UCL Institute of Child Health

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Neurological damage: treatment, management & prevention

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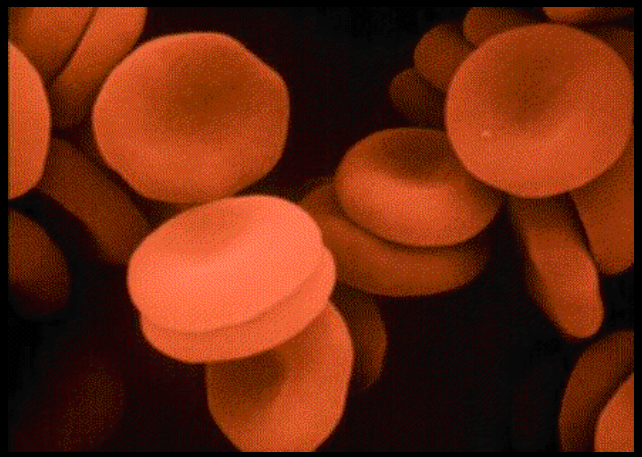
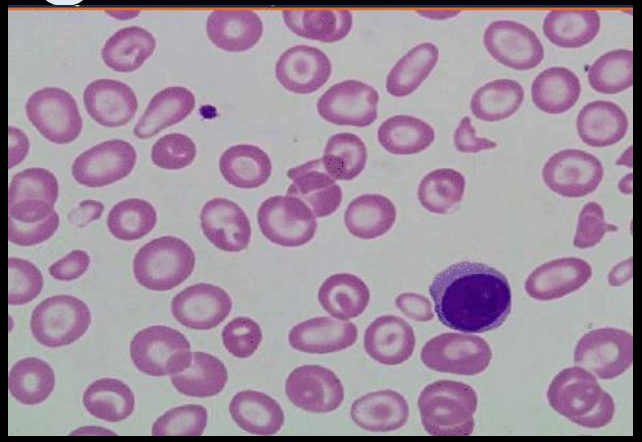
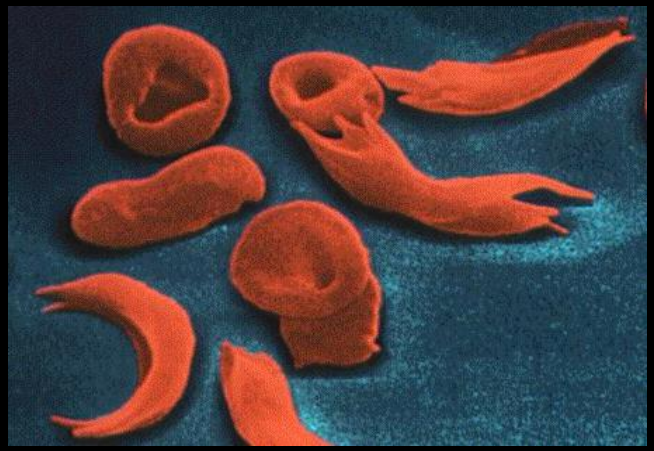
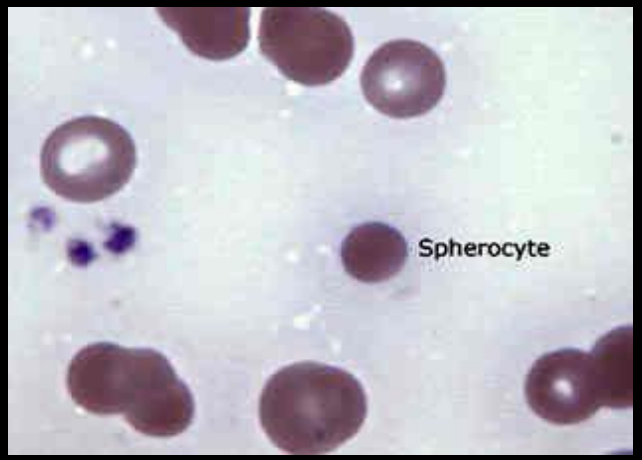
Red cell haematology for neurologists



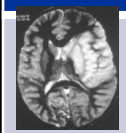
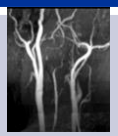
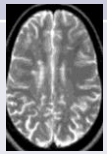
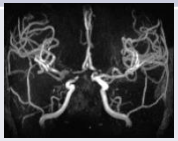
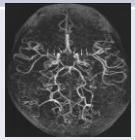
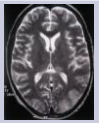
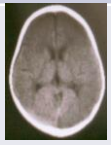
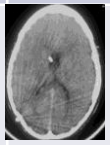
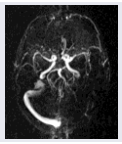
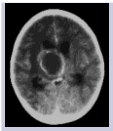
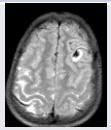
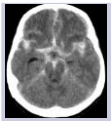
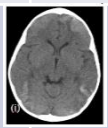
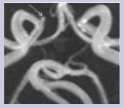
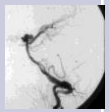


Low
O_2

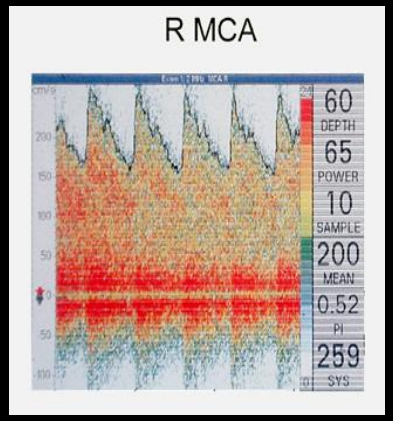




Acute neurology in sickle cell disease for the uninitiated ;-)

MRI	Vascular: MRA/MRV	Clinical and pathological findings	Treatment
	 	Sudden onset **stroke** with arterial territory infarct: stenosis, occlusion, dissection ICA, MCA. Exclude shunting	Transfuse, O2, Intensive care Stroke Unit -TL
	 	**Silent cerebral infarction**: no stroke but may have had seizures. Stenosis, occlusion, moyamoya ICA,MCA. Shunt	?Transfuse; ?Hydroxyurea
		**PRES: Posterior reversible encephalopathy syndrome** after rapid transfusion, acute chest, hypertension	Treat seizures, hypertension, hypoxia
	 	**Venous sinus thrombosis**: presents c hemiplegia, seizures, coma. CT : empty delta, thrombus, CTV /MRV	?Transfuse; rehydrate, anticoagulate
		**Abscess:** seizures, headaches, coma, raised intracranial pressure, fever	Antibiotics Neurosurgeon Intensive care
		**Intracerebral haemorrhage:** sudden onset very severe headache, coma. Venous , hypertension, aneurysm	Neurosurgeon Intensive care
	  	**Subarachnoid haemorrhage:** sudden onset very severe headache, coma . Aneurysm, venous , hypertension e.g. chest crisis	Neurosurgeon Intensive care
		**Subdural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care
		**Extradural haemorrhage:** headache, coma, raised intracranial pressure, skull infarction. Exclude trauma /NAI	Neurosurgeon Intensive care

Primary prevention of stroke in sickle cell disease



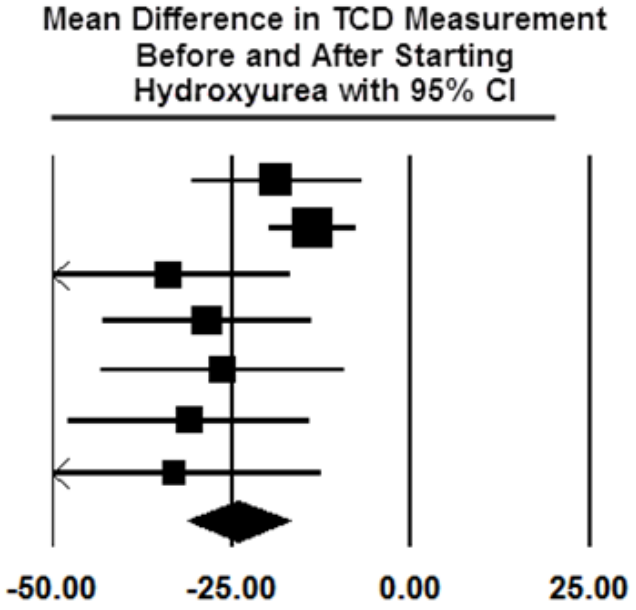
Grade A evidence!

STOP I and STOP II

- 130 children with 2 TCDs maximum time averaged mean ICA/MCA velocity > 200 cm/s
- Randomly allocated to
  - Blood transfusion (n=63; 10 dropouts)
  - No treatment (n=67; 2 crossed over)
- 10 infarcts and 1 haemorrhage in no treatment arm compared with 1 infarct in transfused arm (92% risk reduction, $p<0.001$
- STOP II: cannot stop!

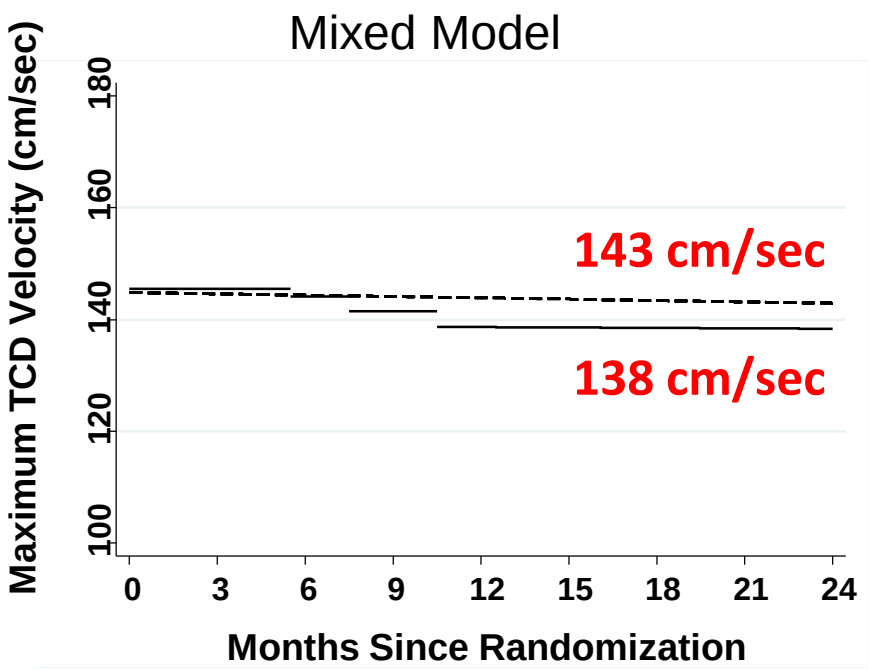
Hydroxyurea to reduce TCD?

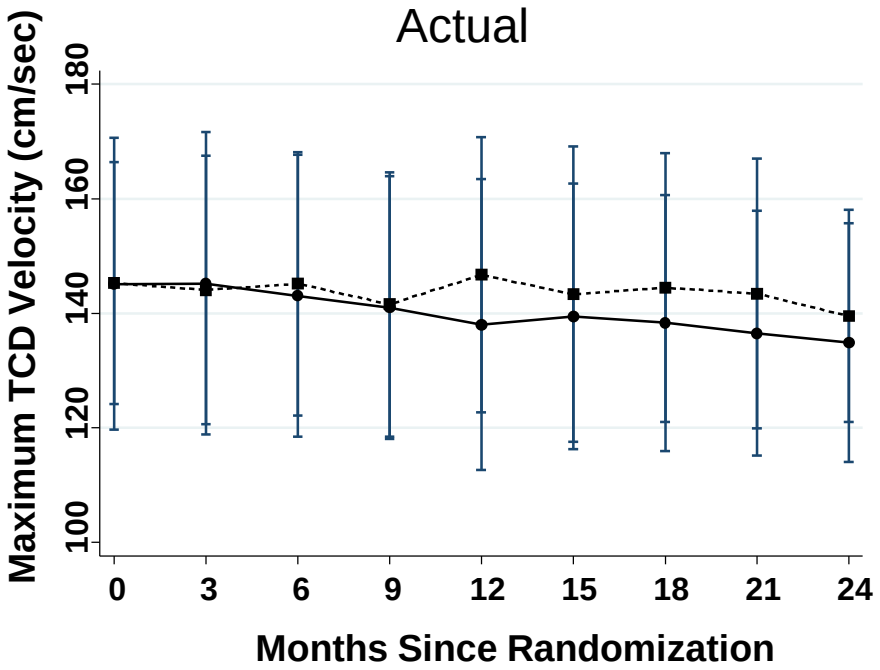
Study Name	Mean Time on Hydroxyurea (months)	Mean Dose of Hydroxyurea (mg/kg/day)
Galadanci, 2015	3.0	20.0
Kratovil, 2006	6.0	23.3
Lagunju, 2015	12.0	24.0
Zimmerman, 2007	12.0	27.9
Thornburg, 2009	25.0	MTD
Gulbus, 2005	33.6	≤ 20
Lefevre, 2008	37.2	Low to moderate
Pooled analysis, random		



Primary Endpoint

Standard - - - - - - Alternative ——





ITT per-protocol non-inferiority comparison ($p=8.82 \times 10^{-16}$)

Additional post-hoc analysis for superiority ($p=0.023$)

Primary stroke prevention for children with sickle cell disease living in high- and low-income settings

ASH guideline Recommendation 1.1. Strong

For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years), the ASH guideline panel recommends annual TCD screening

ASH Recommendation 1.2. Conditional

For children who have compound heterozygous sickle cell disease other than HbSC and have evidence of hemolysis in the same range as those with HbSS, the ASH guideline panel suggests TCD screening

Primary stroke prevention for children with sickle cell disease living in high- and low-income settings

ASH guideline Recommendation 2.1. Strong For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years) who have abnormal TCD velocities and live in a well-resourced setting (where regular blood transfusion therapy is feasible), the ASH guideline panel recommends regular blood transfusion for at least a year (versus no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke

ASH Recommendation 2.2. Conditional For children who have compound heterozygous SCD other than HbSC, who have evidence of hemolysis in the same range as those with HbSS, have an abnormal TCD velocity, and live in a high-income country (where regular blood transfusion is feasible), the ASH guideline panel suggests regular blood transfusion for at least a year (versus no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke

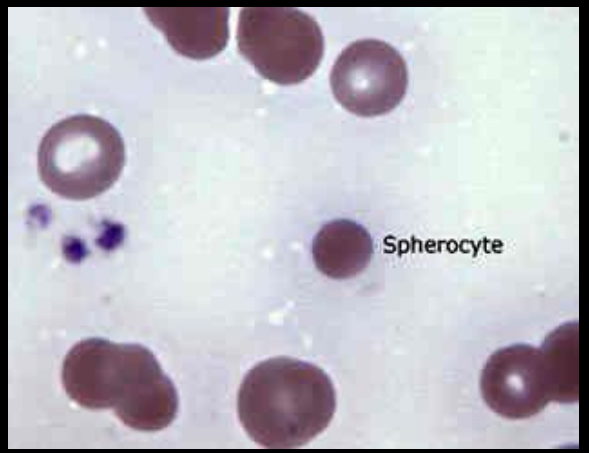
ASH Recommendation 2.2. Conditional For children with SCD (ages 2 to 16 years) and abnormal TCD results who have been receiving transfusion therapy for at least one year and are interested in stopping transfusion, according to the clinical trial risk stratification with an MRI and MRA of the brain, suggests hydroxyurea treatment at maximum tolerated dose can be considered to substitute for regular blood transfusions

What clinical neurological syndromes do we recognise?

Arterial ischaemic events

Stroke

Transient events e.g. Limp, Ataxia



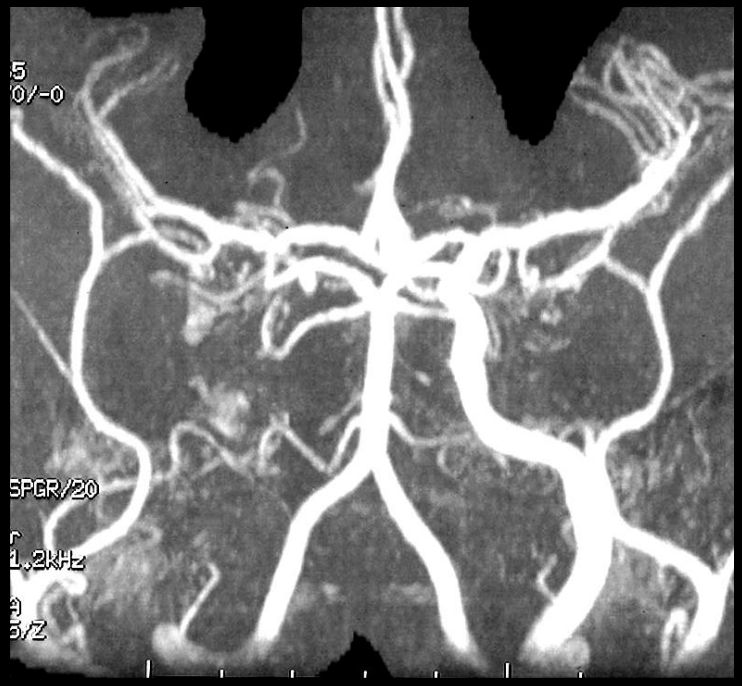
Acute stroke

TIAs, Stroke, Coma

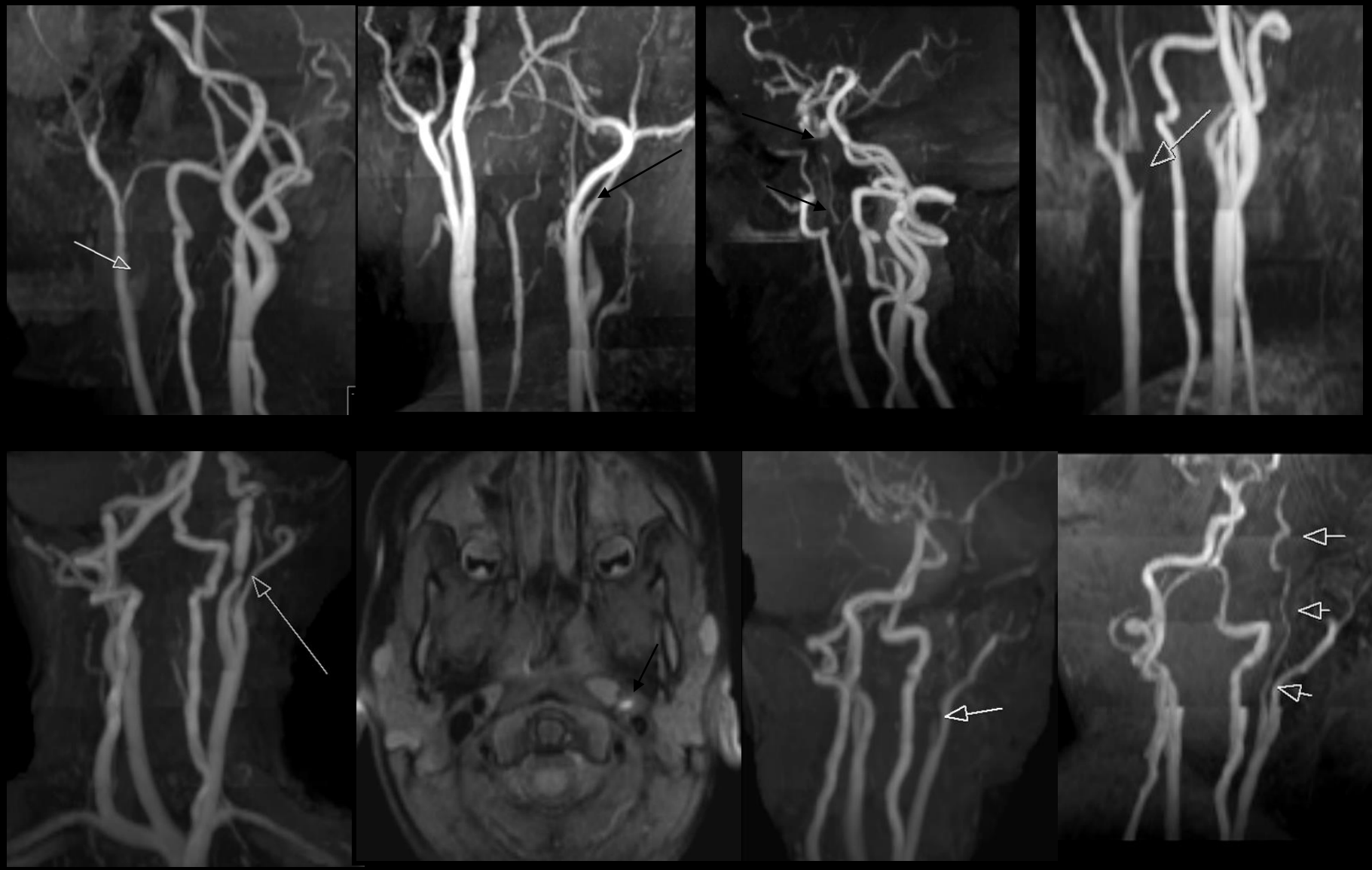
9y girl HbSS, previously well, ‘Top of class’

TIA then stroke: ICA occlusion

- Ataxia aged 5 yrs
- Low TCD
- Settled, not Tx
- Progressive cognitive difficulties
- L hemiparesis aged 16
- ICA occluded in neck



Telfer et al 2011

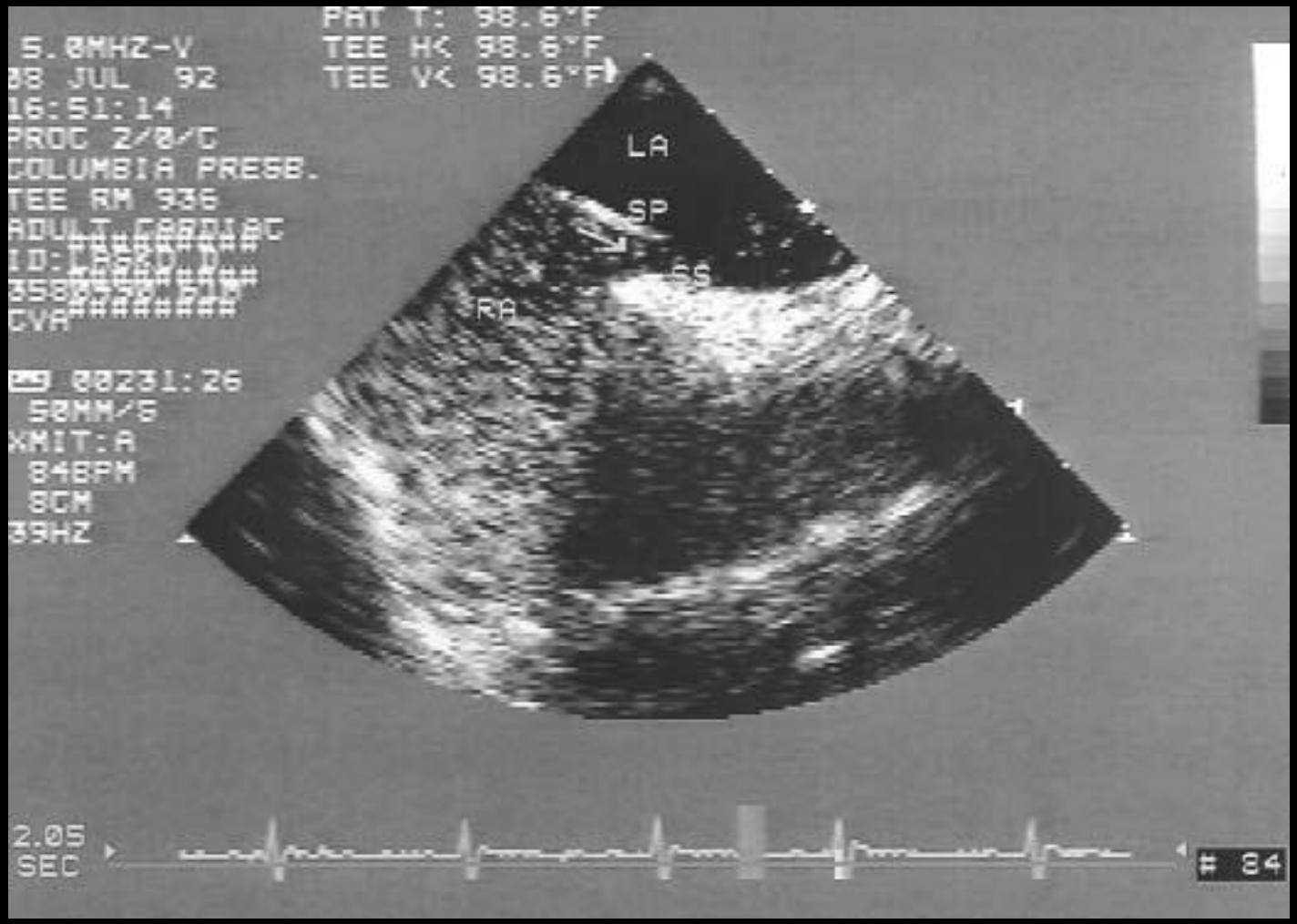


Telfer et al 2011

Infant with with compound heterozygosity

- Acute hemiparesis aged 6 months
- MRI shows small infarct caudate nucleus
- MRA normal
- Echo

?Shunting right to left



PFAST: Inclusion/Exclusion Criteria

- Inclusion criteria for SCD patients
  - Age 2-19 with SCD
  - Overt ischemic stroke confirmed by CT/MRI
  - IV access for another indication= IRB requirement
- Inclusion criteria for Controls
  - Age 2-19 without SCD
  - No known history of overt stroke or congenital heart disease
  - IV access for another indication= IRB requirement
  - Not undergoing TTE for TIA, headache, or other neuro indication
- Exclusion criteria for all
  - Clinically unstable for echo
  - History of PFO closure

PFAST: Prevalence of Potential Shunting

Detection Method	SCA/Stroke # (%)	Control # (%)	p
2D Imaging	3/139 (2.2%)	0/122 (0%)	0.250
Color Doppler	9/139 (6.5%)	8/122 (6.6%)	0.978
Contrast w/o Valsalva	22/146 (15.1%)	19/122 (15.6%)	0.909
Contrast w Valsalva	24/145 (16.6%)	19/118 (18.7%)	0.922
Potential Intracardiac Shunting	32/147 (21.8%)	23/123 (18.7%)	0.533
Potential Intrapulmonary Shunting (Late Bubbles)	35/147 (23.8%)	7/123 (5.7%)	<0.001
Any Potential Shunting	67/147 (45.6%)	29/123 (23.6%)	<0.001

- Increased prevalence of potential right-to-left shunting in SCD/stroke compared to Control patients

Dowling, et al., 2016

Acute management of ischemic strokes and the use of tissue plasminogen activator (tPA) for adults with SCD presenting with stroke symptoms

ASH guideline Recommendation 4.1. Strong For children or adults with SCD and acute neurological deficits, including transient ischemic attack, the ASH guideline panel recommends prompt blood transfusion. The transfusion should be given immediately upon recognition of symptoms without delay beyond several hours of acute neurological symptom presentation. The type of transfusion (simple, modified exchange or apheresis) is dependent on individual patient factors and local transfusion resources Please please please transfuse slowly

ASH guideline Recommendation 4.2. Conditional For children or adults with SCD and acute neurological deficits including transient ischemic attack, the ASH guideline panel suggests exchange transfusion versus simple transfusion (see details for exceptions). When exchange transfusion is not available within two hours of presentation for medical care and hemoglobin is ≤8.5 g/dl, simple transfusion can be performed to avoid delays in treatment while a manual exchange transfusion or an automated apheresis is planned

Acute management of ischemic strokes and the use of tissue plasminogen activator (tPA) for adults with SCD presenting with stroke symptoms

ASH guideline Recommendation 7. Conditional For adults with SCD presenting with symptoms of acute ischemic stroke and being considered for intravenous tPA (age ≥ 18 years, no hemorrhage on CT scan, within 4.5 hours of onset of symptoms/signs and without contraindications for thrombolysis), the ASH guideline panel suggests management using a shared decision-making approach that follows these principles.

a. In all patients, the administration of tPA should not delay prompt simple or exchange blood transfusion therapy.

b. Patients may be considered for intravenous tPA based on its established inclusion and exclusion criteria detailed in stroke management algorithms.

c. The following factors suggest likely benefit from intravenous tPA: older age, atrial fibrillation, diabetes, hypertension, and hyperlipidemia. Management of younger patients without these risk factors should emphasize early transfusion.

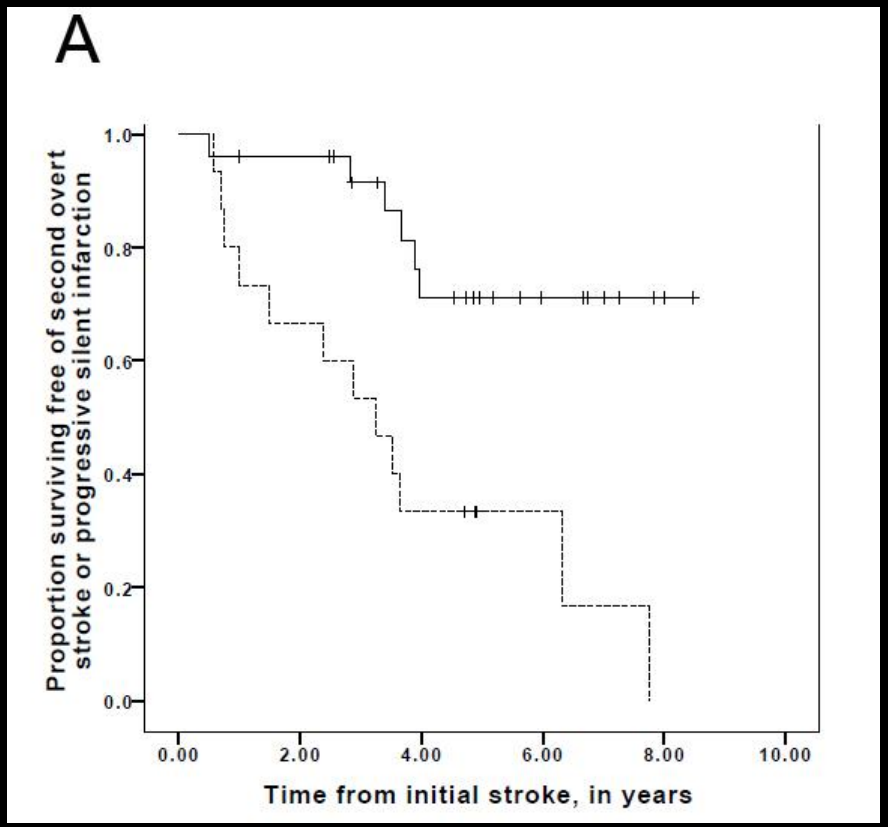
d. There are no validated risk stratification or reliable age cutoffcut-off criteria to guide the choice of initial therapy. Intravenous tPA is not recommended for children with SCD (<18 years of age).

Can we prevent recurrent stroke in those who have already had a first stroke?

Neuro-Heme consortium

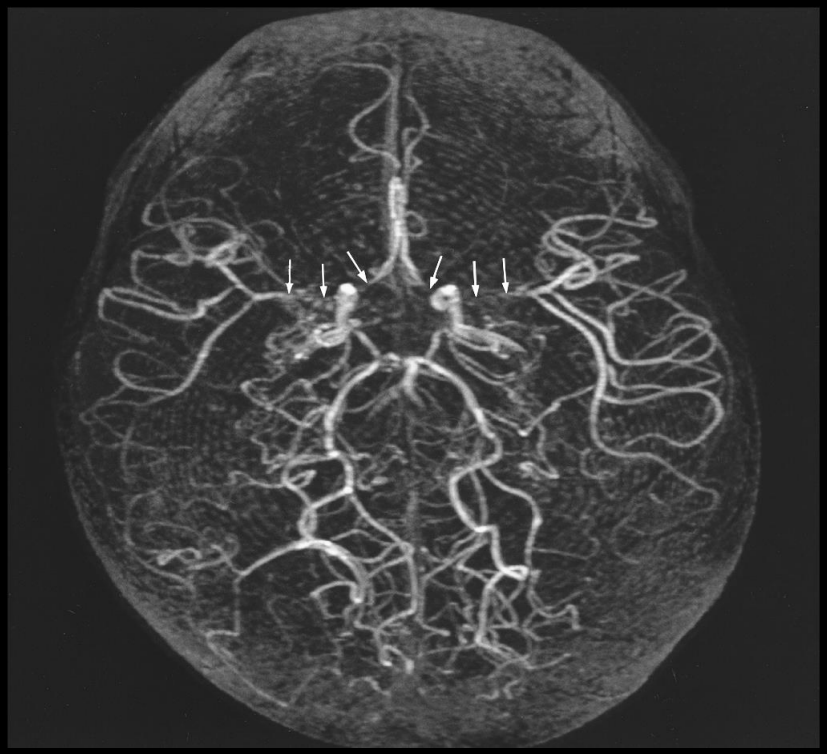
n=40 SCD transfused after stroke at least every 6 weeks to HbS<30%

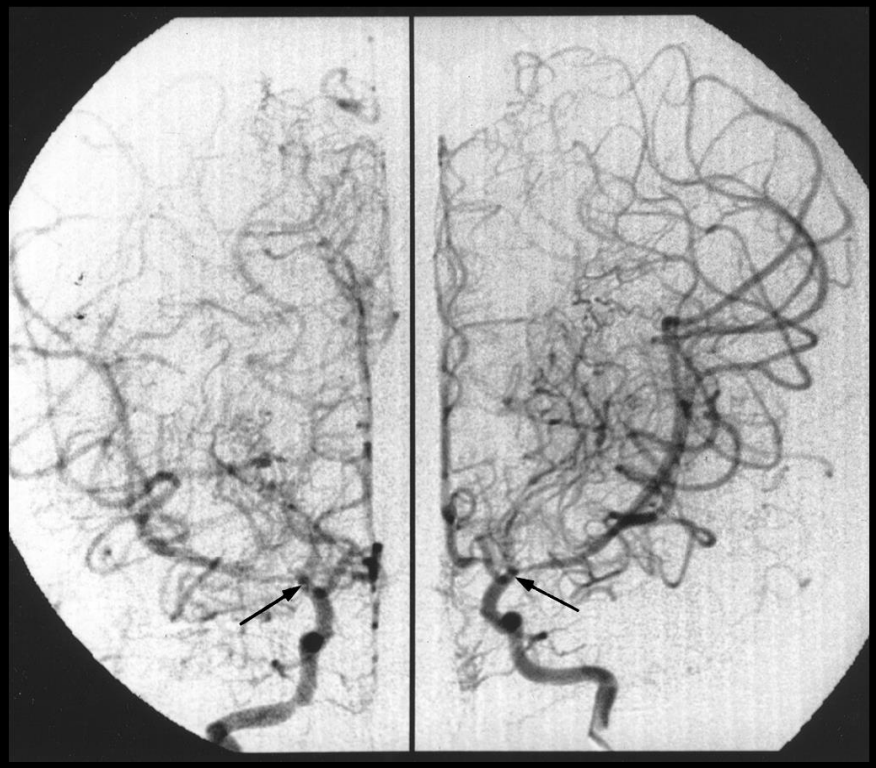
Hulbert et al 2010



Overt and covert stroke

Moyamoya

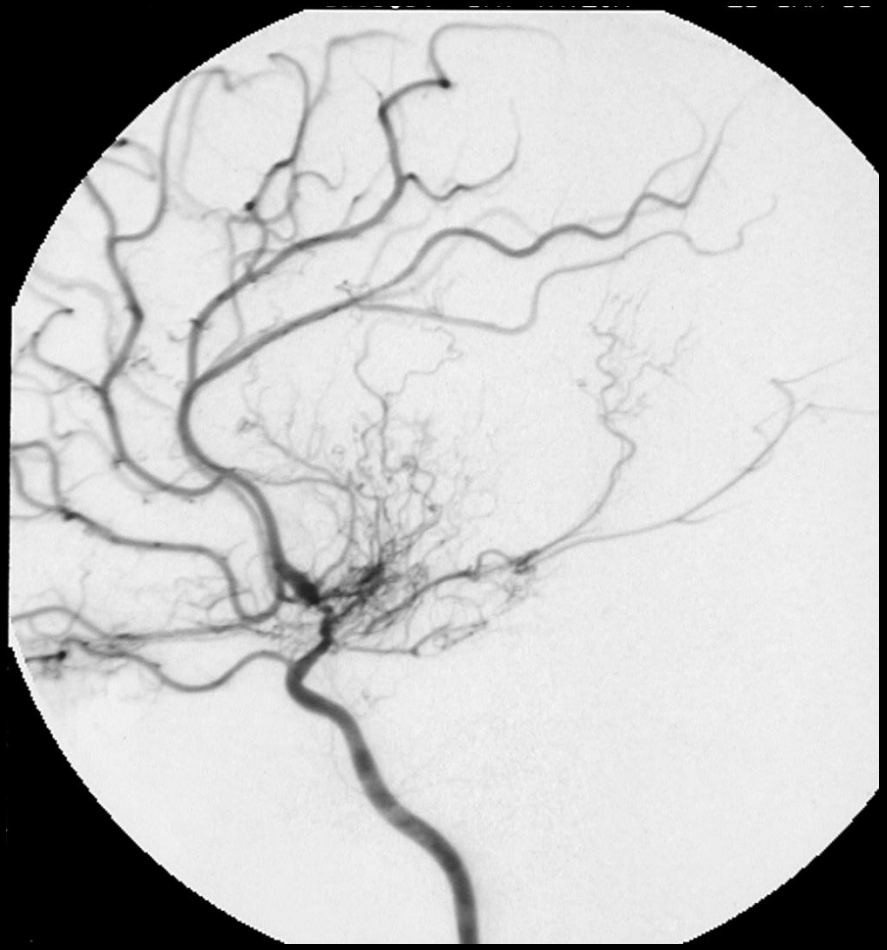




Severe stenosis or occlusion of the terminal internal carotid artery / proximal middle cerebral artery with collateral vessels *Yoon 2000*

Long term secondary prevention

- Transfuse for 3 years to HbS <30%
- Lifelong transfusion to HbS <50%
- Bone marrow transplantation?
- Revascularisation for moyamoya?
- Hydroxyurea + phlebotomy? SWITCH



Secondary prevention of ischemic strokes in children and adults with HbSS or HbSβ0 thalassemia

- **ASH guideline Recommendation 5. Strong** For children with HbSS or HbSβ^0 thalassemia and a history of prior ischemic stroke, the ASH guideline panel recommends that blood transfusion goals for secondary stroke prevention be to increase the hemoglobin above 9 gm/dl at all times and to maintain the HbS level at <30% of total hemoglobin until the time of the next transfusion
- **ASH guideline Recommendation 6. Conditional** For adults and children with SCD, moyamoya syndrome and a history of stroke or transient ischemic attack, the ASH guideline panel suggests evaluation for revascularization surgery in addition to regular blood transfusion

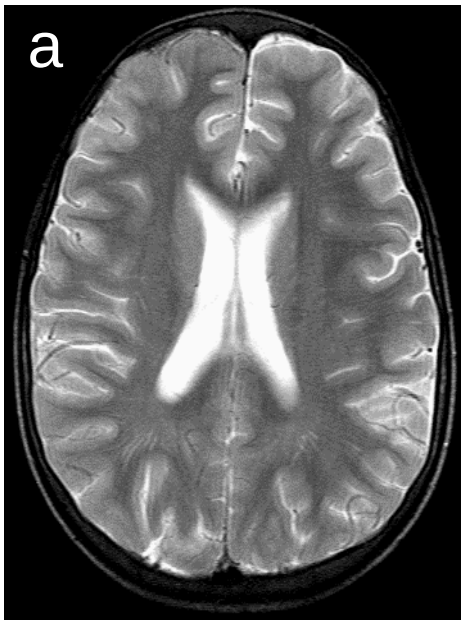
Acute severe headache

Child recently arrived from Africa

- First acute chest crisis
- Sudden onset very severe headache
- TCD: abnormal
- MRI: no infarct
- MRA: narrowing

Headaches post chest crisis

a



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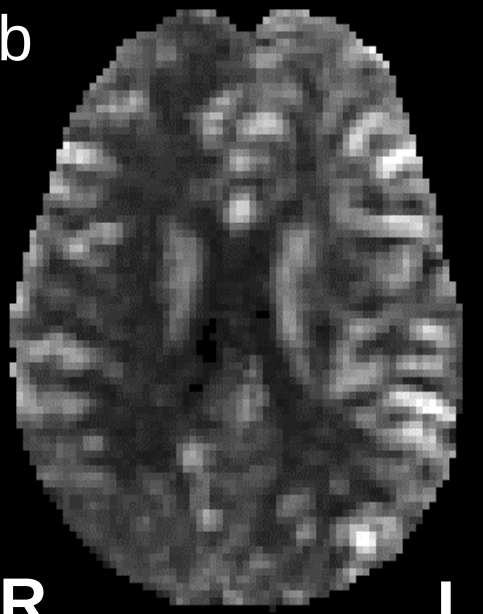

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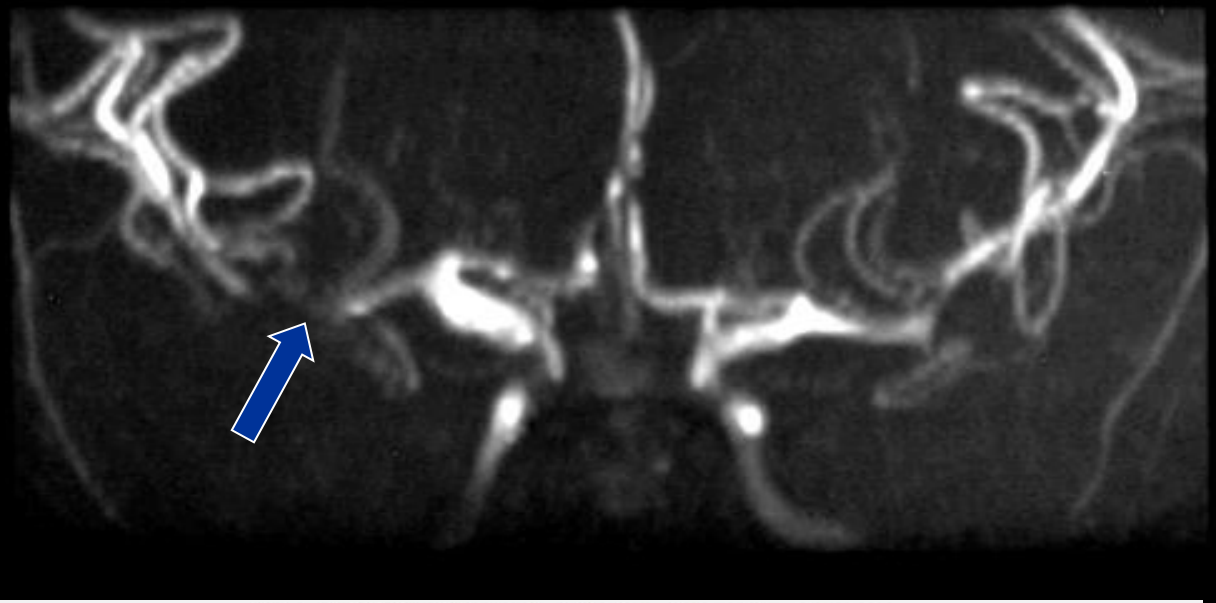

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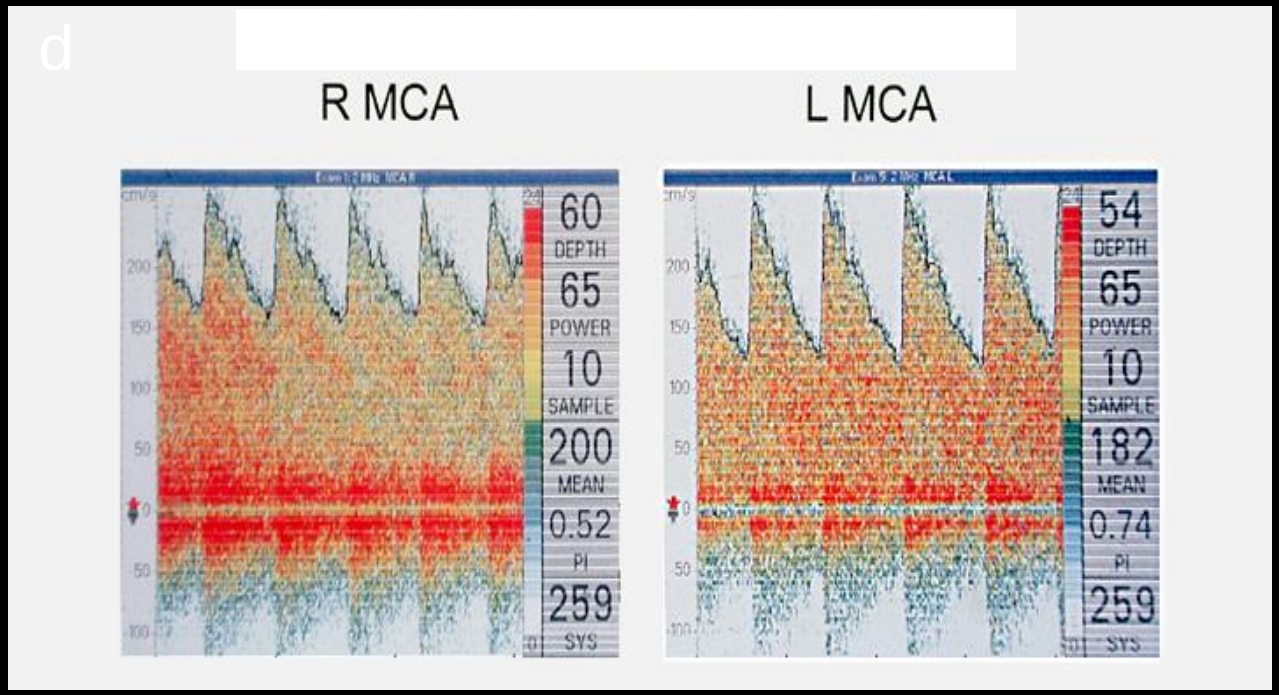
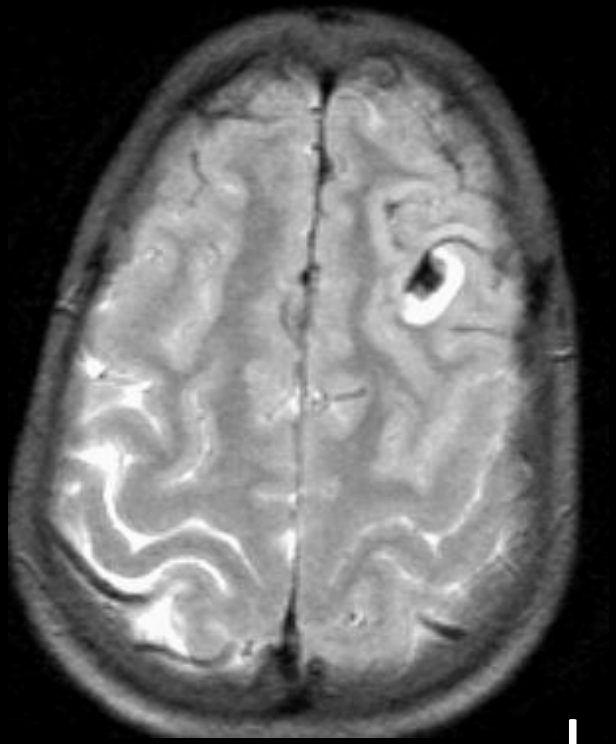


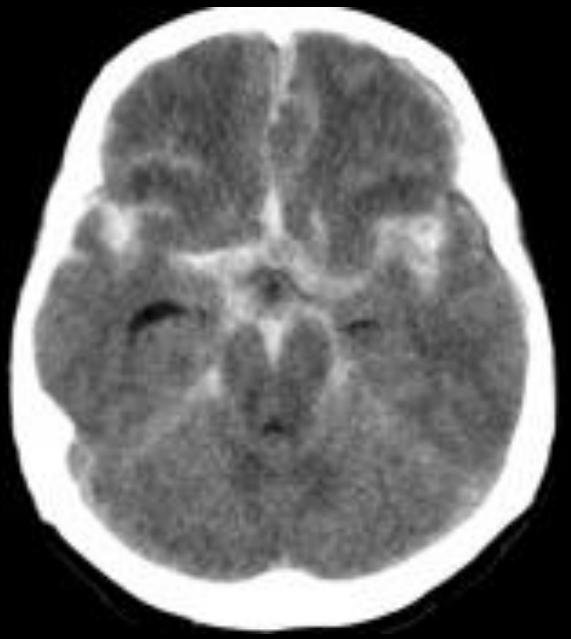
Haemorrhagic stroke

Subdural

Intracerebral

Subarachnoid

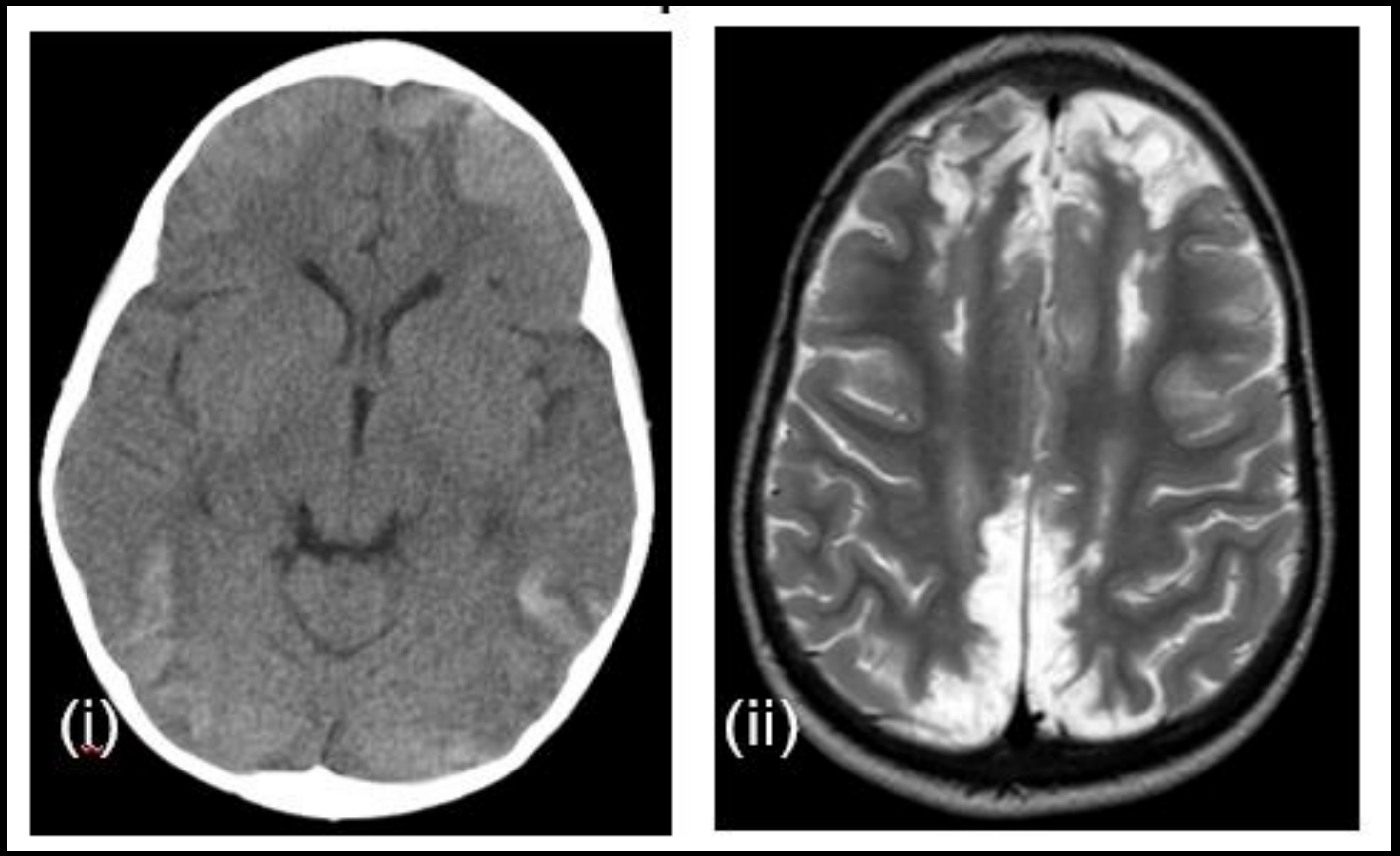




R

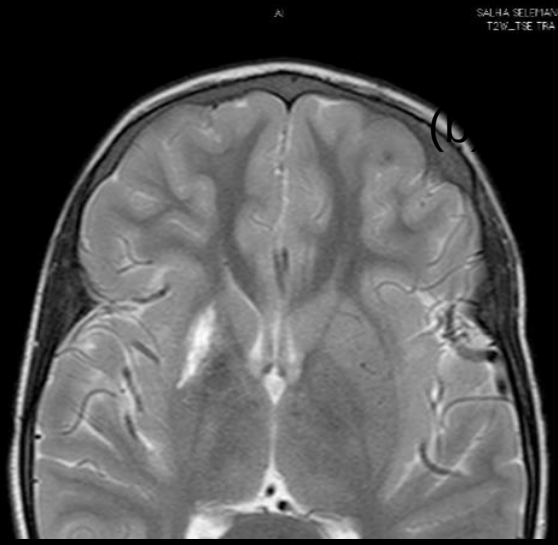
L

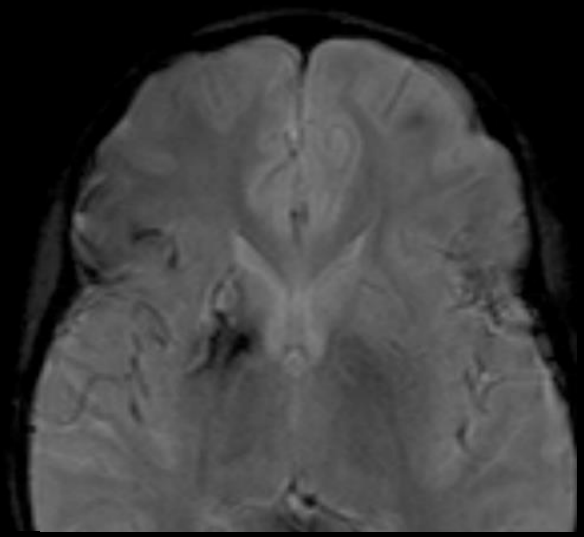
Severe headache after ACS



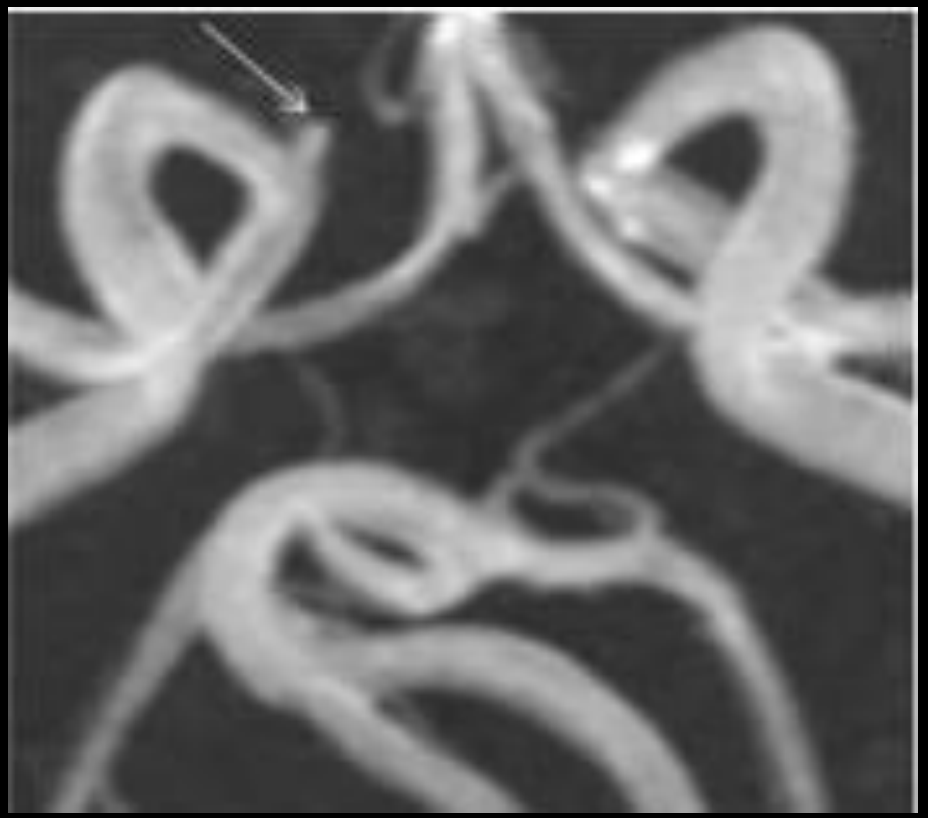
Top up transfused from Hb 50 g/L to 14 g/L over 4 hours

Haemorrhage associated with ischaemic stroke on gradient ECHO MRI





Cerebral aneurysm

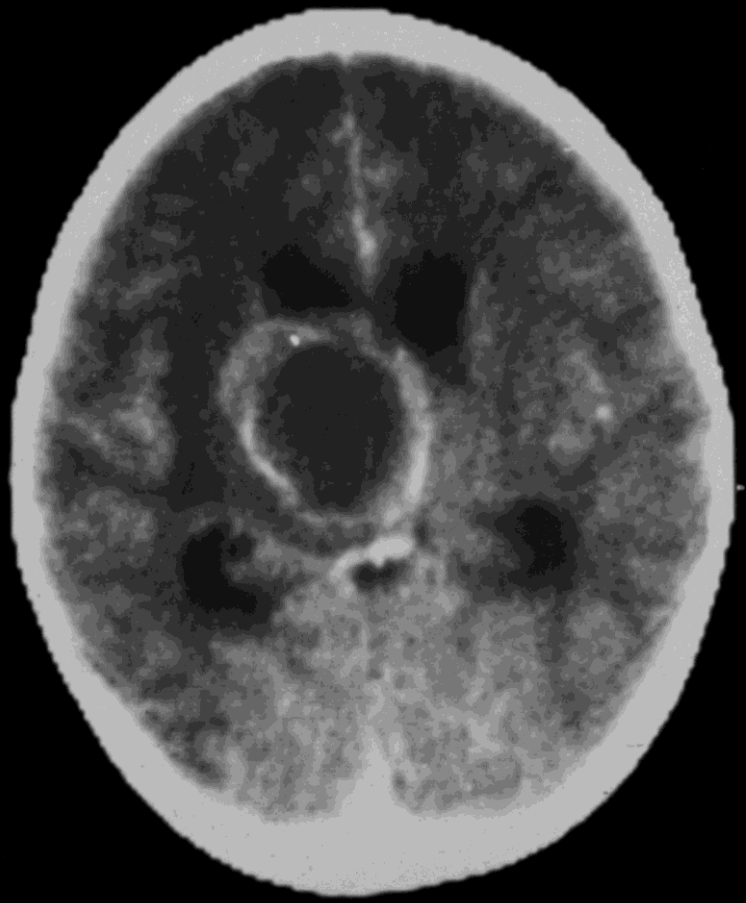


1st acute severe headache in SCD

- Manage as a neurological emergency
- Urgent neuroimaging
  - CT
  - MRI with gradient ECHO/ SWI and MRA
- If haemorrhage contact
  - neurosurgical unit
  - Paediatric or adult neurologist
- If infarct emergency transfusion
- If no haemorrhage/infarct ?migraine

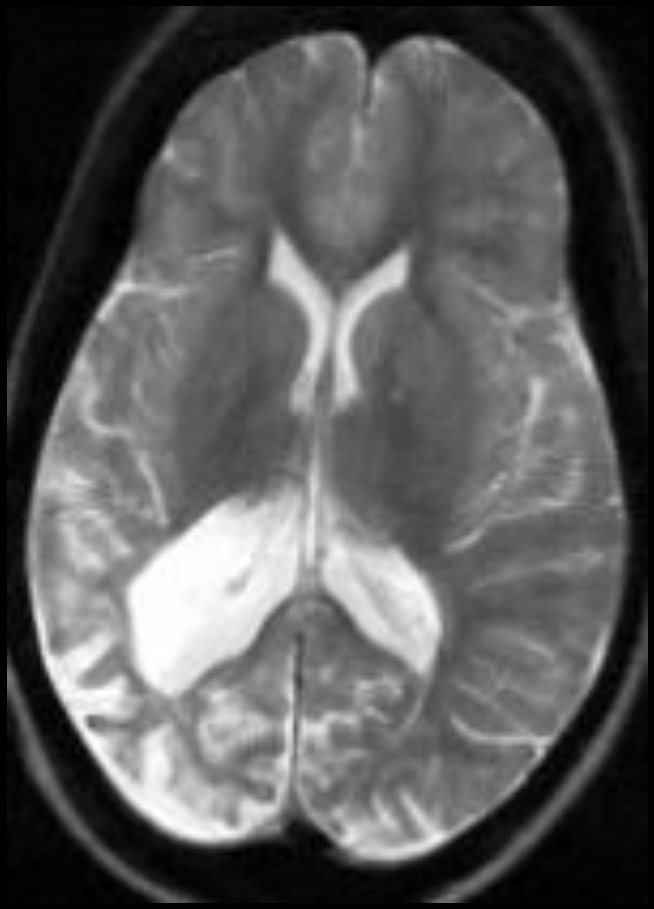
Acute seizures

18 months ‘febrile convulsion’



Sagittal sinus thrombosis

Pneumococcal meningitis, longstanding epilepsy



Straight sinus thrombosis

HbSC, unexplained hydrocephalus in infancy, headache, seizures, coma

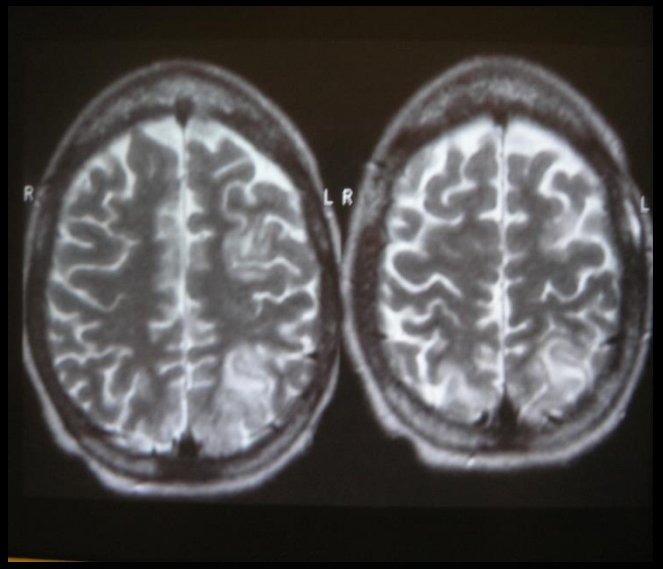
Sébire 2005

Straight sinus thrombosis

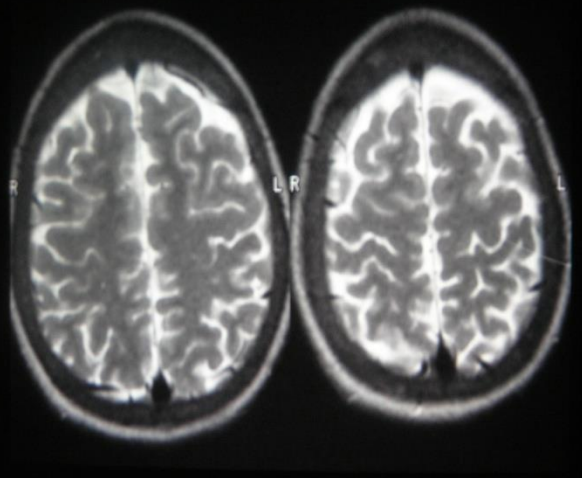
‘Reversible posterior leukencephalopathy’

Henderson 2003, Solh 2016

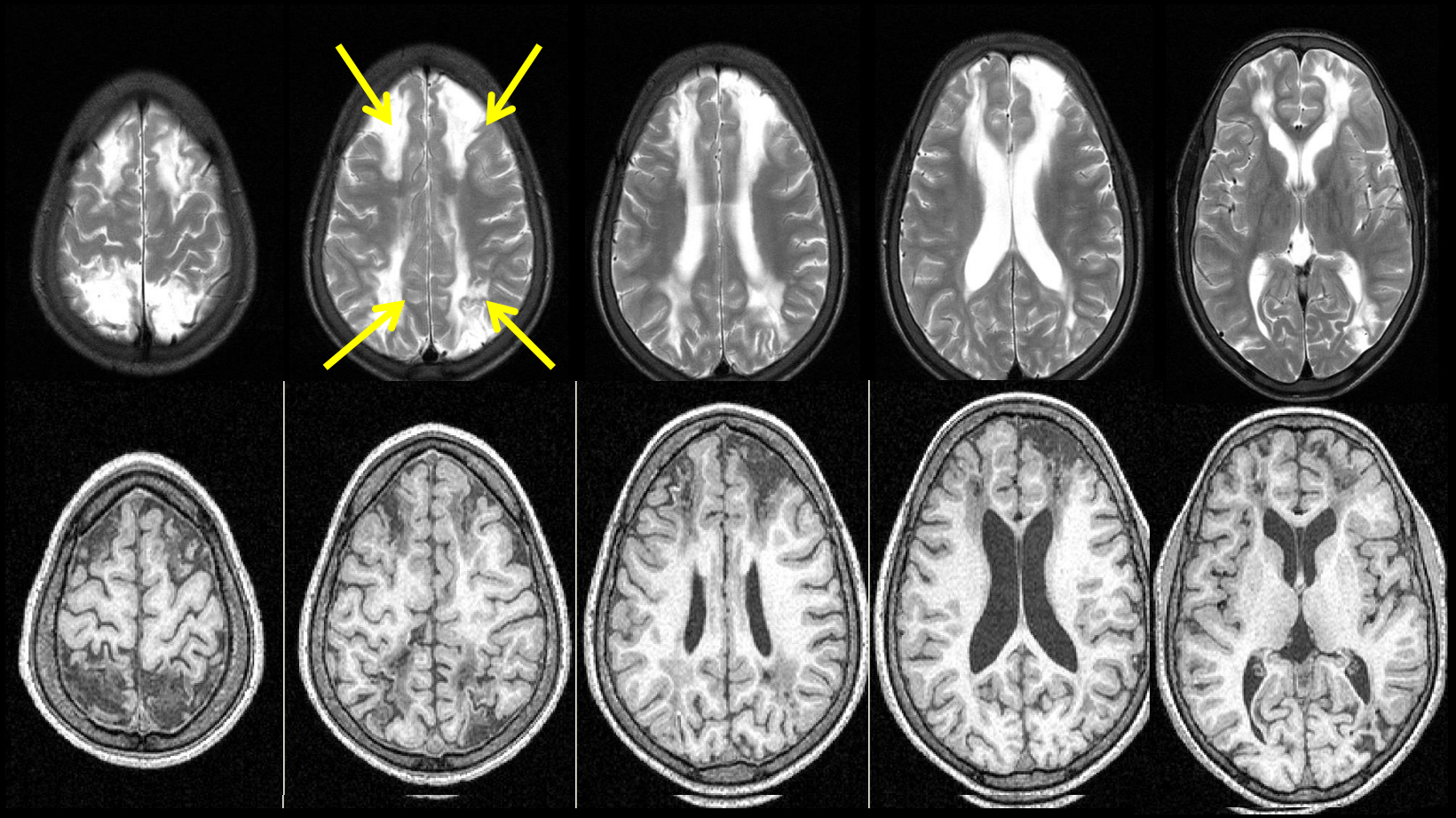
Chest crisis
Seizures
Coma



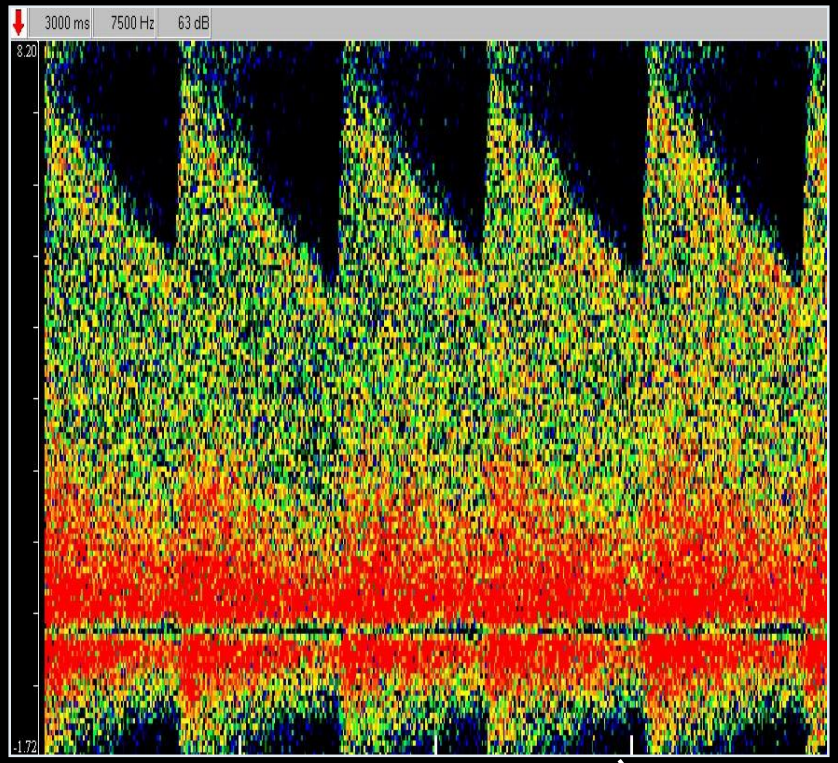
Chronic epilepsy

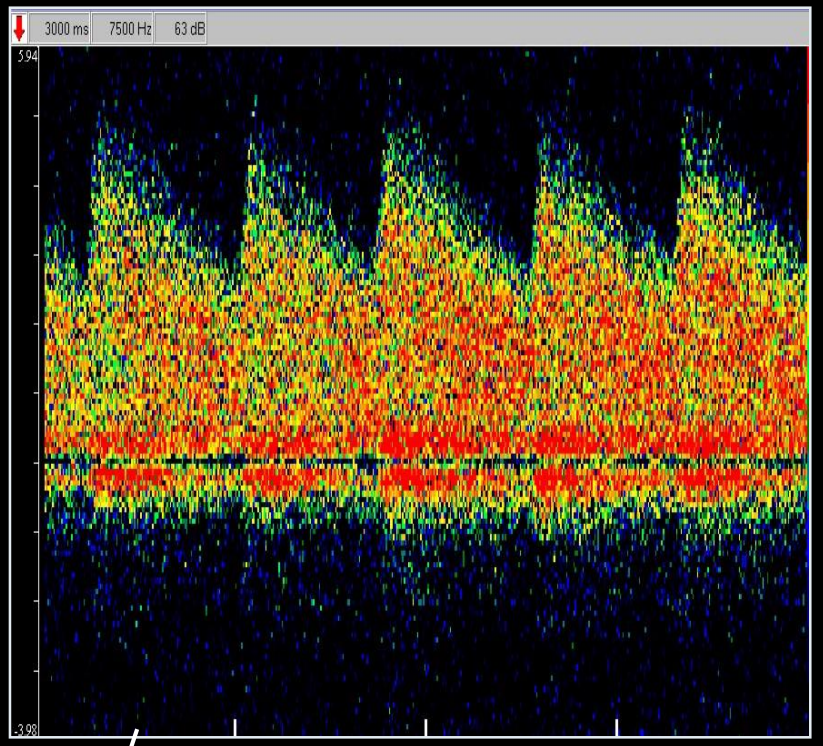


Bilateral borderzone infarction

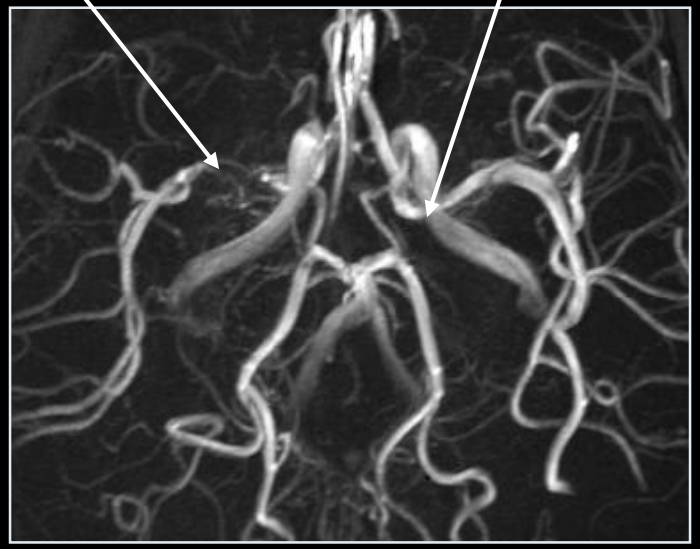


Facial infection, seizures





Right MCA
220 cm/sec



Left MCA
130 cm/sec

Seizures & TCD

Prengler 2005

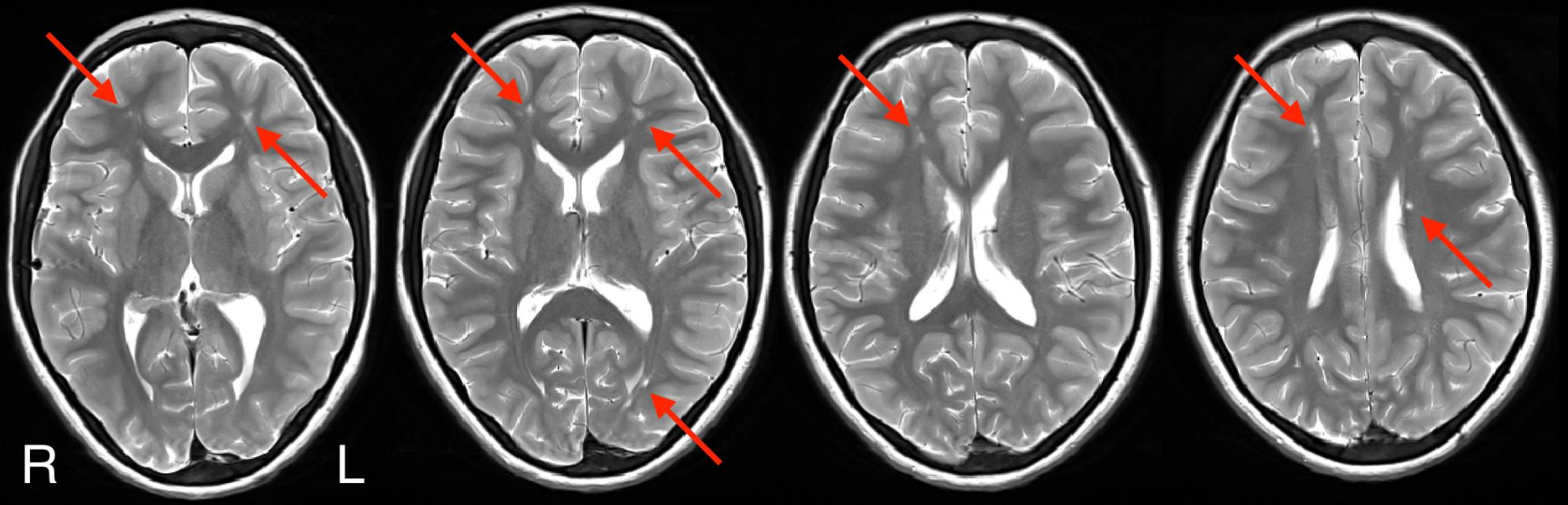
1st acute seizure in SCD

- May be presenting feature of
  - Stroke
    - Arterial
    - Venous
  - Posterior reversible encephalopathy syndrome
  - Cerebral abscess
- Emergency MRI for 1st seizure if GCS not 15
- TCD
- Epilepsy 10 times as common as general paediatric population

What about ‘silent’ (covert) infarction

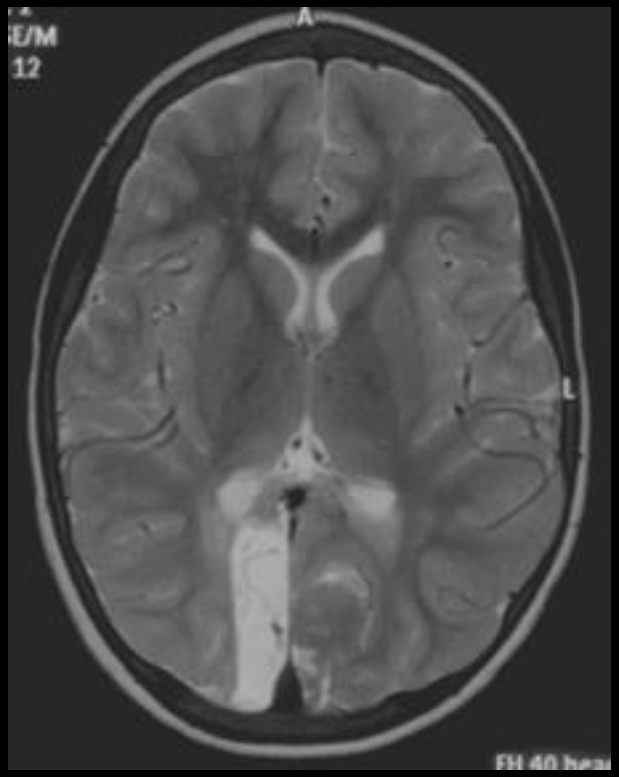
Silent cerebral infarction

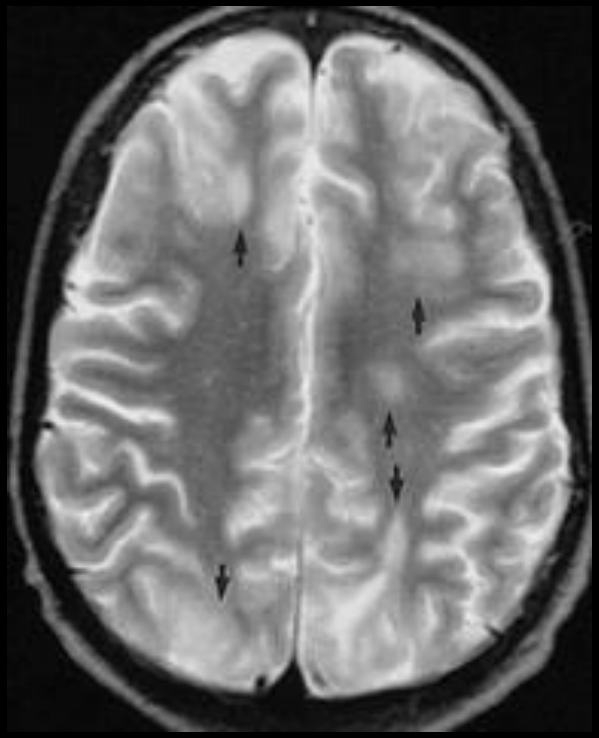
= “at least 3mm in diameter, seen in two planes of T2-weighted MRI” (SIT trial 2010)



12 year old boy with HbSS

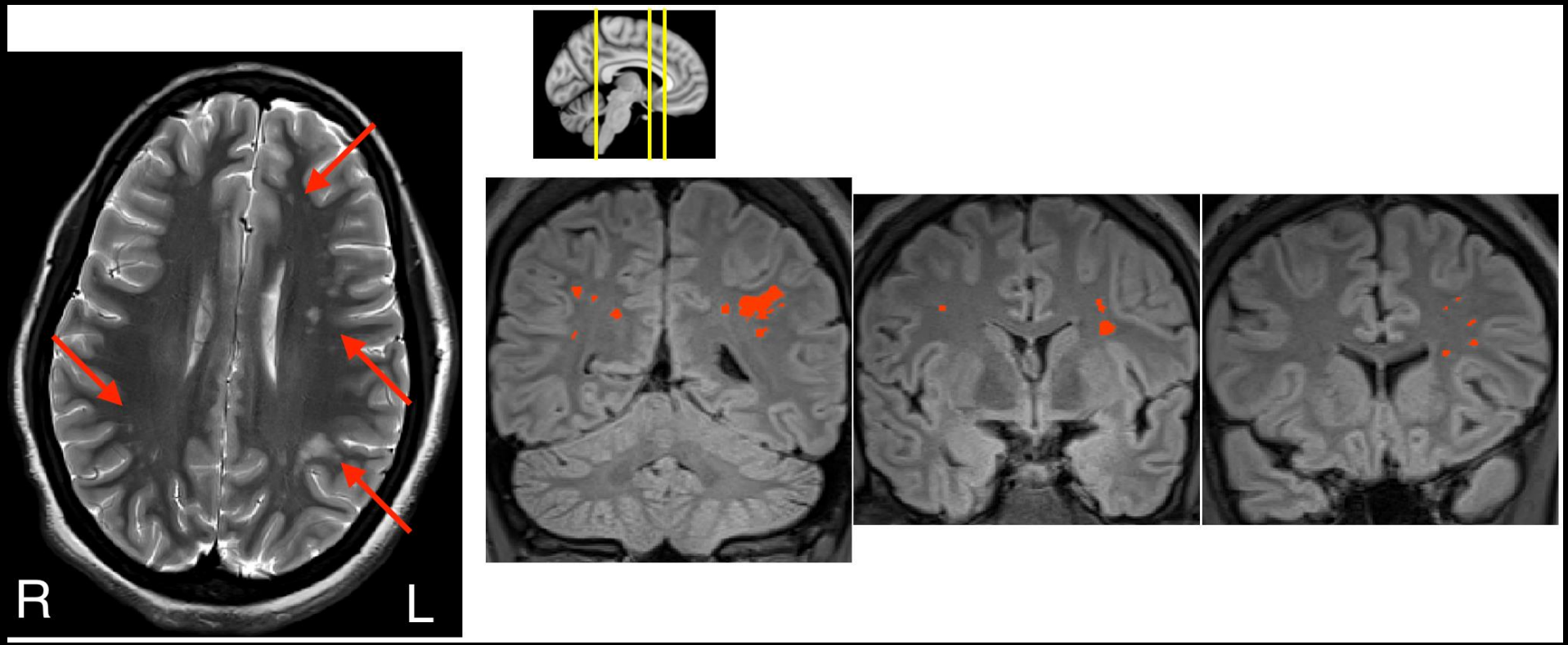
‘Silent’ cerebral infarcts (SCI+)





Progressive SCI

Bilateral frontal and parietal SCI *Kawadler & Kirkham 2016 IN-TECH*



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

M.R. DeBaun, M. Gordon, R.C. McKinstry, M.J. Noetzel, D.A. White, S.A. Sarnaik, E.R. Meier, T.H. Howard, S. Majumdar, B.P.D. Inusa, P.T. Telfer, M. Kirby-Allen, T.L. McCavit, A. Kamdem, G. Airewele, G.M. Woods, B. Berman, J.A. Panepinto, B.R. Fuh, J.L. Kwiatkowski, A.A. King, J.M. Fixler, M.M. Rhodes, A.A. Thompson, M.E. Heiny, R.C. Redding-Lallinger, F.J. Kirkham, N. Dixon, C.E. Gonzalez, K.A. Kalinyak, C.T. Quinn, J.J. Strouse, J.P. Miller, H. Lehmann, M.A. Kraut, W.S. Ball, Jr., D. Hirtz, and J.F. Casella

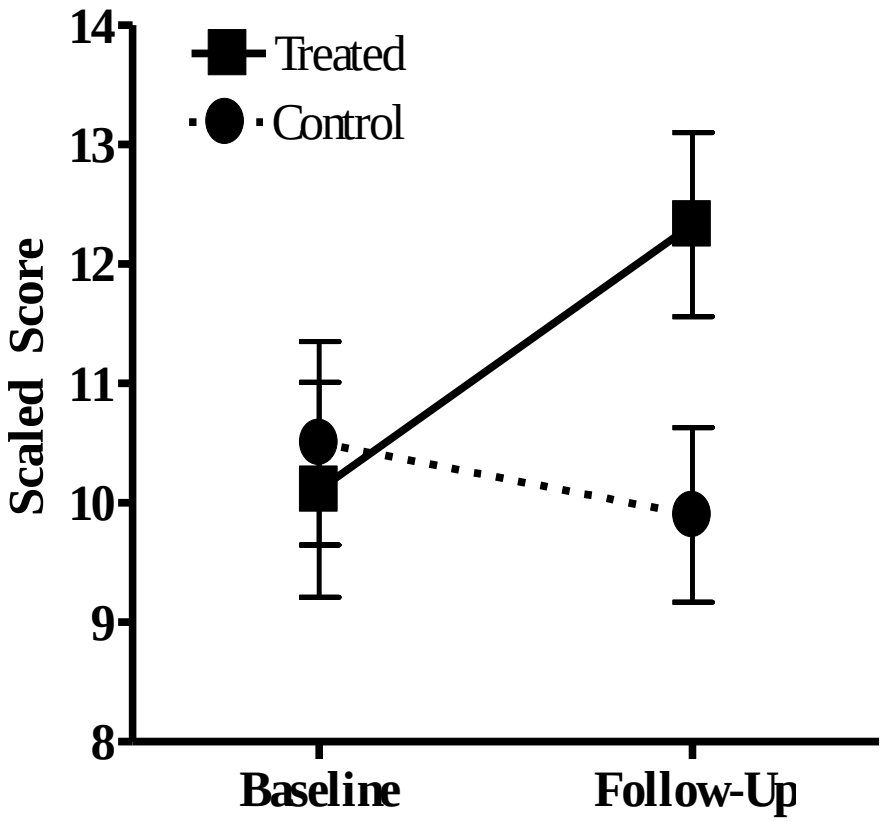
Screening for silent cerebral infarcts in children and adults with HbSS or HbSβ0 thalassemia

- **ASH guideline Recommendation 10.1** **Strong** Given the high prevalence of silent cerebral infarcts in children with HbSS or HbSβ^0 thalassemia (1 in 3) and their association with cognitive impairment, poor school performance, and future cerebral infarcts, the ASH guideline panel recommends at least a one-time MRI screening without sedation to detect silent cerebral infarcts in such early-school-age children, when MRI can be performed without sedation
- **ASH guideline Recommendation 10.2.** **Conditional** Given the high prevalence of silent cerebral infarcts in adults with SCD HbSS or HbSβ0 thalassemia (1 in 2) and their association with cognitive impairment, poor school performance and future cerebral infarcts, the ASH guideline panel suggests at least a one-time MRI screening without sedation to detect silent cerebral infarcts in these adults

Other preventative strategies?

- Transfusion for silent infarction?
- Hydroxyurea for primary prevention?
- Monoclonal antibodies?
  - Crizalinumab
- Anti-polymerisation
  - Voxelator
- Bone marrow transplant
- Gene therapy
  - LentiGlobin incr HbA / CRISR to incr HbF

Overnight Auto-adjusting Positive Airway Pressure / cancellation



Conclusions

- Several stroke syndromes
- Brain compromise in SCD complex
- Primary and secondary prevention of stroke and SCI with blood transfusion for life!
- Hydroxyurea – TWiTCH suggests after 1 year prophylaxis for high TCD with no MRA
- Primary prevention with hydroxyurea?
- Revascularisation an option for moyamoya
- Bone marrow transplant an option
- ASH guidelines 2020