NEUROLOGICAL
CONSIDERATIONS IN
SICKLE CELL DISEASE &
THALASSAEMIA
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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 3<sup>rd</sup> decade

Epidemiology of Stroke in SCD

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

- HbSS > HbSβ<sup>0</sup> > HbSβ<sup>+</sup> > 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

CVA = cerebrovascular accident.

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 (ICA)
- Identify those at risk of stroke – primary prevention
  - Normal: < 170 cm/sec
  - Abnormal: >200 cm/s
  - Conditional: 170-200 cm/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 (>200 cm/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
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:
    \[
    \text{Dose /kg body weight (mg/kg)} = \frac{<0.025}{\text{Ferritin mcg/l}}
    \]
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 haemopoietic 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 haemopoiesis
  - Patients need to be told of need to report symptoms and undergo regular screening