Haemoglobinopathies

Haemoglobin Structure

Different haemoglobins are synthesized in the embryo, fetus, and adult. All tetrameric with two different pairs of globin chains, each attached to one haem molecule:
In embryos: HbPortland ($\zeta_2\gamma_2$), HbGower 1 ($\zeta_2\varepsilon_2$), HbGower2 ($\alpha_2\varepsilon_2$).
In fetus: >90% HbF ($\alpha_2\gamma_2$, where γ-chains may be $^{Gly}\gamma$ or $^{Ala}\gamma$), 10% HbA at birth, <1% after2y
Adult: normally ~98% HbA, 2% $\alpha_2\beta_2$ or HbA_2, $\alpha_2\delta_2$, <1% HbF.
There are 2 loci on Chr16 for the two α-chains & 1 locus on Chr11 for the β-chain.

Genetic disorders of Hb

Thalassaemias - Reduced rate of production of one or more of the globin chains.
Structural disorders – a globin chain change may → to instability or abnormal O_2 transport
Hereditary persistence of fetal haemoglobin – rare and harmless.

Thalassaemia

Epidemiology

Decreased production rate of Hb chains → abnormal Hb → instability & haemolysis → anaemia.

Classification

According to which chain of the globin molecule is affected → α-thalassaemia & β-thalassemia
Terms thalassaemia major/minor/intermedia is based on clinical severity.

Epidemiology

The name thalassaemia is derived from Greek words for sea (Mediterranean) and blood.
Carrier prevalence: 1:10 (Greek), 1:10-20 (Indians). Type varies geographically: β-thalassemia most common form around Mediterranean, North Africa, Middle East, India, and Eastern Europe. α-thalassaemia is more common in SE Asia, India, the Middle East, and Africa.
Overall carriage 3% of world pop. Clinical disease in 0.3% of world pop.

Alpha Thalassaemia

2 genes control α-chain on Chr16. Disease depends on how many of 4 alleles affected:

- 1 allele: Silent carrier. Asymptomatic
- 2 alleles: α-Thalassaemia trait (cis [Asians] or trans [black] alleles). Microcytosis only.
- 3 alleles: HbH disease: Mod. anaemia & reticulocytosis. HbH (β_4) & HbBarts (γ_4).
- 4 alleles: Incompatible with life – intrauterine hydrops fetalis. HbBarts (γ_4) only.

Beta Thalassaemia

More common than α-thalassaemia. Only 1 gene on Chr11 (2 alleles) to be affected:

- 1 allele: Thalassaemia minor. Low MCV for decrease in Hb. Slight ↑HbA2
- 2 alleles: Thalassaemia major. Presents in infancy. >90% HbF. Fe overload. HSM. Bone #/deformities, recurrent infections, endocrine failure.

Investigations

Blood: FBC, film, EPG, iron studies
Imaging: Skeletal survey – marrow expansion, hair-on-end skull XR, maxilla overgrowth, rib/long & flat bone deformities. CXR may show cardiomegaly. CT/MRI – hepatic iron content.
Other tests: ECG/Echo to monitor cardiac fn. HLA typing for BMT. Liver biopsy to assess Fe deposition. If given desferrioxamine may need eye & hearing tests

Management

Non-Drug

- Genetic counselling.
- Avoid food rich in iron. Tea and coffee can reduce the absorbtion of iron.
- Transfusion if Hb<9, but Cx iron overload. Use leucocyte poor blood esp if BMT planned.

Drugs

- Iron chelation - Desferrioxamine to treat haemochromatosis
- Folic acid and vitamin E deficiency may both need treating.

Surgical

- Consider splenectomy if hypersplenism.
- BMT

Complications

- Iron overload even if they are not transfused.
- Bleeding tendency, susceptibility to infection, & organ dysfunction related to Fe overload.
- Repeated transfusions increase the risk of blood borne diseases
- Infection with rare opportunistic organisms in iron overload e.g. Yersinia enterocolitica.
- Osteoporosis common and pamidronate is an effective treatment.
- Hyperuricaemia sometimes produces gout.
- With increasing length of survival, hepatocellular carcinoma is increasing.

Prognosis

- Depends upon the severity of the disease.
- In the β thalassaemia major 80% die in the first 5 years of life from disease Cx.
- The introduction of iron chelating agents has increased life expectancy dramatically.

Sickle-Cell Disease / Sickle Cell Anaemia

Genetics

AR inherited sickle cell haemoglobin (HbS) has glu replaced by val at position 6 in β-chain. Polymerisation of HbS→ RBC membrane damage → rigid sickling → sequelae.

Sickle cell trait

- Heterozygotes (one normal & 1 abnormal β gene → HbAS): ~60% HbA and 40% HbS.
- Asymptomatic unless marked hypoxia, e.g. anaesthesia or non-pressurised flying.
- May have renal Cx: papillary necrosis, haematuria, UTI or poor concentrating ability.
- FBC and film are normal; diagnosis is made by a positive sickle test or Hb electrophoresis.
- Sickle cell trait protects against malaria.
- Screening all those of African descent is essential before general anaesthesia.

Sickle cell anaemia

Occurs when homozygous for gene HbSS (sickle cell disease) or if compound heterozygote with one sickle β gene and the other gene having a different mutation or deletion):

- *HbS/beta^0 thalassaemia:* clinically similar to sickle cell anaemia i.e. severe
- *HbSC disease:* intermediate clinical severity
- *HbS/beta+ thalassaemia*: mild to moderate severity
- *HbS/hereditary persistence of fetal Hb (S/HPHP*): very mild phenotype or symptom-free
- *HbS/HbE syndrome:* very rare and generally very mild clinical course
- *Rare combinations of HbS:* with HbD Los Angeles, HbO Arab, G-Philadelphia, etc.

Epidemiology

Prevelance: ~ 1:5000.
Race: African (1:4), Afro-Caribbean (1:10), Middle Eastern, Mediterranean and Indian (HbS protects somewhat against malaria).

Presentation

The symptoms usually begin >6mo when HbF levels are falling.

- Chronic haemolytic anaemia, jaundice, pallor, lethargy, and general weakness
- Increased susceptibility to infections, dactylitis
- Bone marrow hyperplasia → thin cortices, frontal skull bossing, biconcave vertebrae
- Growth retardation & delayed puberty
- Splenomegaly initially but recurrent splenic infarcts may → autosplenectomy
- Others: CCF, gallstones, hepatomegaly, renal (papillary necrosis, haematuria, ↓concentrating ability), lower limb skin ulcers, ischaemic CNS events.

Sickle cell crises

Preciptants: idiopathic, cold, infection, dehydration, exertion, stasis, acidosis or hypoxia

Vaso-occlusive crises

- MSK - bone infarction, osteomyelitis, avascular necrosis femoral head
- Abdominal - mesenteric sickling and bowel ischaemia, gallstones, hepatic crisis
- Pulmonary – infarction (PE inv not helpful) ± secondary infection. Significant mortality.
- CNS - Variable presentation, including fits and focal neurological signs. Cerebral infarction is commoner in children. Haemorrhage from microaneurysms around infarctions ('moya moya') is more common in adults.
- Priapism

- Renal - infarction, papillary necrosis may cause renal colic or severe haematuria
- Eye problems - hyphaema, retinal haemorrhage and retinal detachment.

Aplastic crisis:

- Usually precipitated by infection with parvovirus B19
- Causes sudden lethargy and pallor, may → high-output congestive heart failure

Sequestration crisis:

- Splenic - Mainly in children<2y. Rapid ↑liver & spleen → death can occur 2° sev. anaemia.
- Chest syndrome: Usually post-puberty. Due to sequestration of sickle cells in the pulmonary circulation. Sig. mortality. Acute SOB, pleuritic pain, infiltrates on CXR.

Infectious crisis:

- Orgs: pneumococcus, salmonella, E.coli, mycoplasma, H.influenzae, Yersinia
- Sig. mortality in children.

Hyper-haemolytic crisis: uncommon; during painful crises can be ↑↑haemolysis rate with ↓Hb.

Differential diagnosis

Other causes of haemolytic anaemia.

Investigations

Bloods: FBC (Normally Hb 60-90, WCC 12-18, ↑plt, all lower in aplastic crisis), film (sickle cells, Howell-Jolly bodies), retics, ESR (may not be helpful as sickle cells don't form rouleaux)
CXR: if fever or respiratory symptoms.
Specific: Hb EPG, sickling test (e.g. mixing drop of blood with 2% sodium metabisulphite)
Screening: before anaesthesia, before conception, neonatal.
Prenatal diagnosis: pre-implantation, amniocentesis, CVS and fetal blood sampling.

Management

General

- Parental and patient education: avoiding precipitants, avoiding EtOH & smoking.
- Bone marrow transplantation: Curative in >80%.
- Hydroxyurea: ↑HbF, ↓crises, ↓need for Txf, ↓hospital admissions. But 40% don't respond.
- Folic acid supplementation may be required.
- Infection: Oral penicillin prophylaxis. Immunisation (pneumococcal, meningococcal, Hib)
- Blood transfusions: if ↓↓Hb, or parital exchange to ↓HbS if Hb relatively high.
- Other Rx: Valproate (↑HbF), decitabine (↑HbF), L-arginine (NO precursor)

Crises

- Hydration – oral fluids or IV (5% dextrose or NS)
- O_2 if hypoxic, NIPPV/IPPV may occasionally be required.
- Analgesia – IV morphine PRN
- Antibiotics if signs of infection
- Transfusion if acute sev. anaemia.
- Treat underlying cause

Prognosis

- Life expectancy >40yrs in Western countries.
- Highest mortality in young children from infections. CVA more common >10y.
- Sustained high concentrations of HbF is associated with a longer life expectancy.