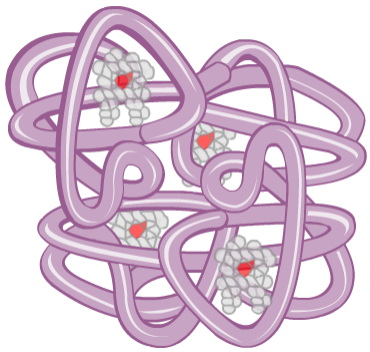
An overview of Thalassaemias and Complications

Haemoglobin

Haemoglobin is the most abundant protein in blood, and exists as three main types in normal adults:

- HbA ($\alpha_2\beta_2$) - 97%
- HbA_2 ($\alpha_2\delta_2$) - 2.5%
- HbF ($\alpha_2\gamma_2$) - 0.5%

Approximately 400 different haemoglobin variants have been identified with 1 - 5% individuals in the world having a haemoglobin variant.



Definitions

- Thalassaemia
  - Quantitative defects in globin chain synthesis
    - alpha globin expressed in fetus and throughout life
    - beta globin expressed not expressed in fetus
- All forms of thalassaemia seem to give some degree of protection against malaria

Thalassaemia Syndromes

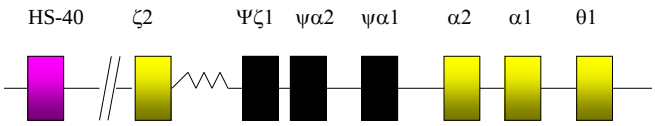
- Thalassaemia major
  - results in death without regular blood transfusions from an early age
  - also called transfusion-dependent thalassaemia
- Thalassaemia intermedia
  - Significant anaemia and splenomegaly, but managed without regular, monthly transfusions
  - Also called non-transfusion dependent thalassaemia
- Thalassaemia carrier
  - Asymptomatic but changes on blood count
  - Also called thalassaemia trait, thalassaemia minor

α thalassaemia

- Commonest single gene disorder in world
- alpha thalassaemia trait - very mild anaemia, small red cells
- HbH disease - moderate hemolytic anemia, rarely needing transfusions
- Hb Bart's Hydrops fetalis - severe intra-uterine anaemia causing fetal death

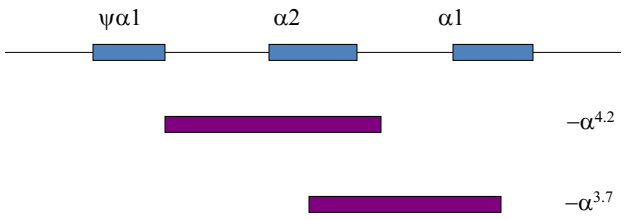
α–globin Gene Cluster

- On chromosome 16p

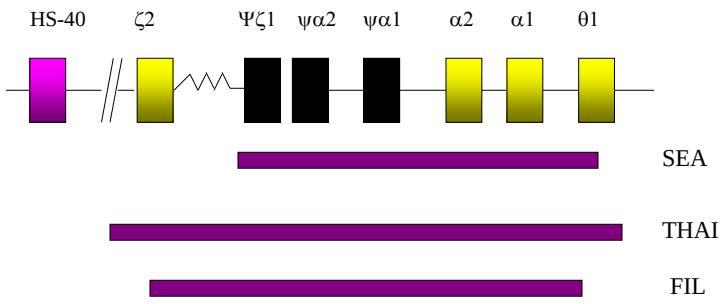


α^+ thalassaemia due to deletions

- Most forms of thalassaemia result from large deletions



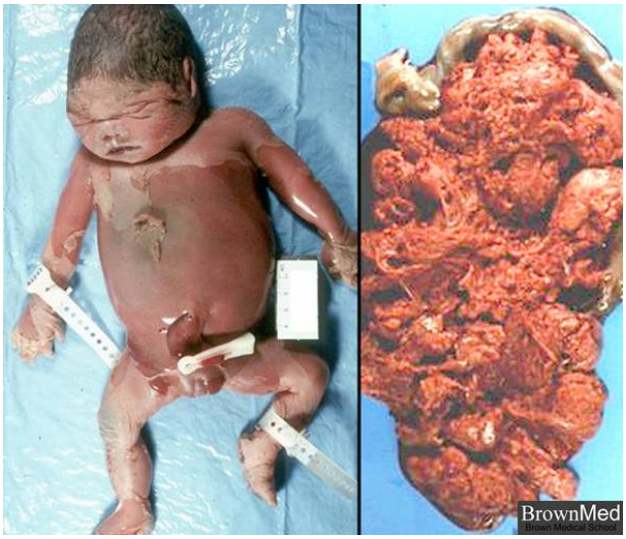
α^0 thalassaemia due to large mutations



Pathophysiology of α thalassaemia

- Hb Bart's Hydrops Fetalis
  - No functioning α globin genes
  - Fetus unable to synthesise fetal haemoglobins from about 8 weeks gestation
    - γ chain tetramers form (Hb Bart's) which do not release oxygen
    - Progressive fetal anaemia and death at 20-30 weeks gestation
- HbH disease
  - One functioning α globin gene (or equivalent)
  - Moderate/mild haemolytic anaemia
- alpha thalassaemia carrier
  - 3 or 4 functioning α globin genes
  - asymptomatic

Hb Bart's Hydrops Fetalis



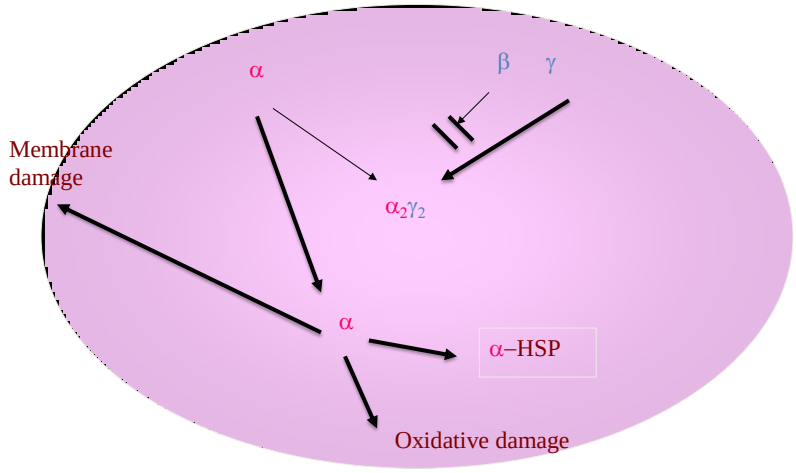
Diagnosis of α thalassaemias

- Carriers identified by
  - Low MCH and MCV
  - Normal HbA2 level
  - No iron deficiency
  - Confirmed if necessary by DNA analysis
- HbH disease
  - Parents carriers
  - Blood film + HbH bodies
  - DNA analysis
- Hb Bart's hydrops fetalis
  - Parents carriers
  - Fetal anaemia on scans
  - DNA analysis

Beta thalassaemia syndromes

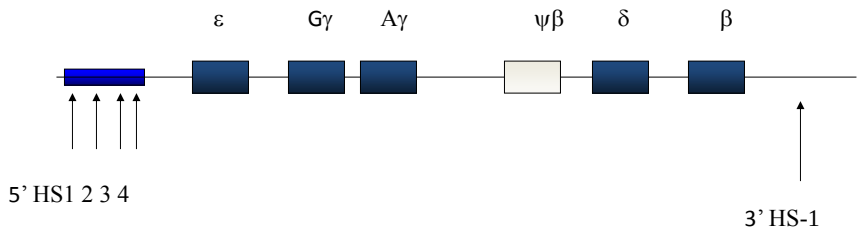
- Reduced beta globin production, but alpha globin continues to be made at same rate
- unpaired alpha globin damages developing erythroblasts
  - membrane
  - enzyme defects
- ineffective erythropoiesis
  - death of developing red cells
- moderate reduction in life-span of circulating red cells (haemolysis)

Pathophysiology of Beta Thalassemia



β globin cluster

- Found on short arm of chromosome 11
- Two main types of mutation
  - β^0 thalassaemia – no beta globin produced
  - β^+ thalassaemia – beta globin production reduced



Genetics

- More than 150 different beta thalassaemia mutations
- Different mutations predominate in different parts of the world
- Some common mutations
  - HbE (codon 6, GAG-AAG, glu-lys) (beta^{++})
  - IVS 1-5, G-C (severe beta^{+})

Severity of beta thalassaemia

- β^0 mutations produce usually produce more severe forms of thalassaemia, but not possible to reliably predict severity from genotype
- Thalassaemia major: β^0/β^0, β^0/β^+
- Thalassemia intermedia: β^0/β^+, β^+/β^+, β^+/β^{++}
- Some factors known to lessen severity
  - co-inheritance of α thalassemia
  - increased ability to make HbF

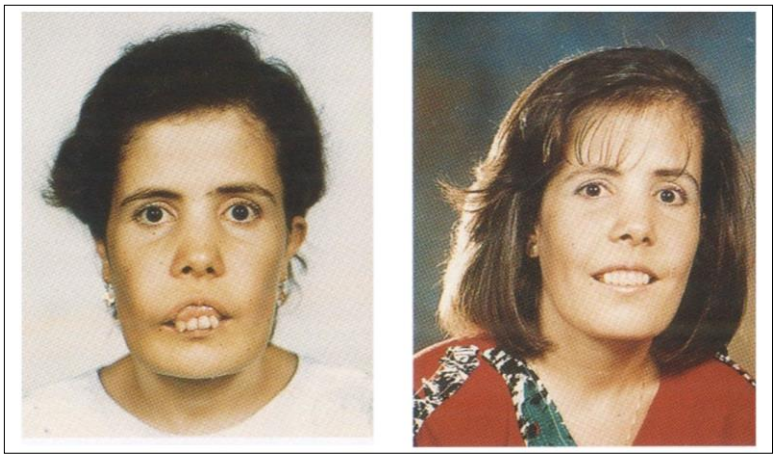
Diagnosis of beta thalassaemia major

- Neonatal screening - no HbA present in cord/neonatal blood
  - Most cases picked up in UK on neonatal screening
- Family studies - parents, siblings
- DNA analysis
- Blood tests - high/100% HbF, severe anaemia, microcytosis, nucleated reds
- Clinical picture

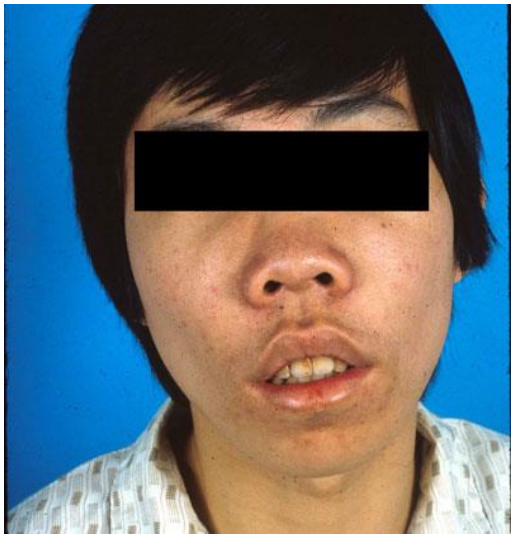
Clinical Features of beta thalassaemia major

- Failure to thrive/poor growth
- pallor, jaundice
- hepatosplenomegaly
- if not transfused
  - bone disease - expanded skull, maxillary hyperplasia, pathological fractures
  - extramedullary haemopoiesis
  - heart failure, death

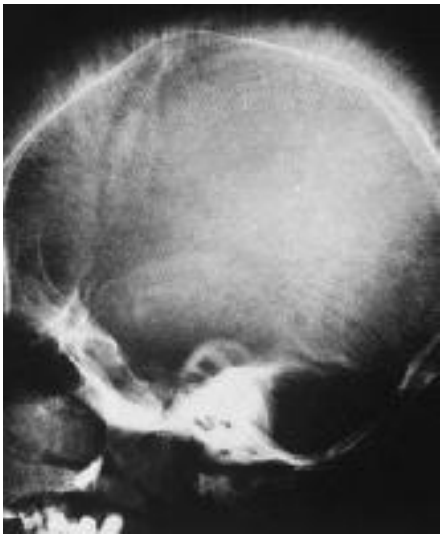
Facial features of thalassemia major



Beta Thalassaemia Major



Beta Thalassaemia Major



Blood Transfusion in Beta Thalassaemia Major

- When to start
  - clinical decision, not based purely on haemoglobin level
  - usually between 6-12 months
  - poor growth, feeding
  - development of hepatosplenomegaly
  - steadily falling Hb with increasing age
- Frequency
  - 2-5 weekly, usually 4 weekly in UK
  - determined by symptoms, social factors

Blood Transfusion in Beta Thalassaemia Major

- Volume of transfusion
  - aim for pre-transfusion Hb 9-10.5g/dl
  - post-transfusion <15g/dl
  - vol = desired increment x mass in kg x 3 (if haematocrit of transfused blood 65%)
  - usually 10-15 ml/kg over 3-4 hours
- Hepatitis B vaccinations before starting transfusions

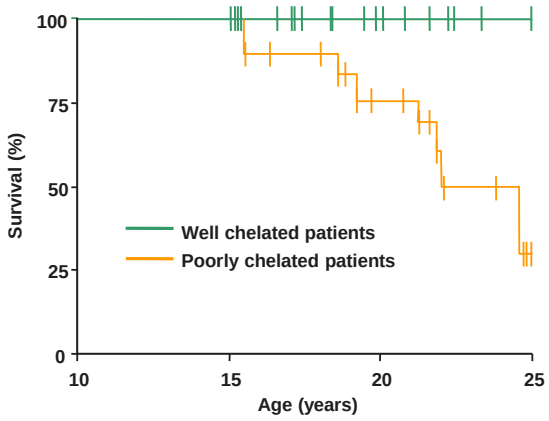
Blood Transfusion in Beta Thalassaemia Major

- Type of blood
  - leucodepleted
  - matched for ABO, Rhesus D, CcEe, Kell
  - negative for any alloantibodies
- Automated red cell exchange
  - reduces frequency of transfusions, iron loading
  - increases cost, donor exposure, infection risk

Iron Chelation in Beta Thalassaemia Major

- Each unit blood contains about 250mg iron
- Without chelation, majority of patients die before 20 yrs
- Starting
  - ferritin >1000microg/l
  - 10-20 transfusions
  - three years old

Chelation therapy and survival



The probability of survival to at least 25 years of age in poorly chelated patients was just one-third that of patients whose iron levels were well managed

Splenectomy in Beta Thalassaemia Major

- Optimal transfusion from an early age often avoids splenomegaly
- Periods of reduced transfusion can result in irreversible splenomegaly
- Splenectomy if LUQ pains, transfusion requirement >220ml/kg/year, hypersplenism
- Vaccinations, penicllin

Other Treatment Options

- Increased HbF production
  - butyrates/short-chain fatty acids
  - hydroxyurea
  - Erythropoietin
- Haematopoietic stem cell transplantation
- Emerging treatments
  - Gene therapy
  - Activin receptor Iib ligand traps

Cardiac Complications

- Severe heart disease can be asymptomatic
- symptoms include palpitations, breathlessness, epigastic pain etc
- investigations - CXR, ECG, echo, MUGA, MRI
- treatment - continuous iv dfo, ACE inhibitors, diuretics, digoxin, amiodarone

Endocrine Complications

- Poor growth - multifactorial
- Delayed puberty - hypogonadotrophic hypogonadism
- Hypothyroidism - severe iron overload
- Impaired glucose tolerance
- Hypoparathyroidism - usually in adults
- Infertility - common in women
- Osteoporosis

Osteoporosis

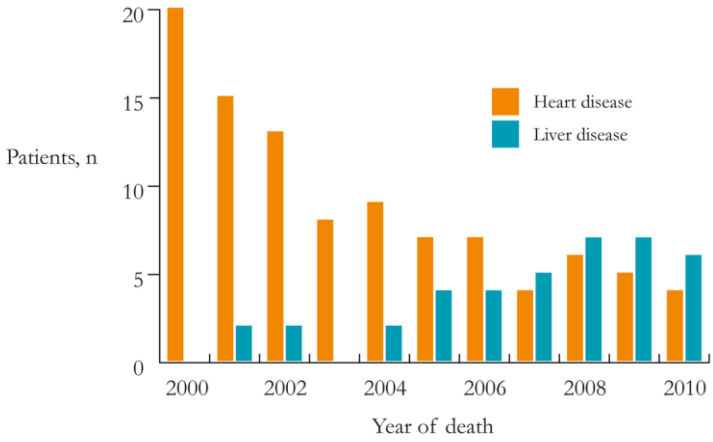
- Increasingly recognised in optimally treated patients
- Nearly all patients have low BMD on DEXA scanning
- Lower BMD if diabetic, male, hypogonadal
- Exact significance unclear, although pathological fractures increasesd
- Increased BMD following bisphosphonates

Causes of Death in Thalassaemia

Cardiac causes	171	71%
Infections	28	12%
Liver disease	15	6%
Tumors	7	3%
Endocrine complications	6	3%
Thrombosis	3	1%
Unknown	3	1%
Anaemia	2	1%
Other causes	*5*	*2%*

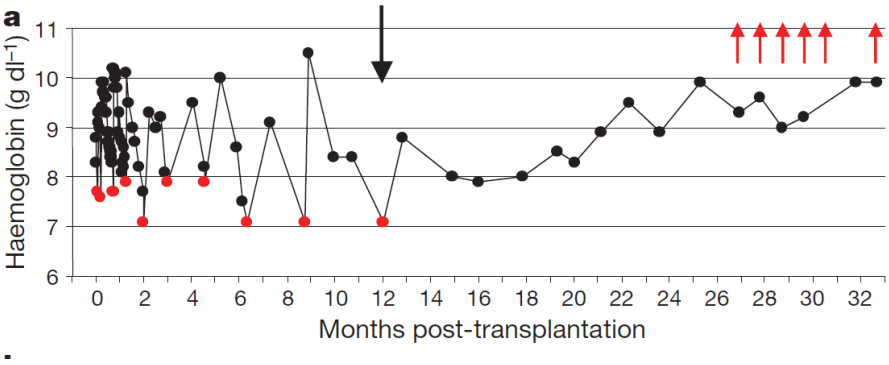
(Italian patients born from 1960-1984)

Deaths in Greece in Thalassaemia Major



Gene Therapy

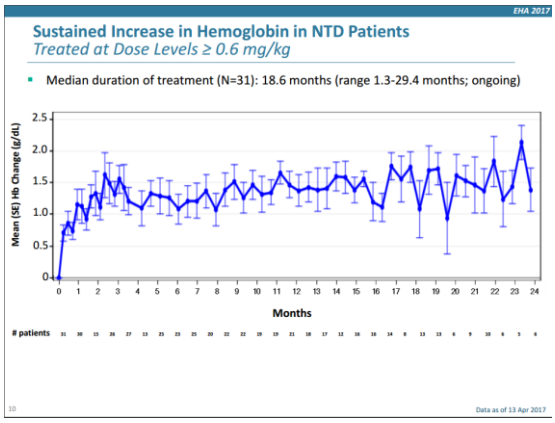
- Lentiviral β globin gene transfer to adult with transfusion dependent HbE/β thalassaemia
- Transfusion independent for more than two years
  - Hb9-10g/dl
  - 1/3 derived from gene transfer
- Emergence of dominant clone due to activation of HMGA2 by vector insertion
  - Concerns about long-term risk of malignancy
  - Unclear how much success depends on chance activation of proto-oncogene



Cavazzana-Calvo et al.
Nature 2010:467;318-323

Luspatercept

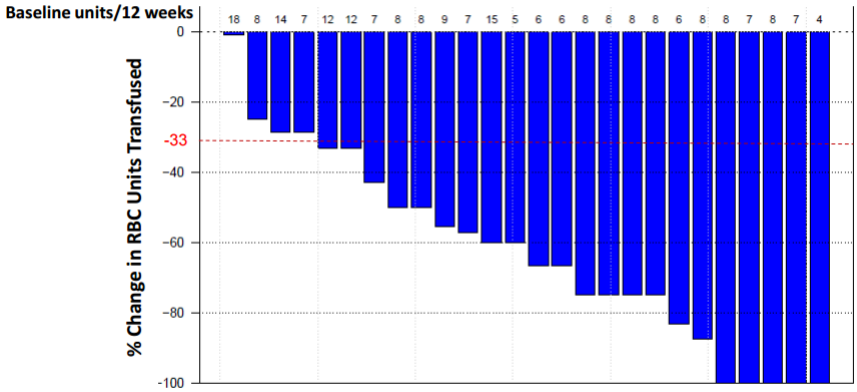
- Trap for TGF-β superfamily ligands
  - Reduces ineffective erythropoiesis



EHA 2017

Reduction in Transfusion Burden in TD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

- Median duration of treatment (N=32): 14.2 months (range 0.7-27.2 months; ongoing)



*6 patients discontinued before completing 12 weeks, not shown

- Transfusion reduction from 12 weeks pre-treatment to any 12-week interval on treatment

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Data as of 13 Apr 2017

Summary

- Thalassaemia common worldwide but relatively rare in UK
- Alpha thalassaemia
  - HbH disease which is usually mild
  - severe fetal anaemia and death
- Beta thalassaemia
  - thalassaemia major requiring regular transfusions and iron chelation
  - new treatments being developed