Sickle Cell Disease in Children - an overview

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9th April 2019
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What is Sickle Cell Disease (SCD)?

- **Chronic inherited** autosomal recessive condition
- Commonest genetic condition worldwide
- First described in 1910
- The pathophysiology of SCD arises from **haemolytic anaemia** and acute **vaso-occlusion**; organ damage develops from recurrent red cell sickling, chronic **haemolysis** and progressive endothelial vasculopathy.
- SCD has a significant impact on morbidity and mortality.
- It is **unpredictable** with crises of **variable severity**.
- Clinical presentations can be acute or chronic.
- Despite having a common genetic basis and similar pathophysiology, individual patients with SCD have a highly variable clinical course.
- Life expectancy is **beyond childhood** and with increased morbidity.
Pathophysiology of SCD

Glutamic acid → Valine

HbA

Point mutation

HbS

Oxygenated → HbS solution → HbS polymers

Deoxygenated → Irreversibly sickled

Reversibly sickled

Infarct (e.g., bone marrow)

Venous sinus

Microvascular occlusion by sickle cells

Normal red cell

Sinusoid

Sickle cell

Macrophage

Splenic cord

Endothelium

Vascular occlusion

SPLEEN → Hemolysis, congestion, infarction

Infarct (e.g., lung)

Inflammation

Transudation of fluid

Cell adhesion

Microvascular occlusion by sickle cells

© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com
Inheritance Pattern

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>S</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Hb AA</td>
<td></td>
</tr>
<tr>
<td>Sickle Cell Carrier</td>
<td>Hb AS</td>
<td></td>
</tr>
<tr>
<td>Sickle Cell Anaemia</td>
<td>Hb SS</td>
<td></td>
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</table>
Screening for SCD

• Full blood count (FBC)
• Reticulocyte count
• Blood film examination
• Hb S solubility test
• HPLC (High Performance Liquid Chromatography)
• Capillary Electrophoresis
• Iso-Electric focusing

N.B: AT LEAST TWO METHODOLOGIES MUST BE USED
Normal red blood cells

Sickle cells
Diagnosis

- Neonatal screening
- Early diagnosis improves outcomes
- Referral to a specialist centre
- Commence parent education
- Penicillin prophylaxis
- Spleen palpation
Penicillin prophylaxis

Prophylaxis with oral penicillin in children with sickle cell anaemia
Gatson, MH et al 1986 NEJM

Multicentred randomised, double-blind placebo-controlled trial

Objective:
To determine if regular daily administration of oral penicillin would reduce the incidence of documented septicaemia due to Strep pneumoniae in children with sickle cell anaemia who were under 3 years old

Children under 3 years of age
Dose: 125mg penicillin v potassium v placebo twice daily

Results:

<table>
<thead>
<tr>
<th></th>
<th>Penicillin group (N= 105)</th>
<th>Placebo group (N= 110)</th>
</tr>
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<tbody>
<tr>
<td>Infection</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

• Conclusion: All patients with sickle cell anaemia should receive prophylactic therapy with oral penicillin by 2 months of age
Vaccinations

• Childhood vaccinations

• Pneumococcal vaccines

• Hepatitis vaccines

• Annual influenza vaccine

• Pre/post-splenectomy vaccines

• Travel vaccines
Complications of SCD

- Hematology
  - Anaemia
- Growth and maturation
- Pain
  - Acute/Chronic
- Infections
- Psychological problems
- Priapism
- Jaundice
- Sickle retinopathy
  - Stroke, silent infarcts, and CNS function
- Cardiac function
  - ACS
  - Pulmonary hypertension
- Splenic function
  - AVN
  - Splenomegaly
  - Gallstones
- Enuresis
- Leg ulcers
- Nephropathy/renal failure
Fever

• If patient present with a fever-ADMIT

• Investigations-
  Bloods-FBC/Retics/GXH, renal/liver/bone profile, CRP
  Blood cultures
  Urine
  and chest x ray (if indicated) and throat swab/NPA (if indicated)
  virology (if indicated)

• Cover using IV Ceftriaxone

• If chest symptoms- include macrolide antibiotic to cover atypical
  organisms (PO Clarithromycin)

• Change antibiotics depending on patients clinical status and blood culture
  results. Involve ID team

Parent/patient education-use of a thermometer, early review
Acute splenic sequestration crisis

- Defined as an acute enlargement of the spleen with a drop in Hb level of at least 2g/dl from baseline
- In severe cases it may result in hypovolaemic shock and death in a matter of hours
- Can occur as early as 3 months of age
- Urgent bloods
- Spleen measurements
- Blood transfusion
- Parent education (recurrence can occur in up to 50% children)
- If repeated episodes, elective splenectomy (vaccines)
Vaso-occlusive Crisis (Pain)

- **The hallmark** acute clinical manifestation of SCD characterised by the sudden onset of discomfort and pain.
- Often occurs without a specific trigger
- Any bone can be affected
- Hands and feet in younger children—dactylitis
- Incidence variable
- Pain is variable in severity
- Rapid clinical assessment
- Involve patient

The primary goal of management is to achieve prompt and safe pain control.
Vaso-occlusive Crisis (Pain)

- The first dose of an appropriate potent analgesic must be administered within 30 mins. of presentation to ED.
- Regular and continuous assessment of pain and pain relief during an acute episode must be assessed at regular intervals along with vital signs and recorded using a standard pain assessment tool for adults.
- Pain severity should be managed according to the **WHO step ladder** of non opioid and opioid analgesia.
- Preferences to particular analgesic should be based on history of successful previous exposure, patients choice or adverse events.
- Recognition and management of side effects e.g. nausea, pruritus, respiratory depression, urinary retention.

**Acute pain**
People presenting with acute sickle pain should be rapidly assessed, and receive a first dose of effective analgesia within 30 minutes of arrival, with the aim that pain should be controlled within 2 hours. Pain and sedation scores should be recorded systematically and treatment adjusted accordingly.
Acute Chest Syndrome (ACS)

• ACS is the 2\textsuperscript{nd} most common cause of hospitalisation.
• Characterised by intrapulmonary ischaemia and infarction, systemic hypoxia and pulmonary infiltrates on cxr.
• Hypoxia and decline in respiratory status (often within 24 hours) is a useful predictor of severity and outcome.
• Accounts for 25% of deaths with an 80% recurrence rate.
Acute Chest Syndrome (ACS)

- Prevention (incentive spirometry for VOC)
- Antibiotics
  - Cephalosporin and macrolide
- Pain relief
  - “adequate to prevent hypoventilation”
- Supplemental oxygen (keep O2>95%)
- IV fluids- do not exceed 80% of maintenance
- Simple (top up) transfusion
  - for hypoxia
  - Deterioration in respiratory status
  - ↓Hb level ≥ 2g/dl below baseline
- Exchange transfusion
  - If Hb over 9g/dl
  - worsening status despite the above
- ICU admission + supported ventilation
Cerebrovascular events

• SCD confers a higher risk of childhood stroke than any other paediatric disease.
• 11% of patients with SCD develop an overt stroke by the age of 20 years.
• Other complications-silent infarct, TIA, seizure
• Studies-STOP, STOP 11, SIT trial, SWiTCH, TWiTCH
• Urgent imaging and exchange blood transfusion
• Primary stroke prevention-TCDs and MRI/A brain imaging
• Secondary stroke prevention
Stroke Prevention Trial in Sickle Cell Anaemia (STOP 1 Trial)

• A total of 130 children with SCD were enrolled (Hb SS or S/Beta ° Thalassaemia)
• No prior history of stroke
• All had a TCD reading of above 200cm/sec on 2 studies
• Randomly assigned to observation or a transfusion programme (goal to keep Hb S% < 30%)
• Trial terminated early (at 20 months)

<table>
<thead>
<tr>
<th></th>
<th>Transfusion group</th>
<th>Observation group</th>
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</thead>
<tbody>
<tr>
<td>N = 63</td>
<td></td>
<td>N = 67</td>
</tr>
<tr>
<td>Cerebral Infarction</td>
<td>1 infarction</td>
<td>10 infarctions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cerebral haematoma</td>
</tr>
</tbody>
</table>

90% difference in the rate of stroke
Transcranial Doppler Studies (TCDs)

TCDs results
- Normal < 170cm/sec
- Conditional 170-199cm/sec
- Abnormal ≥200cm/sec

TCDs
Ages 2 -16 years
Surgery

- Perioperative management of patients with SCD is complicated.
- Many SCD patients require surgery particularly abdominal, orthopaedic, and ENT procedures.
- The rate of perioperative complications varies but overall complications related to SCD are common.
- **Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study**

- Close collaboration between surgical and haematology teams to optimise management.
- Elective procedures should not take place if the patient is febrile or has a sickle cell crisis.
- Bloods
- IV fluids when fasting
- Normothermic
- Oxygen saturations
- Blood transfusion-top up or exchange (TAPS study)
- Incentive spirometry
- CPAP may be indicated
- Adequate analgesia
Specific therapies for SCD

• Hydroxycarbamide therapy
• Chronic blood transfusion prog
Hydroxycarbamide Therapy

Mechanisms of action
1. Increase the production of Hb F
2. Reduction in the neutrophil count and reticulocytes
3. Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes
4. Reduced haemolysis through improved red cell hydration, macrocytosis and reduced intracellular sickling
5. NO release with potential local vasodilatation and improved vascular response
Mechanisms of action

- Reduced cellularity
- Increased proportion of nucleated red cells

- Increased hemoglobin F
- Macrocytosis
- Increased hydration
- Fewer sickled cells
- Fewer reticulocytes

- Reduced adherence
- Improved endothelial function
**Baby HUG**

- RCT (double blind)-13 centres in USA
- Oct 2003-Sept 2009

<table>
<thead>
<tr>
<th></th>
<th>Hydroxycarbamide N=96</th>
<th>Placebo N =97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>177 events in 62 patients</td>
<td>375 events in 75 patients</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>24 events in 14 patients</td>
<td>123 events in 42 patients</td>
</tr>
<tr>
<td>ACS</td>
<td>8 events in 7 patients</td>
<td>27 events in 18 patients</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 events</td>
<td>1 event in 1 patient</td>
</tr>
<tr>
<td>Hospitalisation rates</td>
<td>232 events in 69 patients</td>
<td>324 events in 84 patients</td>
</tr>
<tr>
<td>Transfusion</td>
<td>35 events in 20 patients</td>
<td>63 events in 33 patients</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 events</td>
<td>0 events</td>
</tr>
</tbody>
</table>
Blood transfusion

• Red cell transfusion may be required in SCD either as an emergency measure or as prevention of the short and long-term complications of SCD.
• Red cell alloimmunisation is relatively common amongst transfused SCD patients.
• All SCD patients must have their ABO group and full red cell phenotyping performed at the first opportunity.
• Red cell units should be ABO compatible and also matched for D,C,E,c,e and Kell to minimise alloimmunisation.

Iron overload—iron chelators
  – Desferroxamine (DFO) (Desferal)
  – Deferiprone (DFP)(Ferriprox)
  – Deferasirox FCT(DFX) (Exjade FCT)
Further developments

- Haemopoietic stem cell transplant (HSCT)
- Gene therapy
Psychosocial issues

- Unique set of challenges
- Stigma
- Racism
- Unpredictable
- Pain and coping; PICA; Enuresis
- Higher risk of neurocognitive deficits that impact QOL
- Higher number of school days missed
- Wanting to feel normal
- Psychological adjustment-high rates of anxiety and depression
- Impacts both the child and their families-work, finances, parental and sibling relationships
- Transitioning to adult services
Conclusion

• SCD is a chronic red blood cell disorder that results in significant morbidity and premature mortality.

• Acute and chronic complications

• SCD is not just about pain management

• SCD requires lifelong specialist MDT input to reduce morbidity and mortality
References

- Howard and Telfair (2015) Sickle Cell Disease in Clinical Practice
- NICE guidelines-Sickle Cell Acute Painful Episode: management of Acute Painful Sickle Cell Episode in Hospital (2012)
- Sickle Cell Disease in Childhood: Standards and Guidelines for Clinical care (2010)
- Ware R E (2010) How I use Hydroxyurea to treat young patients with sickle cell anaemia Blood 115 (26) 5300-5311
Annual SCD study day

Caring for a child with Sickle Cell Disease
19th November 2019

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for further information