Brief report

Inverse correlation between cerebral blood flow measured by continuous arterial spin-labeling (CASL) MRI and neurocognitive function in children with sickle cell anemia (SCA)

John J. Strouse, Christiane S. Cox, Elias R. Melhem, Hanzhang Lu, Michael A. Kraut, Alexander Razumovsky, Kaleb Yohay, Peter C. van Zijl, and James F. Casella

Overt stroke, clinically “silent” cerebral infarct, and neurocognitive impairment are frequent complications of sickle cell anemia (SCA). Current imaging techniques have limited sensitivity and specificity to identify children at risk for neurocognitive impairment. We prospectively evaluated 24 children with SCA and normal MRI, complete blood count, transcranial Doppler ultrasound (TCD), measurement of intelligence quotient (IQ), and magnetic resonance imaging (MRI) with measurement of cerebral blood flow (CBF) using continuous arterial spin-labeling (CASL) MRI. Average CBF to gray matter was 112 ± 36 mL/100 g/min. We identified a strong inverse relationship between performance IQ and CBF (−1.5 points per 10 mL/100 g/min increase in CBF, P = .013). Elevated steady-state white blood cell count (≥ 14 × 10⁹/L [14 000/µL]) was associated with lower full scale IQ (86 ± 9 vs 99 ± 10, P = .005). CASL MRI may identify children with neurocognitive impairment, before damage is evident by structural MRI or TCD.

Study design

Study population

We prospectively enrolled children aged 6 to 12 years with homozygous sickle cell disease (HbSS) or sickle β-null thalassemia from our pediatric hematology clinic. We excluded children with previous traumatic brain injury, seizure disorders, abnormal TCDs (>200 cm/sec), stroke, other identified causes of cognitive impairment, and those receiving scheduled transfusions.

Study procedures

At the initial study visit, children had a standardized exam by a pediatric neurologist, a TCD, a brain MRI at 1.5 Tesla, neuropsychologic testing, and venous blood collected. All testing, except for the neurologic exam, was repeated at 12-18 months follow-up. TCD studies were performed with a 2-MHz pulsed ultrasound probe (Intraview; RIMED, Raanana, Israel) per published methods. MRIs (fluid-attenuated inversion recovery [FLAIR], transverse relaxation time [T2], diffusion-weighted sequences, and MR angiography) were assessed by 2 neuroradiologists for the presence of SCI (T2 or FLAIR hyperintensities ≥3 mm in diameter consistent with ischemia and seen in 2 planes). IQ was measured by a licensed neuropsychologist using established methods. The neurologists, neuroradiologists, and neuropsychologist were masked to the results of other studies. CBF was measured using continuous arterial spin-labeling (CASL) MRI, a technique that was studied in the present work.

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that labels water molecules in blood by a radiofrequency pulse as they pass through a plane in the upper neck. Labeled images are subtracted from control (unlabeled) images to estimate CBF. We obtained and processed the images per Oguz et al, but substituted specific values for the spin-lattice relaxation time (T1) of blood at 1.5 T based on packed-cell volume (PCV).11,12

The vascular distributions of the major cerebral arteries11 were independently outlined by 2 investigators and used to calculate regional CBF to gray matter. Blood studies, including PCV, white blood cell (WBC) count, and platelet count, were performed using an automated analyzer (Sysmex SE 9500; Roche, Indianapolis, IN) when the patients were in their usual state of health. The study was approved by the Johns Hopkins Medicine Institutional Review Board, and we obtained consent from the parent/guardian and assent from the child.

Statistical analysis

We converted CBF velocity to standardized values. We calculated the Statistical analysis guardian and assent from the child. We studied 24 children from July 2000 to January 2004. Seventeen returned for their scheduled follow-up visit at 12 to 18 months, and 4 also returned at 6 months (Table 1). All children had SCA, and 2 were taking hydroxyurea. Their mean age at the first visit was 8.5 ± 2.0 years. Five of the 21 children had mild abnormalities detected by neurologic exam, including residual left facial nerve palsy after a documented Bell palsy (1), right carotid bruit (1), subtle pyramidal deficits (2), and mild cerebellar signs (1), without corresponding abnormalities on imaging. Ten children had 1 or more of the following: abnormalities of attention (7), received special services in school (6), or repeated a year of school (5). Only 1 of 36 TCDs was conditional by established standards for SCA.15

Of 24 children with 38 interpretable MRIs and MRAs, 1 child had SCA and irregularity at the trifurcation of the left middle cerebral artery (MCA) on 2 studies. The right-sided CBF. These brain areas are essential for the organizational and visual spatial skills used in block design and matrix reasoning, 2 subsets of performance IQ.10 Overall, regional CBF was highly correlated (r = 0.87-0.99) which explains the similar relationship between CBF by region and IQ. Children with WBC counts in the highest quartile (≥ 14 X 109/L [14 000/µL]) had significantly lower full scale IQ (86 ± 9 vs 99 ± 10, P = .005), whereas children with low PCV (< 20%) or elevated platelet count (≥ 500 X 109/L [500 000/µL]) did not. To our knowledge, an association between WBC count and IQ has not been described previously, although increased WBC count at baseline was associated with increased risk of early death in a large cohort study of SCA.17 WBC count may serve as a marker of inflammatory mediators, which have been associated with increased risk of stroke and cognitive impairment in adults,18 or of decreased splenic function and severe disease in SCA.1

Results and discussion

We studied 24 children from July 2000 to January 2004. Seventeen returned for their scheduled follow-up visit at 12 to 18 months, and 4 also returned at 6 months (Table 1). All children had SCA, and 2 were taking hydroxyurea. Their mean age at the first visit was 8.5 ± 2.0 years. Five of the 21 children had mild abnormalities detected by neurologic exam, including residual left facial nerve palsy after a documented Bell palsy (1), right carotid bruit (1), subtle pyramidal deficits (2), and mild cerebellar signs (1), without corresponding abnormalities on imaging. Ten children had 1 or more of the following: abnormalities of attention (7), received special services in school (6), or repeated a year of school (5). Only 1 of 36 TCDs was conditional by established standards for SCA.15

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Table 1. Linear regression with accounting for clustering of observations by patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. observations (no. patients)</th>
<th>Full-scale IQ</th>
<th>Performance IQ</th>
<th>Verbal IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef.</td>
<td>P</td>
<td>Coef.</td>
<td>P</td>
</tr>
<tr>
<td>Age, y</td>
<td>37 (24)</td>
<td>0.047</td>
<td>.51</td>
<td>0.058</td>
</tr>
<tr>
<td>CBF, mL/100 g/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>19 (16)</td>
<td>-0.13</td>
<td>.30</td>
<td>-0.14</td>
</tr>
<tr>
<td>Left</td>
<td>19 (16)</td>
<td>-0.14</td>
<td>.07</td>
<td>-0.15</td>
</tr>
<tr>
<td>Right</td>
<td>19 (16)</td>
<td>-0.13</td>
<td>.04</td>
<td>-0.14</td>
</tr>
<tr>
<td>Total</td>
<td>19 (16)</td>
<td>-0.14</td>
<td>.05</td>
<td>-0.15</td>
</tr>
<tr>
<td>PCV, %</td>
<td>37 (24)</td>
<td>1.2</td>
<td>.21</td>
<td>0.34</td>
</tr>
<tr>
<td>Platelets, per 10^9/L</td>
<td>35 (23)</td>
<td>-0.01</td>
<td>.37</td>
<td>-0.003</td>
</tr>
<tr>
<td>WBC count, per 10^9/L</td>
<td>35 (23)</td>
<td>-1.4</td>
<td>.05</td>
<td>-0.8</td>
</tr>
<tr>
<td>Maximum CBFV</td>
<td>36 (24)</td>
<td>0.57</td>
<td>.82</td>
<td>2.0</td>
</tr>
<tr>
<td>Hemoglobin F</td>
<td>30 (22)</td>
<td>0.33</td>
<td>.53</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CBFV indicates cerebral blood flow velocity (z score); Coef., coefficient.
increased CBF in a cohort of patients with SCD more than 15 years ago using xenon inhalation. They proposed that increased CBF resulted from adaptive vasodilatation and that it caused a reduction in cerebrovascular reserve. Further demand (eg, fever) or decrease in oxygen delivery (eg, worsening anemia or a drop in perfusion pressure) in patients with the high CBF could cause distal infarction. The increase in CBF in their report was greater than what expected based on the severity of anemia, and decreased more than expected after transfusion with sickle-negative blood. This implies that hemoglobin S has an independent effect on CBF. Increased CBF may result from abnormal vasoregulation secondary to the effects of hemolysis and free hemoglobin on nitric oxide.

limitations of this study include small sample size, convenience sampling, and limited longitudinal measurement of CBF. Our sample of patients, while not deliberately selected for these characteristics, had a lower prevalence of SCI and conditional TCDs and, on average, higher IQ than the general population of children with HbSS. However, it is striking that we still found an inverse correlation between CBF and IQ that was not explained by SCI or worsening anemia. CASL MRI can be performed successfully without sedation and will become more sensitive and more available to clinical practice with the advent of higher magnetic fields (3T). Measurements of CBF by CASL at 1.5 T are reproducible (coefficient of variation of 6% for measurements repeated the same day) and correlate well with PET studies of CBF in a cortical strip (64 ± 12 ml/100g/min vs 67 ± 13 ml/100 g/min). Our results suggest that globally increased CBF, perhaps preceding focal stenosis, may be a risk factor for CNS complications. CASL MRI is a promising modality that allows measurement of CBF noninvasively and without exposure to radiation. CASL MRI, by detecting increased CBF, may allow interventions to modify the risk of neurocognitive impairment from SCA, potentially before SCI or abnormal CBF velocity develop. Larger studies with additional follow-up are necessary to validate the results of this pilot study, and to further evaluate CASL MRI.

References

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