The case of a patient with sickle cell disease is presented in which neuropsychological and magnetic resonance imaging studies were completed prior to and after a right hemispheric stroke. The contribution of a new MR perfusion technique in understanding the neurological complications in this patient is discussed. This case illustrates the complex pathophysiology of neuropsychological deficits in SCD and underscores the need to develop models that better reflect this complexity.

Sickle cell disease (SCD) is the homozygous state for a hemoglobinopathy in which deoxygenation distorts red blood cells. These “sickled” cells may occlude blood vessels in various organs of the body resulting in ischemia, pain, and impaired functioning. It is an inherited disorder in which heterozygotes (sickle cell trait) demonstrate no symptoms. Among African-Americans, it is estimated that one in 12 is a carrier of the trait and that the disease afflicts one in every 500 to 600 live births (DesForges, Milner, Wethers, & Whitten, 1978).

Stroke is one of the major complications of SCD, occurring in 5%-17% of homozygous (SS) patients. Average age for occlusive stroke is 7 years, with the greatest risk being before the age of 15 years (Powars, Wilson, Imbus, Pegelow, & Allen, 1978). Hemorrhagic rather than ischemic strokes are more likely in adulthood. Fifty percent of patients with SCD surviving a stroke will suffer a subsequent stroke within 35 months (Portnoy & Herron, 1972). Although the risk of repeated strokes can be decreased substantially by monthly transfusions, there are multiple risks associated with chronic transfusions including iron overload, viral infection, red cell alloimmunization, and transfusion reactions. Discontinuation of transfusion therapy is not without risk of cerebral vascular accident, even in those patients transfused for more than 5 years (Wang et al., 1991).
Sickling and occlusion of the small cerebral vessels was originally believed to be the primary pathological process in the occurrence of stroke in these patients (Adams, Nichols, McKie, McKie, Milner, & Gammal, 1988). Recent angiographic and pathological evidence, however, implicates large vessel disease (Adams et al., 1988; Pavlakis et al., 1988). Lesions of the intima of the major cerebral vessels are well documented, and contemporary theories propose some form of direct damage to the endothelium due to abnormal adherence properties of erythrocytes in SCD.

Although much attention has shifted to the investigation of large vessel disease, impairment of flow through the microvasculature or decreased cerebral perfusion resulting from altered hemodynamics in the arterioles (Pavlakis et al., 1988), remain viable alternate mechanisms in the pathophysiology of SCD-related deficits. Positron emission tomography (PET) studies (Rogers, Clark, Larson, Rapport, & Nienhuis, 1988) have demonstrated decreased glucose metabolism (and by inference, perfusion) in the frontal lobes of patients with SCD. Cerebral blood flow (CBF) by Xenon-133 inhalation method has also been shown to be diffusely low in sickle cell patients (Huttenlocher, Moohr, Hohns, & Brown, 1984).

Four recent controlled studies have reported neuropsychological dysfunction in SCD patients having no history of cerebral vascular accidents (Brown et al., 1993; Fowler, Whitt, Lallinger, Nash, Atkinson, Wells, & McMillan, 1988; Swift et al. 1989; Wasserman, Wilimas, Fairclough, Mulhern, & Wang, 1991). Some of these studies found lower overall IQ in patients with SCD (Swift et al., 1989; Wasserman et al., 1991), while others found evidence of more specific deficits in academic skills (Brown et al., 1993; Fowler et al., 1988), attention (Brown et al., 1993; Fowler et al., 1988), and visual-motor coordination (Fowler et al., 1988).

One shortcoming of many of these studies has been an overreliance on “level of performance” data analysis procedures. In a disease where lesion size, location, and chronicity vary, such heterogeneity would obscure real differences between SCD and control groups. This is particularly true when using omnibus IQ indexes on which unilateral lesions have differing impact depending upon age of insult (e.g., Riva & Cazzaniga, 1986).

Thus, patients with SCD who have not suffered overt clinical strokes may, nevertheless, exhibit compromised neurocognitive development. Our understanding of the underlying pathophysiology of such impairment is incomplete. It may be that such developmental deviations and clinical strokes have a common basis in large vessel disease. It is also possible that alternate mechanisms, such as chronic anemia (Brown et al., 1993) and small vessel disease/occlusion may account for these neuropsychological findings.

The study of cerebral blood flow and metabolism may help elucidate possible pathophysiological mechanisms. We report on the investigation of a patient using a new magnetic resonance (MR) perfusion technique (rapid sequence T$_2$-weighted MR perfusion images) (Edelman et al., 1990; Tzika, Massoth, Ball, Majumdar, Dunn, & Kirks, 1993). This procedure involves the intravenous injection of a compact bolus of a paramagnetic contrast agent (gadolinium-DTPA) and rapid MR imaging. Perfusion is evaluated on T$_2$-weighted images as a transient signal intensity loss in and around blood vessels. This easily performed method of imaging blood flow characteristics may make such a capability more widely available in the future, although its clinical correlates need to be explored further.

The case reported below presents a unique opportunity to examine the neuropsychological status and imaging findings of a patient with SCD shortly before and after she suffered a stroke.

CASE STUDY

Background

AB was an 11 year 11-month-old female with SCD when she suffered a stroke affecting the left leg, arm, and face. She was alert, oriented, and responsive when examined in the
Stroke in Sickle Cell Disease

Medical records indicated that AB was born at 37 weeks of gestation by caesarean-section due to maternal preeclampsia. She was found to have homozygous sickle cell anemia (Hgb SS) by routine newborn screening. Otherwise, her neonatal course was unremarkable. Developmental milestones were attained within normal limits. On the clinical classification criteria for SCD developed by Cameron, Christian, Lobel, and Gaston (1983), AB’s disease was rated as severe, although there was no previous history of neurologic symptoms.

The patient lived with her mother and two siblings. The parents were divorced and mother reported 2 years of posthigh school education. At the time of the hospitalization, she worked as a typing clerk. The occupational and educational status of the father was unknown.

At the time of AB’s hospitalization, she was completing the 8th grade in a regular class with no history of retention or special education placement. Her teacher was sent a Teacher Report Form (TRF; Achenbach & Edelbrock, 1986) to document AB’s premorbid scholastic adjustment. She reported grade level performance in reading and health, but somewhat below grade level performance in math, science, and social studies. Also noted on the TRF were frequent absences due to illness and high average scores on standardized achievement tests. There were no elevations (defined as T greater than or equal to 70) on any of the clinical scales (Withdrawn, Somatic Complaint, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior).

Prestroke Neuropsychological and MRI Studies

Neuropsychological data obtained 5 weeks prior to the stroke (as part of a prospective study of neuropsychological correlates of MR perfusion abnormalities in SCD patients) and 3 weeks after the stroke are presented in Table 1. For ease of comparison, scores were converted to the same scale, with a mean of 100 and standard deviation of 15 (low scores indicating greater impairment). Because of the absence of published norms for the Kagan Matching Familiar Figures Test (MFFT), the results of this test are presented in raw score form.

When seen for the prestroke testing, the patient was cooperative, attentive, and engaging. She put forth good effort on the tasks presented to her, and had no difficulty understanding instructions. She demonstrated a consistent preference for the right hand, and evinced no difficulty manipulating test materials. Examination of Table 1 indicates that prestroke performances were generally well within normal limits. In fact, AB’s psychometric intelligence was considerably above some reported estimates in this population (Swift et al., 1989). While there was a trend toward a difference between the Verbal and Performance IQs, this would not be considered clinically significant because 20% of the Wechsler Intelligence Scale for Children — Revised (WISC-R: Wechsler, 1974) standardization population demonstrated discrepancies of this size or larger (Sattler, 1988). Individual subtest scores ranged from above average to low average except for a below average score on Block Design.

Achievement scores on the Wide Range Achievement Test — Revised (WRAT-R: Jastak & Wilkinson, 1984) were low average in reading and spelling but above average in arithmetic. Selected subtests from the Wide Range Assessment of Memory and Learning (WRAML: Sheslow & Adams, 1990) demonstrate average short-term figural memory but superior short-term verbal memory. No difficulties were encountered on the MFFT (Kagan, Rosman, Day, Albert, & Phillips, 1964) with the patient demonstrating good attention to pictorial detail and a reflective problem solving style. The only clear abnormality found in this protocol, in regard to level of performance, was on the left hand score of the Purdue
TABLE 1
Pre- and Post-Stroke Neuropsychological Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Prestroke Score</th>
<th>Poststroke Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Similarities</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Comprehension</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Digit Span</td>
<td>110</td>
<td>105</td>
</tr>
<tr>
<td>Picture Completion</td>
<td>100</td>
<td>115</td>
</tr>
<tr>
<td>Picture Arrangement</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td>Block Design</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>Object Assembly</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Coding</td>
<td>105</td>
<td>100</td>
</tr>
<tr>
<td>Mazes</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>99</td>
<td>103</td>
</tr>
<tr>
<td>WRAT-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>86</td>
<td>89</td>
</tr>
<tr>
<td>Spelling</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>110</td>
<td>88</td>
</tr>
<tr>
<td>WRAML</td>
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<td></td>
</tr>
<tr>
<td>Design Memory</td>
<td>105</td>
<td>90</td>
</tr>
<tr>
<td>Sentence Memory</td>
<td>120</td>
<td>110</td>
</tr>
<tr>
<td>Kagan MFFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Errors</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Mean Latency(s)</td>
<td>10.25</td>
<td>20.10</td>
</tr>
<tr>
<td>Purdue Pegboard</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hand (Dominant)</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>Left Hand</td>
<td>70</td>
<td>Untestable</td>
</tr>
<tr>
<td>Beery VMI</td>
<td>85</td>
<td>80</td>
</tr>
</tbody>
</table>

Pegboard Test (Spreen & Strauss, 1991). Figure copying was low normal on the Beery Visual Motor Integration Test (Beery, 1982).

Overall, nearly all of the prestroke test results were within the normal range, and in many cases above average. The lower Performance IQ than Verbal IQ could reflect right hemispheric or more diffuse neuropsychological impairment, though the left hand fine motor deficit would support the interpretation of right lateralized impairment.

A conventional MRI scan (spin echo T2-weighted images) conducted on the same day as the premorbid neuropsychological testing was interpreted by a neuroradiologist (WSB) as demonstrating atrophy of the right cerebral hemisphere greatest in the frontal and parietal lobes (see Figure 1). MR perfusion studies demonstrated delayed perfusion in both frontal lobes as well as areas of increased signal in the white matter bilaterally (right greater than left) suggestive of old infarction.

Poststroke Neuropsychological and MRI Studies

When seen 3 weeks after the stroke (8 weeks after the first testing), the patient was, again, cooperative, alert, friendly, and well motivated. However, she exhibited an awkward gait and dense left upper extremity paresis. Affect and impulse control were judged to be age-appropriate. On readministration with the same battery of tests, the patient showed good preservation of psychometric intelligence. With a reported average gain of over nine points in Performance IQ with retesting after 1 month (Kaufman, 1979), AB's increase on this scale is consistent with practice effects. The greatest increase (one standard deviation)
FIGURE 1. (A) Premorbid MRI scan showing widening of the extra-axial fluid spaces over the frontal convexity on the T2-weighted image (open arrows). Abnormal increased signal within the white matter (arrows) is compatible with ischemic injury and demyelination. (B) Dynamic T2-weighted image showing decreased perfusion in both frontal lobes (arrowheads) compared to the rest of the brain.

occurred on the Block Design Subtest, which was AB's lowest score at the first testing. Therefore, regression toward the mean may also have been a factor in the improved score on poststroke testing.
Achievement skills were unchanged in reading and spelling but significantly reduced in arithmetic. There was a mild decrease in short-term memory, with nonverbal memory being slightly more affected. This, combined with an absence of the expected increase in scores due to practice effects, would argue for a significant decline in memory functioning post-stroke. More errors and longer latencies were found on the MPFT. Examination of the pattern of errors on this test indicated a strong preference for choices at the extreme right, even though on previous testing a mild left-sided preference was noted. This is consistent with left hemispatial neglect, resulting in more errors and longer search times. Error analysis of the Arithmetic Subtest of the WRAT-R also showed occasional neglect of digits to the left of midline and it was this, more than calculation errors, that accounted for AB’s decreased performance on the Arithmetic Subtest.

While a mild decrease in AB’s score on the Mazes Subtest may have resulted from impaired planning and response inhibition, it is noteworthy that on this test the “exit” in two of the last three mazes is positioned on the left side. Thus, left-sided neglect may have contributed to her poorer performance on this task as well.

MRI studies conducted a few days following the stroke showed an acute evolving infarction in the right anterior temporal lobe and central parietal lobe in the vascular distribution of the middle cerebral artery (see Figure 2). There was decreased prominence of the extra-axial fluid spaces over the frontal convexities perhaps as a result of mild brain swelling following infarction. There was also some improvement in perfusion within the frontal lobes, but a new perfusion defect was found corresponding to the middle cerebral artery infarction.

An angiogram performed 3 weeks after the stroke demonstrated complete occlusion of the right internal carotid artery at the origin (Figure 3), with increased collateral flow between the internal and external carotid arteries on the right and increasing intraparenchymal collaterals between the posterior and middle cerebral artery distribution. The left internal carotid was normal.

DISCUSSION

This case illustrates a number of methodological and theoretical complexities in the study of SCD, including; (1) the unknown incidence and impact of subclinical strokes/ischemia in SCD; (2) the relative roles of large vessel disease, small vessel disease, and rheologic factors in accounting for the neurodevelopmental morbidity reported in these patients; and (3) the intricate relationships between abnormalities on imaging studies and neurobehavioral measures.

The fact that AB’s prestroke MRI and perfusion studies demonstrated ischemic injury to the white matter and frontal lobe hypoperfusion despite the absence of a clinically discernible event underscores the potential clinical and research utility of this technique. It also lends credence to the notion that the neurodevelopmental problems reported in at least some patients with SCD are a consequence of such subclinical events (Craft, Schatz, Glauser, Lee, & DeBaun, 1993). Others have reported MRI abnormalities in neurologically normal patients with SCD (El Gammal et al., 1986; Kugler et al., 1993), although most neurodevelopmental investigations in this population (Fowler et al., 1988; Swift et al., 1989; Wasserman et al., 1991) have not correlated their findings with neuroradiologic data. It, therefore, remains unclear to what degree their results can be accounted for by such a process.

This case also illustrates the importance of examining “pattern of performance” or indexes of abnormal “scatter” reflecting irregularities across neuropsychological domains/tests. In the case of AB, such configural approaches were more revealing than were “level of performance” scores on the individual tests.
FIGURE 2. (A) Poststroke MRI showing an infarction in the distribution of the right middle cerebral artery (arrows) on the T2-weighted image. Note a decrease in the prominence of the extra-axial fluid spaces over the frontal convexities. (B) Dynamic T2-weighted image showing some improvement in perfusion within the frontal lobes, but a new perfusion defect (arrowheads) corresponds to the right middle cerebral artery infarction.

This patient exhibited initial perfusion abnormalities in the frontal lobes, which then normalized on the follow-up studies. Possible explanations for this include: (1) unreliability of this new MR technique (although similar defects reported on PET scans and blood flow...
FIGURE 3. A cerebral anglogram was performed by injection into the right common carotid artery. (A) There is complete occlusion of the right internal carotid artery at its origin (arrow). There is a prominent middle meningeal artery (arrowheads) indicating increased collateral flow between external and internal carotid circulations. (B) A vertebral injection reveals retrograde filling of the distal right internal carotid artery to the origin of the ophthalmic artery (arrow). Note extensive collaterals between middle and posterior cerebral artery territories (arrowheads).

studies would support the accuracy of these findings); (2) changes in autoregulation consequent to the stroke; and (3) improved perfusion secondary to poststroke transfusion therapy. The absence of consistent neuropsychological evidence for frontal lobe impairment in AB
despite the perfusion abnormality on the first series may reflect the insensitivity of the neuropsychological battery used in this investigation and the inherent difficulties in measuring the complex behaviors ascribed to these areas of the brain, particularly in children. Alternately, it may suggest that, rather than a static state, the abnormality was a transient phenomenon reflecting a state of perfusion instability.

Thus, the case of AB illustrates an occult neurologic process of unknown origin and duration that eventuated in a clinical event. The ischemic injury and/or hypoperfusion found in AB may have been a consequence of large vessel disease (distal insufficiency), small vessel disease, abnormal rheology, or (more likely) a complex combination of all of these factors. Recent formulations of neurologic morbidity in SCD emphasize the role of large vessel disease but are based largely on pathologic and angiographic evidence of patients suffering completed strokes. It would seem inappropriate to simply assume that lesser degrees of morbidity are a consequence of an identical process when there is mounting evidence implicating other factors that may act in additive or interactive ways in these patients.

This case further demonstrates the challenges facing researchers attempting to relate imaging studies to neuropsychological data. Whereas significant advances have been made in quantifying imaging data (Turkheimer, Yeo, Jones, & Bigler, 1990), constantly emerging technology (such as MR perfusion) present new challenges. Also, researchers must match sophistication on the imaging side with improved means of quantifying and representing behavioral data (Bigler, 1991), other than through simple level of performance approaches. In the case of AB, both the prestroke neuropsychological studies and the patient's history demonstrated surprising resilience to neurologic insults evident on MRI and MR perfusion. This case, thus, highlights the difficulties one faces in attempting to correlate imaging and neuropsychological information. Such efforts are hampered by limitations of instrumentation (i.e., what functions to measure and how best to measure them), optimal and comprehensive ways of representing neuropsychological data (i.e., levels of performance, patterns of performance, variability in performances, and pathognomonic signs), and how abnormal neurological processes become expressed behaviorally over time, taking into account subject (e.g., age) and lesion (e.g., age, momentum, process) factors.

It is clear that prospective studies utilizing both sophisticated neurobehavioral methods and state of the art imaging technology are needed to advance our understanding of the full range of pathophysiological processes in SCD and how they account for the varied neurodevelopmental outcomes of these patients. Comprehensive models also need to take into account psychosocial factors mediating cognitive-behavioral vulnerability (Thompson, Gil, Abrams, & Phillips, 1992) and should consider how concepts of threshold and brain reserve capacity (Satz, 1993) may elucidate clinicopathological relationships as they unfold over time. Improved risk–benefit determinations resulting from such research will promote more effective management of this disease in the future.

REFERENCES


