The Other Side of Abnormal: A Case Series of Low Transcranial Doppler Velocities Associated With Stroke in Children With Sickle Cell Disease

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Summary: The prevalence of cerebrovascular events in sickle cell disease (SCD) can be as low as 10% by the age of 18 for overt cerebral infarction or strokes, up to 35% for silent cerebral infarction, and as high as 43/100 patient years for acute silent cerebral ischemic events. These events typically occur during childhood with a peak incidence between the age of 4 and 7 years. The cumulative risk of central nervous system events in SCD increases with age. Transcranial Doppler (TCD) ultrasonography is an established screening tool for detecting children with SCD at highest risk for stroke by measuring the flow velocity in the large intracranial vessels. Velocities are considered abnormal with readings >200 cm/s and chronic red cell transfusions are recommended to reduce further risk or progression. Red cell transfusions have reduced the rate of cerebrovascular accidents by 90%. We describe the case of 5 children with sickle cell anemia, whose antecedent screening TCD velocities were measured to be ≥ 70 cm/s in the study. All patients developed some form of cerebral insults, an overt cerebral infarctions, silent stroke or transient ischemic attack, and are now receiving chronic transfusion to prevent further progression. On the basis of these cases, low TCD velocities may identify another group of children at risk for cerebrovascular disease. We suggest TCD velocities <70 cm/s in major vessels (MCA, ACA, and ICA) be considered another type of "abnormal," prompting more sensitive evaluations (such as a brain MRI and MRA) for the presence of central nervous system disease, and, if negative, decrease intervals between subsequent TCD assessments.

Key Words: sickle cell disease, strokes, Transcranial Doppler Ultrasonography, cerebrovascular accidents, cerebral infarction

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Central nervous system (CNS) complications associated with sickle cell disease (SCD) include acute hypoperfusion or ischemic cerebrovascular accidents, silent cerebral infarctions with definitive changes on magnetic resonance imaging (MRI) with no identifiable clinical event, cerebral artery stenosis or tortuosity causing moyamoya collaterals that predispose to intracerebral hemorrhage, and the newly recognized acute silent cerebral ischemic events in which there are no lasting changes found on MRI.[1] The prevalence of these events range from as low as 10% by the age of 18 for overt infarctions or "strokes" up to 35% for silent cerebral infarcts, and as high as 43/100 patient years for acute silent cerebral ischemic events.[1,2] These events typically occur during childhood with a peak incidence between the age of 4 and 7 years, however, the cumulative risk of CNS events in SCD increases with age.[2,3] Long-term outcomes after these CNS events range from no obvious sequelae to poor school performance, behavior aberration, hemiplegia, aphasia, seizure disorders, to a prolonged vegetative state, and even death.[4] The overall impact of CNS events on quality of life has resulted in a comprehensive approach toward primary and secondary stroke prevention and is an important focus of comprehensive care for pediatric patients with SCD.

The results from the sentinel SCD Stroke Prevention Trial (STOP) has established transcranial Doppler (TCD) screening as an effective screening tool for identifying those children with SCD who are at highest risk for stroke.[5,6] This noninvasive test measures the mean average flow velocity in the large intracranial vessels of the circle of Willis, primarily the internal carotid artery (ICA), middle cerebral artery (MCA), and the anterior cerebral arteries (ACA). Cerebral angiographic comparisons have confirmed that severe stenosis of any one of these vessels is associated with TCD flow velocities that are 2 to 3 times higher than normal.[6] In addition, increased TCD velocities have been associated with focal vascular stenosis that leads to high linear shear stress through the major arteries and therefore correlates with an increased risk of stroke.[7,8] The STOP trial was designed to determine the efficacy of prophylactic red blood cell transfusions in preventing arterial-occlusive strokes in children with SCD in whom mean TCD velocities were Z 200 cm/s in assessed intracerebral arteries.[5,7] In the original STOP Trial, children with TCD velocities >170 cm/s but <200 cm/s were categorized as a "conditional" risk group who necessitated close follow-up within 6 months. The study concluded that children with TCD velocities of Z 240 cm/s through the ICA were more likely to have MRI lesions when compared with those with velocities of 200 to 239.6 cm/s. Furthermore, it confirmed findings of earlier studies that TCD velocities of Z 200 cm/s were associated with a 40% risk of a stroke within 3 years.[9] The implementation of red cell transfusions for individuals with abnormal TCD velocities has reduced the incidence of acute strokes by 90%, with a concurrent improvement in quality of life.[4]

The STOP trial provides guidance for the monitoring and preventive management of children who have TCD velocities Z 170 cm/s. However, it was not designed to assign risk, nor does it provide recommendations for those who were found to have low TCD velocities. In addition, it does not clearly define the lower limits of flow velocity that

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should be considered normal. In this case series, we describe 5 cases of children with SCD and TCD velocities of < 70 cm/s in the ACA and MCA who were found to have cerebral insults (cerebral infarction, cerebral artery abnormalities, or neurological symptoms) with accompanying MRI or MRA abnormalities.

METHODS

Between January 2005 and February 2011, we reviewed the medical records of 5 identified children with sickle cell anemia who developed acute stroke or were found to have cerebral artery stenosis on neuroimaging in the face of normal antecedent screening TCD velocities. The appropriate Institutional Review board approvals were obtained from Children's Healthcare of Atlanta. All TCDs were performed according to standard criteria established by the STOP study and by a STOP-certified ultrasonographer. Our institution performs screening TCDs yearly on every pediatric patient with homozygous SS or S-b1-thalassemia, beginning at the age of 2 years through the age of 16 years.

CASE REPORTS

Case 1

A 5-year-old female with hemoglobin SS presented acutely with right-sided weakness of the upper and lower extremities, slurred speech, and facial asymmetry. Neuroimaging (Fig. 1) reveals a large area of infarction involving the left cerebral hemisphere with stenosis involving the Left ACA and MCA. Her most recent TCD was performed 4 weeks before acute event and demonstrated flow velocity of 60 cm/s in the left ACA. After an initial exchange transfusion, the patient has been maintained on monthly red blood cell transfusions with residual right-sided hemiparesis.

Case 2

A 7-year-old female presented with hemoglobin SS and significant past medical history of recurrent acute chest syndrome (ACS) and chronic hypoxia secondary to obstructive sleep apnea. She also had a history of an abnormal sleep study with severe snoring and oxygen desaturations to 86% secondary to obstructive sleep apnea. Tonsillectomy and adenoidectomy was performed 2 years before her index TCD. At the time of her TCD she was receiving hydroxyurea (HU) for ACS prevention. Her TCD velocities were low in the left ACA (68 to 72 cm/s). Although clinically asymptomatic, brain MRA was performed and showed stenosis and diminished flow involving the left ICA and MCA, respectively (Fig. 1). Her brain MRI was normal, with no evidence of new or old cerebral infarcts. HU was discontinued and she was begun on monthly red cell transfusions for primary stroke prevention. She continues to be asymptomatic, but is scheduled for neurocognitive testing for school placement.

Case 3

An 8-year-old male presented with hemoglobin SS, low baseline hemoglobin of 6.8 g/dL, chronic hypoxia, and recurrent ACS. Conditional TCD velocities involving left MCA were detected at the age of 5 years (171to 178 cm/s) and he was monitored closely. The patient was started on HU for recurrent ACS. At the age of 7 years, his TCD velocities in the left MCA decreased significantly to 66 to 69 cm/s. One year later, neuroimaging (Fig. 1) was performed prompted by a decline in academic performance, and confirmed the presence of "silent" cerebral infarcts involving the left temporal lobe in a watershed distribution corresponding with the area of low TCD velocities. He is currently maintained on chronic red blood cell transfusions.

Case 4

A 13-year-old female presented with hemoglobin SS, who was started on HU therapy for recurrent severe ACS and pain, and had a brisk fetal hemoglobin response to 16.8%. She presented with left-sided weakness and slurred speech. Neuroimaging (Fig. 1) demonstrated bilateral cerebral infarcts in the left ACA/MCA watershed region, parieto-occipital infarcts, and significant narrowing of the left supraclinoid ICA. A month prior, she had an antecedent TCD that showed flow velocities of 58 to 70 cm/s in left ACA. She is maintained on chronic red cell transfusions and is receiving ongoing speech and physical therapy rehabilitation.

Case 5

A 15-year-old female with hemoglobin SS on HU therapy for frequent painful episodes and ACS presented with daily headaches without other neurological symptoms. Neuroimaging (Fig. 1) demonstrated microangiopathic changes and bilateral patchy foci of increased flair signal in the white matter of the deep watershed region between the ACA and MCA region bilaterally. Eight months later, she developed transient aphasia and weakness. A TCD at this point revealed flow velocities of 40 to 70 cm/s in the left MCA with inability to detect flow in the right MCA. She agreed to chronic monthly red cell transfusion. After 1 year, on therapy, she discontinued regular transfusions and refused HU therapy as well.

DISCUSSION

Screening TCD has proven to be sensitive and specific in the identification of patients with SCD who are at risk for CNS events due to occlusive intracranial vasculopathy.[7] Classification of TCD velocities as conditional or abnormal has centered on velocities > 170 cm/s, due to the strong correlation between high TCD velocity in the ACA and MCA with the risk of stroke among these patients. Narrowing of the arterial lumen may be present on angiography when the cerebral flow velocity is markedly elevated. However, significant reduction in the cerebral blood flow velocity would be expected if there is near-occlusion of corresponding vessels.

Before the STOP study, a pilot study compared the sensitivity of TCD with cerebral angiography in predicting the specific location of stenotic arterial lesions.[8] The criteria for an "abnormal" TCD study to screen for the risk of CNS events were defined as: (1) a mean velocity of Z 190 cm/s in any artery; (2) an abnormally low velocity in the MCA defined as MV < 70 cm/s and an MCA ratio (lower/higher) of r 0.5; (3) an ACA/MCA ratio of Z 1.2 on the same side; or (4) the inability to record an MCA flow velocity in the presence of a demonstrated ultrasound window.[8] The TCD screening study was determined to have a sensitivity of 90% and a specificity of 100% when compared with traditional angiography in 25 pediatric SCD patients. Interestingly, lower than normal flow or non-detectable velocities (< 70 cm/s) were described in 11 subjects, with 100% concordance with the presence of an occluded or stenotic vessels demonstrated by angiography. In addition, 5 (45%) patients with low TCD velocities had cerebral infarctions, and 3 (27%) had collateral circulation in the circle of Willis or leptomeninges. The authors concluded that the presence of cerebral infarction may be accompanied by reduced cerebral blood flow demand on the affected side, leading to lower flow velocities even though arterial narrowing may not be present.

Our study confirms the observations of Minniti et al[10] that some SCD patients with low TCD velocities also experience cerebral infarcts. Our report demonstrates that

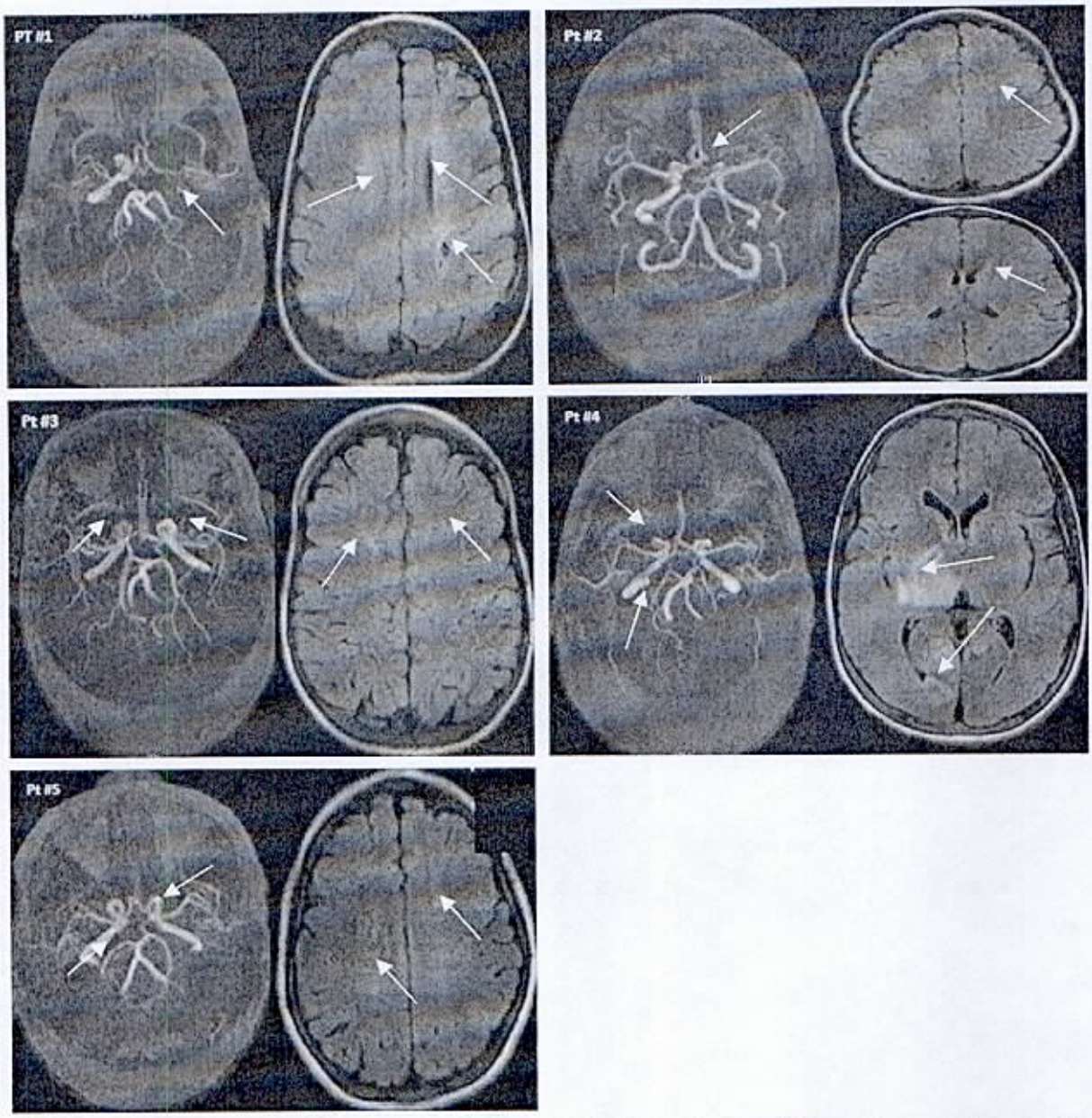

FIGURE 1. Neuroimaging (MRA and MRI) results for each subject. ↗ identifies impaired vascular flow and corresponding parenchymal views.

low TCD velocities may precede the occurrence of a stroke and may also contribute to the increased risk of stroke in children with SCD. However, currently, there are no clinical management guidelines for those SCD children with low TCD velocities (< 70 cm/s).

The recording of low TCD velocities in the presence of normal bone windows may have several explanations. Although not necessarily a complete list of possibilities, lower than normal TCD velocity may reflect complete occlusion of a previously stenotic artery, development of collaterals with resultant decrease in flow in the major artery, and/or decrease in demand due to infarction in that arterial distribution. Others have also found low velocities in the MCA associated with overt stroke. Seibert et al[11] reported 11 abnormal categories of TCD findings (both high and low flow velocities) in SCD patients with a clinical history of prior stroke, compared with controls. Kogutt et al[12] studied 14 SCD patients using these criteria and the STOP criteria and confirmed the association between a resistive index of < 40% and a lower maximum velocity in the MCA compared with the ACA with the presence of brain MRI and/or MRA findings, particularly if these abnormal findings involved either the ACA or the MCA. They concluded that although high velocities of flow suggest focal stenosis, low velocities might be due to imaging blood flow that has already passed through a more stenotic

TABLE 1. Subject's TCD Velocities, Neuroimaging Findings, and Other Characteristic Clinical Data

Case #	Age (y)/Sex	MCA Velocity	ACA Velocity	ICA Velocity	MRA/MRI Findings	Other
Case 1	4/F	L 86-149 R 130-135	(L 60)* R 125-129	L 124-136 R 77-139	Large area of abnormal diffusion in L ACA and MCA distribution with diminished flow Moyamoya	Asthma, ACS, frequent VOC
Case 2	7/F	L 103-152 R 114-137	(L68-72)* R 127-140	L 101-105 R 121-127	Mild stenosis of ICA Diminished flow of L MCA	Asthma, ACS, OSA, HU therapy, hypoxia
Case 3	8/M	(L66-69)* R 87-118	L111-112 R 76	L104-110 R 83-84	L CVA	Asthma, ACS, HU therapy, hypoxia
Case 4	13/F	R 70-96 (L 95-145)	R82-84 (L59-60)*	(R69-78)* L 110-112	Bilateral ACA/MCA watershed distribution Narrow L supraclinoid ICA Acute R PCA infarction	Asthma, ACS, frequent VOC, HU therapy
Case 5	15/F	(L 40-70)*	N/A	N/A	Deep watershed chronic microangiopathic changes	ACS, poor school performance, HU therapy, hypoxia

*Identified low TCD velocity recording.
ACA indicates anterior cerebral artery; ACS, acute chest syndrome; F, female; HU, hydroxyurea therapy; ICA, internal carotid artery; L, left; M, male; MCA, middle cerebral artery; OSA, obstructive sleep apnea; R, right.

proximal vessel and should raise concern for increased stroke risk.

CONCLUSIONS

In the 15 years since the STOP study, some of the "nuances" in interpreting TCD velocities and associated CNS risk have been lost due to the overall decrease in the rates of strokes in children with SCD. We are now seeing a new population of children with stroke associated with low TCD velocities. The 5 cases presented suggest that low TCD velocities in the ACA or MCA circulations may identify a group of children with SCD who are at significant risk for cerebrovascular disease (Table 1).

Perhaps they are at higher risk than those with velocities >200 cm/s as patients with low flow velocities on TCD may be misdiagnosed as "normal," allowing progressive cerebrovascular disease to go undetected until a symptomatic stroke event occurs. This report will serve as an important reminder that those children with SCD with low velocities need urgent recognition, with consideration of additional diagnostic studies, such as brain MRI/MRA, to rule out cerebral artery stenosis or subacute cerebral infarcts. This series is limited as it cannot answer the question of how often low TCD velocities correlate with severe cerebrovascular disease on angiography or the magnitude of the additional stroke risk for each patient. However, it may be prudent to broaden TCD stroke risk criteria, for clinical practice, to include measurement of MCA, ACA, and ICA flow velocities, including their depth. If the velocities are lower than normal (< 70 cm/s), health care providers should institute the same recommendations for those identified as having high TCD velocities to hasten the detection of cerebral artery stenosis or subacute cerebral infarctions.

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