Update on Thalassaemia and Sickle Cell Disease

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Haemoglobinopathies

- Global Health problem
- Traditionally disorders found in malaria endemic regions
- But global Migration → changing distribution of genes
- Incidence in Australia traditionally low but will mimic immigration patterns
- Previous migrants from Mediterranean and South East Asia → introduced more thalassemia carriers
- Anecdotal current increase in Sickle Cell disease
- Carrier state asymptomatic
- Difficult to monitor prevalence
Queensland Refugee Population

- Clinical Audit - 1460 individuals HbEPP results
- 2009-2012

Pie chart showing:
- Normal Results - 84%
- Indeterminate (HbA2 3.3-3.5%) - 5.8%
- Hb Lepore Trait - 0.2%
- HbC Trait - 0.2%
- Likely Beta Thal Trait - 1.3%
- HbE Trait - 1.4%
- Beta Thal Trait - 2.8%
- HbS Trait - 4.4%
Clinically Significant Haemoglobinopathies

<table>
<thead>
<tr>
<th>Haemoglobin Bart's hydrops fetalis</th>
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<tbody>
<tr>
<td>β thalassaemia major and intermedia including that resulting from β thalassaemia/haemoglobin E compound heterozygosity</td>
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<tr>
<td>Sickle cell disease</td>
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<tr>
<td>Sickle cell anaemia</td>
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<tr>
<td>Sickle cell/haemoglobin C disease</td>
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<td>Sickle cell/β thalassaemia</td>
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<td>Sickle cell/haemoglobin Lepore</td>
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<tr>
<td>Sickle cell/haemoglobin D-Punjab</td>
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<tr>
<td>Sickle cell/haemoglobin O-Arab</td>
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Tonight's Talk

• Common Hb disorders
  • Sickle cell disease & Compound heterozygote disease
  • Beta thalassaemia
  • Alpha thalassaemia

• Inheritance and risk assessment for pregnancies

• Screening – Who/When

• Diagnostic testing

• Clinical presentation

• Management
Sickle Cell Disease
**Sickle Cell Disease**

- Inherited group of disorders
- Characterised by severe pain crisis due to vasoocclusive phenomena and haemolytic anaemia.
- Mutation in beta globin gene $\rightarrow$ HbS
- HbS polymerises to filaments when deoxygenated
- Symptomatic due to homozygous or compound heterozygous state
Sickle Cell Disease inheritance

**Both parents are carriers of haemoglobin S (HbS)**

- $\beta^+ \rightarrow$ functional $\beta$-globin genes
- $S \rightarrow$ abnormal haemoglobin (HbS)

**For every pregnancy the chances are:**

- 25% with SC disease (HbS/HbS)
- 50% carriers of HbS
- 25% with functional $\beta$-globin genes

**One parent is a carrier of haemoglobin S (HbS) and the other is a carrier of $\beta$-thalassaemia**

- $\beta^- \rightarrow$ non-functional $\beta$-globin genes
- $S \rightarrow$ abnormal haemoglobin (HbS)

**For every pregnancy the chances are:**

- 25% with compound haemoglobin pattern (HbS/$\beta$)
- 25% carriers of a non-functional $\beta$-globin gene (i.e., carriers of $\beta$-thalassaemia)
- 25% carriers of HbS
- 25% having functional $\beta$-globin genes (i.e., two functional $\beta$-globin genes)
Screening – who to test

- Family history
- Ethnicity
  - Up to 1:5 carrier rate in Africa
  - HbS gene most prevalent in persons of African, Arabian, and Asian-Indian ancestry
- Unexplained anaemia
- +/- signs of haemolysis - ↑LDH, ↑bili, ↑retics
  ↓haptoglobin
- May have normal FBC

NOTE: Sickle cell disease does not cause a microcytosis unless coexistent thalassaemia trait
Diagnosis – sickle Hb

- Haemoglobin electrophoresis (HbEPP)
- Parents – if both carriers refer for Genetic counselling, also if carriers of other beta globin mutations or deletions
- Normal Adult
  - HbA → $\alpha_2\beta_2 = 95\text{-}98\%$ of all haemoglobin
  - HbF → $\alpha_2\gamma_2 = <1\%$
  - HbA2 → $\alpha_2\delta_2 = 2\text{-}3.5\%$
  - HbS → $\alpha_2S_2 = 0\%$
Sickle cell disease presentation

• Asymptomatic at birth
• First presentation may be with life threatening event
• Overwhelming sepsis
• Pain crisis
• Acute chest syndrome
• Acute Splenic sequestration
• Stroke
Treatment of sickle cell disease

- Vaccinations – functionally asplenic – spleen.org.au
  - Pneumococcal
  - Haemophilis influenzae
  - Meningococcal
- Prophylactic penicillin
  - Daily amoxicillin until at least age 5yrs
  - Emergency supply of Augmentin
- Avoid triggers to pain crises
  - Avoid dehydration, extremes of temperature, Hypoxia (smoking, altitude, intensive exercise), infections
- Hydroxyurea
  - ↑increases HbF, increases NO → improved survival, decreased frequency of pain crisis
- Folate
### Asplenia/Hyposplenism – Paediatric Guidelines

**Age 0 to 18 years**

#### Additional IMMUNISATIONS for people with Asplenia or Hyposplenism

- NIP – national immunization program

#### Vaccination Guidelines

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Pneumococcal Vaccines*</th>
<th>Meningococcal Vaccines</th>
<th>Haemophilus influenza type b (Hib) Vaccine</th>
<th>Influenza Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brands</strong></td>
<td>Prevenar13</td>
<td>Pneumovax23*</td>
<td>Menevac#</td>
<td>InfanrixHexa Menitorix</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>&lt; 2 years of age</td>
<td>Pneumococcal Conjugate Vaccine 13vPCV</td>
<td>Pneumococcal Polysaccharide Vaccine 23vPPV</td>
<td>Meningococcal Quadrivalent Conjugate Vaccine 4vMenCV_A CWY</td>
<td>Bexsero</td>
</tr>
<tr>
<td></td>
<td>Primary course as per NIP</td>
<td>1 dose at 4-5 years of age</td>
<td>&gt;6 weeks to ≤6 months 3 doses (8 weeks apart) 4th dose at 12 months of age</td>
<td>Note: Requires prophylactic paracetamol%</td>
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<tr>
<td></td>
<td>1 additional dose at ≥12months of age</td>
<td>7 to ≤24months 2 doses (8 weeks apart)</td>
<td>&gt;6weeks to ≤6 months 3 doses (8 weeks apart) 4th dose at 12 months of age</td>
<td>&gt;6 months to &lt; 9 years of age</td>
</tr>
<tr>
<td>2-5 years of age</td>
<td>Primary course as per NIP</td>
<td>1 dose at 4-5 years of age</td>
<td>7 to ≤12months 2 doses (8 weeks apart) 3rd dose at 12 months (or 8 weeks post previous dose, whichever is later)</td>
<td>2 doses</td>
</tr>
<tr>
<td></td>
<td>1 additional dose at &gt;12months of age</td>
<td>2 doses (8 weeks apart)</td>
<td>&gt;13 to ≤ 24 months 2 doses (8 weeks apart)</td>
<td>Recommend seasonal influenza vaccine Every year (one dose)</td>
</tr>
<tr>
<td>&gt;5 years of age</td>
<td>1 dose (if no previous doses as &gt; 12 months at age)</td>
<td>2 doses (8 weeks apart)</td>
<td>2 doses (8 weeks apart)</td>
<td>See ATAGI guidelines annually</td>
</tr>
<tr>
<td>Boosters</td>
<td>Nil required</td>
<td>Booster 5 years post 1st dose</td>
<td>Booster 3 years post primary course Review ongoing boosters every 5 years</td>
<td>Booster requirements currently unknown, review every 5 years</td>
</tr>
</tbody>
</table>
Beta Thalassaemia
Beta thalassaemia inheritance

- One Beta Globin Gene, two copies
  - $\beta^0\beta^0$ – BT major
  - $\beta\beta^0$ – BT trait
  - $\beta^0\beta^+$ or $\beta^+\beta^+$ BT intermedia

**RISK LIKELY TO BE IDENTIFIED EARLY AS AT LEAST ONE PARENT HAS BETA THAL MAJOR**

**MOST LIKELY CASE TO BE MISSED DUE TO LACK OF SCREENING AND BOTH PARENTS ASYMPTOMATIC CARRIERS**
Beta Thalassaemia Trait

- When to suspect
  - Microcytic, hypochromic anaemia in Iron replete patient
  - Family history
  - Ethnicity

- How to test
  - Haemoglobin EPP – Haemoglobin studies
  - Raised HbA2 >3.5% is diagnostic beta trait

- Who/when to test
  - diagnosis microcytosis – to avoid erroneous iron prescription
  - Planning pregnancies – to determine risk of beta thal major
  - Family history of beta thal or sickle cell or HbC/HbE
Beta thalassaemia intermedia

• “highly diverse” group of beta thalassaemia
• red cells survival sufficiently short-lived to cause anaemia but without patients requiring regular blood transfusions
• Mutation → reduction but not absence of beta globin production
• Beta plus syndromes
• Present later in childhood
Beta Thalassaemia Major

• Severe haemoglobinopathy - Transfusion Dependent
• Ideally risk of an child being born affected by Beta thal major should be predicted prenatally
• Couples at risk of an affected child should be referred for genetic counselling preconception
• If already pregnant
  • Assess risk – test both parents
  • If both parents carriers – 25% risk with every pregnancy
• Is early termination of pregnancy an option – gestation?
  • And would the couple consider it if diagnosis was confirmed
  • Yes – then CVS (10-14 weeks) and beta gene testing
  • No – await birth
• Diagnostic test after birth
  • Gene test, HbEPP less accurate in neonates as HbA very small amounts at birth
• But there is no routine maternal or newborn screening in Australia
• So ...... when will these kids present
Presentation of Beta thal Major

• Healthy at birth

• Signs and symptoms by 6 to 12 months of age
  • pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice
  • severe hemolytic anemia with markedly abnormal hypochromic, microcytic red cells

• If left untreated – bony abnormalities due to extramedullary haematopoiesis – chipmunk facies

• Diagnosis
  • Confirmed by HbEPP –
  • absence or severely reduced HbA
  • only HbF and HbA2 present
Management of Beta thal Major

- Transfusion
  - stops marrow expansion – bony deformities, improves growth
- Iron Chelation
  - Critical to improved survival
- If had splenectomy – (minority)
  - Vaccinations
  - Prophylactic antibiotics

Complications of beta Thal major
- Osteoporosis, Extramedullary hematopoiesis, Hypogonadism, Cholelithiasis, Thrombosis, Pulmonary hypertension, Abnormal liver function, Leg ulcers, Hypothyroidism, Heart failure, Diabetes mellitus

Endocrinologist, cardiologist, ophthalmologist involved
Alpha Thalassaemia
Alpha thalassemia

- When to suspect
  - Microcytic, hypochromic anaemia in Iron replete patient
  - And beta thalassaemia has been excluded (Normal HbEPP)
  - Or family history

- Who/when to test
  - Planning pregnancies - Most important time to test is to predict risk of hydrops fetalis
  - Symptomatic/abnormal RBC indices
  - Deletions of 1 gene (silent/alpha thal minima) or 2 gene (alpha thal minor/trait) cannot be excluded based on normal FBC indices

- Alpha gene test is not covered by medicare - cost $70-100

- Test cost covered by Mater Pathology for patients that are referred from public specialist outpatients or antenatal clinic
Risk of alpha thalassaemia major

Assess Risk - Parents Genotypes
• Need to inherit two mutated alpha genes from each parent
• Two asymptomatic carriers of 2 gene deletions can cause hydrops fetalis in offspring
  • Only if on same chromosome ie Cis --/αα
  • Cis deletion more common if Asian descent
  • (Trans deletion α-/α- more likely African descent)

Alpha Thalassaemia Major/ HbBarts/ Hydrops fetalis
• Deletion of all 4 alpha globin genes --/--
  • Incompatible with extra uterine life
  • Unable to form any Fetal or Adult haemoglobin
  • Causes hydrops fetalis
  • Associated with increased maternal morbidity and mortality

• If risk of hydrops based on parents genotypes then couple should be offered, preconception counselling, early pregnancy diagnosis and therapeutic termination of pregnancy
Alpha Thal inheritance/risk

- Both parents carriers of 2 gene deletions
- but deletions are on different chromosomes
- “Trans” deletion
- NO RISK OF HYDROPS
- All offspring carriers
ONE PARENT WITH HbH DISEASE (3 NON-FUNCTIONAL α-GLOBIN GENES) AND THE OTHER A SILENT CARRIER OF α-THALASSAEMIA (αα-THAL) (1 NON-FUNCTIONAL α-GLOBIN GENE)

FOR EVERY PREGNANCY THE CHANCES ARE:

25% CARRIERS OF αα-THALASSAEMIA (trans)
25% CARRIERS OF αα-THALASSAEMIA (cis)
25% CARRIERS OF αα-THALASSAEMIA (SILENT CARRIER)
25% WITH HbH DISEASE

"cis" deletion

25% or ¼ risk of hydrops in offspring
HbH disease

Not considered critical to diagnose before birth but can cause clinically significant disease

- $\alpha-/--$ deletions of 3 of the 4 $\alpha$-globin genes
- Excess beta globin chains form $\beta4$ tetramers called HbH
- Diagnosis – Alpha gene testing
- Variable phenotype
  - Haemolytic anaemia during gestation
  - Symptomatic at birth - Jaundice and anaemic
  - Stigmata of chronic haemolytic anaemia,
    - hepatosplenomegaly,
    - ↑indirect hyperbilirubinemia, ↑LDH, ↓ haptoglobin,
    - leg ulcers,
    - osteopenia,
    - premature biliary tract disease (pigmented gall stones)
- Usually not transfusion dependent
  - May require transfusions during times of increased stress (inter-current illness, pregnancy, oxidative medications)
- Prone to iron accumulation due to ineffective erythropoiesis
HbH disease - Management

• Key Management
  • Monitor Haemoglobin if increased symptoms of anaemia
    • Refer for transfusion if required
  • Folate supplementation during haemolysis exacerbations
  • Avoid additional iron unless proven deficiency ferritin <20
  • Chelation considered if evidence of iron loading

• Preconception counselling
  • Partner of any patient with HbH planning children should have genetic test done.
  • 25% Risk of hydrops if partner has 2 gene deletion on one chromosome (cis deletion)
1. Assess risk before 10 weeks’ gestation
   One of:
   • High-risk ethnicity*
   • Unexplained microcytosis/hypochromia (MCV, ≤80fL or MCH, ≤27pg)
   • Family history or biological parent with known haemoglobinopathy†
   • Unexplained anaemia

2. Request on pregnant mother‡
   • FBC (haemoglobin level, MCV, MCH)
   • Ferritin test
   • Haemoglobinopathy screening tests
   AND document:
   • Gestation, ethnicity and indication for testing

   Haemoglobinopathy unlikely
   → No further action

   Haemoglobinopathy† confirmed or not excluded in mother
   → 3. Test father‡
   • FBC (haemoglobin level, MCV, MCH)
   • Ferritin test
   • Haemoglobinopathy screening tests
   AND document:
   • Ethnicity, partner name and date of birth

   If both parents are haemoglobinopathy carriers

   If only one parent is a haemoglobinopathy carrier
   → No further action§
Key points

• FBC indices
  • Thalassaemias – microcytosis
  • Sickle cell anaemia – Not microcytic

• Presentation
  • Alpha thal major – in gestation
  • Beta thal and beta Variants – after birth (>6months)

• Diagnosis
  • Beta (thal/sickle/HbC/HbE/HbD/HbO) → HbEPP
  • Alpha thalassaemia -> gene testing

• All haemoglobinopathies → iron overload, avoid supplements unless deficient

• Pre-pregnancy screening ideally