

Extracranial internal carotid arterial disease in children with sickle cell anemia

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ABSTRACT

Background

Sickle cell anemia is one of the commonest causes of stroke in children. It is usually, but not always, associated with intracranial vasculopathy. We have assessed the value of ultrasound screening for extracranial internal carotid artery disease.

Design and Methods

Using Doppler ultrasound scanning, we assessed peak systolic blood velocity, tortuosity and stenosis in the extracranial internal carotid arteries of 236 children with sickle cell anemia. Seventeen of the children had previously had a stroke. All measurements were performed as part of routine clinical care.

Results

The median extracranial internal carotid artery velocity was 148cm/s (5th centile 84, 95th centile 236). Higher velocities were significantly correlated with younger age, higher white blood cell counts and higher rates of hemolysis. Fourteen (5.9%) had tortuous extracranial internal carotid arteries and 13 (5.4%) had stenosis or occlusion. None of the children with tortuous vessels but 8 of those with stenosis had previously had a stroke; the presence of stenosis was strongly associated with overt clinical stroke (OR 35.9, 95% C.I. 9.77-132, $P < 0.001$). In 6 children, extracranial stenosis was part of extensive intracranial vasculopathy, but in 2 there was no evidence of intracranial disease. Stenosis seemed to be more common in older children.

Conclusions

Extracranial internal carotid artery stenosis is strongly associated with stroke in children with sickle cell anemia, and may explain some cases of stroke without overt intracranial vasculopathy. Doppler ultrasound scanning of extracranial internal carotid arteries is non-invasive and fairly quick to perform and may identify children at increased risk of stroke who would otherwise be missed. The value of extracranial internal carotid artery scanning should be studied prospectively.

Key words: sickle cell anemia, internal carotid artery, Doppler ultrasound scanning.

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Introduction

Sickle cell anemia (SCA) results from the coinheritance of the β^s allele from both parents (HbSS). Cerebrovascular disease is an important complication in children with this condition. In sickle cell anemia, the peak incidence of overt stroke is 1.02 per 100 patient years between the ages of two and five years.¹ Although children often make a good motor recovery, significant cognitive impairment is almost inevitable.² Most cases of stroke in children with sickle cell anemia are associated with narrowing of large intracranial arteries. Transcranial Doppler (TCD) scanning demonstrated that high blood velocities in the middle cerebral artery (MCA) were strongly associated with increased risk of stroke.³ A subsequent randomized controlled trial, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, showed that regular blood transfusions reduced the risk of stroke by about 90% in children with increased intracranial blood velocities.⁴ It is not fully understood why this vasculopathy occurs, although endothelial damage related to anemia, hypoxia, hemolysis, abnormal rheology and changes in red cell adhesion is increasingly implicated.⁵ Increased blood velocities identified by TCD scanning typically precede any apparent stenoses on angiography, and it has been suggested that failure to regulate blood flow to the brain is one of the primary problems, with vasculopathy developing secondary to this.⁶ In addition to overt stroke, up to 20% children with sickle cell anemia develop clinically silent, small brain infarcts detected on MRI.⁷

The significance of extracranial internal carotid artery (ICA) disease in children with sickle cell anemia is not known, although abnormalities are well described in cerebrovascular disease in adults without sickle cell anemia.⁸ Some strokes in children with sickle cell anemia occur without detectable intracranial vasculopathy;⁵ for example, a study using angiography found that 4 out of 14 children with sickle cell anemia and strokes had normal intracranial angiograms.⁹ Extracranial internal carotid artery abnormalities may explain some of these strokes in children without obvious intracranial vasculopathy. In theory, extracranial internal carotid artery stenosis may either cause cerebral ischemia directly or mask intracranial disease by normalizing TCD measurements despite intracerebral vasculopathy. For the last six years, children with sickle cell anemia at our hospital have undergone annual TCD scanning, which has also included Doppler ultrasound assessment of the extracranial internal carotid arteries. We have reviewed these data to assess whether it is potentially useful to screen for extracranial internal carotid artery abnormalities.

Design and Methods

Patients

The data were collected as part of an audit of TCD scanning at King's College Hospital. Since 2004, all children at King's College Hospital with sickle cell anemia have been offered annual TCD scans between the ages of two and 16 years. Routine laboratory tests are also performed in the steady-state either on the same day as the TCD scan or at the next clinic appointment. In patients on regular transfusions, laboratory and TCD readings were used from before the start of transfusions. In 6 children, all with strokes, measurements were only available after starting

transfusions: in these cases TCD velocities were analyzed but laboratory data were not included. Some children also had MRI and MR angiography of the head. The diagnosis of sickle cell anemia was confirmed in all cases by hemoglobin analysis, family studies and DNA analysis where necessary.

Doppler measurements

Scans were performed in the Vascular Laboratory at King's College Hospital using TCD imaging. Color duplex scanners (Siemens Sequoia and Aspen, Philips iU22) were used with 2 MHz phased array transducers to record time averaged maximum mean velocity (TAMMV) for the middle cerebral artery, anterior cerebral artery, bifurcation, distal internal carotid artery and posterior cerebral artery on both sides. Previous evaluation of TCD imaging *versus* TCD scanning had shown that both methods gave similar results when used according to strict, established protocols.¹⁰ Extracranial carotid and vertebral arteries were routinely scanned during the examination. Although this did not form part of the scanning protocol in the STOP trial when non-imaging TCD was used, it has been used routinely in our center to provide additional information on the cerebral circulation. Vascular Laboratory staff have extensive experience of carotid scanning in adults and the inclusion of this typically added less than five minutes to the examination. The extracranial arteries were scanned with high frequency linear arrays (typically from 6-9 MHz). Angle corrected peak systolic velocities (PSVs) were recorded in the left and right internal carotid arteries and the vessel assessed for stenosis, abnormally low or absent flow, or tortuosity leading to locally increased velocities.

Empirical definitions of stenosis and tortuosity were used, based on our experience of Doppler ultrasound scanning in this population. Stenosis was reported if there was a 2-fold increase in PSV at the stenosis and the absolute velocity was 300cm/s or more, or if the vessel was occluded with no flow. Low velocities were reported if there were velocities less than 60 cm/s and a greater than 50% discrepancy between R and L ICA PSVs. Curvature in the distal extracranial internal carotid artery is a common finding; tortuosity was reported if there was evidence of significant angulation ($> 120^\circ$) with changes in PSV through the curvature.

Statistical analysis

The links between extracranial internal carotid artery measurements, laboratory and clinical parameters were assessed using the statistical programme SPSS 17.0 (Chicago, IL, USA). The extracranial internal carotid artery PSV velocities were skewed (Kolmogorov-Smirnov test) but normalized by logarithmic transformation; therefore, velocities were either analyzed non-parametrically or logarithmically transformed to produce normally distributed data. Results with $P < 0.05$ were considered statistically significant. Analyses included Pearson's correlation coefficients, linear and logistic regression.

Results

Peak systolic velocities in extracranial internal carotid arteries

Extracranial internal carotid artery velocities were measured in 236 children with sickle cell anemia. Twenty-seven children had either stenosis or tortuosity (Figure 1). In normal vessels, there were no significant differences between the left and right sided velocities (Table 1) and the highest value was used for further analysis; the

median PSV velocity was 148cm/s (5th centile 84, 95th centile 236).

Determinants of extracranial ICA velocities in arteries without stenosis or tortuosity

Pearson's correlation coefficients were calculated for logarithmically transformed extracranial internal carotid artery PSVs against factors known to influence intracranial velocities or risk of cerebrovascular disease: age, hemoglobin, white cell count, AST, LDH, TAMMV (highest intracranial blood velocity on TCD), MCH (marker of α thalassemia status), reticulocyte count and HbF %. There was significant correlation ($P<0.05$) between extracranial internal carotid artery PSV and age, lactate dehydrogenase (LDH), white cell count, reticulocyte count, AST and TAMMV (Table 2). Linear regression was then performed against significant factors from univariate analysis, using LDH as the marker of hemolysis, and only age ($P<0.001$) and LDH ($P=0.014$) remained significant.

Stenosis and tortuosity of the extracranial ICA

Two hundred and nine children with sickle cell anemia had normal extracranial internal carotid arteries, 14 (5.9%) had tortuous vessels and 13 (5.4%) had stenosis or occlusion

Table 1. PSVs in the left and right extracranial internal carotid arteries, and maximal TCD velocities in 209 children with sickle cell anemia and no evidence of abnormalities of the extracranial ICA.

	Median	5 th centile	95 th centile
Right extracranial ICA (cm/s)	125	73	207
Left extracranial ICA (cm/s)	134	80	223
TAMMV (cm/s)	124	89	192

TAMMV is the time-averaged mean of the maximum velocity and the highest figure from the middle cerebral artery, distal internal carotid artery and bifurcation is used in the analysis (relevant vessels from the STOP study).⁴

(Figure 1). In 4 of the 13 with stenotic/occluded vessels, there was no measurable blood velocity due to occlusion. The PSV in stenotic vessels (excluding occluded vessels with no flow) was not significantly higher than that in tortuous vessels, although it included some low readings due to severe stenosis; 6 of those with stenotic vessels were being transfused at the time of the internal carotid artery measurements which may have lowered the values (Figure 2).

Cerebrovascular disease and extracranial internal carotid artery

Seventeen children with sickle cell anemia had suffered clinical stroke, confirmed in all cases by MRI imaging of the brain. Eight of these with stroke had stenosis/occlusion of the extracranial internal carotid artery. The presence of extracranial internal carotid artery stenosis/occlusion was associated with an increased risk of stroke (logis-

Table 2. Correlation of maximum PSV in the extracranial ICA (excluding stenosis and tortuosity) with other clinical and laboratory parameters.

	Number	R	P
Age (years)	209	-0.359	<0.001
Hb (g/dL)	209	-0.102	0.144
Wbc (10 ⁹ /L)	209	0.226	0.001
Retic (10 ⁹ /L)	207	0.137	0.049
MCH (pg)	209	0.111	0.110
HbF (%)	189	0.100	0.169
LDH (IU/l)	198	0.285	<0.001
AST (IU/l)	209	0.145	0.037
TAMMV (cm/s)	212	0.153	0.026

The PSVs were not normally distributed, and correlations were performed against the natural logarithm of the velocity.

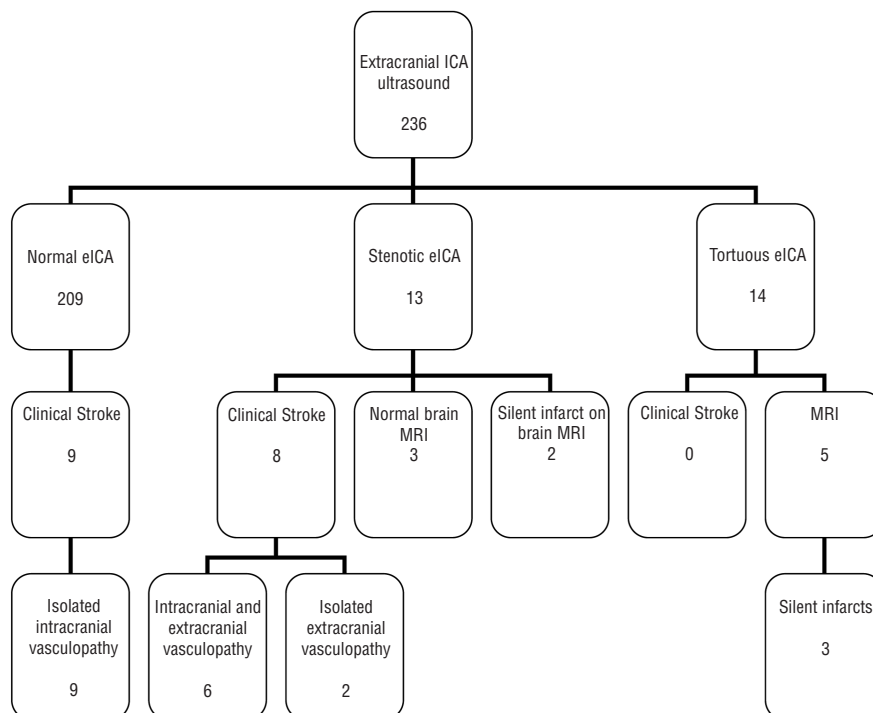


Figure 1. Flow diagram showing numbers of children with stroke and different extracranial ICA ultrasound results. (eICA: extracranial internal carotid artery).

tic regression analysis, OR 35.9, 95% C.I. 9.77-132, $P < 0.001$). Five children without overt stroke but with stenosis/occlusion of the extracranial internal carotid artery underwent MRI/MRA of the brain; 2 of these had silent infarcts (Figure 1; Table 3).

In 6 of the 8 children with stroke and extracranial internal carotid artery stenosis, there were also extensive intracranial arterial abnormalities, shown on MRA and TCD. These were older children who suffered strokes before the introduction of routine TCD and had already developed marked cerebrovascular damage before starting blood transfusion. Importantly, in 2 children, extracranial internal carotid artery stenosis preceded stroke in the absence of overt intracranial vasculopathy (patients 7 and 9 in Table 3).

Patient # 7

A boy with sickle cell anemia had been followed at our hospital since early childhood and had suffered few problems related to his condition. Age 11, his TCD scan was normal with a TAMMV of 87cm/s in the left MCA and all readings in the normal range. However, Doppler ultrasonography at that time showed a tight stenosis of the left extracranial internal carotid artery, 2cm from the bifurcation, with a PSV greater than 400cm/s; the right internal carotid artery was normal. A repeat scan six months later showed essentially the same result, although the TAMMV had increased to 120cm/s in the left MCA. A brain MRI/MRA scan at that time showed no major abnormality. Age 12, he presented with acute leg pain and complained of blurred vision; ophthalmological examination showed appearances of bilateral ciliary branch retinal artery occlusion, and a marked reduction in his visual acuity. Urgent exchange transfusion was performed. His TCD results were unchanged but with increased PSV in the left internal carotid artery of 590cm/s. Brain MRI/MRA showed two new acute infarcts in the right caudate and

frontal lobes which were clinically silent. CT angiography confirmed the bilateral extracranial internal carotid artery problems. Echocardiography showed a patent foramen ovale but no embolic source was identified. A thrombophilia screen was normal. Four weeks later, Doppler ultrasound showed stenosis of both extracranial internal carotid arteries a few centimeters from the bifurcation. Since this event, he has been transfused regularly for the last three years, maintaining his HbS at less than 30%. His brain MRI/MRA shows minor narrowing of the distal internal carotid artery on the right and of the medial adjacent right A1 segment, with appearances unchanged over several years. TCDs and PSVs have also remained unchanged; he has had no further clinical problems but remains severely visually impaired.

Patient # 9

Age 14, this girl had routine TCD imaging which showed normal intracranial velocities, with a peak velocity of 118cm/s at the intracranial bifurcation of the left internal carotid artery. Doppler ultrasound showed stenosis of the left extracranial internal carotid artery with a PSV of 334cm/s; the right extracranial internal carotid artery was normal. She had few previous complications of sickle cell anemia and no neurological symptoms. Because of the normal intracranial results, TCD imaging was not repeated. Age 17, she presented with sudden onset weakness of her right arm and dysphasia. There was no antecedent illness. An urgent exchange transfusion was performed. Brain CT and MRI/MRA showed infarction of the left cerebral hemisphere, particularly involving the frontal lobe, with no flow in the left internal carotid artery. TCD scanning showed low readings, with velocities of 63cm/s in the left MCA and 81cm/s in the right MCA; stenosis of the left extracranial internal carotid artery was again noted. She made a good motor recovery and has continued on regular exchange

Table 3. Clinical details of patients found to have stenotic extracranial internal carotid arteries on ultrasound screening.

	Age (years) at TCD	Sex	Stroke	Age at stroke	Extracranial ICA PSV (cm/s)		TAMMV (cm/s)	Brain MRI/MRA	Other features
					Right	Left			
1	8	m	no	-	99	380	147	Normal	
2	9	m	no	-	450	224	150	Not done	
3	10	f	no	-	180	400	131	Normal	
4	13	m	no	-	69	370	110	4-5 small infarcts	
5	10	f	no	-	23	0	168	Bilateral small infarcts; right dICA stenosis	
6	16	m	yes	5	0	0	0	Bilateral large infarcts; left dICA stenosis	
7	12	m	yes	12	254	420	80	Right frontal lobe infarction	Bilateral retinal artery occlusion
8	18	f	yes	10	0	0	128	Right hemisphere infarction	
9	17	f	yes	17	104	334	118	Left hemisphere infarction	
10	16	f	yes	14	110	42	114	Left frontal lobe infarction	Stroke followed ACS
11	16	m	yes	13	0	400	73	Right parietal infarction	Moyamoya and inadequate TCDs
12	10	m	yes	1.5	0	0	95	Right frontal lobe infarction	Moyamoya; inadequate TCDs
13	10	m	yes	1.5	0	0	58	Right frontoparietal lobe infarction	Stenosis of right MCA

ACS : acute chest syndrome. DICA: distal, intracranial carotid artery. MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

transfusions with no further neurological complications.

None of the 14 children with tortuous vessels suffered a clinical stroke. Five underwent brain MRI/MRA scanning. Three of the scans showed two or more silent infarcts in the deep/superficial watershed region, with the other two scans being normal.

Determinants of stenosis and tortuosity

Binary logistic regression analysis was used to assess which of the following factors were associated with stenosis of the extracranial internal carotid artery: sex, age, LDH, G6PD deficiency, hemoglobin, MCH, white cell count, reticulocyte count, creatinine and HbF%. The only significant associations were with older age ($P=0.003$, OR 0.77, 95% CI 0.645-0.916), lower hemoglobin ($P=0.044$, OR 1.86, 95% CI 1.018-3.399) and higher reticulocyte count ($P=0.045$, OR 0.995, 95% CI 0.990-1.000). All these maintained their significance when combined in multiple regression. LDH was not associated with stenosis.

Similarly binary logistic regression was used to assess the association of the same factors with tortuosity of the extracranial internal carotid artery. Tortuosity was significantly associated only with younger age ($P=0.014$, OR 1.195, 95% CI 1.037-1.377) and lower creatinine ($P=0.003$, OR 1.152, 95% CI 1.050-1.264). Creatinine increases significantly with age and it is likely that this is the origin of its association with tortuosity.

Discussion

Routine transcranial Doppler studies are accepted as important in the care of children with sickle cell anemia, identifying those at increased risk of preventable stroke. Regular blood transfusion in children found to have abnormal TCDs reduces the risk of stroke by 90%⁴ and this approach has been linked to the falling incidence of overt cerebrovascular disease in this population.¹¹ However, TCD screening has limitations, including the failure to identify all children at increased risk of stroke.⁹ Some strokes may be missed due to difficulties assessing the distal extracranial, petrous, and cavernous internal carotid artery using the STOP protocol.

The significance of extracranial carotid disease in children with sickle cell anemia has not been established, although it is an important cause of stroke in the non-sickle adult population.³ Several earlier studies using cerebral angiography found little evidence of extracranial vasculopathy.^{9,12} However, there is evidence that some strokes are of extracranial origin. Gorman *et al.* evaluated the use of submandibular TCD, and identified 4 out of 131 children with abnormalities of the internal carotid artery not detectable with standard TCD through the temporal window.¹³ A recent study measured extracranial internal carotid artery velocities in 56 children with sickle cell anemia and found mean PSVs of 113cm/s and 121cm/s in the left and right extracranial internal carotid artery, respectively, similar to our findings; this study did not include any children with strokes or internal carotid artery abnormalities.¹⁴ Four patients with sickle cell disease and extracranial internal carotid artery stenosis were previously reported by Bhattacharya *et al.*; all stenoses were detected by MRA which was performed because of acute stroke in 3 cases and raised TCD velocities in one.¹⁵ There is also a report of a 19-year old man with sickle cell anemia who presented

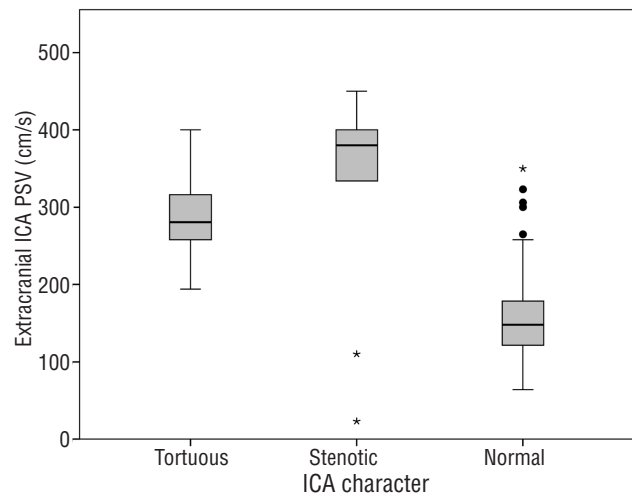


Figure 2. Box plots of PSVs in children with SCA and normal, tortuous and stenotic extracranial ICAs. Occluded vessels are excluded from the analysis. Dots are >1 standard deviation and stars are more than 2 standard deviations above the mean.

with a stroke due to stenoses of extracranial internal carotid artery and vertebral arteries.¹⁶ Increased extracranial internal carotid artery velocities have also been linked to exposure to particulate air pollution in children with sickle cell disease.¹⁷

In this study, we found that extracranial internal carotid artery PSVs were significantly higher in younger children with sickle cell anemia, and also in those with higher rates of hemolysis, as shown by LDH, AST and reticulocyte count (Table 2); in children over the age of two years, age and hemolytic rate show a similar relationship with intracranial velocities measured by TCD, suggesting that to some extent the same processes might be contributing both to intracranial and extracranial vasculopathy.¹⁸ Interestingly, in those under the age of two, intracranial TCD velocities seem to increase with age, suggesting that peak velocities occur at about the age of two years.¹⁹

In our study, PSV in the extracranial internal carotid arteries were markedly elevated for two reasons: either because the extracranial internal carotid artery was tortuous or because it was significantly narrowed. None of those with tortuous internal carotid arteries suffered an overt stroke or had abnormal TCDs, but 3 out of 5 had silent infarcts on brain MRI, compared to the reported prevalence of about 20% in children with sickle cell anemia;⁵ the significance of this is difficult to determine because of the small numbers involved although it seems appropriate that children with tortuous extracranial internal carotid arteries should have full neurological and neuropsychometric assessment. Although tortuosity of the internal carotid artery has been studied in older adults, relatively little is known about its occurrence and significance in childhood; it is thought that the tortuosity results from congenital elongation of the internal carotid artery.²⁰

In contrast, stenosis/occlusion of the extracranial internal carotid artery was strongly associated with intracranial vasculopathy and stroke (OR 35.9, 95% C.I. 9.77-132). This was found mostly in older children who also had marked intracranial abnormalities, and presented with overt stroke

before routine TCD screening was introduced. However, 2 children in our series suffered overt strokes with no detectable intracranial disease. It is not clear whether strokes due to extracranial disease are preventable by regular blood transfusions. Stenosis was significantly associated with older age and lower hemoglobin. This may be partly due to a cohort effect involving older children who developed florid vasculopathy before routine TCDs were introduced; however, both children who had strokes with isolated extracranial disease were also over the age of 12 years. It seems possible that the pathological processes causing stenosis of the extracranial internal carotid artery are different in some ways to those causing stroke due to intracranial disease; for example, the latter is characterized by a peak incidence at 2-5 years of age and a strong association with LDH levels.^{1,18}

Extracranial assessment using duplex ultrasound takes five to ten minutes and in general is well tolerated. It is acknowledged that when using a duplex scanner with a linear or curvilinear array to image the internal carotid artery, only the proximal 4-5 cm is typically imaged, depending on the level of the bifurcation. For the petrous portion of the internal carotid artery, a phased array TCD transducer could be used with a submandibular approach to detect raised velocities. Duplex scanning permits angle-correction of velocities where the carotid arteries are often near parallel to the skin. In contrast, non-imaging TCD methods rely on uncorrected velocities since the beam/vessel cannot be determined. When using non-imaging TCD with a submandibular approach, Gorman *et al.* used a threshold of uncorrected TAMMV of 160 cm/s to indicate a stenosis in the extracranial internal carotid artery.¹⁵ In this study, we used angle corrected peak systolic velocity and changes in PSV to indicate stenosis. There are currently no established protocols.

Our data suggest that Doppler ultrasound of the extracranial internal carotid artery is a potentially useful screening

tool to identify children at increased risk of stroke who may not be detected using routine TCD. It is non-invasive, fairly quick and cheap to perform, and does not require any anesthesia or sedation. Extracranial analysis should exclude stenosis of the internal carotid artery, look for tortuosity and measure PSV. If stenosis is detected, full brain and neck imaging should be organized. In some cases extracranial internal carotid artery disease seems to be an extension of overt intracranial vasculopathy, although it can also occur in isolation. MRI/MRA of children with sickle cell anemia and neurological problems should routinely include the neck to look for extracranial vasculopathy. Preliminary data from our study suggest that extracranial internal carotid artery stenosis affects older children and is not obviously related to increased hemolytic rates. Further prospective studies may elucidate the value of screening for internal carotid artery stenosis, and could potentially assess the role of interventions such as hydroxycarbamide and blood transfusion in stroke prevention in these circumstances.

Authorship and Disclosures

CRD performed TCD and Doppler studies, analyzed the data and helped write the manuscript; DG performed TCD and Doppler studies, analyzed the data and contributed to the manuscript; JB collected and analyzed data, and contributed to the manuscript; KREP collected clinical data, contributed to analysis and the manuscript; SEH helped collect clinical data and contributed to the manuscript; NS and JJ contributed radiological data, studies and discussions, and contributed to the manuscript; SLT collected and analyzed clinical data, and helped write the manuscript; DCR devised the study, collected and analyzed data, and wrote the manuscript. None of the authors have any conflict of interests to declare.

References

- Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cooperative study of sickle cell disease: cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91(1):288-94.
- Hariman LM, Griffith ER, Hurtig AL, Keehn MT. Functional outcomes of children with sickle-cell disease affected by stroke. *Arch Phys Med Rehabil*. 1991;72(7):498-502.
- Adams RJ, McKie VC, Nichols FT, Carl E, Zhang DL, McKie K, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. *N Engl J Med*. 1992;326(9):605-10.
- Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339(1):5-11.
- Switzer JA, Hess DC, Nichols FT, Adams RJ. Pathophysiology and treatment of stroke in sickle-cell disease: present and future. *Lancet Neurology*. 2006;5(6):501-12.
- Prohovnik I, Hurler-Jensen A, Adams R, De Vivo D, Pavlakis SG. Hemodynamic etiology of elevated flow velocity and stroke in sickle-cell disease. *J Cereb Blood Flow Metab*. 2009;29(4):803-10.
- Bernaudin F, Verlhac S, Fréard F, Roudot-Thoraval F, Benkerrou M, Thuret I, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. *J Child Neurol*. 2000;15(5):333-43.
- Goldstein LB. Extracranial carotid artery stenosis. *Stroke*. 2003;34(11):2767-73.
- Gerald B, Sebes JI, Langston JW. Cerebral infarction secondary to sickle cell disease: arteriographic findings. *AJR Am J Roentgenol*. 1980;134(6):1209-12.
- Neish AS, Blews DE, Simms CA, Merritt MA, Spinks AJ. Screening for stroke in sickle cell anaemia: comparison of transcranial Doppler imaging and nonimaging US techniques. *Radiology*. 2002;222(3):709-14.
- Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. *Blood*. 2004;104(2):336-9.
- Russell MO, Goldberg HI, Hodson A, Kim HC, Halus J, Reivich M, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. *Blood*. 1984;63(1):162-9.
- Gorman MJ, Nyström K, Carbonella J, Pearson H. Submandibular TCD approach detects post-bulb ICA stenosis in children with sickle cell anemia. *Neurology*. 2009;73(5):362-5.
- Pawlak MA, Krejza J, Rudzinski W, Kwiatkowski JL, Ichord R, Jawad AE, et al. Sickle cell disease: ratio of blood flow of intracranial to extracranial cerebral arteries – initial experience. *Radiology*. 2009;251(2):525-34.
- Bhattacharya A, Newell H, Evanson J, Kirkham F, Telfer P. Extracranial carotid artery occlusion in children with sickle cell disease. *Br J Haematol*. 2007;137:73 (Supplement 1).
- Calviere L, Viguier A, Guidolin B, Tall P, Larue V. Cervical artery stenoses in sickle cell disease. *Eur Neurol*. 2007;58(2):120-1.
- Mittal H, Roberts L, Fuller GW, O'Driscoll S, Dick MC, Height SE, et al. The effects of air quality on haematological and clinical parameters in children with sickle cell anaemia. *Ann Hematol*. 2008;88(6):529-33.
- O'Driscoll S, Height SE, Dick MC, Rees DC. Serum lactate dehydrogenase as a biomarker in children with sickle cell disease. *Br J Haematol*. 2008;140(2):206-9.
- Pavlakis SG, Rees RC, Huang X, Brown RC, Casella JF, Iyer RV, et al. Transcranial doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the BABY HUG trial. *Paediatr Blood Cancer* 2010; 54(2):256-9.
- Leipzig TJ, Dohrmann GJ. The tortuous or kinked carotid artery: pathogenesis and clinical considerations. *Surg Neurol*. 1986;25(5):478-86.