#  Transcranial Doppler and Magnetic Resonance in Tanzanian children with sickle cell disease

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ABSTRACT

**Background and Purpose:** We determined prevalences of neurological complications, vascular abnormality and infarction in Tanzanian children with Sickle Cell Disease (SCD).

**Methods:** Children with SCD were consecutively enrolled for Transcranial Doppler (TCD); those with slightly elevated (>150cm/s), low (<50cm/s) or absent cerebral blood flow velocity (CBFv) were invited for brain MRI and MRA.

**Results:** Of 200 children (median age 9; range 6-13 years; 105 (52.5%) boys), 21 (11%) and 15 (8%) had previous seizures and unilateral weakness respectively. Twenty-eight (14%) had elevated and 39 (20%) had low/absent CBFv, all associated with lower haemoglobin level, but not higher indirect bilirubin level. On multivariable analysis CBFv>150cm/s was associated with frequent painful crises and low haemoglobin level. Absent/low CBFv was associated with low hemoglobin level and history of unilateral weakness. In 49/67 children with low/absent/elevated TCD undergoing MRI, 43% had infarction while 24/48 (50%) MRAs were abnormal. One had hemorrhagic infarction; none had microbleeds. Posterior circulation infarcts occurred in 14%. Of 11 children with previous seizure undergoing MRI, 10 (91%) had infarction (5 silent) compared with 11/38 (29%) of the remainder (p=0.003). Of 7 children with clinical stroke, 2 had recurrent stroke and 3 died; 4/5 had absent CBFv. Of 193 without stroke, one died and one had a stroke; both had absent CBFv.

**Conclusions**: In one third of Tanzanian children with SCD, CBFv is outside the normal range, associated with frequent painful crises and low hemoglobin level but not hemolysis. Half have abnormal MRA. African children with SCD should be evaluated with TCD; those with low/absent/elevated CBFv should undergo MRI/MRA.

# BACKGROUND

Although there are few data available from sub-Saharan Africa, stroke and silent cerebral infarcts (SCI) detected by magnetic resonance imaging (MRI) are common in untreated sickle cell disease (SCD) elsewhere.1,2 Arterial ischemic stroke (AIS) in the territories of the middle and anterior cerebral arteries and their borderzones is typical.3,4 Posterior reversible encephalopathy syndrome has been reported5 and is not always reversible although residual occipital or cerebellar infarction is rarely reported in cross-sectional studies. Hemorrhagic stroke (HS) occurs in the context of hypertension6 and aneurysm formation,7 but the prevalence of microbleeds remains uncertain.

Magnetic resonance angiography (MRA) detects intracranial arteriopathy.8 Stenosis or occlusion of the intracranial arteries may be detected with transcranial Doppler (TCD), measuring cerebral blood flow velocity (CBFv); abnormal ICA/MCA CBFv (>200 cm/sec) occurs in 2.8 to 10% of children9,10 and predicts clinical stroke.11 Low ACA and MCA CBFv may also predict stroke and SCI12 but there is an overlap with those with ‘inadequate’ TCD;10 there are few data comparing TCD with MRA in this group.

Data from Africa on the prevalence in SCD of TCD outside the normal range (50-149 cm/sec)13 are scarce although conditional (>170 and ≤200 cm/s) and abnormal CBFv (>200cm/s) have been reported in 4% and 7% respectively;14 there appears to be considerable variability. Of 105 Kenyan children only 3% had conditional and none had abnormal CBFv.15 A Nigerian study of 145 children found that 5% had CBFv >200cm/s and 20% had CBFv >150cm/s16 while in Cameroon, 22% had abnormal MCA CBFv.17 MRI was not performed in any of these studies.

We conducted a cross-sectional study to determine the prevalence of elevated/absent/low CBFv in Tanzanian children with SCD and imaged those with abnormal TCD to determine whether there was an association between elevated or low CBFv and silent infarction or microbleeds in the anterior or posterior circulation on MRI or cerebrovascular disease on MRA.

# METHODS

Ethical clearance and permission to conduct this study was obtained from the Senate Research and Publications Committee of Muhimbili University of Health and Allied Sciences (MUHAS) and Muhimbili National Hospital. All parents/guardians of the children gave written consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

The inclusion criteria for the study were: children with SCD (confirmed with hemoglobin electrophoresis; no HbSC in this cohort) aged between 6 and 13 years enrolled in the Muhimbili Sickle Cohort18 who consecutively attended the SCD outpatient clinic of the Muhimbili National Hospital in Dar-es-Salaam, Tanzania from June 2010 to March 2011. Penicillin was prescribed and use of insecticide treated nets was emphasized to prevent malaria infections but chloroquine and hydroxyurea were not prescribed and no child was on a chronic blood transfusion regime. A structured questionnaire was used to determine demographic characteristics and clinical events and all children had a complete general and neurological examination. We used a recall period of two years for admissions and blood transfusions and one year for painful crises to minimize bias. Blood pressure, oxygen saturation and hemoglobin were measured on the day of the TCD examination when the child was well.

The basal cranial arteries (MCA, ACA, ICA) were insonated with a 2 MHz probe and non-imaging TCD (Viasyss Health Care). All examinations were performed by one author (EK), with CN checking the recordings outside the normal range. The CBFv in the MCA/ICA was classified as follows: low (CBFv <50cm/s), normal (50–149 cm/s),13 slightly elevated (150–169cm/s), conditional (170–199cm/s) and abnormal (CBFv≥200 cm/s).11 Children who had a TCD exam outside the normal range (no signal, CBFv <50cm/s or CBFv >150cm/s) were scheduled to have brain MRI/MRA brain (supplementary Figure I).

MRI scanning was performed on a Phillips Achieva 1.5 Tesla MRI scanner, using an 8-channel head coil, at a median duration of 5 months (range 3-7 months) after the TCD examination. The scanning protocol included: T1-weighted spin echo (TR/TE/flip angle = 596ms/15ms/69°), T2-weighted fast spin echo (TR/TE/flip angle=4424ms/100ms/90°), T2\* weighted gradient echo (T2\*GE; TR/TE/flip angle=700ms/23ms/18°), fluid-attenuated inversion recovery (FLAIR; TR/TE/TI/flip angle=11000ms/140ms/ 2800ms/90°), diffusion weighted imaging (DWI; b=0, 500, 1000 s/mm2) and susceptibility weighted imaging (SWI; TR/TE/flip angle=35ms/50ms/15°), all acquired in the axial plane, and 3D time-of-flight MR angiography (MRA; TR/TE/flip angle=35ms/5ms/20° and 0.7mm slice thickness).

T2-weighted, FLAIR and DWI images were used to determine the presence of infarcts and atrophy. Images were reviewed independently by three neuro-radiologists (DS, SB, TC); where there was disagreement, the scans were reviewed by DS and consensus was achieved when 2 neuro-radiologists agreed.

SCI were defined as one or more focal MRI signal abnormalities of at least 3 mm in one dimension visible in two views on FLAIR/T2-weighted images in the absence of a focal neurological deficit.2 T2\*GE and SWI were inspected for hemorrhage. MRA maximum intensity projections (MIPs) were used to determine the presence of intracranial artery abnormality using a previously reported grading system.18

Children were followed until censoring at stroke or death or 31st March 2014.

The data were analysed in SPSS v22. Skewed data were summarized with median and interquartile range. Association between variables was determined using Chi-square test and Fisher’s exact tests. Univariable and multivariable logistic regression were used to determine clinical predictors of elevated/absent/low CBFv. Mann-Whitney and Kruskal-Wallis tests were used to compare the distribution of variables between two and more than two variables respectively. Inter-observer variability between the neuro-radiologists was analysed using the method of Fleiss with the web-based programme of Geertzen (<https://mlnl.net/jg/software/ira/>). A P-value <0.05 was considered as statistically significant.

# RESULTS

From June 2010 to March 2011, 200 consecutive children (median age 9; range 6-13 years; 105 (52.5%) boys) meeting the inclusion criteria were enrolled. Fifteen (8%) had a history of unilateral weakness and 21 (11%) had a history of seizures (Table 1). TCD examination was outside the normal range in 67 (34%) children, of whom 28 (14%) had elevated CBFv>150cm/s and 39 (20%) had CBFv<50cm/s (n=10) or absent signal (n=29) (Table 1). Sixteen had slightly elevated CBFV (150-169 cm/s), 11 (5.5%) had conditional CBFv (170-199 cm/s) but only one, who had already had a clinical stroke, had an abnormal high CBFv (>200cm/s). Elevated CBFv was more common in children <12 years old. Hemoglobin was lower in those with low/absent and elevated CBFv, but there was no association with indirect bilirubin as a marker of hemolysis (Table 1).

**Risk factors for low CBFv or absent MCA signal**

Compared to those with normal velocities, children with absent/low CBFv or MCA signal were more likely to have a history of focal weakness and seizures (Table 2). In multivariable analysis low hemoglobin and history of focal weakness were independent predictors of absent/low CBFv (Table 2).

**Risk factors for elevated CBFv**

Compared with children with normal CBFv, those with elevated CBFv>150cm/s in the MCA were more likely to have a history of seizures but not focal weakness. They also had more frequent painful crises in the previous 2 years compared to those with normal CBFv (Table 1). In multivariable analysis low hemoglobin and frequent painful crises were independent predictors of elevated CBFv (Table 2).

**Patients who had MRI scans**

Of the 67 children with TCD examinations outside the normal range, 18 (27%) did not return for MRI (supplementary Figure I). There was no difference in the demographic or clinical features of those children who did not return for the scans compared to those who did (Supplementary Table I). For documentation of infarction among the three observers, kappa was 0.629 (good agreement); while for determination of normal MRA and definite MRA abnormality, kappa was 0.849 (excellent agreement).

Of the 49 children who had MRI, 21 (43%) had abnormal scans (Figures 1 and 2; Supplementary figures II and III), i.e. at least 21/200 (11%) of the overall sample. Most infarcts occurred in the anterior circulation, in deep white matter and basal ganglia (Table 3) but 7 (14%) had occipital and/or cerebellar infarcts or atrophy (Table 3, Figure 1). All but one had large vessel disease, mostly involving the terminal cavernous and carotid arteries; in two, the posterior circulation infarction was associated with generalised disease. Seven patients had had clinical stroke (14% of those undergoing MRI, 4% of the total and 70% of those with a history of focal weakness). SCI occurred in 14 (29% of those undergoing MRI or at least 7% of the overall sample). SCI were present in 8/21 (38%) of the children who had CBFv>150 cm/s, and in 6/24 (25%) of the children with absent signal, but there were no SCI in the 4 with low CBFv. One patient with slightly elevated CBFv had hemorrhage associated with basal ganglia infarction (Figure 2) but no microbleeds were detected on T2\*GE or SWI.

Twenty-four patients with TCD outside the normal range had abnormal MRA (Figures 1 and 2; Supplementary figures II and III; Table 4), 50% of the 48 scanned (1/49 with clinical stroke and abnormal CBFv>200 cm/s failed MRA). This represents at least 36% of the 67 with elevated/low CBFv and the majority had stenosis/occlusion (Grades 2/3).18 One patient had moyamoya (Grade 4;18 Supplementary Figure II). Turbulence without definite narrowing or occlusion (Grade 1;18 Supplementary Figure III) was not counted as abnormal. MRA was more likely to be abnormal in those with infarction on MRI (χ2=12.34; p=0.00044). Of the 6/7 children with clinical stroke who had MRA, all were abnormal, while of the 14 children with SCI who also had MRA, 10 (71%) were abnormal. Abnormal MRA was documented in 8/24 with absent TCD signal (33%), 1/4 with CBFV<50 cm/sec (25%) and 9/20 (45%) with CBFV>150 cm/sec.

Although abnormal ICA/MCA velocity (>200 cm/sec) was rare in this cohort, absent or low velocities were common in those with previous clinical presentations and those with abnormal MRA (Supplementary Table II). Of the 7 with clinical stroke, 2 had elevated and 5 had absent CBFv. Of the 14 with SCI, 8 had elevated CBFv and 6 had absent CBFv. Three patients died, 2 of whom had prior strokes with absent CBFv and one with absent CBFv and normal MRI who died during an episode of severe anemia. Four children had a subsequent stroke, one with absent CBFv and SCI and 3 with previous stroke (2 with elevated CBFv, 1 with absent CBFv). The remaining 13 children with SCI did not experience subsequent strokes and, although 2 of the 11 with conditional TCD and the one child with abnormal TCD had had previous neurological symptoms, these 10 children did not experience stroke during follow-up.

Of 11 children with a history of seizures undergoing MRI, 10 (91%) had infarction (5 silent) compared with 11/38 (29%; 10 silent) of those with no history of seizures (Fisher’s Exact test p=0.0003); 7/10 also had MRA abnormality compared with 17/38 of those without seizures (Fisher’s Exact test p=0.14). Seven of 9 children (78%) with a history of contralateral weakness had stenosis or occlusion of the basal cranial arteries on MRA compared to 17/39 (44%) of those without weakness (p=0.137).

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# DISCUSSION

More than a third of Tanzanian children with SCD had TCD recordings outside the normal range (<50 or >150cm/s), consistent with cerebrovascular disease or, for those with elevated CBFv, cerebral hyperemia. Although 12 (6%) had CBFv>170 cm/sec, only one patient (0.5%) had abnormally high CBFv>200 cm/s. Frequent painful crises in the previous year and lower hemoglobin was associated with a CBFv>150cm/s. Low hemoglobin and focal neurological deficits were associated with low/absent velocities. The proportion of children with elevated, low or absent CBFv who had infarction on MRI was 43%, with SCI comprising 31% of this selected group.

The prevalence of TCD outside the normal range was similar to most of the previous studies in Africa.14-17 ~~The lower proportion of abnormal high CBFv (>200cm/s) may be due to rapid progression of the disease in Africa, with progressive stenosis of internal carotid and MCAs leading to occlusion with lower CBFv distally, consistent with our finding of a high prevalence of absent/CBFv, particularly in those with clinical presentations.~~ The high mortality for the children with clinical stroke undergoing MRI (2/7) is consistent with the possibility that those with progressive cerebrovascular disease died at a younger age; African survival cohorts may therefore appear to have less severe CVD. We documented stenosis and occlusion on MRA, although only one child had moyamoya collaterals. MRA of the neck might reveal additional stenosis or occlusion.19

The prevalence of focal weakness was similar to studies of stroke from the pre-TCD screening era in North America,1 and the prevalence of seizures is similar to data from Nigeria,20 although a little higher than in the Jamaican cohort.21 As the patients with elevated/low/absent CBFv were selected for MRI, the minimum prevalence of SCI of 7% is likely to be an underestimate. Although there is a previously documented association between abnormal high CBFv>200 cm/s and SCI, most with SCI have normal TCD.22 Our observed SCI prevalence in mid-childhood (at least 7% of the total population and 29% of those scanned for elevated/low/absent CBFv), appears lower than that in unselected populations elsewhere.2 A larger study of unselected patients will be required to determine whether this holds for those with CBFv within the normal range as well as those with elevated or low CBFv. This is important as one study found that children with normal TCD velocities and no SCI had a lower rate of neurological events compared to those with SCI and a normal TCD.23 This is a survival cohort with high prevalence of alpha thalassemia14 and Central African Republic haplotypes, which are associated with reduced risk of stroke, so it is biologically plausible that SCI are less common.

The distribution of infarction in the basal ganglia and deep white matter is similar to that reported in other studies,24 but we also report occipital and cerebellar infarction typical of a posterior circulation distribution; the anterior cerebrovascular disease associated may reflect the severity of disease in untreated children with SCD. The absence of corresponding posterior large vessel disease in children with posterior circulation infarcts may reflect the lack of imaging of the vertebrobasilar system in this cohort but also raises the possibility of an alternative aetiology such as poor oxygen delivery or cardiac embolic source.

Interestingly, abnormal MRA was documented in more than half of the children with CBFv>150 cm/sec, including 8/11 with CBFv 150-169 cm/sec as well as 4 of 9 with conditional TCD (the child with abnormal TCD failed MRA). Absent/low CBFv in the ICA/MCA may be secondary to extracranial stenosis or occlusion with low distal flow (not excluded as neck vessel imaging was not performed), as well as intracranial disease, demonstrated on MRA in 50% of low and 42% of absent TCD in this study, or to difficulties in obtaining signal through a thick skull.10

In our study, all of those with overt stroke, and nearly three quarters of those with SCI, had abnormal MRA, apparently higher than in previous USA studies. MRA abnormality was reported in 58% of children with clinical stroke in the SWiTCH study,8 in 16% of those with SCI in the SIT trial22 and in 25% of children with SCD in the STOP study of children with abnormal CBFV>200 cm/sec.25 In the Tanzanian children, the most common MRA abnormality found in children with elevated/low/absent CBFv was stenosis, similar to the studies in the American children.25 In contrast to children with stroke, in whom MRA abnormality was only seen in those with absent/low CBFv,8 we also documented abnormal MRA in children with CBFv>150 cm/sec.

Seizures were more common in children with elevated/absent/low CBFv, consistent with previous UK data.26 In our study, children with elevated/low/absent CBFv and a history of seizure had a higher proportion of infarcts than children who did not have a history of seizure. The CSSCD study of American children also found that seizures were associated with stroke and SCI,27 but did not report TCD or MRA. Prengler et al. found no association between abnormal MRA findings and history of seizure although CBFv was higher in those with seizures.26 Cerebrovascular disease should be excluded in children with SCD and seizures, although seizures may occur early in an active pathophysiological process, when CBFv is abnormal but MRA is not.

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# Study limitations

Some of the clinical parameters are prone to recall bias despite the relatively short period. Given the high mortality of children with SCD in Tanzania within the first 5 years of life,28 the children with the most severe disease may have died and the data may not be generalizable. MRI and MRA were obtained at a mean of 5 months after the TCD, during which time CBFv may have changed. Children were recruited from outpatient clinics when clinically well, leading to a potential for bias in excluding sicker children which may account for the lack of children with abnormal TCD, although Routine Outpatients is also typically the setting for TCD screening in the North. As a result of their relative rarity in this cohort, it was not possible to explore any differences in effect of conditional or abnormal CBFv compared with slightly elevated CBFv, nor to determine whether elevated TCD was associated with abnormal MRA. A quarter of children with CBFv outside the normal range did not return for MRI, which may have introduced selection bias, although there was no evidence for selection of children by age or with a history of neurological problems. Children with SCD and normal TCD examinations did not undergo MRI, while MRA of the neck was not included so the proportions of SCI and MRA abnormality are minimum estimates. The prevalence of abnormalities may be different but our inter-observer variability for MRI reporting was good, similar to that reported from the SIT trial29 with the same definition,2,30 and that for the MRA abnormalities was even better.

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# Conclusions

This study shows that elevated/absent/low CBFv and MRI abnormalities are common in children with SCD in Africa, and that frequent painful crises in the past year and low hemoglobin are independent risk factors for these abnormalities in addition to seizures and clinical stroke. TCD may be useful in centres in Africa that do not have access to MRI, provided that evidence-based treatment for Conditional or Abnormal CBFv is available; there is now some evidence that hydroxyurea, which is relatively low cost, reduces CBFv. Longitudinal studies are required to determine the outcome and neurocognitive functioning of children with TCD outside the normal range and abnormal MRI/MRA.

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**Disclosures**: None

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Normal CBFv** | **Low CBFv/No Signal** | **Elevated CBFv#** |
|  | **No** | **%** | **No** | **%** | **P value\***  | **No** | **%** | **P value\***  |
| **Age group(yrs)** |  |  |  |  |  |  |  |  |
|  6 – 8 | 54 | 40.6 | 17 | 43.6 | 0.565 | 13 | 46.4 | 0.053 |
|  9 – 11 | 48 | 36.1 | 16 | 41.0 | 14 | 50.0 |
|  12 + | 31 | 23.3 | 6 | 15.4 | 1 | 3.6 |
| **Sex** |  |  |  |  |  |  |  |  |
|  Male | 70 | 52.6 | 20 | 51.3 | 0.882 | 15 | 53.6 | 0.928 |
|  Female | 63 | 47.4 | 19 | 48.7 | 13 | 46.4 |
| **History of Admissions** |  |  |  |  |  |  |  |  |
| No admission | 54 | 40.6 | 15 | 38.5 | 0.488 | 14 | 50.0 | 0.138 |
|  2 -3 | 59 | 44.4 | 15 | 38.5 | 7 | 25.0 |
|  >3  | 20 | 15.0 | 9 | 23.0 | 7 | 25.0 |
| **History of Blood Transfusions** |  |  |  |  |  |  |
|  No BT | 47 | 35.3 | 11 | 28.2 | 0.407 | 12 | 42.9 | 0.453 |
|  BT | 86 | 66.7 | 28 | 71.8 | 16 | 57.1 |
| **History of Seizures** |  |  |  |  |  |  |
|  Yes | 8 | 6.0 | 8 | 20.5 | 0.011 | 5 | 17.9 | 0.052 |
|  No | 125 | 94.0 | 31 | 79.5 | 23 | 82.1 |
| **History of Weakness** |  |  |  |  |  |  |  |
|  Yes | 4 | 3 | 8 | 20.5 | 0.001 | 3 | 10.7 | 0.102 |
|  No | 129 | 97 | 31 | 79.5 | 25 | 89.3 |
| **Number****of Painful crises in past 2 years** |  |  |  |  |  |
| Median (IQR) | 3 (1, 5) | 3 (1, 6) | 0.718 | 6 (3, 10) | 0.002 |
| **Hemoglobin**  |  |  |  |  |  |
| g/dl mean± sd  | 7.5 ±1.2 | 7.0 ±1.6 | 0.025 | 6.8 ±0.9 | 0.003 |
| **O2 saturation** |  |  |  |  |  |
| %: median (range) | 98 (96,99) | 98 (97,100) | 0.201 | 98 (97,100) | 0.321 |
| **~~Systolic BP~~** |  |  |  |  |  |
| ~~mmHg mean ± sd~~ | ~~96 ± 8.9~~ | ~~98 ± 8.9~~ | ~~0.359~~ | ~~98 ± 9.5~~ | ~~0.563~~ |
| **~~Diastolic BP~~** |  |  |  |  |  |
| ~~mmHg mean ± sd~~ | ~~58 ± 6.5~~ | ~~60 ± 5.8~~ | ~~0.131~~ | ~~59 ± 6.2~~ | ~~0.954~~ |
| **Indirect Bilirubin** |  |  |  |  |  |
| g/dl median (IQR) | 31.7(16.4, 54.5) | 31.4(20.9, 55.5) | 0.655 | 37.3(22.9, 60.2) | 0.441 |

**Table 1: Patient characteristics by Cerebral Blood Flow velocity category**

IQR :Inter-Quartile Range sd Standard deviation \*for comparison with normal #Elevated includes Slightly elevated (CBFv 150-169 cm/s), Conditional (CBFv 170-199 cm/s) and Abnormal (CBFv >200 cm/s)

**Table 2: Risk factors for No Signal/Low CBFv and Elevated CBFv**

|  |  |  |
| --- | --- | --- |
|  | **Univariable analysis** | **Multivariable analysis** |
| Variable | OR | 95%CI | P value |  OR |  CI | P value |
| **NO SIGNAL/LOW CBFv** |
| **History of Seizures** |
| Yes | 3.53 | 1.16-10.57 | 0.023 | 2.37 | 0.71-7.78 | 0.153 |
| **History of weakness** |
| Yes | 7.28 | 2.07-29.28 | 0.003 | 5.64 | 1.50-23.54 | 0.011 |
| **No of Painful crises in past 2 years** |
|  | 1.04 | 0.95-1.13 | 0.279 | - |  - | - |
| **Hemoglobin level** |
| g/dl | 0.73 | 0.54-0.98 | 0.038 | 0.74 | 0.53-1.00 | 0.051 |
| **ELEVATED CBFv** |
| **Seizures** |  |  |  |  |  |  |
| Yes | 3.40 | 0.96-11.14 | 0.046 | 1.83 | 0.39-7.34 | 0.409 |
| **History of weakness** |
| Yes | 5.38 | 1.20-24.18 | 0.023 | 2.73 | 0.46-14.78 | 0.242 |
| **No of Painful Crises in past 2 years** |
|  | 1.14 | 1.05-1.26 | 0.003 | 1.13 | 1.03-1.25 | 0.009 |
| **Hemoglobin level** |
| g/dl | 0.55 | 0.35-0.81 | 0.004 | 0.59 | 0.37-0.90 | 0.020 |

**Table 3: MRI findings in 49 children with abnormal TCD**

|  |  |  |
| --- | --- | --- |
| **Finding** | **Number patients** | **%**  |
| **Any abnormality** | 21 | 43 |
| **Generalised atrophy** | 5 | 10 |
| **Infarction**UnilateralBilateral*Focal arterial infarction**Anterior circulation* ACA MCA Both ACA and MCA*Posterior circulation* Occipital  Cerebellar  Occipital and cerebellar*Watershed territory infarcts*Deep white matterTemporal Basal gangliaNormal | 2141740317421212428 | 43835806214842424857 |

Key: ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, WM = white matter. Some individuals had more than one outcome on MRI

**Table 4: Relationship between Clinical, TCD, MRI and MRA findings**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Normal MRA****N=24** | **Abnormal MRA****N=24** | **P1** |
| **Clinical** |  |  |  |
| No previous history | 19 (79%) | 15 (62.5%) | 0.13 |
| Focal weakness only | 3 (12.5%) | 2 (8.5%) |
| Seizures only | 2 (8.5%) | 2 (8.5%) |
| Focal weakness + seizures | 0 (0%) | 5 (20.5%) |
| **TCD** |  |  |  |
| No signal | 14 (58.5%) | 10 (41.5%) | 0.4 |
| CBFv<50 cm/sec | 2 (8.5%) | 2 (8.5%) |
| CBFv 150-170 cm/sec | 3 (12.5%) | 8 (33%) |
| CBFv 170-200 cm/sec | 5 (20.5%) | 4 (17%) |
| CBFv>200 cm/sec | 0 (0%) | 0 (0%) |
| **MRI** |  |  |  |
| Normal | 20 (83%) | 8 (33%) | 0.00044 |
| Overt stroke | 0 (0%) | 6 (25%) |
| Silent cerebral infarction | 4 (17%) | 10 (42%) |

 *1 Fisher exact test comparing proportions*

**Legends**

Figure 1 A. Axial T2-weighted magnetic resonance image showing mature right MCA/PCA watershed territory (black arrow) and left MCA territory infarcts. Bilateral deep grey and deep white matter watershed lesions are seen bilaterally. B. A small left cerebellar infarct (white arrow) is seen in the same patient. C. The magnetic resonance angiogram reveals an occluded left MCA (short arrow) and a narrow right MCA (long arrow). The PCAs appear normal. Marrow expansion of the skull vault is noted. MCA = middle cerebral artery, PCA =posterior cerebral artery



Figure 2. (a) Hemorrhagic basal ganglia infarct in a 16 year old girl. The subtle hemorrhagic change is seen as a dark blush on the T2-weighted sequence but is well seen on the (b) T2\* sequence (white arrows). (c) A magnetic resonance angiogram revealed severe stenosis of the right middle cerebral artery with reduced filling of the distal vessels.



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