

## Cerebral Vasculopathy in Sickle Cell Anemia: Diagnostic Contribution of Positron Emission Tomography

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Children with sickle cell anemia (SS) have an increased risk for cerebral vasculopathy with stroke (CVA) and cognitive impairment. The present study examines the extent to which adding positron emission tomography (PET) to magnetic resonance imaging (MRI) can improve the detection of cerebral vasculopathy. Whereas MRI has been the prime modality for showing anatomical lesions, PET excels at assessing the functional metabolic state through glucose utilization 2-deoxy-2 [<sup>18</sup>F] fluoro-D-glucose (FDG) and microvascular blood flow ([<sup>15</sup>O]H<sub>2</sub>O). Forty-nine SS children were studied. Among them, 19 had clinically overt CVA, 20 had life-threatening hypoxic episodes or soft neurologic signs, and 10 were normal based on neurological history and examination. For the entire sample of 49 subjects, 30 (61%) had abnormal MRI findings, 36 (73%) had abnormal PET findings, and 44 (90%) showed abnormalities on either the MRI or the PET or both. Of the 19 subjects with overt CVA, 17 had abnormal MRI (89%), 17 had abnormal PET (89%), and 19 (100%) had either abnormal MRI or PET or both. Among the 20 subjects with soft neurologic signs, 10 (50%) had abnormal

MRI, 13 (65%) had abnormal PET, and 17 (85%) had abnormal MRI and/or PET. Six (60%) of the 10 neurologically normal subjects had abnormal PET. Among the 30 subjects with no overt CVA, 25 (83%) demonstrated imaging abnormalities based on either MRI or PET or both, thus, silent ischemia. Lower than average full-scale intelligence quotient (FSIQ) was associated with either overt CVA or silent ischemic lesions. Four subjects who received chronic red blood cell transfusion showed improved metabolic and perfusion status on repeat PET scans. In conclusion, (1) the addition of PET to MRI identified a much greater proportion of SS children with neuroimaging abnormalities, particularly in those who had no history of overt neurologic events. (2) PET lesions are more extensive, often bihemispheric, as compared with MRI abnormalities. (3) PET may be useful in management as a tool to evaluate metabolic improvement after therapeutic interventions, and (4) the correlation of PET abnormalities to subsequent stroke or progressive neurologic dysfunction requires further study.

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**N**EUROVASCULOPATHY in sickle cell anemia (SS) is clinically manifested as cerebral infarction with paresis during childhood and intracranial hemorrhage in older children and adults.<sup>1-7</sup> In addition to regional central nervous system (CNS) infarction with overt stroke, a subclinical diffuse cerebral microvasculopathy also occurs as best shown by regional or global cerebral atrophy on computed tomography (CT) imaging scans. One consequence of this microvasculopathy is a variety of cognitive impairments, which usually becomes evident by middle school age.<sup>8-14</sup>

At the present time, CT and magnetic resonance imaging (MRI) are the accepted imaging modalities used to confirm a clinical diagnosis of cerebral infarction, intracranial hemorrhage, or neuronal damage in SS children.<sup>3,6,7,15-21</sup> MRI provides high resolution anatomical delineation, whereas positron emission tomography (PET) can gauge the functional activity of the cerebral tissues by using radioactive tracers to indicate glucose metabolism 2-deoxy-2 [<sup>18</sup>F] fluoro-D-glucose (FDG) and evaluate microvascular blood flow ([<sup>15</sup>O]H<sub>2</sub>O) as demonstrated in a normal PET study (Fig 1). Stenosis or occlusion of the large intracranial vessels of the Circle of Willis, particularly the middle cerebral artery (MCA),<sup>22-27</sup> detected by transcranial doppler (TCD)<sup>24-26,28,29</sup> or magnetic resonance angiography (MRA)<sup>19,25,29,30</sup> can be used to predict an increased risk of clinical infarctive stroke.

The application of PET in SS subjects was published in 1988 when investigators at the National Institutes of Health (NIH) reported a preliminary study using FDG PET technology on six adults with sickle cell anemia who had normal CT scans and no known neurological events.<sup>31</sup> These subjects were found to have significant hypometabolism in the frontal areas of the brain. A second study showed that brain oxygen extraction ratios were normal in six nontransfused anemic adults along with lower oxygen consumption.<sup>32</sup> In two subjects with abnormal CT scans, although blood flow was similar to the level of normal

children, blood perfusion seemed to be decreased. PET studies have detected incipient stroke and identified risk regions of the brain for subsequent infarction based on ipsilateral increased cerebral oxygen extraction fraction in adults with carotid artery stenosis.<sup>33</sup> The combined use of PET and MRI should better identify the extent of the physiologic dysfunction in relation to anatomic loss of neuronal tissue.<sup>34-36</sup>

We report findings on a group of 49 subjects with SS evaluated to assess the combined use of MRI and PET in detecting cerebral dysfunction. The study hypothesis is that metabolic imaging would provide additional information on the neurophysiologic status of the patient. The ultimate aim is to

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*Submitted January 5, 1998; accepted September 1, 1998.*

*Supported in part by the USC Comprehensive Sickle Cell Centers Grant No. NHLBI No. P60 HL48484 and the California Children's Services.*

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0006-4971/99/9301-0023\$3.00/0

identify patients at high risk for stroke or functional neurologic deficits, thus allowing for timely therapeutic interventions.

## MATERIALS AND METHODS

**Patient population.** Subjects with sickle cell anemia were recruited from a Southern California regional consortium of pediatric hematologists investigating stroke in SS children. Hemoglobinopathy diagnosis was based on hemoglobin electrophoresis, column chromatography, or molecular biologic techniques. Pediatric hematologists were the primary care physicians for these patients and knew them essentially from birth. Neurologic examinations were performed by consulting neurologists at the participating institutions. Three groups of children were recruited. The first group (Category I) included those who had clinical neurologic events with overt cerebral vascular accidents (CVA). The second group (Category II) was those subjects who had a prior hypoxic illness requiring hospitalization or showed soft neurologic signs with poorer fine motor coordination according to the Zurick Neuromotor Examination or the Movement ABC Test Scale (modified for children), similar to that compiled by Mercuri et al.<sup>37</sup> A third comparison group (Category III) was composed of those who had no history of neurologic events including seizures and no soft neurologic signs. The following patients were excluded from this study: (1) those who had been hospitalized for head trauma, (2) those who could not stay motionless inside the MRI imaging equipment, and (3) those who were severely brain damaged after stroke and were in custodial care. Some subjects were too cognitively impaired for complete neuropsychological testing.

**Imaging methods.** PET scans were performed using the Siemens (ECAT, Knoxville, TN) 953/whole body scanner, located in the University of Southern California PET Imaging Science Center, with axial FOV of 10.4 cm, plane slice thickness of 3.375 mm and in-plane resolution of 4 mm. Image reconstruction was done using the filtered back projection technique with calculated attenuation correction. The radiopharmaceuticals used were FDG (maximum dose-10 mCi) for measuring glucose metabolism and ( $^{15}\text{O}$ )  $\text{H}_2\text{O}$  (maximum dose 70 mCi) for measuring cerebral blood flow (CBF). Interpretation was performed using multiple dimensional scan images in black and white. Figure 1 shows normal FDG and ( $^{15}\text{O}$ )  $\text{H}_2\text{O}$  PET scans. PET scans were reviewed using visual inspection by two expert neuroradiologists and results were reported without knowledge of the clinical history, results of other imaging modalities, doppler studies, or the findings of neuropsychologic testing. The criterion for abnormalities was the decrease of neuronal function (glucose utilization) or blood perfusion in the gray matter regions.

MRI was performed using  $T_1$  and  $T_2$  weighted spin-echo techniques. No intravenous contrast agents were used. A General Electric (Milwaukee, WI) Signa 1.5 Tesla 5-X Scanner with a 6.1 software platform, located in the University of Southern California Magnetic Imaging Center, was used. Infarction was defined as an area of abnormally increased signal intensity on the  $T_2$  weighted pulse sequences and was classified by size and anatomic location in the cerebrum, cerebellum, thalamus, or basal ganglia. The MRI abnormalities were classified as to

gray matter or white matter involvement of the corona radiata and watershed regions.

**Neuropsychological assessment.** As part of a comprehensive neuropsychological battery of tests, age-appropriate Wechsler scales were used to assess intelligence, including the Wechsler Pre-School and Primary Scales of Intelligence-Revised (WPPSI-R) for ages 3 to 5 years,<sup>38</sup> the Wechsler Intelligence Scales for Children-third edition (WISC-III) for ages 6 to 16 years,<sup>39</sup> and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) for ages 17 to 19 years.<sup>40</sup> Findings on the full-scale intelligence quotient scores (FSIQ: normative mean, 100; standard deviation, 15) are presented in this report.

Testing was conducted at the patient's clinic or hospital or at the Sickle Cell Disease Research Foundation by one of two advanced graduate students in Clinical Psychology who were experienced in psychological and neuropsychological assessment and additionally trained by a senior neuropsychologist. Informed consent for participation in neuropsychological assessment was obtained for 15 of the 19 subjects in Category I (CVA), 16 of the 20 subjects in Category II (soft signs), and 9 of the 10 subjects in Category III (neurologically normal). Testing and scoring were conducted without knowledge of the participant's stroke status except in cases where sensorimotor damage was evident. Administration of the entire battery was typically completed in one session that took approximately 3 hours, including rest breaks between tests. Participants had no narcotic analgesic intake in the preceding 48 hours and reported no pain on the day of the assessment.

**Statistical analysis.** Between group differences in proportions of subjects with abnormal findings on the MRI, PET, or FSIQ scores were tested for significance by the  $\chi^2$  test. Between group differences in mean FSIQ scores were tested by analysis of variance with Bonferroni adjustment for multiple paired comparisons.<sup>41</sup>

## RESULTS

**Subject characteristics.** A total of 49 subjects, 26 males and 23 females, with SS were included in the study: 19 patients who had known CVA (Category I), 20 children who had soft neurologic signs (Category II), and 10 children who had no clinical indication of neurologic dysfunction (Category III).

Among the 19 patients in Category I, 15 had neurologic deficits with hemiparesis and/or spasticity, two had brainstem strokes with prolonged coma, one had an intracranial hemorrhage, and one had repeat episodes of transient parietic ischemic attacks requiring several hospitalizations. Their age of onset of the first clinical neurologic event ranged from 1.8 to 16.3 years. One subject died subsequent to the MRI and PET study at age 11 years, 45 days post bone marrow transplant (Fig 2)<sup>42</sup> and another survived a successful engraftment after bone marrow transplantation. Seventeen of the 19 were treated with chronic red blood cell transfusion therapy aimed at maintaining a sickle

**Fig 1.** Normal metabolic (FDG) and perfusion ( $^{15}\text{O}$ ) $\text{H}_2\text{O}$  PET scans in a neurologically normal SS child. The red areas on the PET represent regions with high activity of metabolism (FDG) and perfusion ( $^{15}\text{O}$ ) $\text{H}_2\text{O}$ . Yellow represents less activity. Green and blue denote progressively lower activity levels. Black represents no measurable metabolic neuronal function.

**Fig 2.**  $T_2$  Weighted MRI shows multiple punctate high signal white matter lesions at different cranial (CRAN 39.1 and 47.9) image levels in the left corona radiata and right centrum semiovale. On PET, subtle decreased metabolism (FDG) and perfusion ( $^{15}\text{O}$ )  $\text{H}_2\text{O}$  is seen bilaterally in the frontal and occipital cortices. Hypoperfusion is more severe in the right occipital cortex (arrowhead). Visual evoked potentials (not shown) showed severe postchiasmal deficits of the right occipital area.

**Fig 3.**  $T_2$  weighted MRI demonstrating multiple white matter and watershed bright lesions in the frontal white matter and in the corona radiata, slightly more on the left. Metabolic (FDG) PET imaging shows a severe left frontal gray matter deficit (middle panel, arrowhead). There is hypoperfusion ( $^{15}\text{O}$ ) $\text{H}_2\text{O}$  of the right hemisphere most marked in the right superior parietal lobe (right panel, arrowheads). The subject has recovered from a left hemiparesis, but is cognitively impaired.

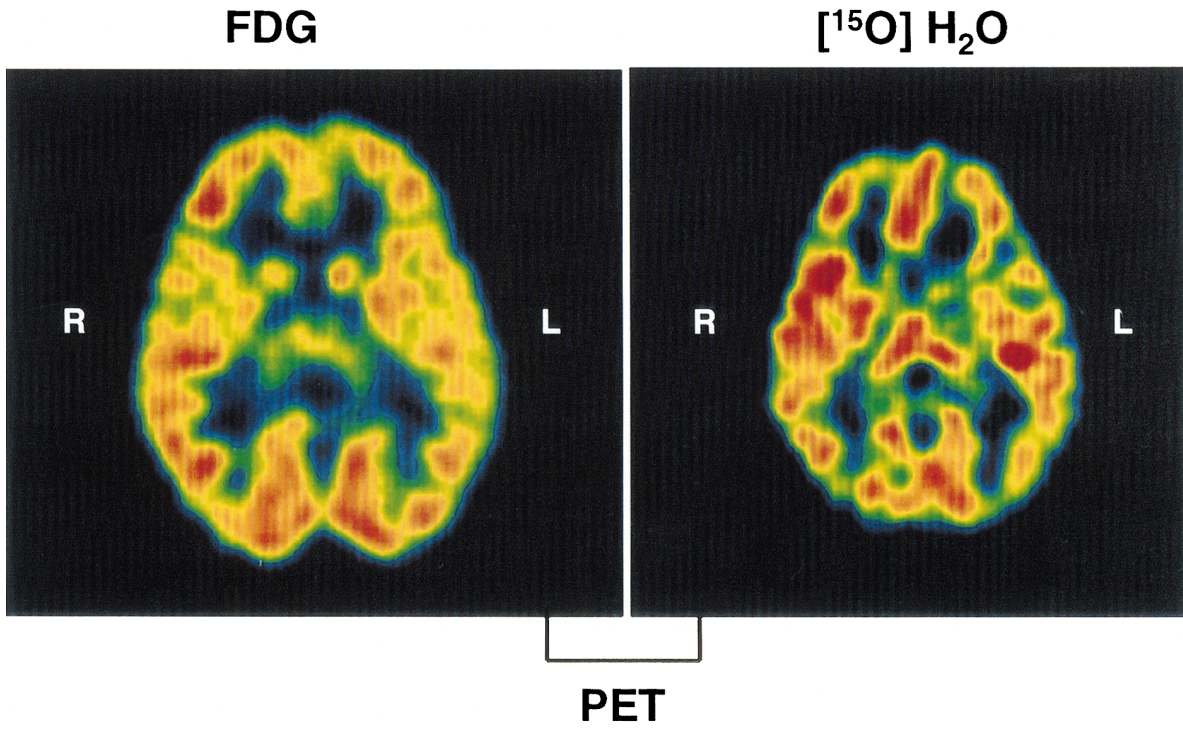


Fig 1.

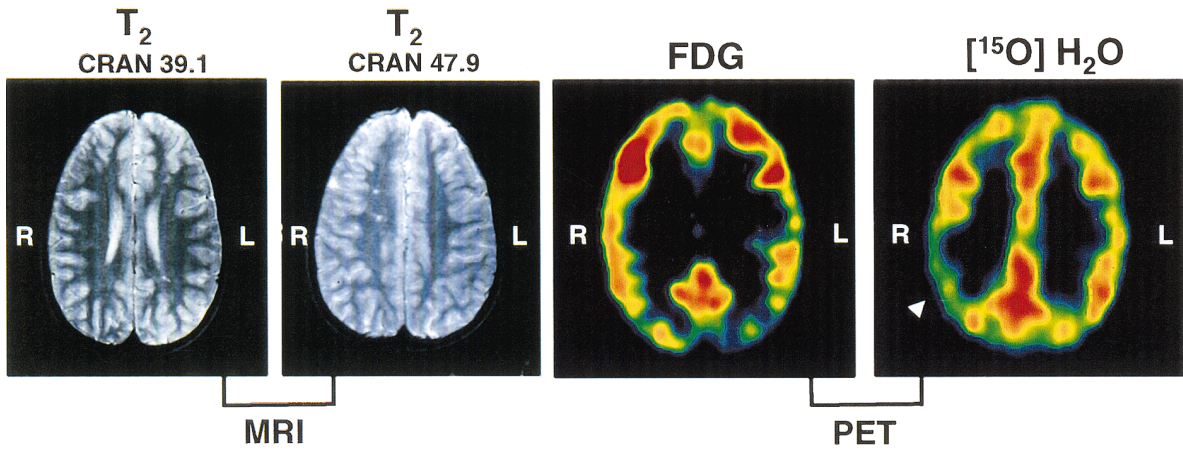


Fig 2.

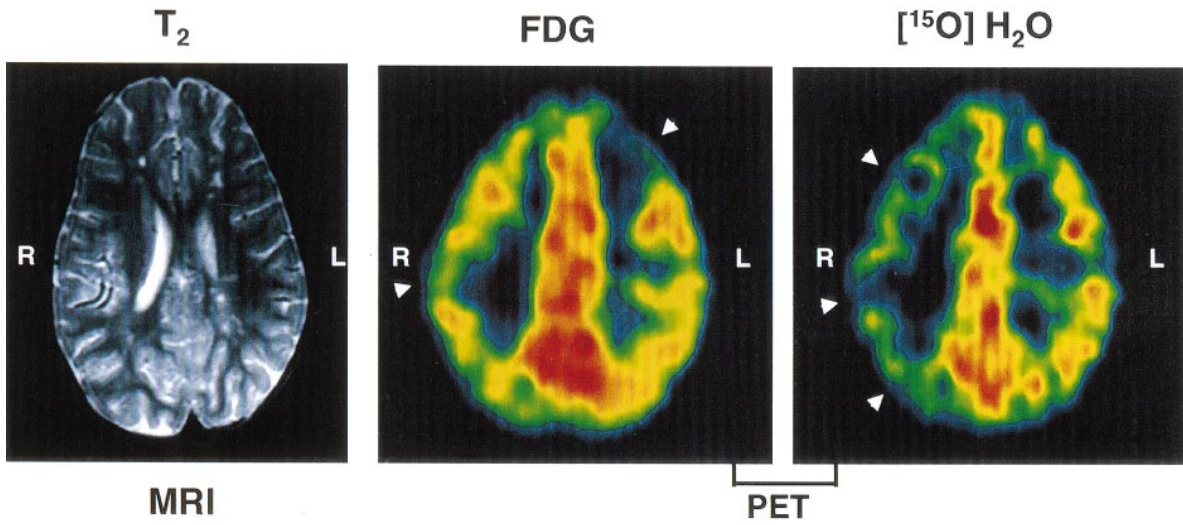


Fig 3.

cell hemoglobin (HbS) at less than 30%. None received hydroxyurea.

Of the 20 Category II patients, none showed overt neurophysiological abnormalities. Seven had acute chest syndrome with CNS hypoxia marked by a  $P_{aO_2}$  of less than 60 mm Hg, two had proven pneumococcal meningitis/septicemia, three had severe behavior disorders, four had a progressive decline in cognitive ability identified by the school, two had episodes of observed sleep apnea, one had an episode of life-threatening aplastic crisis (hemoglobin nadir at 1.9 g/dL) with apnea and hypoxia, and one had repeat complex seizure disorder without fever or another known precipitating cause. Of the 10 neurologically normal Category III children, two had siblings with parietic stroke and three others had elevated Trans Cranial Doppler velocities.

**Correlation of clinical status with MRI and/or PET findings.** Among the entire group of 49 subjects, 30 (61%) had MRI white and/or gray matter lesions, 36 (73%) had abnormal PET findings, and 44 (90%) had either an abnormal MRI or abnormal PET or both (Table 1). Of the 19 CVA subjects (Category I), 17 (89%) had abnormal imaging findings on MRI or PET when considered independently, 19 (100% sensitivity) when considered in combination. Performing MRI alone would have left two of 19 patients (11%) who had overt clinical CVA undetected (normal MRI; abnormal PET). Of the 20 patients in Category II, 10 (50%) had abnormal MRI, 13 (65%) had abnormal PET, and 17 (85%) had either abnormal MRI or PET or both. Three (30%) of the 10 Category III patients had abnormal MRI, 6 (60%) had abnormal PET, and 8 (80%) had an abnormality on either MRI or PET or both.

Silent infarction has been defined as unexpected abnormalities on MRI in subjects with no overt neurophysiological abnormalities, Categories II and III subjects in this study.<sup>15,16</sup> Based on the MRI, we found 13 subjects with silent infarction including 10 from Category II and three from Category III. When the definition of silent infarction is extended to include metabolic imaging abnormalities, PET identified 12 additional subjects to have silent ischemic lesions who were normal on MRI, including seven in Category II and five in Category III. Thus, combining the findings of MRI and PET, there was a total of 25 (83%) of the subjects in Categories II and III found to have silent ischemic lesions. Two subjects with silent ischemic lesions have subsequently developed overt clinical strokes: one with an MRI white matter lesion and PET hypoperfusion and

hypometabolism developed a bilateral frontal intracranial hemorrhage 3.5 years after initial imaging studies and the other developed left leg paresis 2 years after the PET showed FDG hypometabolism.

**Type of abnormal PET findings.** Of the 36 abnormal PETs, 28 (78%) had both hypoperfusion and hypometabolism, 6 had only focal hypometabolism (FDG), and 2 had only focal hypoperfusion (CBF) (Table 2). The percentage of subjects with both hypoperfusion and hypometabolism progressively increased with increasing severity of abnormal neurologic findings: 2 of 6 (33%) in Category III, 10 of 13 (77%) in Category II, and 16 of 17 (94%) in Category I. Overall, 14 of the 36 patients with abnormal PETs (39%) had a normal MRI.

**Correlation of PET findings with MRI gray and white matter lesions.** The concordance between abnormal PET and MRI scans where abnormalities were found in both gray and white matter was 11 of 12 (91.7%) (Table 3). The concordance between PET and MRI was 80.0% for MRI identified abnormal gray matter lesions. Concordance was lower at 53.8% for abnormal white matter lesions on MRI without gray matter involvement because of the low glucose utilization in the white matter (corona radiata and watershed). A normal PET was found in 6 of 13 subjects with MRI watershed abnormalities. Among the non-CVA subjects (Categories II and III), PET was abnormal in 4 of 9 (44%) of those with MRI watershed white matter lesions. In our PET studies, we confirmed the observation by Steen et al<sup>21</sup> based on  $T_{1q}$  MRI mapping and  $T_2$  MRI by Moser et al<sup>15</sup> of occasional dysfunction of the thalamus ( $n = 9$ ). We also identified dysfunction of the parahippocampal gyrus and uncus in one neurologically normal Category III patient. Figure 3 is a good example of the added information derived from FDG and ( $[^{15}O]H_2O$ ) PET images when correlated with the MRI. The FDG shows a large left frontal lobe deficit much greater than seen on ( $[^{15}O]H_2O$ ) perfusion, whereas perfusion is markedly decreased in the right superior parietal lobe. MRI shows white matter bright lesions in the frontal regions and in the corona radiata slightly more on the left side. In all cases with abnormal MRI, the abnormality identified on PET, as measured by glucose metabolism and perfusion defects, was more extensive than indicated by MRI alone (Fig 4).

**Transfusion and PET.** Four of our study subjects who were placed on a chronic transfusion program (HbS maintained at  $<30\%$ )<sup>43-46</sup> had improvement in glucose metabolism and perfusion on repeat PET scans. The first PET scan was performed

**Table 1. Number and Percent of PET and/or MRI Findings Analyzed According to Clinical Evidence of Neurologic Disease**

	CVA Category I (n = 19)		Soft Neurologic Signs Category II (n = 20)		No Neurologic Events Category III (n = 10)		All Categories (n = 49)	
MRI abnormal	17	89%	10	50%	3	30%	30	61%
MRI normal	2	11%	10	50%	7	70%	19	39%
Total	19	100%	20	100%	10	100%	49	100%
PET abnormal	17	89%	13	65%	6	60%	36	73%
PET normal	2	11%	7	35%	4	40%	13	27%
Total	19	100%	20	100%	10	100%	49	100%
Either PET or MRI or both abnormal	19	100%	17*	85%	8*	80%	44	90%
Both PET and MRI normal	0	0%	3	15%	2	20%	5	10%
Total	19	100%	20	100%	10	100%	49	100%

\*Number of silent ischemic lesions in subjects clinically categorized according to soft neurologic signs or no known neurologic events ( $n = 25$ ).

**Table 2. Type of PET Abnormality Analyzed According to MRI Findings and Clinical Evidence of Neurologic Disease**

PET Abnormality	Category I CVA (17 Abnormal PET)		Category II Soft Neurologic Signs (13 Abnormal PET)		Category III No Neurologic Events (6 Abnormal PET)		All Categories (36 Abnormal PET)	
	MRI Normal	MRI Abnormal	MRI Normal	MRI Abnormal	MRI Normal	MRI Abnormal	MRI Normal	MRI Abnormal
	CBF* and FDG† abnormal	2	14	6	4	2	0	10
CBF* normal and FDG† abnormal	0	1	1	2	1	1	2	4
CBF* abnormal and FDG† normal	0	0	0	0	2	0	2	0
Total abnormal PET	2	15	7	6	5	1	14	22

\*CBF uses [ $^{15}\text{O}$ ]H $_2$ O).†FDG is 2-deoxy-2 [ $^{18}\text{F}$ ]fluoro-D-glucose.

within a month of entry into the study. One of the four was an asymptomatic patient with a normal MRI and an elevated screening TCD. Her PET showed significant metabolic and perfusion hypofunction. Repeat PET was used to monitor transfusion effect and showed normalization after 16 months of transfusion therapy. The MRI has been repeatedly normal and FSIQ was stable near the original 129. The second subject with sleep apnea and a normal MRI had hypometabolism of the thalamus on PET. After a year of transfusion, all PET studies had reverted to normal. The third patient had a fixed left hemiparetic stroke with both MRI and PET evidence of infarction in the distribution of the right middle cerebral artery (RMCA). After transfusion for 3 years, repeat PET showed improvement of both metabolism and perfusion in the contiguous anterior regions of the RMCA. Clinical status was unchanged. The fourth subject had a normal MRI 2 years before an encephalopathic episode. The PET scan performed during this comatose episode showed left hemispheric multifocal areas of decreased glucose metabolism and blood perfusion. During that same hospital admission, a second MRI showed a small ill-defined anterior watershed abnormality on the left. PET scans performed at 6-month intervals after the initiation of a transfusion program showed near normalization in glucose metabolism and improvement in perfusion (Fig 5). The patient has significant cognitive deficiencies and poor adaptive behavior. In these four patients, improvement in neuronal metabolic function and microvascular perfusion was demonstrated by repeat PET imaging.

**Table 3. Correlation of PET and MRI Findings of Gray and White Matter Abnormalities**

MRI Findings	Total	PET Normal	PET Abnormal	% PET Abnormal
Gray abnormal, white abnormal	12	1	11	91.7
Gray abnormal, white normal	5	1	4	80.0
Gray normal, white abnormal	13	6	7	53.8
Gray normal, white normal	19	5	14	73.7
Total	49	13	36	73.5

$\chi^2$  test *P* value is .258 comparing the percentage of PET abnormalities among the four MRI groupings.

*Neuropsychological findings.* Impairments were found in several areas including intelligence, school achievement, motor and psychomotor speed, and adaptive behavior. In the present communication, findings on the FSIQ are presented to illustrate the impairment of Category I, Category II, Category III, and the silent ischemia group. The mean ( $\pm$  SD) of FSIQ scores was significantly different among the three patient groups 82 ( $\pm$ 13) for Category I, 78 ( $\pm$ 19) for Category II, and 99 ( $\pm$ 23) for Category III. Pair-wise comparison of the means by one-tailed *t*-test showed that the difference was significant ( $P < .01$ ) between Categories I or II and III. The proportion of subjects below the normal mean of 100 was similar for Categories I (CVA) and II (soft neurological) children, but significantly lower among Category III (no neurological signs) subjects: 14 of 15 (93%) for Category I, 15 of 16 (94%) for Category II, and 4 of 9 (44%) for Category III. Among the 25 subjects in Categories II and III who had silent ischemia on the MRI or PET or both, 20 participated in neuropsychological assessment. Their mean FSIQ score was 84 ( $\pm$ 23), and 16/20 (80%) of the IQs were below 100; these values were not significantly different from those of Category I (CVA group). In those whose silent ischemic lesions were diagnosed by an abnormal PET in the face of a normal MRI ( $n = 11$ ), the mean FSIQ was 86 ( $\pm$ 22) and 8 of 11 (73%) were below the normal mean.

## DISCUSSION

Forty-nine children with sickle cell anemia were studied by a combination of PET and MR imaging techniques, which identified a high percentage of anatomical and/or functional brain abnormalities across a spectrum of clinically identified neurologic states. All 19 of the subjects with overt CVA showed at least one imaging abnormality, while 85% of patients who were clinically identified with soft signs of neurologic impairment and 80% of subjects with no CVA or soft neurologic signs did also. The addition of PET to MRI evaluation of the CNS in these SS subjects clearly demonstrated that PET imaging can identify both overt and subtle loss of cerebral neuronal metabolic function when MRI studies show no clear anatomic lesion. Fourteen of the 19 subjects with normal MRIs (74%) were abnormal on PET, five of these identified in the neurologically normal group. This study confirms the original observation of Rodgers et al<sup>31</sup> of silent neuronal dysfunction in adults based on abnormal FDG-PET. The high sensitivity of PET for CNS

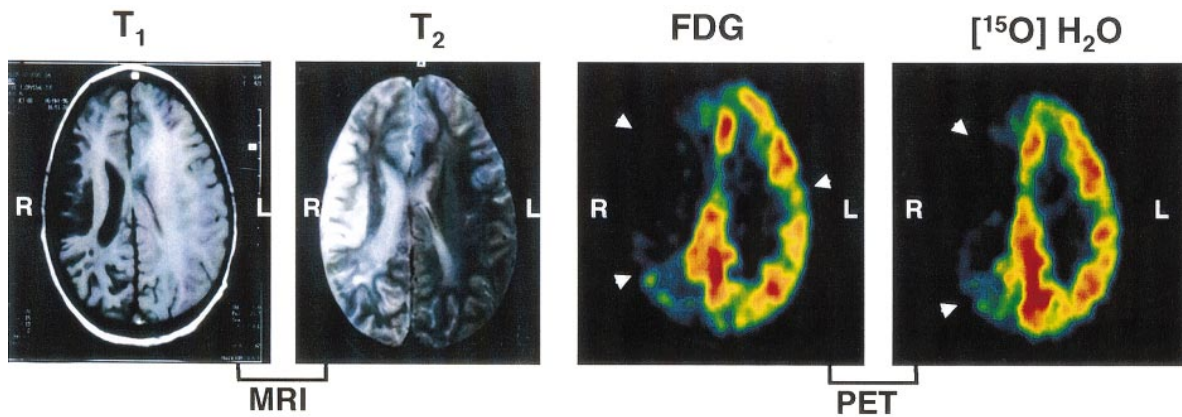


Fig 4. T<sub>1</sub> and T<sub>2</sub> weighted MRI images (left) showing loss of neuronal tissue in the distribution of the RMCA in the right cerebral hemisphere with focal dilatation of the right lateral ventricle. MRA showed absence of blood flow in RMCA and RACA (not shown). Marked FDG (metabolic) and [<sup>15</sup>O] H<sub>2</sub>O (perfusion) deficits on PET imaging (right) are seen throughout the right hemisphere (arrowheads) with near total neuronal loss (infarction). Deficits are greatest in the cerebral cortex of the RMCA distribution. Left cerebral cortex shows focal deficits best seen on FDG-PET (arrowhead).

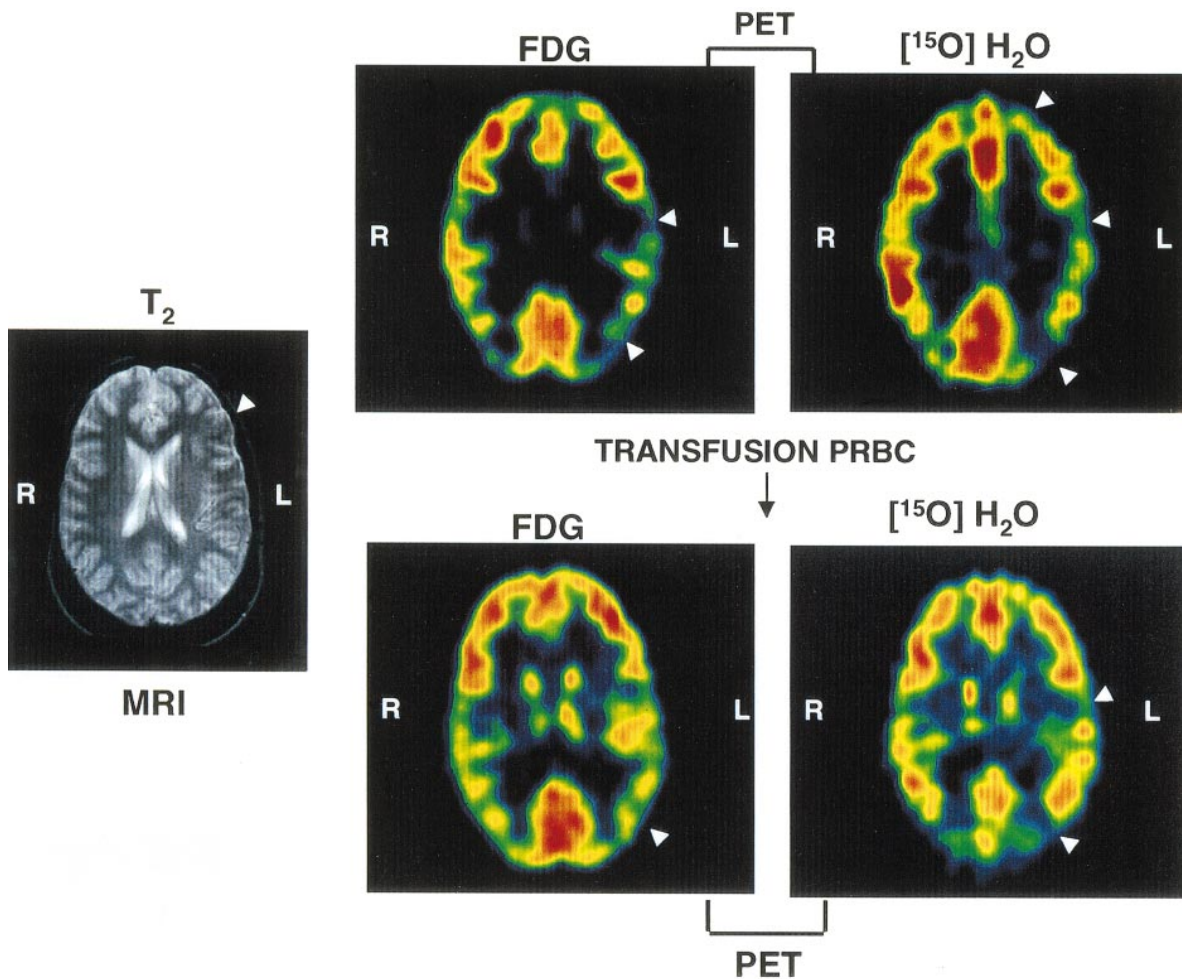


Fig 5. T<sub>2</sub> weighted MRI image (left) shows a small, ill-defined signal in the left genu of the corpus callosum (arrowhead). Maximum velocity (V<sub>Max</sub>) of LACA was 225 cm/sec and LMCA was 252 cm/sec by transcranial doppler. On FDG (metabolic) and [<sup>15</sup>O] H<sub>2</sub>O (perfusion) PET imaging (middle and right upper panels), diffuse hypoperfusion and hypometabolism is demonstrated with multifocal lesions throughout the left cerebral hemisphere. After institution of a hypertransfusion program, repeat PET scans performed at 6 months showed generalized subtle perfusion improvement (middle and right lower panels) with residual low perfusion in left occipital and parietal lobes (arrowheads). There was concurrent normalization of left frontal lobe on FDG PET.

dysfunction is consistent with recent PET studies in subjects with acute traumatic head injuries. These show that areas of functional abnormality are usually greater than the structural neuronal loss defined by MRI or CT and can be found associated with a normal MRI or CT.<sup>47,48</sup> In like manner, PET showed more extensive bilateral hemispheric dysfunction than was demonstrated by MRI in our SS subjects with known clinical ischemic events. This may account for the high risk of extension of the cerebral vasculopathy into previously presumed nonaffected areas. We suggest that the definition of the MRI identified silent infarction status be extended to include unexpected metabolic or perfusion ischemic lesions on PET.

The use of MRI in SS patients is well established. Pavlakis et al<sup>6,16,20,31</sup> examined the MRI results of 73 SS patients. Eighteen had a clinical history of stroke and 16 of them showed MRI abnormalities. The remaining 55 had no history of stroke, but six of them showed infarctions on the MRI. Moser et al<sup>15</sup> evaluated MRI on 215 SS children. Among the 52 children who had abnormal MRI, only 16 had clinical stroke. Thus, 36 had no overt clinical stroke, but had silent infarction.<sup>15</sup> Wang et al<sup>49</sup> found 11% of 36 very young SS children (less than 4 years of age) with no history of CVA already had abnormalities on MRI. No clinical information regarding severe hypoxic or infectious episodes in these subjects with the silent infarction syndrome is reported obviating any clinical parallel comparisons to our PET-defined silent ischemia group. The distinguishing feature of the reported MRI abnormalities was the predilection for lesions to occur in the high cortical convexities in the general regions of arterial border zones between the major cerebral arteries (watersheds) and the adjacent deep white matter. The pattern of the MRI lesions suggested two pathogenic mechanisms: (1) proximal large vessel disease with inadequate cerebral perfusion (distal field insufficiency syndrome)<sup>6,20,50</sup> and (2) distal small-vessel disease (sludging syndrome).<sup>3,6</sup> Wiznitzer et al<sup>19</sup> concluded that a combination of MRI and MRA (magnetic resonance angiography) can provide useful screening for large vessel disease in this population. Recently Wang et al<sup>49</sup> reported three children less than 2.5 years of age who had stenosis of large intracranial vessels on MRA with no MRI abnormalities. In three of our subjects with no MRI abnormalities (data not shown), metabolic perfusion abnormalities on PET were associated with MRA intracranial vessel stenosis.

Watershed abnormalities were indeed originally thought to be incidental findings in patients with SS who were not known to have neurologic involvement. The addition of PET to MRI describes surrounding tissue pathology in some of these patients. In this study, PET was abnormal in 44% of our non-CVA SS subjects who had watershed white matter lesions on the MRI. The finding of cerebral metabolic or diffusion deficits supports the hypothesis that these watershed lesions in non-CVA subjects are associated with a broader region of cerebral dysfunction and may be a prelude to clinical stroke.<sup>33</sup> Further study is needed to evaluate whether the demonstration of abnormalities, by combined neuroimaging, possibly including single photon emission computer tomography (SPECT) or neuroSPECT<sup>36,47</sup> might predict stroke occurrence analogous to the TCD demonstration of increased blood flow velocity in the large cerebral vessels.<sup>24</sup>

PET imaging cannot supplant MRI because of the failure of

PET to identify cerebral atrophy and white matter lesions in the watershed areas.<sup>35,51,52</sup> This is due to the relatively low glucose utilization in the projection fibers of the corona radiata.<sup>32</sup> On the other hand, among some of our patients, a decrease in gray matter metabolism, particularly in the frontal areas, was observed on PET before their white matter lesions were observed on repeat MRI examinations. The combination of PET with MRI better delineated cerebral deficits.

The addition of neuropsychologic evaluation identified subjects with impaired cognitive skills that were clearly associated with decreased cerebral metabolic activity based on PET. Subjects with normal neurological examination and history (Category III) had significantly higher FSIQ as compared with the FSIQ scores of the Category I (CVA) and Category II (soft neurologic signs) subjects. Those in Categories II and III with abnormal imaging (silent ischemia) had lower FSIQ scores with 80% below the normal mean. The present findings suggest that silent ischemic lesions can be nearly as damaging to cognitive function as overt stroke. Cognitive assessment should be conducted for all patients with silent ischemic lesions and supportive educational programs should be provided.

In our small comparison group, the high percentage of CNS abnormalities (80%) was not expected. They were initially recruited solely on the basis of a normal neurologic history and physical examination. Two were siblings of stroked SS subjects and three had subsequent findings of an elevated TCD velocity. The findings in this study group indicate the difficulty of clinically identifying subtle cerebral dysfunction.<sup>37,53</sup>

A few provocative observations were made during the course of this study. Two children with PET abnormalities (one with concurrent MRI lesions) subsequently developed overt CVAs. This supports the concept that PET-defined silent ischemic lesions are not just aberrancies of a very sensitive imaging technique. Four patients with CNS vasculopathy who were treated by chronic transfusion therapy showed improvement in cerebral metabolic activity. This raises the potential for use of PET as a monitoring tool capable of assessing therapy in a more helpful way than counting new infarcts on MRI or observing repeat parietic strokes. Because this study was not designed to assess longitudinal progression of disease, further prospective study will be needed to more systematically define the role of PET in predicting stroke or monitoring therapy.

## CONCLUSION

PET imaging techniques offer additional and detailed delineation of both (1) regional infarction and (2) diffuse cerebral disease.<sup>33,50,54,55</sup> The addition of PET to MRI identified a greater proportion of SS children with neuroimaging abnormalities than MRI alone (90% v 61%). The majority (63%) of these SS children with no overt neurologic events had abnormal PET studies. The prevalence of silent ischemic lesions was much higher than the reported 10% frequency of overt CVA in SS children would imply.<sup>2</sup> PET lesions were also shown to be more extensive, often bihemispheric as compared with MRI. These findings may be helpful in understanding the development of cerebral vascular disease in SS children.

In four of our subjects, chronic transfusion was shown to be beneficial in reversing impaired cerebral metabolic activity. The addition of PET to MRI or neuropsychologic evaluation may help identify subjects with cerebral vasculopathy for early

intervention including bone marrow transplantation or chemotherapeutic intervention and could provide a monitoring tool to assess the effectiveness of therapy.

#### ACKNOWLEDGMENT

We thank Dr Cage Johnson, Director, USC Comprehensive Sickle Cell Center for his advice and encouragement. We greatly appreciate the efforts of the neuroradiology staff and the pediatric neurology staff of the cooperating institutions who forwarded their reports to the principal investigator coupled with copies of the MRI and MRA. We are grateful for the secretarial efforts of Debra Johnson in the preparation of this manuscript.

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