Dr Banu Kaya
Consultant Haematologist
Barts Health NHS Trust
Royal London Hospital, London, UK

SICKLE CELL AND THALASSAEMIA OVERVIEW
Objectives

- Gain awareness of haemoglobinopathy inheritance, pathophysiology and complications
- Screening standards
- Understand aspects of management of sickle cell disease and thalassaemia relevant to community
- Discuss cases
Regions where haemoglobinopathies are endemic
Genetics of haemoglobinopathies

- Thalassaemic changes cause a reduction or absence of globin chain production.
- Structural haemoglobin variants (e.g., Hb S, Hb C etc) result from mutations producing amino acid substitutions in the globin chain. But there is no reduction in amount of globin chain produced.
Inheritance of beta thalassaemia major

Partner who carries beta thalassaemia

Not a carrier
Carrier of beta thalassaemia
Carrier of beta thalassaemia
Child with beta thalassaemia major
The NHS Sickle Cell and Thalassaemia (SC&T) Screening Programme was set up in England in 2001 following Government commitment in the NHS Plan* (2000). It is the world's first linked antenatal and newborn screening programme.
Antenatal Screening Standards

- 95% pregnant women offered screening
- Timely screening - 50% pregnant women offered screening by 10 weeks, 0 days
- 90% of samples submitted to lab with FOQ
- At risk pregnancies identified with partner testing
- 50% prenatal diagnoses performed by 12 weeks, 6 days
- Subsequent action by 13 weeks, 6 days
Antenatal / neonatal screening in Tower Hamlets

Close liaison between:

- GP
- genetic counsellor
- midwives/health visitors
- Laboratory and hospital team
National Haemoglobinopathy Register
Thalassaemia

- Quantitative disorders of Hb synthesis
- Most common autosomal recessive disease worldwide
- Divided into $\alpha$- or $\beta$-thalassaemia depending on absence or reduction of each type of globin chain

- Extent of $\alpha$- / $\alpha$- non chain imbalance determines severity of $\beta$-thalassaemia
Clinical effects of untreated beta thalassaemia major

- Hypochromic microcytic anaemia
- Bone marrow expansion leading to:
  - Bone deformity
  - Extramedullary erythropoietic masses
  - Enlarged liver / spleen
- Failure to thrive from about 6 months of age
- Heart failure and death by age 3-4
Historical thalassaemic facies
Management of Beta Thalassaemia major

- Regular transfusions to maintain adequate Hb and prevent complications
- Preventing end organ damage due to iron loading - Iron chelation therapy
- Dealing with complications
  - Liver fibrosis – cirrhosis – liver failure
  - Cardiac complications
  - Hypogonadotrophic hypogonadism and endocrinopathy
- Curative interventions – BMT / gene therapy
Adapted from B. Modell and V. Berdoukas, 1984
Transfusional Iron Overload in Thalassemia

Iron Load Accumulation From Tx

- Hepatic Fibrosis
- Cardiac arrhythmia
- Hypoparathyroidism
- Hypothyroidism
- Diabetes
- Hypogonadism
- Cardiac Failure
- Death

Thalassemia Centre, Dept. of Pediatrics
University of Turin, Italy
Deaths in thalassaemia patients in the UK

As late as 1999:
- 50% of UK patients died before the age of 35 years
- Heart disease was responsible for 71% of the deaths

BMT = bone marrow transplantation.

Data recording and communication
Decision to start transfusions

- Presentation often insidious
  - Poor feeding
  - Faltering growth
  - Pallor
  - Increased infections
- Usually evident after age 6/12 but variable
- Ensure no correctable factors eg sepsis, G6PD deficiency causing acute anaemia
Evolution of iron chelation therapy

- **1960**: Standard management of iron overload
- **1980**: Deferoxamine (DFO)
- **1999**: Deferiprone (DFP)
  - DFP approved by EMEA
- **2005**: Deferasirox (DFX)
  - DFX approved by FDA
- **2006**: DFX approved by EMEA

**Acronyms:
- FDA, Food and Drug Administration, USA
- EMEA, European Medicines Agency**
Community – aim for long-term home based care

- Health promotion and maintenance
- Routine non specialist prescriptions
- Initial assessment and management of acute complications – eg sepsis
- Management of chronic complications
- General medical management and psychosocial support
Sickle Haemoglobin

- The sickle mutation is GAG-GTG substitution at codon 6 of the beta globin chain
- This gives rise to a substitution of valine for glutamic acid in the beta globin chain
- The ‘sickle haemoglobin’ has a tendency to form polymers when in the deoxygenated state
Sickle Cell Genotypes

- Hb SS
- Hb SC
- Hb S/Beta Thal
- Hb SD
- Hb SO

= Sickle cell disease
Spectrum of SCD Complications

These mechanisms are not mutually exclusive

Hemolysis, endothelial dysfunction

Viscosity, vaso-occlusion

Precapillary arteriole

Smooth-muscle cells

Capillary

Hb

Arg

NO

O₂

ET-1

NO

ET-1

NOS

XO

Monocyte

Platelets

VCAM-1

α₄β₁

Decreased NO bioactivity

Increased vaso-occlusion

Pulmonary hypertension
Leg ulceration
Priapism
Stroke

Pain crisis
Acute chest syndrome
Osteonecrosis
Clinical consequences of sickle cell disease

- Anaemia
- Increased susceptibility to infection (particularly encapsulated bacteria)
- Vaso-occlusive crises (commonest is painful crisis)
- Chronic tissues damage (eg stroke, avascular necrosis of hip, retinopathy)
Steady state Haemoglobin levels in 6 yr olds with HbSS
Sickle complications at different ages

- Pain
- Dactylitis
- Long bones
- Trunk
- Sequestration
- Splenic
- Hepatic
- Chest syndrome
- Mesenteric syndrome
- Infection
- Pneumococcal
- Parvovirus
- Salmonella
- Priapism
- Upper airway obstruction
- Stroke
- Subarachnoid haemorrhage
- Retinopathy
- Gall stones
- Avascular necrosis
- Hyposthenuria
- Delayed growth and development
- Leg ulcers
- Chronic renal failure
- Chronic sickle lung
Management of sickle cell disease

- Infection prophylaxis
- Analgesics for painful crises
- Education, lifestyle, avoidance of precipitants
- Transfusions for specific acute and chronic complications
- Hydroxycarbamide (Increases HbF, reduces painful crises)
- Bone marrow transplantation
Newly diagnosed child

- Important to discuss clinical heterogeneity
- Focus on risk of infection especially < 5 years old
- Importance of immunisation programme and penicillin prophylaxis
- Education – pain management at home, indications for seeking help, recognising severe complications
Role of community services

- Health promotion
- General education
- Supporting pain management at home
- Early recognition and treatment of complications
- Infection prevention
- Psychological support
- Family planning
- Employment / social support
- General screening
- Travel advice
Questions
Case 1

- 3 year old with Hb SS
- Compliance with penicillin V suboptimal
- Management plan?
Case 2

- 22 year old man, known Hb SS
- Presents with 2 hour history of priapism
- Distressed by severe pain
- Management?
Case 3

- 34 year old woman, Hb SC
- Generally well
- Mild documented retinopathy
- 6 / 12 history R hip pain
- Diagnosis? Plan?
Case 4

- Neonatal screening result
- HB F, Hb E only
- Mother’s antenatal results: Hb E, Hb A
- Father’s results unknown
- ?Diagnosis, management?
Case 5

- Antenatal screening
- Hb A, Hb A2 normal
- Results of FBC
- Hb 12 g/dL, MCV 63fl, MCH 22pg

- Is this a concern?
- What info would be useful?
Alpha and beta Globin gene clusters

Chromosome 16-Alpha globin cluster
5’ ζ α2 α1 3’

Chromosome 11-Beta globin gene cluster
5’ δ Gγ Aγ β 3’
Case 6

- 30 year old with beta thal major
- 2 day history of diarrhoea and abdominal pain
- Good compliance with chelation therapy
- Plan?
Thank you