (range, 4–29 years). Eight were initially diagnosed with cerebral infarction, one with intraventricular and one with subarachnoid hemorrhage. The stroke history was based on clinical events that occurred from 2 weeks to 15 years (mean, 4.4 years) before this study. The mean age at the time of cerebral infarction (nine patients) was 6.2 years (range, 3–13 years). Prior angiography was available in three cases, two with infarction and one with subarachnoid hemorrhage.

The nonstroke group contained six females and four males, mean age 14 years (range, 4–32 years). The oldest subject had a history of partial complex seizures since age 19. The youngest subject had been treated for an idiopathic seizure disorder since age 3 months; his development and neurologic examination were considered normal. Another subject, age 6, was included in the study during initial evaluation for a single seizure, without residual neurologic deficit, that occurred 10 days before MR. The remaining nonstroke subjects were neurologically asymptomatic.

All subjects received proton MR (GE 1.5 T Signa Unit) according to the following protocol: sagittal views with T1-weighted images (TR 800, TE 25) with 3-mm slice thickness at 1-mm separation; T2-weighted axial and coronal views (TR 2000, TE 25/50 msec) and 5-mm thickness with 2.5-mm separation between slices. Some patients also had coronal T1-weighted images (TR 800, TE 25 msec). Nineteen patients had CT (GE 9800) within 10 days of MR; all but four were obtained without contrast enhancement. Imaging studies were examined in an unblinded fashion.

RESULTS

Stroke Group

Seven subjects in this group had residual neurologic deficit. The CT, MR, and angiographic data are shown in Table 1. MR consistently demonstrated the major intracranial arteries, including the internal carotid, proximal middle cerebral, and the basilar arteries. The anterior cerebral arteries were less consistently visualized. In some cases, other vessels such as the lenticulostriate, anterior choroidal, and posterior communicating arteries were also seen.

Evaluation of the vasculature was made by examination of adjacent sections in both the coronal and axial views. The appearance of major vessels on MR was abnormal in the following cases: case 1, bilateral distal internal carotid artery occlusions consistent with prior findings on angiography (Fig. 1); case 2, collateral circulation in relation to stenosed right intracranial internal carotid artery, also present on prior angiogram; case 3, left internal carotid artery occlusion ipsilateral

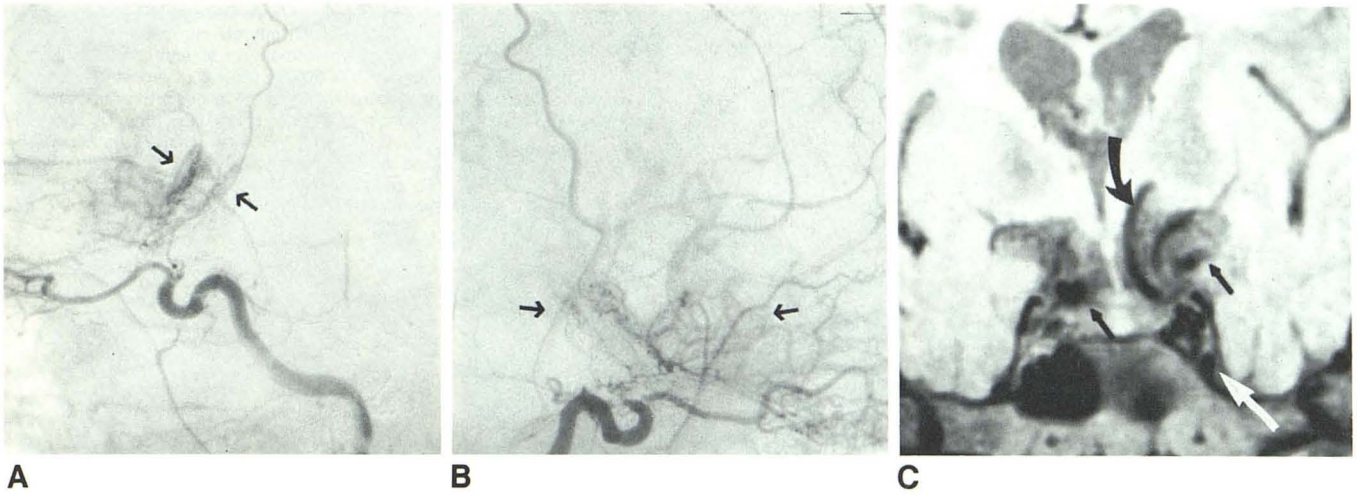

Fig. 1.—Case 1. **A** and **B**, Lateral views of bilateral carotid arteriogram showing complete occlusion of both internal carotid arteries beyond origin of ophthalmic arteries. Collateral circulation with moyamoya pattern noted (*arrows*). **C**, Coronal MR study (TR 2000/TE 25) shows very small left intracavernous carotid artery(*white arrow*) and large left posterior communicating artery (*curved black arrow*). Left terminal internal carotid artery is reconstituted and lies medial to large posterior communicating artery. Low signals noted medial to temporal lobes at level of pituitary stalk most likely represent moyamoya pattern noted on arteriogram (*small black arrows*).

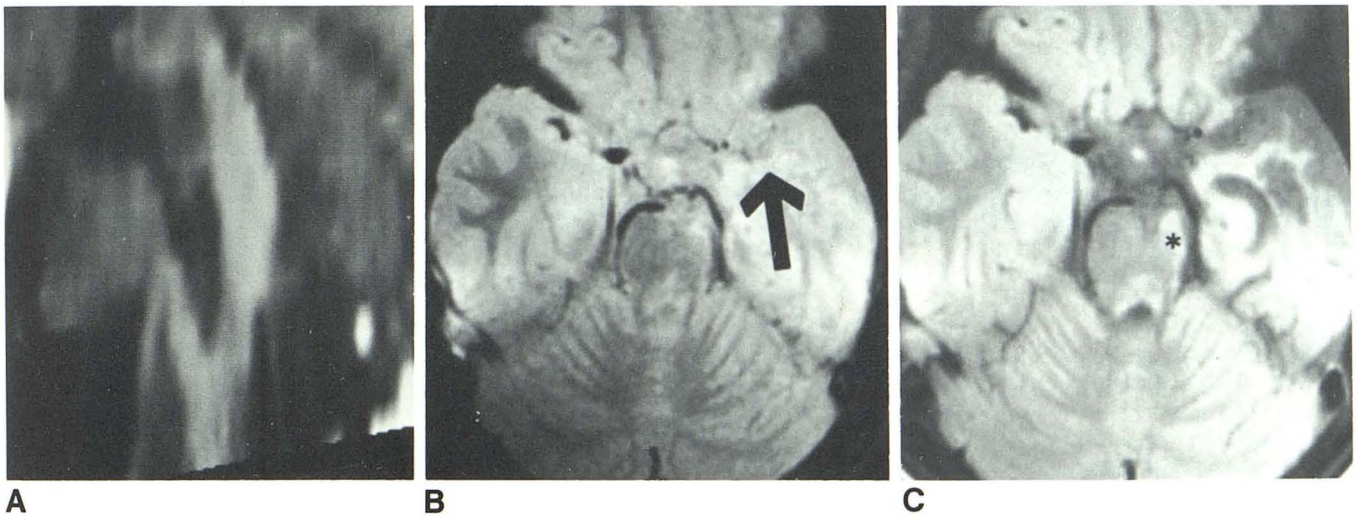

Fig. 2.—Case 3. **A**, Reformatted CT-enhanced image of left side of neck showing normal carotid artery bifurcation. **B**, Transaxial MR shows complete occlusion of left internal and middle cerebral arteries (*arrow*) instead of normal low signal of terminal carotid small vessels. This may represent collateral circulation of moyamoya pattern. **C**, Very small left cerebral peduncle (*asterisk*) secondary to Wallerian degeneration in left hemisphere. Note the significant tissue loss of left temporal lobe.

to massive infarction (Fig. 2); case 4, apparent right middle cerebral artery occlusion ipsilateral to infarction in middle cerebral artery distribution; case 5, severe stenosis of the terminal right internal carotid artery ipsilateral to massive infarction (Fig. 3); case 9, apparent stenosis of right terminal internal carotid artery ipsilateral to infarction in the distal distribution of the middle cerebral artery. Although one patient, case 1, had low signal on MR where previous angiography had demonstrated moyamoya (Fig. 1), a definite MR pattern representing moyamoya could not be established from this study.

There were seven cases with unilateral and two with bilateral infarctions. The anatomic distribution of these lesions suggested major-vessel or branch occlusions except for that of case 5, which showed a pattern consistent with a watershed infarction. Infarction in the distribution of the posterior cerebral artery was seen in one case. Although CT detected all infarctions, MR better demonstrated the location and ex-

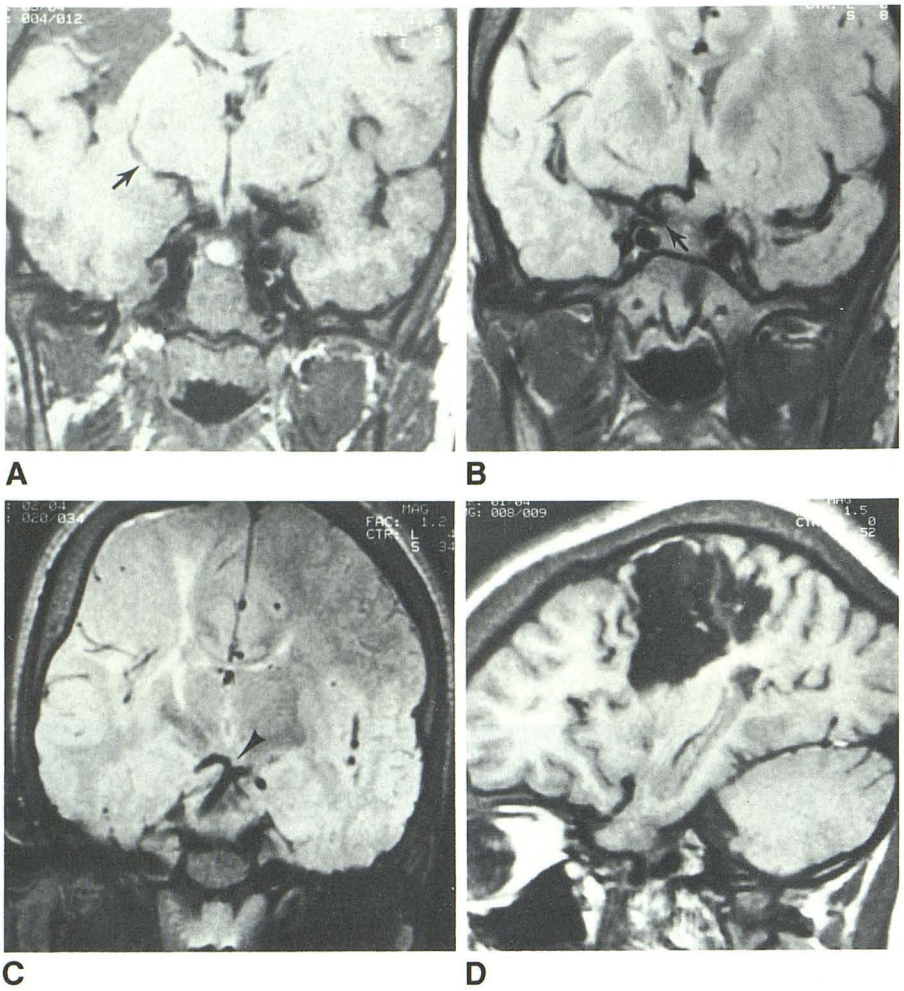

Fig. 3.—Case 5. **A**, Coronal MR shows normal bifurcation of left internal carotid artery. At right, there is hyperatrophy of anterior choroidal artery (*arrow*) (TR 800/TE 25). **B**, Coronal MR shows stenosis of right internal carotid artery (*arrow*) close to origin of anterior choroidal artery (TR 2000/TE 25). **C**, Coronal MR shows normal basilar artery and its bifurcation (*arrowhead*) (TR 2000/TE 50). **D**, Lateral view shows large infarction in right hemisphere (TR 800/TE 25).

tent of these lesions. MR demonstrated hemiatrophy of the cerebral peduncle ipsilateral to large infarctions in three cases; MR did not reveal peri-infarct calcifications detected in one case by CT (Fig. 4).

Seven cases had high-signal white-matter lesions on MR, in a spectrum from small circular plaques to linear patterns extending over several centimeters (Fig. 5). In most cases, these were found in proximity to areas of infarction; however, in three cases with unilateral infarction such signals were present in both hemispheres. The intensity of these lesions did not appear to be related to the age of adjacent infarction, being seen both in recent (1 year) and remote (15 years) stroke. The white-matter abnormalities seen on MR were not revealed by CT scan.

The MR in five stroke patients (cases 1, 3, 4, 5, and 9) revealed low signal in the basal ganglia consistent with increased iron concentration (Fig. 6). Of these five cases, four had previously received chronic transfusion therapy; two of the remaining five stroke cases had been chronically transfused but did not show this pattern.

The MR of case 10 was normal; it was performed 15 days after subarachnoid hemorrhage diagnosed by lumbar puncture and CT, which showed high attenuation in the right sylvian fissure. Angiography was normal.

Nonstroke Group

On neurologic examination, no abnormalities were found in this group. The vessels appeared normal on MR in all cases. Angiographic correlation was available in one case. No infarctions were demonstrated, but one case with seizures and prior angiography showed dilation of the left lateral ventricle suggestive of old infarction. This patient also had high signal plaques in the centrum semiovale bilaterally (Fig. 5A). Another case with no neurologic symptoms also had similar bilateral plaques. Neither case had corresponding lesions on CT, all cases had normal CT.

Discussion

Cerebrovascular disease represents a major cause of morbidity and mortality in sickle cell disease. At present, there are no clinical, hematological, or noninvasive neurodiagnostic

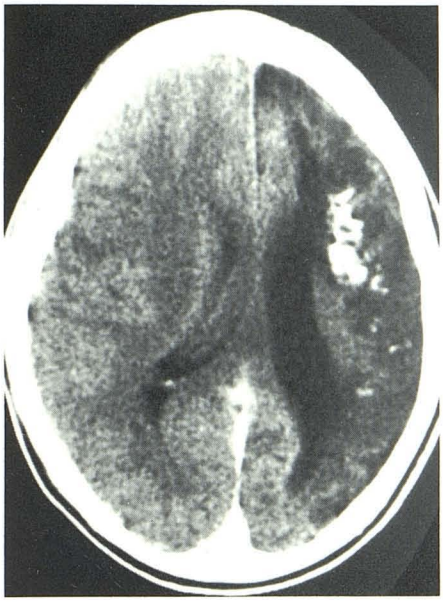

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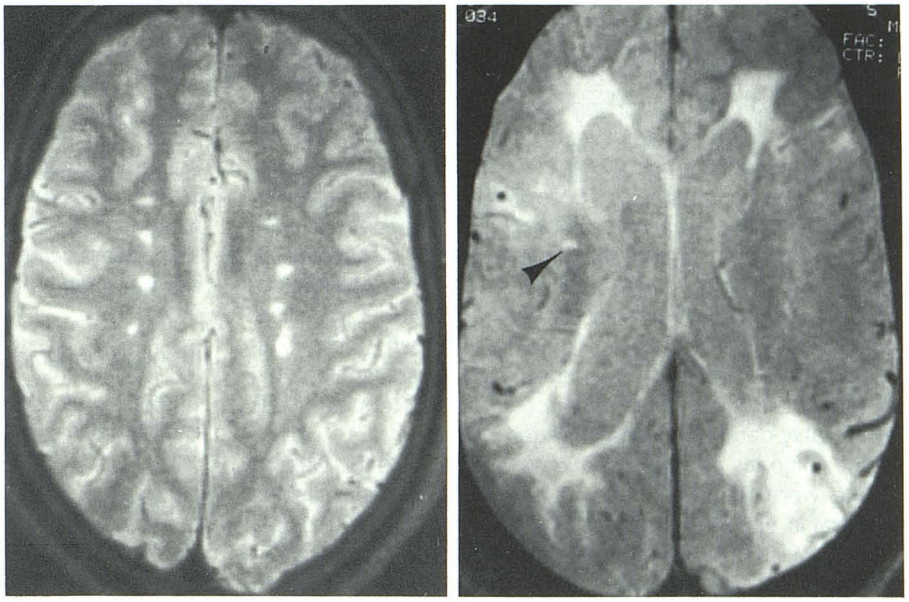
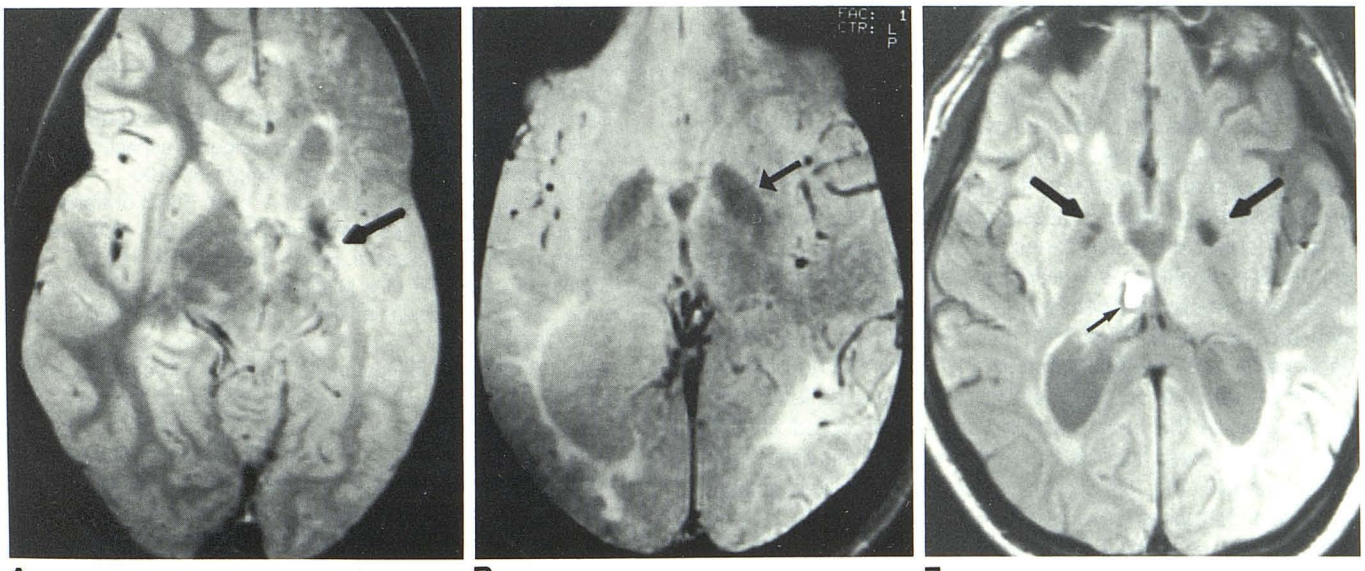
Fig. 4.—Case 3. CT 1 year after initial ischemic episode shows significant hemiatrophy with large area of low attenuation and extensive calcifications that were not seen on MR study.



A B

Fig. 5.—White-matter disease. **A**, 32-year-old woman with no history of stroke shows multiple high-signal lesions in centrum semiovale bilaterally. These were thought to be due to vascular disease and appear identical to those reported in multiple sclerosis. **B**, An example of extensive white-matter disease (Case 9) shows large area of paraventricular high signal in T2-weighted images (TR 2000/TE 50). Multiple small high-signal plaques are also noted (*arrowhead*).



A B 7

Fig. 6.—Low signal in basal ganglia (possibly from increased iron deposition) (TR 2000/TE 25). **A**, Left hemiatrophy and extensive infarction (Case 3). A localized unilateral area of low signal in left globus pallidus is noted (*arrow*). **B**, Bilateral low signal noted in globus pallidi (*arrow*), Case 9.

Fig. 7.—64-year-old white male who was under Coumadin therapy for several years with evidence of subclinical hemorrhage. Transaxial MR shows right old thalamic hemorrhage with high signal surrounded by a ring of low signal, probably due to iron deposition from hemosiderin in the periphery of hemorrhage (*small arrow*). Two areas of abnormal low signal in globus pallidi noted bilaterally (*large arrows*) probably represent iron deposition from older hemorrhages and appear similar to the low signals noted in our cases of sickle cell anemia (TR 2000/TE 25).

means to identify patients who are developing the vasculopathy revealed on angiography [2]. The apparent occlusions and severe stenosis of major vessels detected by MR were consistent with the limited angiographic data available in this series. The other apparent vascular abnormalities detected were ipsilateral to areas of infarction, but angiographic correlation was not available. These findings are encouraging, but further MR studies with angiography are needed to better define the role of MR in detecting mild arterial disease. Moyamoya is thought to develop as a result of progressive stenosis of major intracranial vessels [15], and its identification by noninvasive means would be important clinically in this population as an indirect marker of cerebral vasculopathy. At present, further studies are required to determine if MR can reliably detect moyamoya pattern.

The majority of stroke patients and a minority without stroke were found to have high-signal subcortical lesions identical in appearance on MR to those reported in multiple sclerosis [16]. This unexpected finding was quite variable in appearance and was seen in asymptomatic areas of brain in some cases. Although the presence of these signals in this population suggests a vascular etiology, possibly ischemia from small-vessel occlusion secondary to sickling, their nature is unknown. This finding also raises questions as to the specificity of such MR signals in the diagnosis of multiple sclerosis.

All infarctions were demonstrated on CT where available; however, MR provided better delineation of the anatomy of infarction by virtue of higher resolution and the use of multiple views. The pattern of infarction suggesting major-vessel or branch occlusion is consistent with earlier reports [2]. The pattern of distal insufficiency ("watershed") infarction, seen in one of our cases, is consistent with high-grade stenosis of the internal carotid artery seen on the angiogram in this case. Although repeated episodes of small-vessel occlusion might be expected to produce multiple small infarcts, such a pattern was not observed in this series. The low signal in the basal ganglia of five patients is similar in appearance to that reported in Hallevorden-Spatz disease [17, 18]. Iron and other metallic ions produce a prolonged T1 relaxation time and a correspondingly low T1-weighted signal [19]. There is no basis to implicate abnormal copper metabolism in these patients, and calcification of the basal ganglia was not observed on CT. Accordingly, these signals are presumed to represent iron deposition [20, 21]. Tissue deposition of iron in liver, spleen, and kidney has been observed in this disease [6, 22], but we are unaware of reports documenting iron deposition in the basal ganglia. The cause of this finding in these patients is unclear, although subclinical hemorrhage (Fig. 7) or deposition of iron related to hemolysis and/or transfusion therapy are possibilities.

We believe this is the first study to use MR and cranial CT to look for subclinical manifestations of cerebrovascular disease in sickle cell disease patients with no history of stroke. Two of 10 nonstroke patients had abnormalities on MR suggesting that at least some neurologically asymptomatic patients also experience cerebral vascular complications. More extensive investigations are needed to establish the true incidence of subclinical disease in this group. The development of MR techniques capable of detecting occlusive vasculopathy of the basal arteries and/or moyamoya would be of considerable clinical value allowing noninvasive identification of patients presumed to be at high risk for disabling stroke. It could be used to follow such patients receiving treatment designed to reverse lesions and prevent stroke. Further application of cranial MR in both symptomatic and asymptomatic sickle cell disease patients is warranted.

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