Stroke in adults with Sickle Cell Disease

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Stroke and SCD

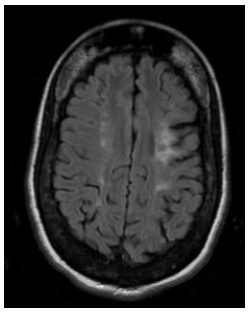
- Children and adults with SCA (haemoglobin SS) have a high prevalence (4.01%) of stroke
- The reported age-adjusted incidence is 0.61 to 0.76 per 100 patient years (ie, 0.61 to 0.76 percent per year)
- Ischaemic stroke is most common in children aged 2 to 9 with a second peak in adults aged 20 to 29. The risk of stroke by the age of 20 is about 11%
- Silent cerebral ischaemic lesions on MRI are common in SCD and present without overt clinical manifestations but probably have a role to play in cognitive functioning

Ohene-Frempong K et al. Blood 1998; 91:288

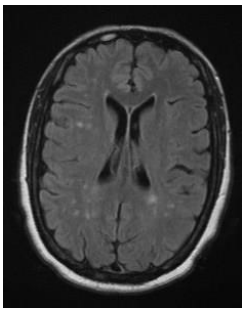
The type of strokes we see in adults

- Cerebral infarction is associated largely with occlusion or stenosis of the large intracranial arteries
- We see a borderzone type cerebral ischaemia even in those without large vessel occlusion and this may be from sludging and occlusion of small vessels by rigid red cells at end vessels in the deep borderzone
- An increase in silent subcortical white matter lesions without overt stroke which studies have shown to associate with cognitive dysfunction

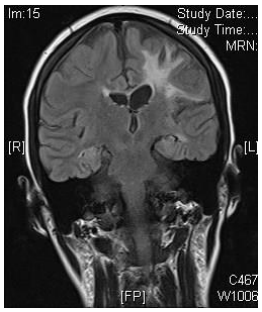
MRI of stroke subtypes in SCD



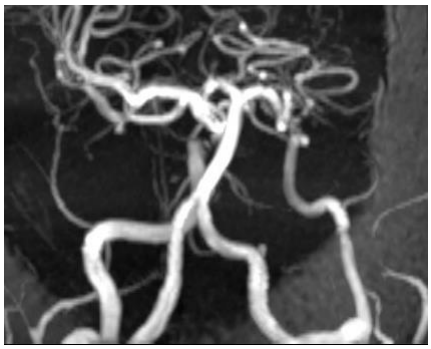
Borderzone ischaemia



'Silent' subcortical WMLs



Left MCA infarct
Occluded left ICA

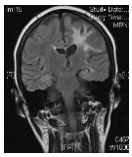


Risk factors for stroke in SCD

- Prior TIA: Relative risk RR 56
- Low steady state haemoglobin: RR 1.9 per 1 g/dL decrease
- Rate of acute chest syndrome: RR 2.4 per event per year
- Episode of acute chest syndrome within the previous two weeks: RR 7.0
- Elevated systolic blood pressure: RR 1.3 per 10 mmHg increase
- Development of moyamoya vessels

Ohene-Frempong K et al. Blood 1998; 91:288

Cerebral infarction – acute management



- Immediate assessment by the haematology and neurology service with shared discussion of the assessment and plan
- Laboratory evaluation to include FBC with reticulocyte count, cross match, PT, APTT, basic metabolic panel, and HbS quantification

Recommended imaging approach (may be institution specific):

- CT scan of the brain to exclude cerebral haemorrhage
- MRI and MRV of the brain after the patient is stable (6 h). Alternatively, only an MRI and MRV of the brain may be performed if the images can be obtained within 60 minutes of evaluation and the scan sequence has been set up to detect cerebral haemorrhage
- Obtain vascular access and prepare for blood transfusion

Acute management - continued

- With acute stroke, we urgently transfuse patients to rapidly lower the HbS concentration. Ideally, this is accomplished by an immediate exchange transfusion to achieve a goal HbS concentration of <30% of total Hb, and a total Hb level of approximately, but > than 10 g/dL
- Urgent simple transfusion may be appropriate if the patient has severe anaemia or there is a delay (>4 hours) to start EBT
- Trials have shown that EBT rather than simple transfusion is associated with a reduced risk of stroke recurrence.
- Supportive care measures including O2 administration to keep oxygen saturation 95% or above and normoglycaemia is important
- If febrile, blood culture, antipyretics, and antibiotics should be administered

Thrombolysis in acute stroke

In acute ischaemic stroke, IV thrombolysis ASAP after 30 minutes of stroke onset

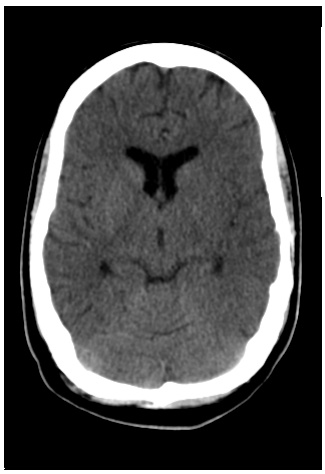
Can be given up to 6 hours but maximum benefit first 1 ½ hours

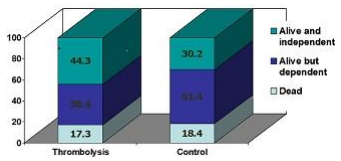
CT before to exclude haemorrhage.

Contraindicated if on anti-coagulants

No published reports regarding the use of thrombolytic agents in adults with SCD

Careful consideration should be given if other causes for stroke e.g. older patient in AF



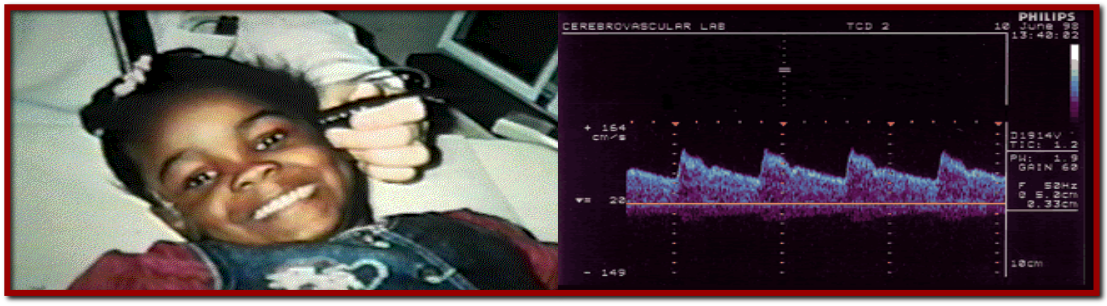


Differences/1000:
141 extra alive and independent (P<0.01)
130 fewer dependent survivors (P<0.01)
12 fewer deaths (NS)

Prevention of secondary stroke

- Recurrent stroke occurs in approximately 2/3 of patients within 2 years
- For ongoing prevention, chronic transfusion protocols are typically used
- Patients who have been stabilised with chronic transfusion therapy may be evaluated for the option of haematopoietic stem cell transplantation
- Based on the safety data from the SWiTCH Trial , hydroxyurea can no longer be considered adequate as the sole therapy
- Chronic transfusion can reduce the incidence of recurrent stroke from approximately 2/3 of patients to below 10 %, when routine monthly red blood cell transfusions are given to maintain the Hb S fraction at less than 30 % of total Hb

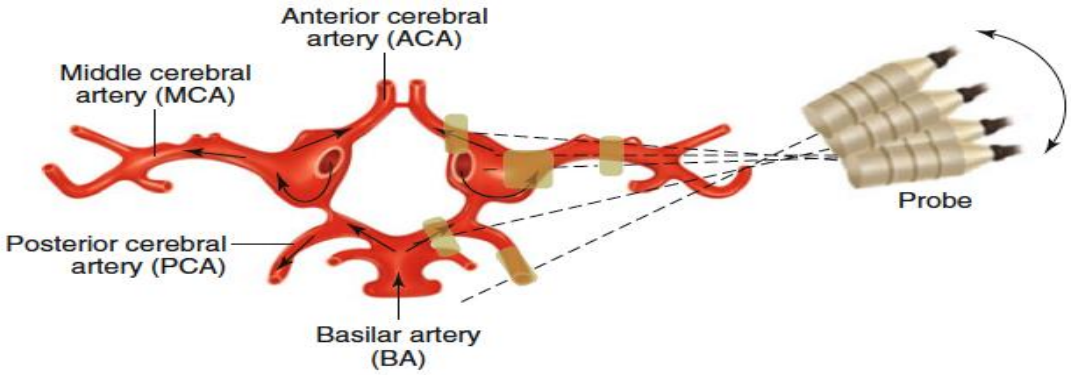
PRIMARY STROKE PREVENTION Raised TCD: Increased stroke risk



TCD Velocity (cm/s)	Interpretation	Yearly Risk of Stroke
< 170	Normal	~1%
≥ 170 and < 200	Conditional	intermediate
≥ 200	Abnormal	~10%

Adams et al 1997

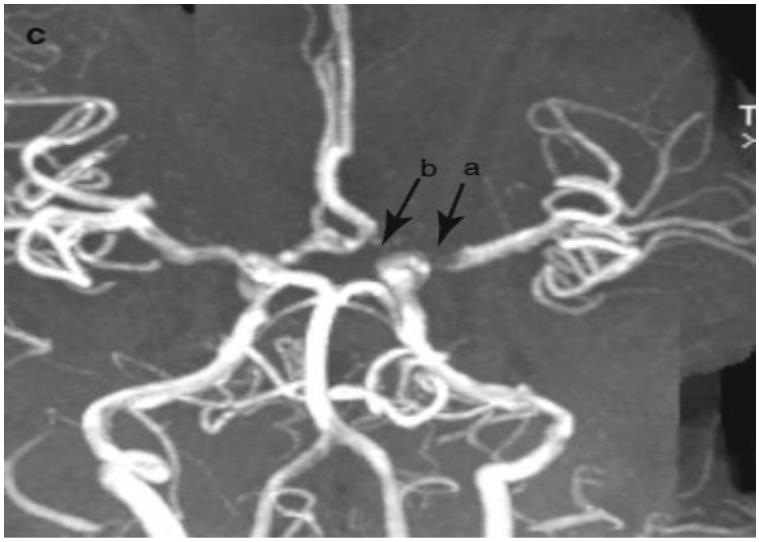
Transcranial Doppler Screening



MRA showing the type of IC stenosis seen

a Proximal MCA

b Proximal ACA



STOP trial

1934 children screened with TCD

Flow in MCA/ICA measured

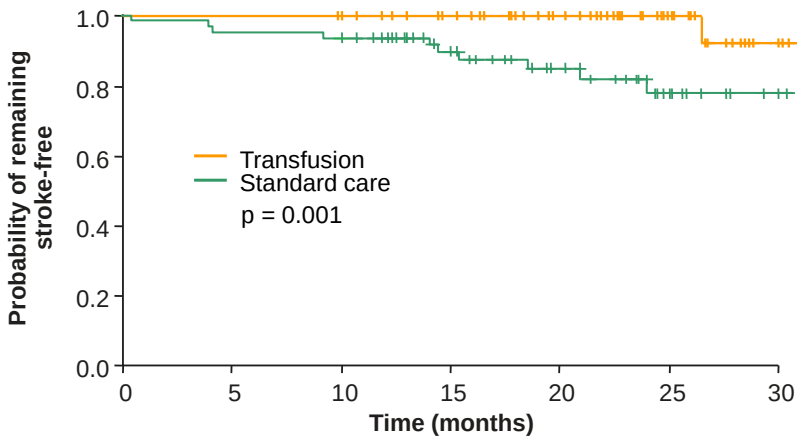
TCD flow >200/sec

Standard Care

Regular Blood Transfusion

S% <30%

Adams et al 1998 NEJM



Transfusion reduces stroke in children with SCD

Adams RJ, et al. N Engl J Med. 1998;339:5-11.

STOP trial

Standard Care	Transfusion
67 patients	63 patients
11 strokes	1 stroke

- 130/ 1934 HbSS children with TCD >200cm/s
- 92% risk reduction <0.01
- Recommend all children screened with TCD
- High TCD flow = offered long term transfusion
- Need to treat approx 11 children to prevent 1 stroke

Effect of Introduction of TCD Screening

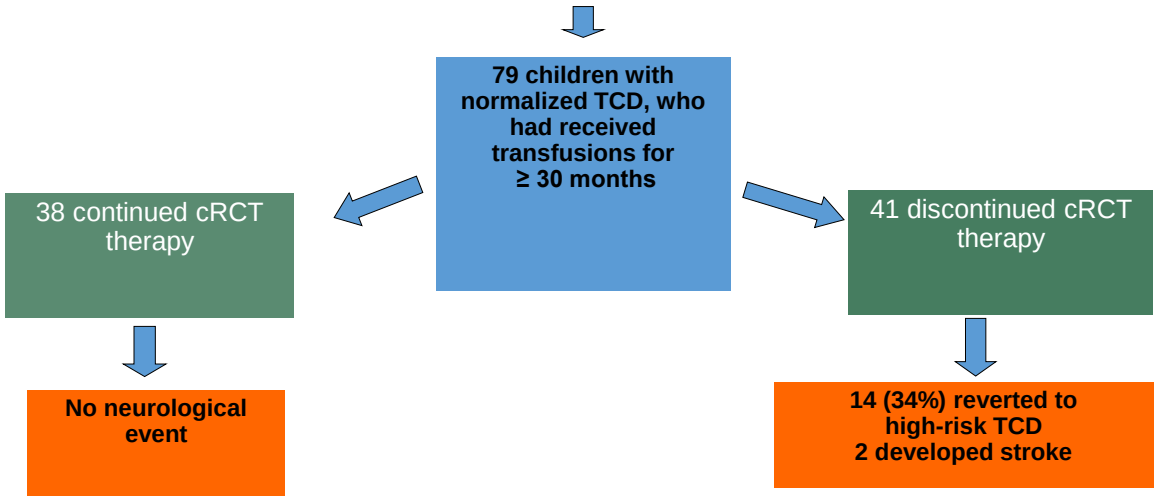
- Retrospective single institution study
- 475 patients followed in 8 years prior to TCD screening
- 530 patients followed in 8 years following introduction of TCD screening

- Pre-TCD: Stroke incidence 0.67 per 100 patient years
- Post-TCD: 0.06 per 100 patient years ($p<0.0001$)

Ennifel-Eghan et al 2010

STOP 2 Trail

- Prospective randomized controlled multicentre treatment trial



Adams RJ, et al. N Engl J Med. 2005;353:2769-78.

TWiTCH study - TCD With Transfusions Changing to Hydroxyurea

- NHLBI funded multi-centre Phase 3 RCT
- 24 months of standard treatment (transfusions) vs alternative treatment (hydroxycarbamide) in children with SCA and raised TCDs (who had received at least 12 months transfusion)
- Excluded if clinical stroke/TIA or severe neuro-vasculopathy. Could be included with abn TCD.
- End-point was 24 month TCD velocity

Ware et al; Lancet. 2015

Results/Conclusion

- Final TCD velocities 143 vs 138 cm/s (transfusion vs hydroxy)
- Non-inferiority shown. Possible superiority in Hydroxy arm (p= 0.046)
- 29 new neurological events. 6 TIAs (3 in each arm). No strokes.
- Raised TCD in one child on transfusion.
- Exit MRI/A abnormal in one child on transfusion (new vasculopathy)

- Hydroxy may represent an effective alternative to indefinite transfusions for the prevention of primary stroke in this high risk population
- As hydroxy is prescribed to more children, the natural history of SCD may change

Silent infarcts

- Silent cerebral ischaemic lesions on MRI are common in SCD
- No overt clinical manifestations
- Have a role to play in cognitive functioning – associated with neurocognitive damage
- 17% of children, 48% of adults
- ? Increase risk of overt stroke

- SITT trial: Does long term transfusion in patients with silent strokes prevent progression to overt stroke?

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Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia

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SST TRIAL

Silent Infarct Transfusion Trial

- Children with SS and SB0thal screened with MRI/A
- If Silent infarct present, randomised to standard care or regular blood transfusion for 3 years
- Primary endpoint – recurrence of infarct (overt stroke or silent infarct)

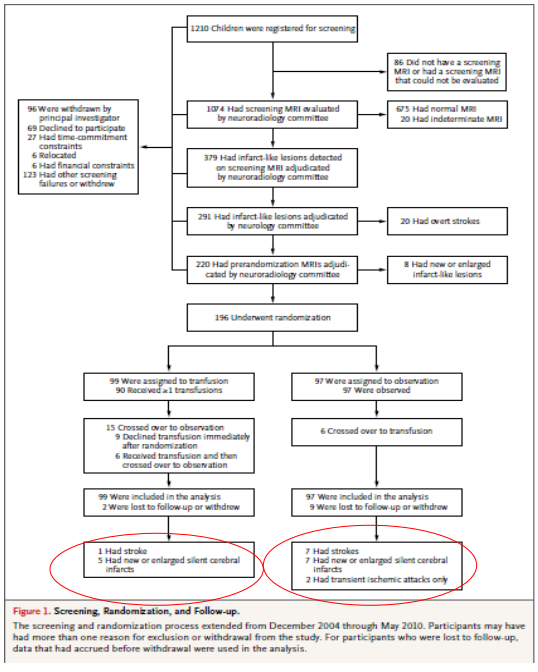

Figure 1. Screening, Randomization, and Follow-up.

The screening and randomization process extended from December 2004 through May 2010. Participants may have had more than one reason for exclusion or withdrawal from the study. For participants who were lost to follow-up, data that had accrued before withdrawal were used in the analysis.

P= 0.04

Primary stroke prevention

- There is evidence that routine use of TCD lowers the risk of stroke
- Transfusion is not without complication
  - Burden of regular transfusion
  - Costs and availability of transfusion
    - $9828-50,852 (Wayne et al)
    - Risk-benefit ratio will be different in countries where blood is not freely available
  - Iron overload
  - Alloimmunisation
- Alternatives to transfusion (Hydroxyurea/Hydroxycarbamide) have been investigated in TWiTCH and SCATE trials
- Results from these trials are yet to be developed into an international consensus
- The role of transfusion to prevent overt strokes in patients with silent infarcts still needs clarification

Acute intracerebral haemorrhage

- Accounts for about 1/3 of strokes in patients with SCD
- The site of bleeding may be subarachnoid, intraparenchymal, intraventricular, subdural, or a combination of these locations
- The peak incidence is between the ages of 20 and 29
- Common presenting features include severe headache, vomiting, stiff neck, and alterations in consciousness
- Angiography should be considered to identify the cause of bleeding and to guide further therapy
- The mortality rate in patients is as high as 24 to 50 %

Subarachnoid haemorrhage

- Commonest case of haemorrhagic stroke in SCD. Usually secondary to rupture of aneuryms; multiple aneurysms present in approx 45 %
- Treatment: close monitoring, prevention of vasospasm with nimodipine and endovascular coiling or surgical clipping of culprit aneurysm
- ISAT Trial clipping higher mortality and morbidity and stopped early
- It appears that although endovascular coiling is associated with a shorter recovery period as compared to surgical clipping, it is also associated with a significantly higher recurrence rate after treatment

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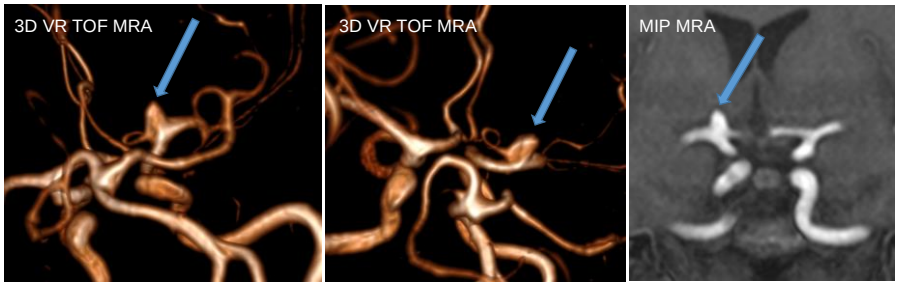

3D volumetric and MIP reconstructions showing a superiorly pointing 6mm terminal right ICA aneurysm (blue arrow)

Intracerebral haemorrhage - continued

- The majority of cases of ICH represent subarachnoid hemorrhage resulting from the rupture of one or more aneurysms; multiple aneurysms are present in approximately 45 % of patients
- Treatment is close monitoring, prevention of vasospasm with nimodipine and endovascular coiling or surgical clipping of culprit aneurysm
- ISAT Trial clipping higher mortality and morbidity and stopped early
- It appears that although endovascular coiling is associated with a shorter recovery period as compared to surgical clipping, it is also associated with a significantly higher recurrence rate after treatment
- In about 30% of patients with ICH a moyamoya picture is seen on angiography

Moyamoya

- Moyamoya disease, a chronic cerebrovascular disease of uncertain aetiology that occurs primarily in Japan and is characterized by severe bilateral stenosis or occlusion of the arteries around the circle of Willis, with prominent collateral circulation
- Patients with SCD who develop moyamoya syndrome appear to be at risk for recurrence of strokes

Dobson et al. Blood 2002; 99:3144

Moyamoya - continued

- The angiographic abnormalities may be the source of haemorrhage
- Retrospective study 44 patients on EBT, 19/44 moyamoya picture
- 58% vs 28% risk stroke recurrence
- Surgical treatment has been used in an effort to restore the circulation of the ischaemic brain area, thereby reducing the risk of ischaemic stroke
- In a report, indirect revascularisation using encephaloduroarteriosynangiosis (EDAS) was performed in 12 patients with SSD and documented moyamoya syndrome. 2/12 had strokes at 47 months f/u
- Although there are no RCT determining the effectiveness of surgical treatment in patients with SCD and moyamoya disease, EDAS is a reasonable option for these patients given their poor outcome

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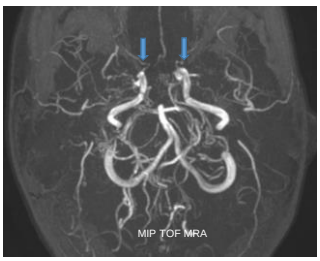
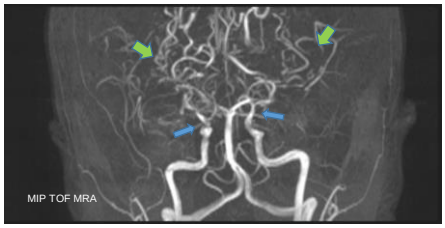
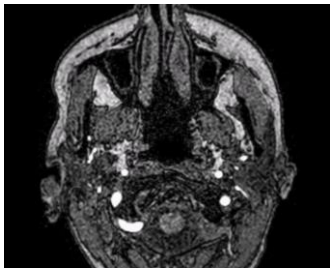




Bilateral occluded ICAs (blue arrows) with extensive "moya moya" collateral formation (green arrows)



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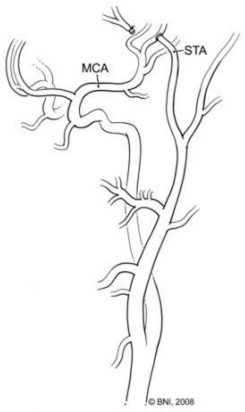
Moyamoya – treatment



Direct Bypass: STA-MCA bypass

Baaj et al., (2009)

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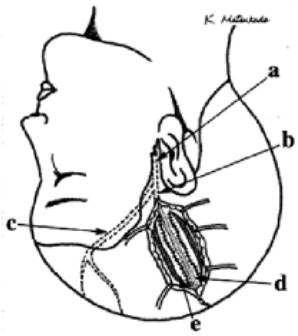
Indirect Bypass: EDAS

The posterior branch of the STA is laid on the brain surface, covered with galea and sutured to the pia.



a. main trunk of the STA
b. posterior branch of the STA
c. anterior branch of the STA
d. galeal flap
e. dura mater

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Comparison of Direct versus Indirect

Indirect (EDAS)

- Useful if inadequate donor artery grafts
- At least several weeks required to form collaterals
- Easier and safer in patients with serious medical comorbities

Direct (STA-MCA bypass)

- Technically difficult; size and progressive MCA occlusion
- Immediate revascularization
- Symptomatic cerebral hyperperfusion, although transient

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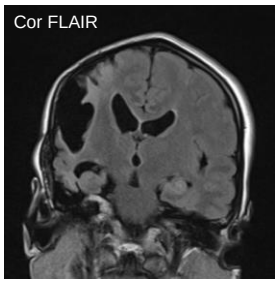
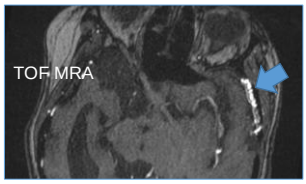
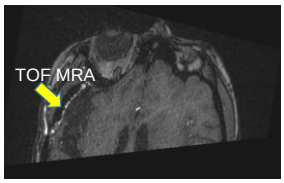
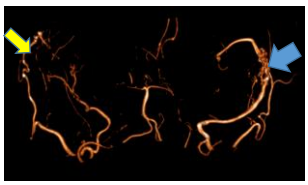
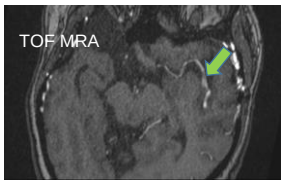


Mature encephalomalacia on right from prior infarct









Left (blue) and right (yellow) sided EC-IC anastomosis with retrograde filling of left MCA (green)

Case presentation

28 year old man

HbSS SCD

Cystic fibrosis

Not on EBT program when we met him

During an acute SCD chest syndrome he developed and acute R hemiparesis

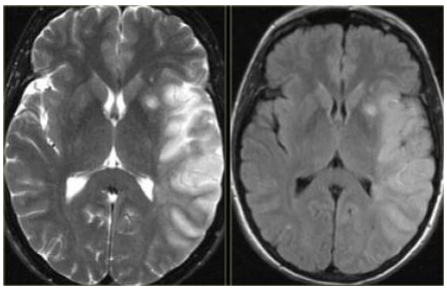
Urgent EBT

Recovered well

MRI left MCA embolic looking stroke

MRA was essentially normal

What would you do?



Seen on our SCD/neurology/neuropsychology MDT clinic

- Decision made to commence EBT
- The stroke appears cardio-embolic and perhaps less typical of the stroke we see in SCD
- We know that there is an increased risk of venous thrombosis in SCD and he was having a chest crisis at the time
- A bubble echocardiogram has shown a large shunting PFO.
- The decision to close in made by a cardiology/stroke/haematology MDT

Other neurological complications

- Infection
- Venous sinus thrombosis
  - Probably more common in patients with SCD
  - Need to consider diagnosis and request MR venography if MRA normal or distribution of infarcts atypical
  - Treat infection, dehydration, seizures. Treat with anticoagulation
- Posterior Reversible Encephalopathy Syndrome (PRES)
  - Severe acute neurological syndrome (visual impairment, seizures, headache)
  - Associated with excessive fluid replacement during acute chest syndrome in children and during pregnancy
  - Exchange transfusion may be of benefit

Conclusions

- The literature and evidence on the management of CVD in adults with SCD is less helpful than in the paediatric population
- TCD does not appear to be a helpful guide in adults
- Many patients transition to adult clinics on EBTs and we continue
- We monitor the extent of vascular change and vessel stenosis by MRI/MRA every 2 years
- There is no evidence for thrombolysis in acute ischaemic stroke in the adult SCD population unless perhaps other clear vascular risk factors are present. Anti-platelet drugs are not clearly indicated in SCD stroke
- Acute EBT is the treatment of choice
- Much of our clinic involves the management of migraine headaches