Common Haemoglobinopathies in the Western Cape

Red Cross War Memorial Children's Hospital

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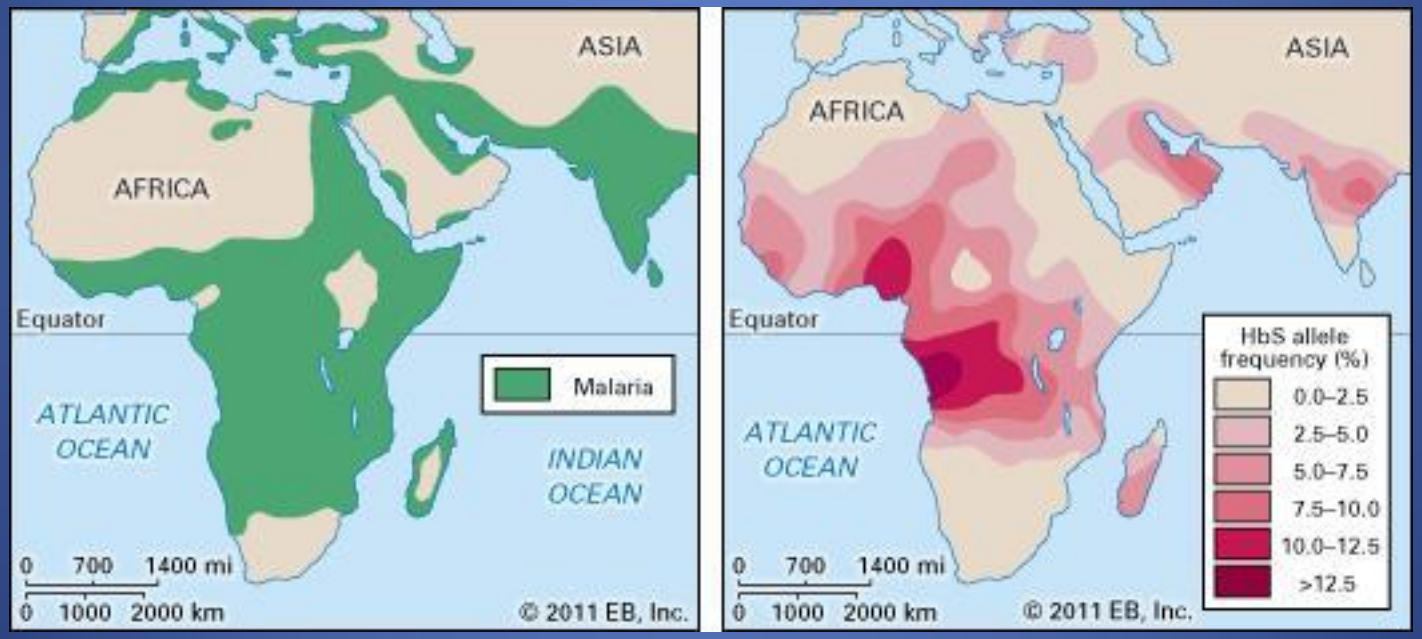
Common Haemoglobinopathies in the Western Cape

- Sickle Cell Disease (Fairly recent development)
- Thalassaemia (Rare)

Sickle Cell Disease: Background



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Sickle Cell Disease: Background

- Sickle Cell Disease (SCD): Autosomal recessive disorder characterised by Haemoglobin S in the patient's Red Blood Cells(RBC's).

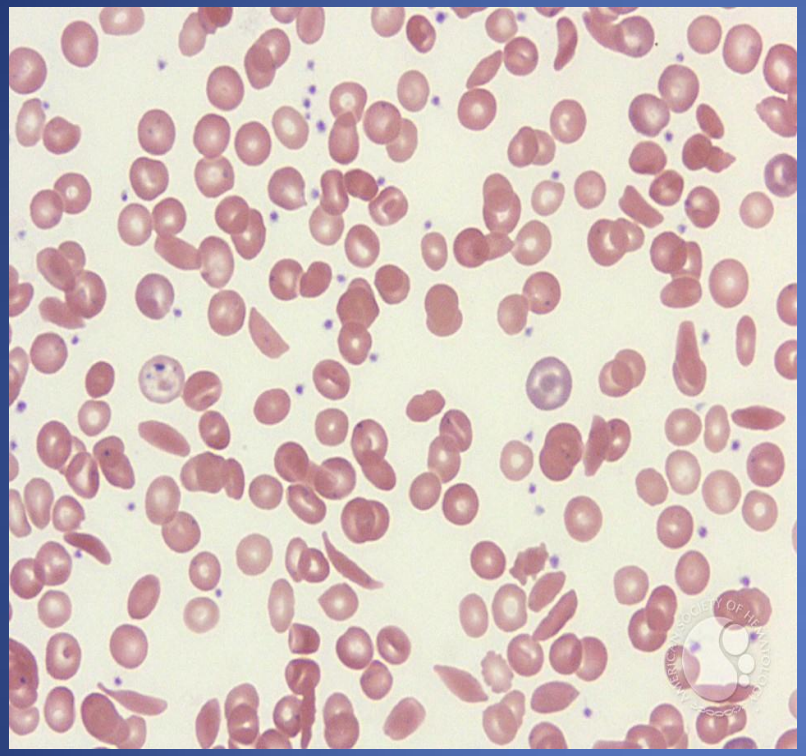
- Haemoglobin S is due to a mutation and deletion of the β globin gene on chromosome 11 resulting in a single amino acid substitution (Valine for Glutamic Acid at position 6) on the β chain.

- The result of this amino acid substitution is that, HbS has a higher electrical charge than HbA and therefore different electrophoretic mobility.

Sickle Cell Disease: Background

- HbS in the reduced form is less soluble than HbA. The molecules form rod like structures that cause the RBCs to sickle.
- Sickle Cells are destroyed prematurely resulting in chronic haemolytic anaemia(lifespan 10-40 days).
- Sickle cells result in increased blood viscosity with impaired blood flow and thrombus formation.

Sickle Cell Disease: Background



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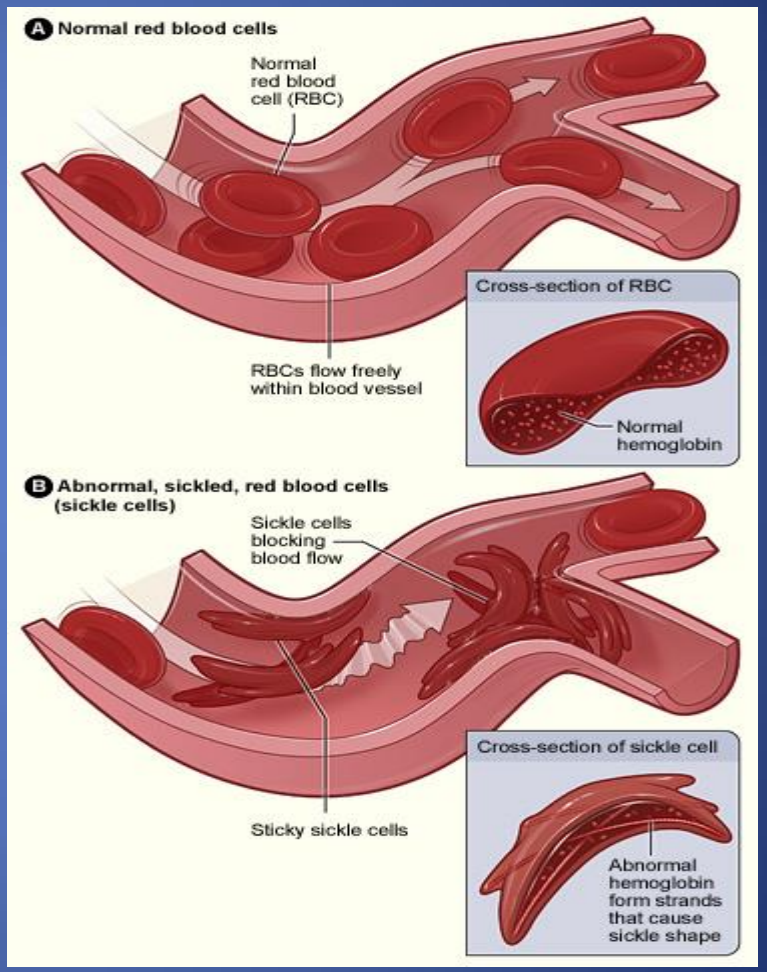


http://www.nhlbi.nih.gov/health/health-topics/topics/sca

Sickle Cell Disease: Background

- Heterozygous individuals are usually asymptomatic carriers(20-40% HbS). Homozygous patients (Hb SS) and compound heterozygous patients are symptomatic for the disease.

- There main genotypes of Sickle Cell Disease are:
  - HbSS
  - HbSC
  - HbS-β Thal Double Heterozygotes

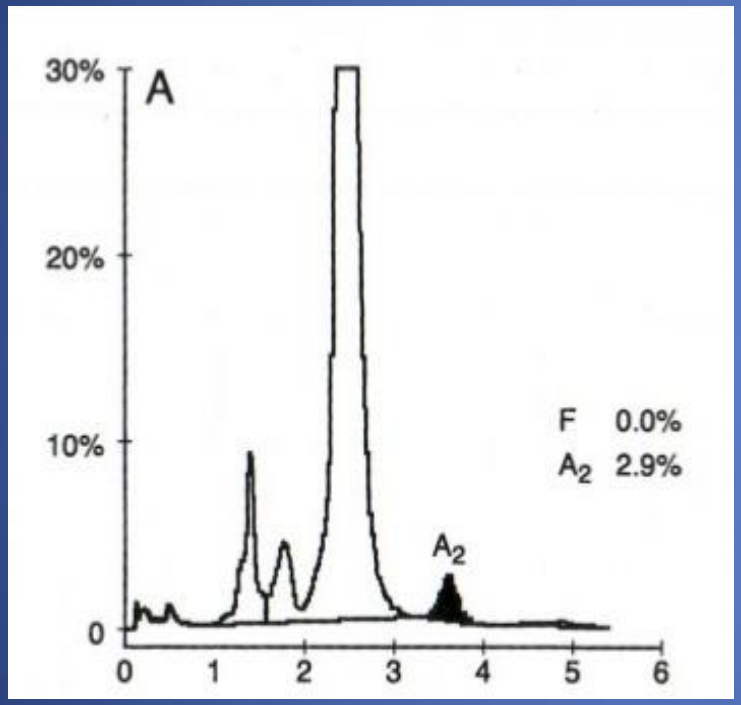
Newborn Screening

- Most babies with SCD are asymptomatic at birth. They are protected by high levels of Hb F and become symptomatic as HbF level falls.

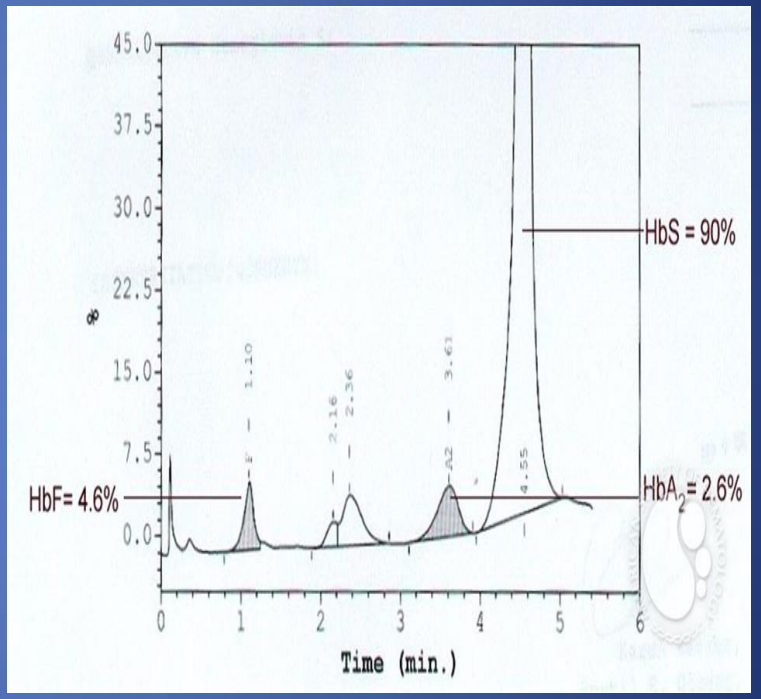
- Acceptable tests for screening include: HPLC and Hb electrophoresis (cellulose acetate and citrate agar).

- Confirmatory tests should be performed within 3 months of age to begin Penicillin prophylaxis timeously and initiate comprehensive care.

High Performance Liquid Chromatography



HPLC Normal Haemoglobin



HPLC Homozygous SCD

Paediatric Presentations of SCD

- Dactylitis
- Aplastic Crisis
- Splenic Sequestration Crisis
- Painful Crisis
- Infection
- Acute Chest Syndrome
- Stroke
- Priapism

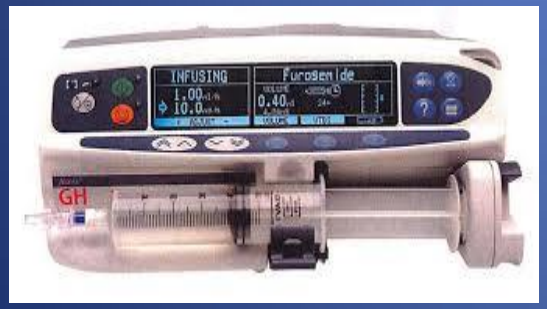
Dactylitis

- Vaso-occlusive disease of the small bones in the hands and feet (Usually from about 4 months of age).
- Very painful, tender swollen hands/fingers or feet.
- Occurs in young children and infants. The younger the child, the more severe the disease.
- Treatment is with IV Fluids(1.5 X Maintenance) and analgesia (NSAIDS and IV opiates).

Painful Crisis

- Severe pain should be considered a medical emergency. It requires timely and aggressive management.
- Sickle pain is managed with hydration(1.5X Maintenance) and pharmacologically.
- Parenteral Opioids are the mainstay of treatment once a child requires admission (continuous morphine infusions or patient controlled administration).
- Opiates are titrated against pain.
- Rarely, ketamine infusions are required to control severe pain.

Painful Crisis

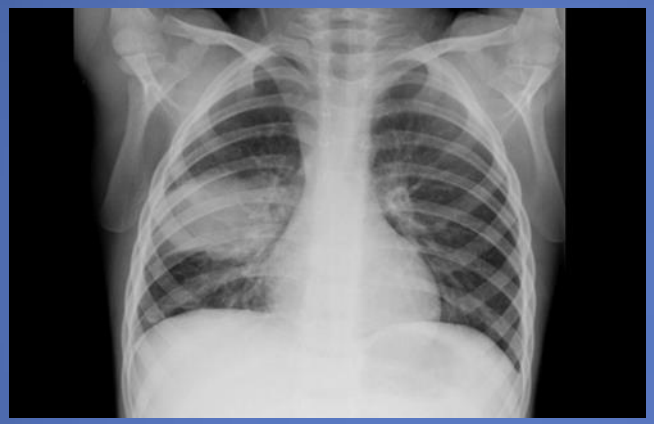


Infection

- Splenic dysfunction can be present from as early as 3 months of age.
- For this reason children with SCD are at increased risk for septicaemia and meningitis caused by pneumococci and other encapsulated organisms like meningococci.
- They are also susceptible to osteitis, not only due to Staph Aureus, but also due to Salmonella species.
- Any fever over 38°C is concerning and children are cultured and commenced on parenteral antibiotics, even in the face of finding a focus of disease e.g. URTI, Otitis media.

Acute Chest Syndrome

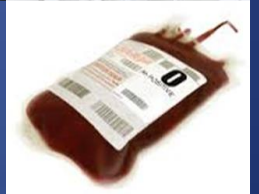
- Patients have preceding /concurrent LRTI symptoms +/- hypoxia and new infiltrates identified on CXR.



- ACS may be present initially during an acute illness or may develop after 2 to 3 days of severe vaso-occlusive pain.
- ACS is a known complication of general anaesthesia and surgery.
- Aetiology includes infection (viral and bacterial, including Mycoplasma or Chlamydia species), pulmonary infarction and pulmonary fat embolism.

Acute Chest Syndrome

- May progress rapidly to pulmonary failure and death.
- Early diagnosis and aggressive treatment with oxygen, analgesics, antibiotics is essential(Remember Atypical cover).
- Transfusions may be life saving.
- Incentive spirometry is important.
- ICU admission often required.



Aplastic Crisis

- Usually there is a history of a preceding viral illness. Viral exanthema is often not present but most cases are due to acute infection with parvovirus B19.
- The child's anaemia is suddenly exacerbated with a markedly low reticulocyte count(Often < 1%).
- Parvovirus is contagious: Isolation is required. Testing of siblings with SCD for concurrent and subsequent aplastic crisis are recommended.
- In order to diagnose: Demonstrate a fall from baseline Hb level and reticulocyte count.
- May need packed RBC transfusion because of heart failure.
- Need to monitor Hb after initial transfusion until patient demonstrated recovery of reticulocyte count.

Sequestrative Crisis

- Acute onset with rapid enlargement of the spleen and Hb level falls > 2 g/dL below the patient's baseline.
- Often associated with a mild to moderate thrombocytopenia.
- Severe cases progress rapidly to shock and death.
- Early diagnosis and treatment with RBC transfusions are life saving.
- Splenectomy to prevent recurrence is often recommended after recovery from life-threatening /recurrent episodes of sequestration.

Stroke

- Any new onset neurological symptoms warrant investigation.
- Common presenting symptoms and signs of stroke include hemi/monoparesis, aphasia or dysphasia, seizures, severe headache, cranial nerve palsy, stupor, and coma.
- Ischemic CNS injury can also present with “soft” neurology (Developmental delay/Decline in school performance).
- Non-contrast CT head or MRI are indicated to exclude haemorrhage.
- MRA can be performed to document large vessel vasculopathy.

Stroke

- 4 important studies re stroke prevention in SCD
  - **Stroke Prevention Trial in Sickle Cell Anaemia(STOP)**
    - Adams et al NEJM 1998; 339: 5-11
  - **Optimizing Primary Stroke Prevention in SCA (STOP 2)**
    - Adams RJ et al. N Engl J Med 2005;353:2769-2778
  - **Stroke With Transfusions Changing to Hydroxyurea(SWiTCH)**
    - Ware R et al. Blood 2012;119:3925 - 3932
  - **Transcranial Doppler (TCD) with Transfusions Changing to Hydroxyurea (TWiTCH)**
    - Ware R et al. The Lancet; Published online December 2015

Priapism

- Mean age at which priapism occurs is 12 years. By 20yrs, up to 89 percent of males with SCD will have experienced ≥ 1 episode of priapism.
- Caused by vaso-occlusion, resulting in obstruction of the venous drainage of the penis.
- Recurrent episodes of priapism can result in fibrosis and impotence, even when adequate treatment is attempted.

Routine General Examination

- Common findings:
  - Hepatomegaly: Not an unusual finding
  - Spleen not always palpable: Auto splenectomy
  - Cardiac Flow Murmurs: Due to anaemia
  - Bone Marrow Expansion: Prominent maxillae
  - Extra medullary hypertrophy: Enlarged tonsils

- Watch out for.
  - Growth and nutrition
  - Hypertension(at risk for stroke)
  - Developmental delay(subclinical strokes)
  - Delayed sexual development

Guidelines: Routine Care

- Every Visit (3 monthly)
  - General examination
  - Growth and development
  - Blood pressure monitoring
  - Intellectual development and school performance.
  - Regular dental care / good oral hygiene.
  - Genetic Counselling
  - Parental Education: Prevention/Medical Care
  - Penicillin prophylaxis
  - Folate 2,5 mg or 5 mg daily. Smaller doses may be required for neonates.
  - Immunization
  - Hydroxyurea

Parental Education

- Genetic Counselling (Autosomal Recessive)
- Penicillin Prophylaxis
- Immunization
- Good Hydration(Especially in the heat/when active), Keeping warm
- Analgesia plan at home
- Help Seeking Behaviour: Fever, pain, dactylitis
- Identify sequestration and seek help urgently

Home Plan for Analgesia

- Non- medical: Hot packs, warm showers, massage, relaxation therapies
- Medical: NSAIDs: Paracetemol, Ibuprofen
  Opiates : Codeine, Morphine
- When to seek medical attention: Fever, uncontrollable pain

Immunization

- All routine immunizations as per national immunization schedule. Prevenar essential.
- Important to receive Meningococcal(Quadrivalent polysaccharide) and Pneumococcal (23-valent polysaccharide and 13-valent conjugate)Vaccines at 2 and 5 years.
- Influenza Vaccine every year in autumn.

Penicillin Prophylaxis

- From as early as 2 months (Major reason for screening)
- Pen VK 125mg bid po. Increased to 250mg bid at 3rd birthday and continues at least until 5yrs of age.
- Alternative to oral penicillin: IMI Bicillin 1.2 million units every 3 weeks.
- Parents can be offered the option of discontinuing Pen prophylaxis after 5 years.
- If Pen Allergy: Erythromycin 20mg/kg/day in bid doses

Treatment: Hydroxyurea

- Hydroxyurea
  - Increases HbF
  - Decreases WCC
  - Increases RBC deformability
  - Improves cation depletion and hemolysis
- Clinically
  - Decreases the incidence of painful crisis and acute chest syndromes.
  - Preserves organ function.
- Start at an oral dose of 15mg/kg. (500mg per capsule). May have to opt for alternate day doses in smaller children or even less than that (e.g. 500mg 2X per week).
- Monitor Hb F levels. Aim for an Hb F level of 10%.
- Need to monitor for myelotoxicity (Dose dependant)
- Side Effects: N+V, Skin rashes/pigmentation, Nail changes, Carcinogenic/leukemogenic.
- Can be commenced as early as 9 months (Baby HUG)

Special Studies

- Transcranial Doppler:
- Measures flow velocity in middle cerebral artery or internal carotid artery
- Blood-flow velocity is inversely related to arterial diameter.
- **From age 2 years:** Annually if normal flow (<170cm/sec) or 4 monthly if marginal (170-200cm/sec).
- Repeat in 2-4 weeks if abnormal(>200cm/sec).
- MRI Brain
- Evaluate for silent strokes.
- Children with abnormal findings need closer monitoring and considering for interventional treatment e.g. Hyper transfusion
- Pulmonary Function Tests
- Especially important in children with recurrent chest syndrome and those who run low sats.

Guidelines: Routine Care

- Ophthalmological evaluation
  - Start at school going age.
  - Repeat every few years.
  - If retinopathy is present then follow up must be more regular
- Adolescents
  - Genetic counselling
  - Sex education
  - Contraception
    - Barrier contraceptives
    - Low dose oestrogen oral contraceptives are safe.

Transfusion

- Acute vs. Long-term
  - Acute: Stabilise acute complications.
  - Long-term: Limit future chronic complications.

- Recommended product: Phenotypically matched, sickle negative, leukocyte depleted packed cells.
- Post transfusion Hct of ≤ 36%is recommended; >36 can be dangerous due to hyperviscosity.
- Transfusions increase O2 carrying capacity and decreases the proportion of sickle cells. This increases microvascular tissue perfusion.

Transfusion in the acute setting

- Management of acute severe anaemia:
  - Splenic Sequestration
  - Aplastic Crisis
  - Acute Haemolysis: Acute Chest Syndrome/Sepsis/Malaria
  - CCF
  - Stroke
  - Acute Chest Syndrome
  - *Painful crisis*(Even if Hb falls from admission value: Can defer transfusion if Retics>20 % and cardio/resp stable)
- Try to maintain Hb S <30%
- Prior to *major* surgery : Aim Hb 10g/dl; Hb S ≤60%
- Not necessary in stable, well patients prior to minor procedures

Transfusion in the chronic setting

- The goal of regular transfusion is to suppress patients own erythropoiesis.
- The goal is a HbS level: 30-50%.
- Transfusions are 3-4 weekly.
- This decreases the risk of stroke, recurrent painful crisis and acute chest syndrome.
- Indications for chronic transfusion:
  - Primary prevention of stroke*
  - Prevention of Stroke Recurrence
  - Chronic Pain/Recurrent Painful Crisis
  - Acute Chest Syndrome
  - Priapism

* Hydroxyurea presenting an alternative in patients with abnormal TCD's

Incorrect use of transfusion

- Contra indications/inappropriate Indications to transfusion:
  - Chronic steady state
  - Uncomplicated pain episodes
  - Infections
  - Minor surgeries/procedures
  - Aseptic necrosis of hip/shoulder

Bone Marrow Transplant

- Only curative option
- Balancing the prevention of sickle cell complications and resulting morbidities and early death vs. risk of severe adverse events post transplant.
- Limited due to:
  - Cost
  - The lack of availability in the developing world.
  - The lack of HLA-matched sibling donors.
  - The complication of transplantation-related morbidity and mortality.

Eligibility for Bone Marrow Transplant

- Inclusions
  - Patient <16yrs with SCA (Hb SS or Hb Sβ° Thal)
  - ≥ 1 of the following complications:
    - Stroke or CNS event lasting >24hrs.
    - Recurrent acute chest syndrome/Early sickle lung disease.
    - Recurrent veno-occlusive crisis or priapism.
    - Impaired neuro-psychologic function with abnormal MRI and angiography.
    - Sickle nephropathy (GFR 30-50% of predicted normal).
    - Osteonecrosis of multiple joints.

Thalassaemia: Background

- Thalassaemia is rare in South Africa.
- β-thalassaemia major affects mainly those of Mediterranean and Indian descent.
- It is a chronic life-long condition that requires management with frequent blood transfusions and chelation therapy to remove excess toxic iron.
- There are several international published treatment guidelines, in SA there is a National consensus statement which aims to ensure optimal, standardised care.

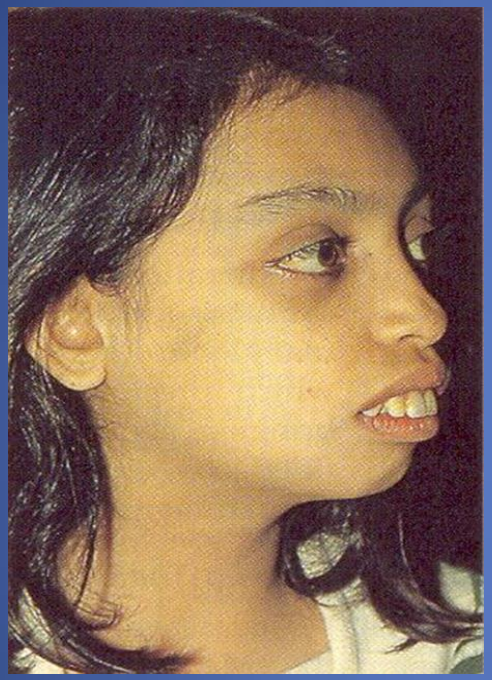
Thalassaemia: Background

- β-thalassaemia major is an autosomal recessive disorder resulting in abnormal haemoglobin (Hb) synthesis.
- Abnormalities in the beta globin gene results in decreased or absent production of beta globin chains with subsequent imbalance between alpha and beta chains.
- The excess alpha chains cause damage to the red cell membrane resulting in markedly shortened red blood cell. This leads to severe anaemia and compensatory marrow hyperplasia.

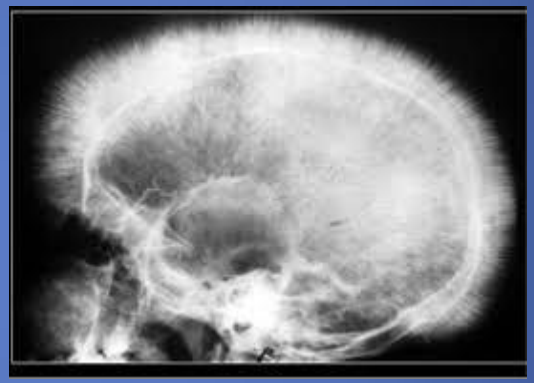
Thalassaemia: Background

- Newborns with β-thalassaemia major are asymptomatic due to high levels of haemoglobin is HbF.
- When HbF falls and they switch to HbA (adult haemoglobin) they become symptomatic (4-6 months of age).
- They present with symptoms of anaemia: poor growth, difficulty in feeding, pallor, cardiac failure, hepatosplenomegaly and recurrent infections.
- Ineffective erythropoiesis results in bone marrow hypertrophy and extra-medullary haemopoeisis.
- If the anaemia is untreated, death usually occurs in the first decade of life.

Thalassaemia: Background



Malar Hyperplasia



Hair-on end Skull X-ray

Thalassaemia: Diagnosis

- FBC including differential count and peripheral blood smear.
- Haemoglobin electrophoresis (including HbF).
- Iron studies, Vitamin B12 level.
- Genetic analysis should be performed where available.

Thalassaemia: Classification

- **Thalassaemia major (TM):** Markedly decreased haemoglobin production resulting in severe anaemia requiring regular transfusion therapy.
- **Thalassaemia intermedia (TI):** Variable reduction in haemoglobin production with mild-to-severe anaemia. Some require frequent transfusions, while others require infrequent or no transfusions.
- **Thalassaemia minor (carrier/trait):** Asymptomatic with mild microcytic hypochromic anaemia.

Thalassaemia Major: Management

- Newly diagnosed infant:
  - Timely establishment of the correct diagnosis.
  - Adequate counselling of the family, referral to a genetic service.
  - Close monitoring (3-4 weekly).

- Monitoring:
  - History: Symptoms of anaemia, abnormal growth and development.
  - Examination: Height, weight and head circumference measurement, facial deformities, bone deformities and hepatosplenomegaly.
  - Full blood count.

- Poor growth, failure to thrive, complications of anaemia and the presence of bone marrow expansion will necessitate regular transfusions.

Thalassaemia Major

- Packed red cell transfusions every 3-4 weeks.
  - Regular transfusions are intended to suppress the patient's endogenous ineffective erythropoiesis, which is causing bone marrow hyperplasia and hepatosplenomegaly.

- Maintaining the haemoglobin at an appropriate level facilitates normal growth and development.

- The major complication that results from regular long-term transfusion therapy is iron overload.

- Allogeneic Haemopoietic Stem Cell Transplant using HLA identical family donors is the only curative option for patients with thalassaemia (ideally between 18 months and 3 years).

Iron Toxicity

- Iron is toxic to many tissues. Excess iron is non-transferrin bound iron in the plasma and results in free radical damage to cells in the intra-cellular compartment.

- It takes 3 to 10 years of chronic exposure to iron before measurable organ dysfunction occurs.

- The most effective strategy is prevention of iron overload and tissue damage. The assessment of iron stores and monitoring their trend over time is key to management.

Iron Toxicity

- Most important organ toxicities:
  - **Cardiomyopathy:** Cardiac iron loading takes 8-10 years to develop
  - **Cirrhosis and liver failure:** Significant iron loading of the liver occurs after 6 months of regular transfusions. Liver damage is seen after 4 years of regular transfusion
  - **Endocrinopathies**: Pancreas, Thyroid, Parathyroid, hypothalamic and pituitary damage

- Monitoring iron overload
  - Indirect measurement
    - **Serum ferritin.**
    - MRI T2* for cardiac iron assessment.
    - MRI T2* and MRI R2 for liver iron assessment
  - Direct measurement: Liver Iron Concentration (LIC) via liver biopsy.

- Aim of all chelation regimens is to attain and maintain an annual average serum ferritin of 1 000 µg/l (+/- 500 µg/l), a liver iron between 3-7 mg/g dry weight and cardiac T2* > 20 ms2.

Chelation

- Chelation therapy should be commenced as soon as the patient becomes significantly iron overloaded.
- Removal of iron from normal tissues can be detrimental, and chelation should not be started without overload.
- In infants, chelation therapy may be delayed beyond the 1st year, due to the toxicity of the chelators.
- Chelation is commenced generally after 10-12 transfusions, when the ferritin is persistently between 1 000-1 500 µg/l.
- Current chelators in use at Red Cross :Deferasirox (Exjade) Advantage is it is an oral medication(No longer require overnight subcutaneous infusions as previously with Desferrioxamine (Deferral).

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