Sickle Cell Disease: Pathophysiology and acute management

joan.walters@kcl.ac.uk
2015

Summary of the session

- In this session the following areas will be covered:
  - The demography and epidemiology of sickle cell disease
  - The pathophysiology of sickle cell disease
  - The clinical manifestations & management of sickle cell disease

Sickle Cell Disease: Global National and Greater London facts

- Affects an estimated 1-2% (120,000) of infants in Africa annually
- 1 in 8-10 African Caribbean’s are carriers for the gene
- 1 in 4 West Africans are carriers for the gene
- Approximately 200-300 foetuses with sickle cell disorders each year
- **Incidence:**
  - Sickle Cell Disease 1:2380
  - Cystic Fibrosis 1:2500
Sickle Cell Disease: Global National and Greater London facts

• 65-70 new births per annum. in LSL in the past 5 years + inward migration
• Approximately 6750 sickle cell sufferers live within the South Thames region - the largest group in the UK and Europe.

What is the structure and function of the red blood cell?

What is the structure and function of haemoglobin?
Haemoglobin

- HAEM (iron)
- GLOBIN (protein)
- 4 main globin chains are - alpha, beta, gamma, delta
- Globin contains approx. 140 amino acids (alpha -141, beta - 146)
- Alpha - chromosome 16
- Beta, gamma, delta - chromosome 11

- One haemoglobin (Hb) molecule consists of four haem-globin combination arrange in two functional pairs e.g. 2 alpha and 2 beta
- In a haemoglobin molecule the four subunits are arrange so that they touch one another

Red Cell Destruction

- What is the process of red blood cell destruction called?
- What happens during this process?

Excessive red cell destruction

What happens if the red blood production does not keep up with red cell breakdown?
Sickle cell disease - a definition

- Sickle cell disease will be considered to consist of all disease states where gene HbS is present. Clinically they give rise to haemolytic anaemia’s of varying severity. Sickle cell anaemia is sickle cell disease in which the patient is homozygous for the HbS gene. This state gives rise to a severe haemolytic anaemia

(WHO Scientific Group Report 1966)

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**Frequency of haemoglobin traits (carriers) in certain ethnic groups**

<table>
<thead>
<tr>
<th>HAEMOGLOBIN TYPE</th>
<th>ETHNIC GROUP</th>
<th>CARRIER FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell trait</td>
<td>Afro-Caribbean’s West Africans</td>
<td>1 in 10 up to 1 in 4</td>
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<tr>
<td></td>
<td>Cypriots Pakistanis, Indians</td>
<td>1 in 100 1 in 100</td>
</tr>
<tr>
<td>C trait</td>
<td>Afro-Caribbean’s Ghanaians</td>
<td>1 in 30 up to 1 in 6</td>
</tr>
<tr>
<td>D trait</td>
<td>Pakistanis, Indians White British</td>
<td>1 in 100 1 in 1000</td>
</tr>
<tr>
<td>Alpha Thalassaemia</td>
<td>Chinese Cypriots Cypriots Asians Chinese Afro-Caribbean’s White British</td>
<td>1 in 5 - 1 in 30 1 in 50 - 1 in 100 1 in 7 1 in 10 - 1 in 30 1 in 30 1 in 50 1 in 1000</td>
</tr>
</tbody>
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**Perceptions of Risk**

Guardian Newspaper May 1998
The Ethnic Question?

Haemoglobinopathies causing sickle cell disease
- Sickle cell anaemia (HbSS)
- Sickle cell beta thalassaemia (HbSβthal)
- Sickle haemoglobin C disease (HbSC)
- Sickle haemoglobin D disease (HbSD)
- Sickle haemoglobin E disease (HbSE)
- Other rare sickle cell disorder e.g. HbSO

Sickle cell disease - the facts
- WHAT IS SICKLE CELL DISEASE?
  A hereditary disorder where there is increased haemolysis of the erythrocytes
- WHAT CAUSES IT?
  HbS is an abnormality of the beta globin chains
  Beta globin is on chromosome 11
  The sixth amino acid in HbA is glutamic acid
  It is substituted for valine
  The newborn infant appear normal at birth until 4-6 months of age when HBF should have converted to HBA
What are the problems?

- The red blood cells are more likely to crystallise with a low oxygen tension or pH, forming a sickle shape.
- When the red blood cell containing the sickle haemoglobin is deoxygenated, the haemoglobin molecule within aggregates into a rod like structure.

What are the problems? (Cont)

- Consisting of a 14 strand cable.
- As the rod grows it deforms the red blood cell into a rigid sickle shape form.
- This leads to blockage of the small capillaries and small infarcts in various parts of the body.
- This is called the painful or infarctive crisis.
- These blood cells on average last 7-20 days therefore there is usually a chronic anaemia.

The pathophysiology of a sickling crisis

- Hypoxia
- Increased blood viscosity
- Inflexible red blood cells
- Fragility of red blood cells
- Reduced red cell solubility
- SLOPING OF BLOOD FLOW THROUGH MICROCIRCULATION
- OCLUSION OF SMALL BLOOD VESSELS
- Infarction and infarct of red blood cells
- Residual debris and dead cells
- Fragility of red blood cells
- Tissue hypoxia and acidosis
- Vital organ infarct
- Further sickling of red blood cells.
Tissue Effects of Sickle Disease

Sickle cell words of wisdom

SICKLE CELL CRISIS
DON'T KNOW YOUR PRECIPITATING FACTORS????
NURSE YOUR PATIENT HAS HAD IT

- H - HYPOXIA
- A - ACIDOSIS
- D - DEHYDRATION
- I - INFECTION
- T - TEMPERATURE CHANGES
- STRESS

Nursing assessment

- CHEST PAIN
- BREATHELESSNESS
The patients' condition is critical if ANY of these
symptoms are present. Contact medical staff immediately
- HYPOXIA (oxygen saturation <90%)
- SHOCK
- ABDOMINAL PAIN
- TEMPERATURE (above 38°C and unwell)
- HEADACHE
- PRIAPISM
Classification of problems

- Haemolysis
- Aplastic
- Infection
- Sequestration
- Vaso-occlusive

Nursing management of the acute crisis in the child with sickle cell disease

- Is the child unwell? with or without pain
- Is sepsis a possibility?
  - Remember sickle cell children are immuno-compromised
- Is the child very pale?
- Is the spleen enlarged?
- Does the child have parathesia?
- Difficulty with speech?
- Weakness?
- Is the respiratory rate increased?
- Does the child have a painful erection?

FBC, retics
Blood cultures
MSU
Lumbar culture
IV access
Antibiotics
ADMIT
Urgent FBC and retics
Urgent crossmatch
Parvovirus titres if spleen not enlarged
IV access
Consider transfusion
ADMIT
Urgent Hb and crossmatch
MRI scan
IV access
Consider exchange transfusion
ADMIT
Pulse oximetry in air
CXR, FBC and retics
Crossmatch if pO2 < 90mm in air
Oxygen
IV access
Antibiotics
Exchange transfusion
ADMIT/REFER
Rehydrate
Analgesia
Hb and crossmatch if > 4 hours
Consider exchange transfusion
ADMIT/REFER
Haemolysis

- RBC's last 7-15 days
- Normal Hb 5.5-9g/dl
- Uncommon in the UK & US, reported in Jamaica & Africa
- Raised reticulocyte count
- Dependent on splenic function
- Severe infection
- ? Exercise
Infection

- Ability to produce opsonins is reduced therefore bacteria/viruses which a healthy individual is able to eradicate can be life threatening (Septicaemia/Bacteraemia Pneumococcus, Haemophilus Influenzae, Salmonella, Parvovirus
- Spleen partially effective
- Known defective opsinisation
- Prone to severe malignant malaria

How should we manage infection?

Aplastic

- Cause usually infective - Parvovirus
- Reticulocytes disappear from peripheral blood and Hb falls
- Transient decrease in WBC (lymphocytes & neutrophils) and platelets
- Symptoms - ? fever, bone pain, rash, drowsiness
- Can be life threatening with Hb as low as 1-3g/dl
How should we manage an Aplastic episode?

Sequestration

- Splenic enlargement more common in SBThal & SC than SS in adults
- Undergoes acute enlargement, entrapping a significant amount of RBC mass, causing a precipitating fall in Hb level and risk of death
- Sequestration can be mild-months; rapid-days to weeks or; life-threatening-hours to a day
- Cause unknown - no preventative treatment available
- Liver sequestration more commonly seen in adults

Sequestration

How should we manage a sequestration episode?
Change in Practice

Hemocue
- Haemoglobin analyzer using finger prick blood samples
- For use at Triage in A&E for all children with SCD
- Will identify patients with severe anaemia
- Cost £500

Vaso-occlusive
- Accounts for 90% of all hospital admissions usually manifesting itself as pain but other organ damage may be occurring i.e. –
  - Dactylitis
  - Aseptic necrosis
  - Cerebrovascular accidents
  - Priapism
  - Sickle chest syndrome
  - Mesenteric crisis
  - Ocular crisis

Dactylitis
Cerebrovascular - epidemiology

- 8-10% of patients with HbSS develop by age 12 have had symptomatic stroke
- 75% ischaemic stroke or cerebral infarction
- 25% intracranial haemorrhage
- 17% will have evidence of asymptomatic stroke with MRI
- Median age for infarctive stroke is 6 years
- Most commonly 3-10 years
- Majority of strokes in childhood are from infarction
- Intracranial or intracerebral haemorrhage more common in later life

Cerebrovascular pathophysiology

- Severe anaemia with chronic cerebral anoxia
- Abnormal adherence of sickled RBC's to the endothelium
- Altered rheology of RBC's
- Reduction in natural anticoagulants and increase prothombic generation
- Impaired liver function
- Cerebral infarction is associated with abnormalities of the large intracranial arteries;
- Histological studies of these lesions reveal fibrotic scars
- Infarction results from occlusion of major cerebral arteries and in reduction in their cerebral blood flow
- Cerebral aneurysm are secondary to vascular damage

Cerebrovascular diagnosis

- Usually hemiplegia although subarachnoid may occur
- May be associated with severe headaches, convulsion and neck stiffness
- Education - falling off of academic achievement or failing to reach expected academic level
- Behavioural problems
- Personality changes
How should we manage infection?

Cerebrovascular management – on going
- Chronic blood transfusion regime
- Hydroxyurea
- Low dose warfarin
- Antiplatelet therapy
- Coil embolization
- Cerebral angiography
  - Open aneurysmal clipping
- Serial scanning
  - I. Transcranial doppler
  - II. Magnetic Resonance Imaging (MRI)
  - III. Computer assisted intravital microscopy (CAIM)

Lungs
- Infarction
- Pneumonia
- ACUTE CHEST SYNDROME
  - Commonest cause of death over the age of 10 years
  - Pain, fever, cough, dyspnoea and abnormal X-ray
  - Can lead to chronic lung disease particularly in SC Disease

ACUTE CHEST SYNDROME
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II. Magnetic Resonance Imaging (MRI)
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Sickle lung

- Infections are more commonly recorded in children than adults
- Only direct lower airway secretions and/or serology can identify these infections. Important infectious causes include: S. pneumoniae, H. influenzae, Staphylococcus Aureus, Klebsiella sp., Mycoplasma pneumonia, Chlamydia pneumonia and Parvovirus
- During the winter when respiratory syntical virus (RSV) and other viruses are more common there is an increased incidence in children.

Sickle lung – hypothesis

- Catecholamines released during stress promote the releases of free fatty acid (FFA), which are then taken by the liver which synthesises and release lipoprotein fat globules.
- These large globules are then filtered by the lung, which causes mechanical blockage of vessels.
- These infiltrates may be confined to one lobe, diffused or bilateral.

Sickle lung- hypothesis

- These globules can also be seen in the eyes, brain and urine
- The FFA accelerates platelet aggregation and activates the coagulation cascade leading to activation of the complement system and disruption of the alveolar capillaries membrane. FFA can also cause inactivation of lung surfactant culminating in acute lung injury.
- Consolidation of the lungs develops with an associated drop in saturation of arterial gases.
How should we manage sickle lung?

Incentive Spirometers

Exchange Transfusion

Manual Exchange Transfusion

Automated Exchange Transfusion (Apheresis)
Cardiac

- Arrhythmia/failure if Hb falls from normal steady state
- Infarction in the absence of atherosclerosis
- Ischaemic heart disease rare - obesity rare, low cholesterol, low BP
- Until recently not reaching the age when these conditions develop

Kidneys

- Inability to concentrate urine (hyposthenuria) seen as young as six months old
- Polyuria, nocturia, enuresis
- Difficult to restrict fluids due to delicate acid base balance
- Haematuria - in AS & SS usually painless with a dull ache
- On investigation - minute ulceration, oedema, renal papillary necrosis
- Urinary tract infection increases during pregnancy in SS women
- Acute infection then atrophy
- Chronic renal failure
- Transplantation

Dehydration

- Most children with SCD fluid requirements will be greater than normal
- A creatinine result in the high normal range in a child with SCD is significant.
- Encourage oral fluids but if not tolerated give iv 0.18% NaCl/4% Dextrose and monitor fluid balance & electrolytes.
- Maintenance iv fluid requirement is approximately 1.5 x normal (Please check this?)
Priapism

- Prolonged penile erection
- The painful erection that does not subside after several hours is an emergency
- Preservation of normal erection is the major goal
- Majority of cases are idiopathic, prolonged erection may be associated with polycythemia.
- Spontaneous detumescence occurs in the majority of cases.

How should we manage priapism?

Skeletal

- As well as acute episodes - chronic joint disability
- Weight bearing joints most affected
- Local damage to small vessels, occlusion most likely in position greatest distance from arterial blood supply e.g., head of femur, also shoulder
- NB Difficulty in sexual relationships
- Peak incidence in late adolescence & early adulthood
- Avascular necrosis of growing epiphysis, shortening digits
- Face - pain, limitation of eye movement, mandible, rib, sternum, vertebrae
Skeletal

- OSTEOMYELITIS (long term antibiotic 3-6 months)
- GOUT
- LEG ULCERS
  - In the WI from the age of 10, 63% have a leg ulcer
  - In the UK most commonly from late teens onwards. Tendency to reoccurrence
  - Incidence 25% higher in SC than SS
  - Can take months to years to heal
  - Some studies show higher incidence in males than females
  - Usually above medial & lateral maleoli
  - Secondary infection inevitable

Chronic pain syndrome in sickle cell disease

- Occult infection
- Aseptic necrosis
- Skeletal infection
- Chronic anxiety & depression
Sickle pain

"FOR ALL THE HAPPINESS MANKIND CAN GAIN IS NOT IN PLEASURE BUT IN REST FROM PAIN"
John Dryden, The Oxford Dictionary of Quotations

Natural history of pain

THE INDIVIDUAL
• Hallmark of sickle cell pain is its extreme variability and unpredictability in timing, location and intensity
• Patients usually follow their own patterns
• Unpredictability is the bane of the patient's existence

DURATION
• On average last 3-5 days
• May be as short as a few hours and as long as weeks
• Children usually have shorter episodes
• Some have daily pain with intermittent acute exacerbation's
• Episode rises, plateaus, and then falls, but the contour may be erratic

Natural history of pain 2

SEVERITY
• From mild to extremely intense
• African terms translated = "body chewing" "body biting" "Beaten up"
• Patient’s who have had surgery or women who have had babies often state that sickle pain is more severe

CHARACTER
• Usually Nociceptive
• Neuropathic syndromes occur but rare in childhood
• Descriptors - "deep" "tiring" "aching"
• Quality is usually consistent from episode to episode
Frequent attendee’s - inability to differentiate pain

- P: It’s hard to differentiate crisis pain and pain being caused by something else, cause its pain, so you wouldn’t really know
- I: You wouldn’t know the difference?
- P: No not really unless it’s maybe muscle pain but then again muscle pain can be caused by a crisis as well, so it’s hard to differentiate whether it’s crisis pain or pain being caused by another problem


Natural history of pain 3

DEVELOPMENTAL
- Can occur as early as 6-9 months
- Some experience no pain until adolescence or early adulthood
- Extremity pain reported more common in children <3
- Adolescents= abdominal pain
- Adults= Back and lower limb pain

REGION
- Any region that contains nociceptors or peripheral nerves
- Involves single or multiple body parts
- May migrate during an episode
- Some patients describe pain episodes involving the whole body

Pain management in the child with sickle cell disease

- O PAIN THE MAIN PROBLEM
- ASSESS SEVERITY WITH ASSESSMENT TOOL
- OBSERVE BEHAVIOURAL SIGNS
- ASK PARENTS HOW CHILD NORMALLY RESPONDS TO PAIN
- ASK CHILD/PARENT WHAT ANALGESIA HAVE BEEN GIVEN AND WHEN
- ADMIT IF PARENTS ARE ANXIOUS ABOUT MANAGING PAIN AT HOME
**Out-patient nursing management**

- Health maintenance clinics - Every 3-6 months
- Transfusion & chelation therapy
- Hydroxyurea follow up
- Leg ulcers
- Joint clinics e.g. neuro, orthopaedic, renal, ophthalmology
- Adolescent/transition clinic
- Nurse counsellor - health education and psychosocial support
- Psychologist - CBT