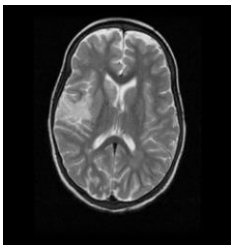
NEUROLOGICAL CONSIDERATIONS IN SICKLE CELL DISEASE & THALASSAEMIA

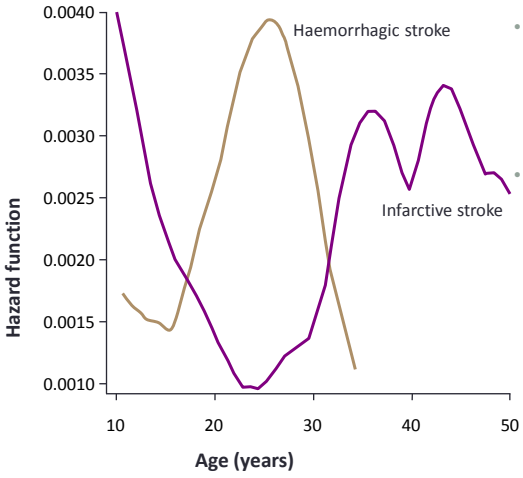
DR MOIRA DICK AND DR SUE HEIGHT



Neurological Complications in Sickle Cell Disease

- CNS is site of major morbidity in SCD
- Complications include
  - Stroke – event lasting >24 hours +/- new areas of abnormality on scan
  - Silent infarcts
  - Transient ischaemic attacks: resolve <24 hours/no change on imaging
  - Intracranial haemorrhage
  - Cognitive impairment
  - Fits
  - Headaches
  - Visual symptoms – can occur in isolation

Stroke subtype by age



- **Infarctive stroke**
  - 54% of CVAs
  - highest in 1st decade and after 30 years
  - peak at 2–5 years
- **Haemorrhagic stroke**
  - during 3rd decade

CVA = cerebrovascular accident.

Epidemiology of Stroke in SCD

Commonest cause of death in adults in UK (NCEPOD 2008)

- HbSS > HbSβ^0 >HbSβ$^+$ > HbSC

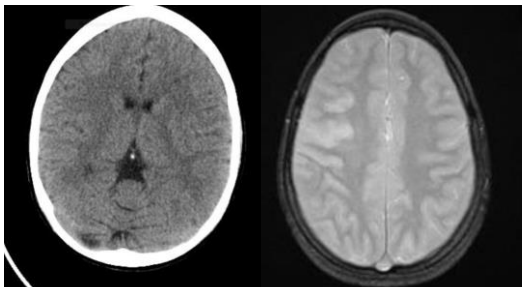
Sickle cell anaemia (HbSS): Commonest cause of stroke in children (not neonates)

- 300x more common than in children who do not have HbSS
- Peak incidence at 2-5 years and > 50yrs
- Overall prevalence 4%
- Marked reduction in children since Doppler screening

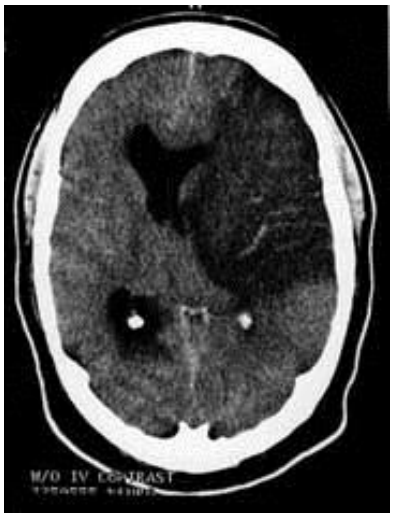
- 'Silent' Stroke – present 37% by the age of 14 years
- cognitive deficiencies and higher overt stroke risk

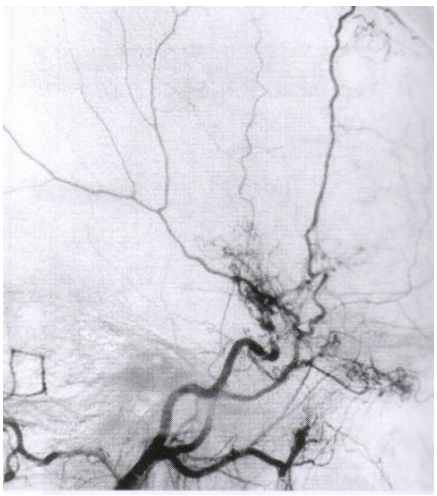
Features of Infarctive Stroke in SCD

- Overt strokes
  - Stenosis of intracranial carotid & middle cerebral arteries
  - Progressive vessel occlusion and moyamoya can occur
  - Anterior cerebral circulation
  - Infarction of 'watershed' areas
  - Pathological basis not clear
    - blockage of vasa vasorum
    - 'endothelial damage'
    - Nitric oxide deficiency/free plasma haemoglobin
    - Aggravated by anaemia
- Aneurysms
- Silent Cerebral Infarcts



Stroke



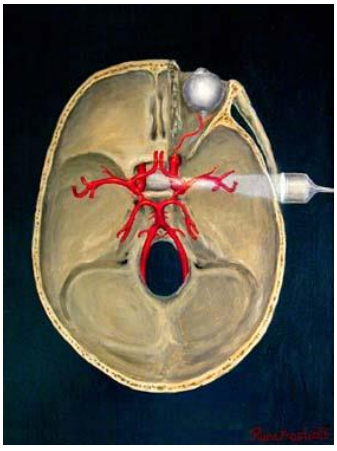


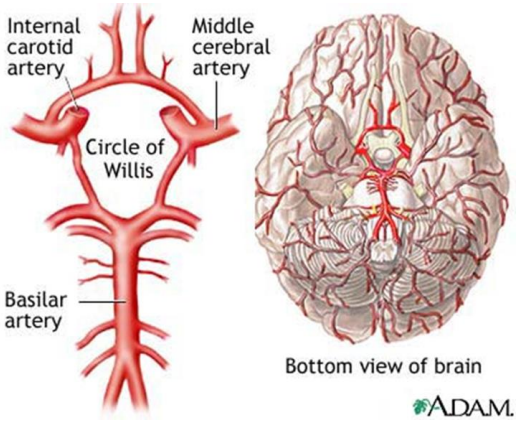
Risk factors for Stroke in SCD

- Previous TIA
- Anaemia*
- Acute Chest Syndrome in last 2 weeks *
- Rise in Systolic BP*
- Family History – affected sibling
- Silent infarcts
- Nocturnal Hypoxia
- Children – Transcranial Doppler Velocities**

- * may occur in inpatients admitted for other reasons

Transcranial Doppler Scanning (2-16 years – standard of care

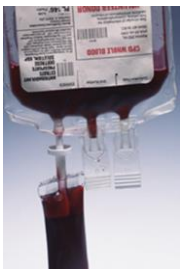




Transcranial Doppler Scan (TCD)

- Measurement of blood velocity – detects stenosis
- Age 2-16yrs annual scans
- Ranges defined by STOP study: velocities in
  - middle cerebral arteries (MCA) or
  - distal internal carotid arteries d(ICA)
- Identify those at risk of stroke – primary prevention
  - Normal: < 170 cm/sec
  - Abnormal: >200cm/s
  - Conditional: 170-200cm/s
  - Inadequate: MCA, dICA, bifurcation not seen
  - Abnormal TCD → stroke risk of 10% per year

Primary Prevention of Stroke in SCD



- Stroke Prevention Trial in HbSS (STOP) Study
  - Abnormal TCDs (>200cm/s)
  - 63 assigned transfusions → 1 stroke
  - 67 standard care →10 strokes, 1 intracerebral bleed
- Optimizing Primary Stroke Prevention in HbSS (STOP 2)
  - children with HbSS, with normal TCDs after >30 months of transfusions for abnormal TCD
  - 41 stopped transfusions →14 redeveloped abnormal TCDs, and 2 strokes
  - 38 continued transfusion → no abnormal TCDs or strokes

Clinical Presentation of Stroke

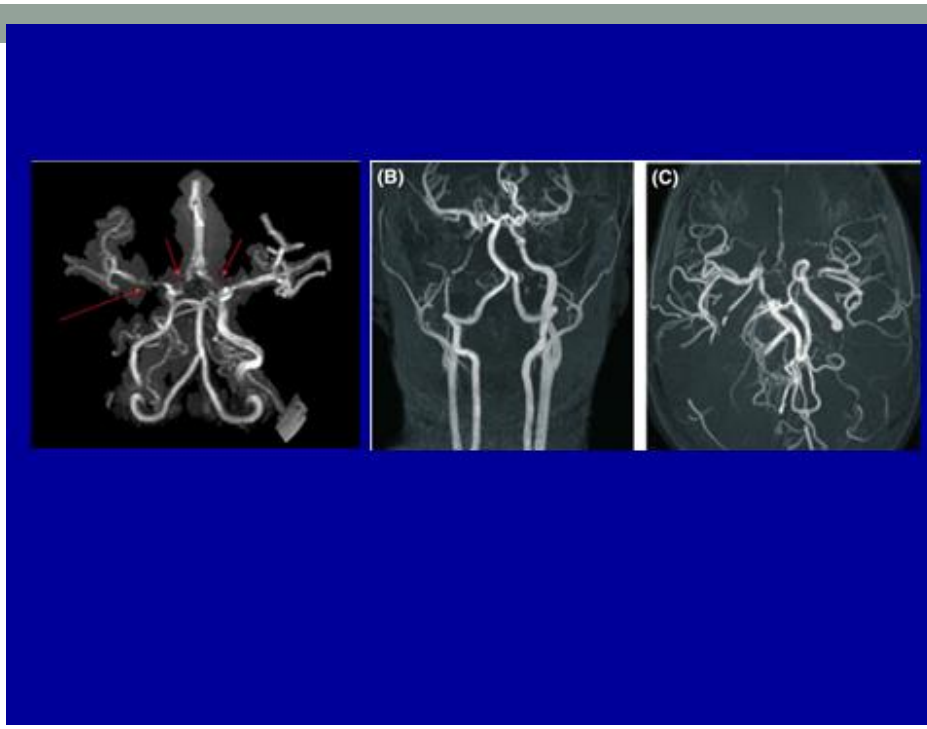
- Weakness
- Aphasia
- Seizure
- **Painless** limp
- Subtle/transient motor changes
- Coma
- Can be difficult in young children
- TIA (transient) – symptoms may resolve by time they are seen
- HIGH INDEX OF SUSPICION

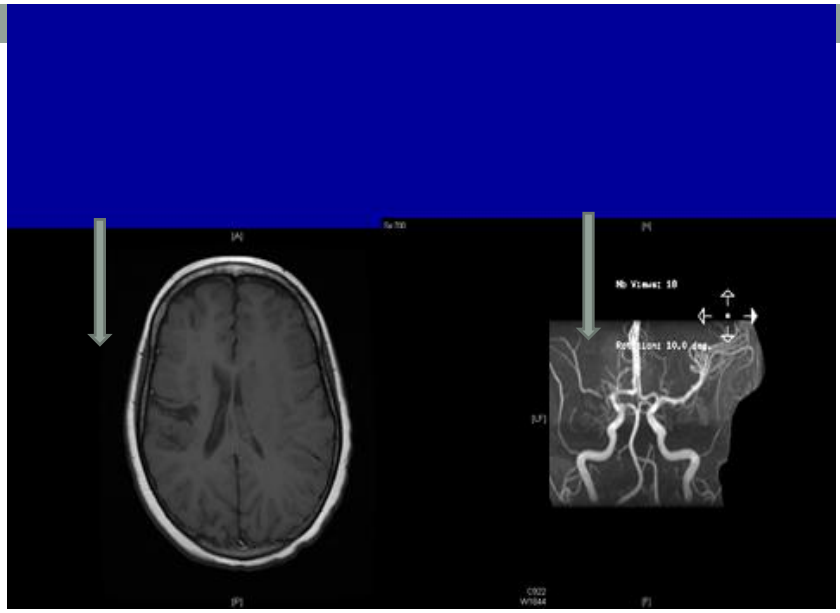
Diagnosis of Acute Stroke

- History, symptoms and signs
- **Awareness of possibility of diagnosis**
- Urgent imaging
  - CT scan to exclude intracranial haemorrhage/space occupying lesion
  - MRI/MRA with diffusion weighting images
  - Child <8 years may need GA
- If abnormal/deteriorating neurology, or strong clinical suspected proceed with treatment whilst awaiting scans

Investigations

- Blood tests urgent
  - FBC & reticulocytes
  - Group and save (will need sickle negative RBCs, ABO and RhD Kell matched)
  - LFTs, U&Es, Glucose, CRP
  - Coagulation screen
  - Consider Malaria Screen, auto-antibodies
  - If not known to King's OR on regular transfusions send HbS%
- Imaging – urgent CT scan
  - ?infarct or bleed …(or Space Occupying Lesion)



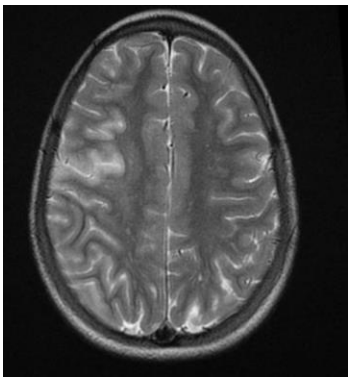


Acute Management of Stroke

- Oxygenation – maintain >96%,
- Adequate hydration –avoid overload
- Regular neurological observations
- Protect airway if necessary
- BP monitoring
- Urgent blood transfusion if Hb <80g/l →100g/l
  - Sickle Negative
  - ABO RhD Kell negative red cells
  - Proceed to urgent exchange transfusion to reduce HbS <30% and increase Hb 12g/l – manual or automated (apheresis).
  - Isovolaemic, avoid fluid shifts, close monitoring

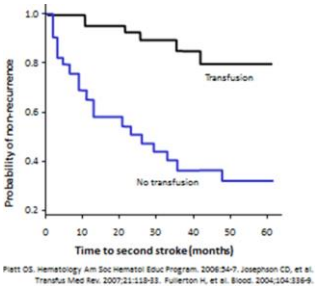
Further management and differential diagnosis to consider

- SALT assessment
- Further imaging/transfusion if continued deterioration
- Consideration of other possible diagnoses, including meningitis, encephalitis, paradoxical embolism
- Rehabilitation
- Further investigations
  - ECHO
  - Sleep Study
  - Neuro-cognitive assessments



Risk of recurrent stroke

- 70% recur in 2 years without transfusion
- 90% reduction of risk with transfusion
- Moya-moya vasculopathy - significant risk even with transfusion
- After 2 years, risk is lower in those who had a prior or concurrent medical illness
- Despite chronic transfusions, overt & silent strokes occur



Platt OS. Hematology Am Soc Hematol Educ Program. 2006:54-7. Josephson CD, et al. Transfus Med Rev. 2007;21:118-33. Fullerton H, et al. Blood. 2004;104:336-9.

Secondary Prevention of Stroke

- Regular blood transfusion
  - Maintain HbS<30%, Hb>9g/dl
  - Reduces risk of recurrence to about 10%
  - Either: 3-4 weekly top-up transfusions or
  - Automated exchanges (apheresis) 6-8 weekly
- Management of complications of blood transfusion
  - Iron overload → iron chelation - Exjade FCT (or Desferrioxamine)
  - Allo-immunisation
  - Transfusion transmitted infections - immunisations
- Sibling allogeneic bone marrow transplantation
  - HLA type full siblings who do not have HbSS

Deterioration on Regular Transfusion

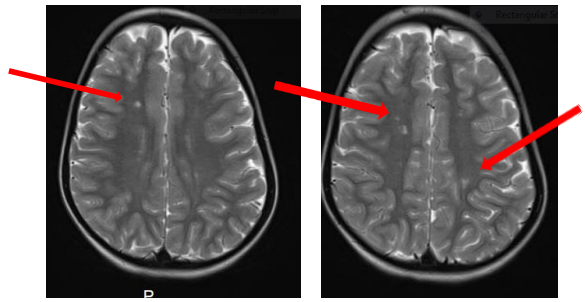
- ~5-10% children have further strokes despite transfusions
  - 40% suffer further cerebrovascular events - TIAs
  - 20% with moyamoya have further strokes
- Therapeutic options
  - Reduce HbS% <10%
  - Add hydroxyurea
  - Correct overnight hypoxia – oxygen, tonsillectomy
  - Aspirin/dipyridamole (but not in moyamoya)
  - Cerebrovascular bypass procedures

Neovascularisation Surgery

- Surgical techniques established for Moyamoya in Japan
- Several case reports showing benefit in progressive sickle vasculopathy
- Different surgical approaches
  - Encephalo-duro-arteriosynangiosis (EDAS)
  - Extracranial-intracranial bypass

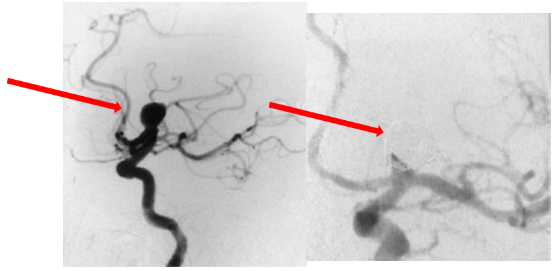
Silent Infarcts ('Silent Strokes')

- Abnormal MRI and no CVA or neurological symptoms>24 hours
- Present in 22% children with HbSS by age 14 years
- Mainly frontal lobes, deep white matter, small vessel disease
- Not clearly linked to large vessel disease or abnormal TCD
- Poor academic attainment
- Increased risk for CVA or new MRI abnormalities
- Seizures
- Headaches
- ?Prevention?



Haemorrhagic Stroke in SCD

- Highest risk in 20-29 year group
  - Cerebral artery aneurysms and MoyaMoya - risk of rupture
  - Multiple, Occur at younger age, common in posterior circulation – develop on background earlier stenosis
  - Overall risk of 0.44 per 100 patient years
  - <20 years: 10% of 1st strokes haemorrhagic vs
  - >20 years: 50% 1st strokes haemorrhagic
  - Mortality 25% - commonest cause of death in adults with SCD
- Associations - more severe anaemia and higher WBC
- Presentation - Stroke, Sudden onset severe headache, seizure
- Investigation
  - Urgent CT scan
  - MRI/MRA
  - Cerebral angiography
- Management
  - Urgent exchange,
  - Interventional radiology,
  - Neurosurgery



Cognitive Impairment in Sickle Cell Disease

- Significantly reduced IQ in cerebrovascular disease
  - Those with CVAs or Silent infarcts: IQ 77
  - With normal MRI - Reduced IQ mean 4.3 lower than normal
- Reduced employment prospects
  - Higher unemployment
  - Lower mean income than matched population

Neurological Complications in Transfusion-Dependent Thalassaemia (Thalassaemia Major) and Thalassaemia Intermedia

- Cord compression
- Peripheral Neuropathy
- Cognitive Impairment
- Complications of Treatment
  - Chelation therapy – monitoring
    - Desferrioxamine
    - Deferasirox (Exjade)

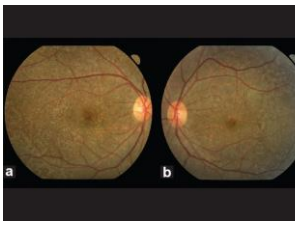
Visual and Auditory problems

- Can occur in Thalassaemia (or SCD) with iron overload as complication of chelation therapy with Desferrioxamine or Deferasirox (Exjade)
- Can be subclinical before symptoms develop
- Need for regular screening – annual
- Patients told to report problems
- For Desferrioxamine the risk of toxicity related to the therapeutic index
  - Maintain therapeutic Index:

$$\frac{\text{Dose /kg body weight (mg/kg)}}{\text{Ferritin mcg/l}} = <0.025$$

Eyes

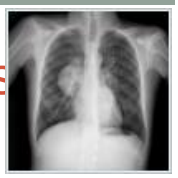
- Early changes can be asymptomatic
- Can be irreversible
- Incidence 1.2% (desferrioxamine)
- Importance of screening
- Symptoms – warn patients to report
  - Loss of colour/night vision
  - Loss of acuity/ change in visual fields/central blind spot
- Clinical
  - Cataracts
  - Retinopathy
  - Macula –
  - Assess before treatment and annually



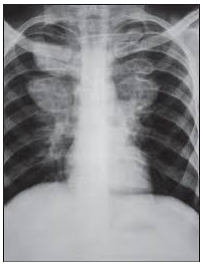
Ears

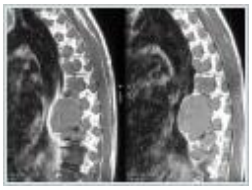
- High Tone Sensorineural Deafness
- Hearing loss
- Risks in higher doses of chelating agents
- Need annual checks of audiometry – can be irreversible.

Other Neurological complications



- Thalassaemia Intermedia
  - Asymptomatic paravertebral masses – extramedullary haemopoeitic tissue
  - Symptoms of Spinal Cord compression,
    - Weakness/Paraesthesiae, Bladder/bowel, Sensory Level
  - Nerve root compression
    - radicular pain, weakness, loss of reflexes
  - May be evident on CXR
  - Urgent MRI spine
  - Emergency –
    - Radiotherapy, hypertransfusion regimen, Hydroxyurea





Summary

- Sickle Cell Disease
  - Cerebrovascular disease – common – starts early
  - Can be ‘silent’ but with significant morbidity
  - Overt disease can be devastating
  - Aim to prevent by identifying those at risk (TCDs)
  - May modify future presentation in those who have had screening if they have had intervention to stop progression….?
  - Acute episodes can occur in the presence of other illness eg Acute Chest Syndrome, severe anaemia
  - High index of suspicion
  - Investigate and treat urgently
- Thalassaemia
  - Mainly a risk of chelation therapy – hearing and vision
  - Rarely due to under-treatment – extramedullary haemopoeisis
  - Patients need to be told of need to report symptoms and undergo regular screening