Alpha-thalassaemia

Key facts

- The thalassaemias are a group of conditions characterised by reduced production of either the alpha (alpha-thalassaemia) or beta (beta-thalassaemia) chain of the haemoglobin molecule.
- There are two clinically significant forms of alpha-thalassemia. The more severe type is known as hemoglobin Bart hydrops fetalis (or Hb Bart) syndrome; the milder form is called HbH disease.
- No treatment is effective for Hb Bart hydrops fetalis. Most patients with HbH disease will present in early childhood and many will not need treatment.
- Alpha-thalassaemia is considered an autosomal recessive disorder, but in fact inheritance is complex because the alpha-globin chain production is controlled by two genes, *HBA1* and *HBA2*.
- Alpha-thalassaemia is most prevalent in sub-Saharan Africa, South and Southeast Asia, the Middle East and regions of the Mediterranean such as Cyprus. Being a carrier of alpha-thalassaemia is thought to convey some protection against malaria.
- Antenatal screening for thalassaemia is available throughout the UK, apart from Northern Ireland. Screening is dependent on the prevalence of the condition in particular geographical areas. At a minimum, laboratory testing will be based on an assessment of risk, which is determined by the ethnic origin of the baby's mother and father.

Clinical features

- Hb Bart syndrome and HbH disease need to be considered independently, as their clinical presentations are so different.
- Hb Bart syndrome presents antenatally with hydrops fetalis, and the majority of babies with this condition will be stillborn or die soon after birth. Pre-eclampsia is common in pregnancies complicated by Hb Bart syndrome.
- HbH disease usually causes a mild to moderate haemolytic anaemia, though very rarely may present with hydrops fetalis.
- The clinical features correlate with the number of affected alpha-globin chains (see below).

Diagnosis

- The diagnosis depends on measuring red blood cell (RBC) indices, a peripheral blood film, detection of RBC inclusion bodies, and qualitative and quantitative haemoglobin analysis.
- DNA testing (see below) may be useful in confirming the diagnosis and for predicting the clinical phenotype.
- The results are complex and need expert interpretation by haematologists or haematology clinical scientists.

Genetic basis

- The production of the alpha-globin protein is regulated by four alpha-globin genes, two (one each of *HBA1* and *HBA2*) on each copy of chromosome 16. The severity of the condition correlates with the number of altered genes and hence the amount of alpha-globin chain production.
- Hb Bart syndrome occurs when there are genetic alterations in all four alpha-globin genes.

- HbH disease occurs when there are genetic alterations in three of the four alpha-globin genes.
- The genetic basis of alpha-thalassaemia is complex, as each person inherits two alpha-globin genes from each parent. However, the principles of autosomal recessive inheritance apply. Because of the complexity, referral to specialist clinical genetics services is recommended.
- Many disease-causing alterations have been identified in the alpha-globin genes. However, more than 90% of cases are caused by small deletions involving one or more of the alpha-globin genes.

Clinical management

- No treatment is known to be effective for Hb Bart syndrome, though intrauterine transfusions and haematopoietic stem cell transplantations have been considered. Pre-eclampsia is common in pregnancies at risk of Hb Bart disease and should be managed appropriately.
- Most patients with HbH disease are well but will have a haematological evaluation every 6-12 months. Occasional red blood cell transfusions may be required, particularly during febrile illnesses when haemolytic crises are more likely.

Genetic testing

Genetic testing can be used to:

- identify the gene alterations in the alpha-globin genes in someone with alpha-thalassaemia;
- provide information about the genetic status of relatives of someone with alpha-thalassaemia through carrier testing; and
- offer prenatal and pre-implantation genetic diagnosis. Prenatal diagnosis is usually possible by chorionic villus sampling (CVS) or amniocentesis. If a couple are considering prenatal diagnosis, referral should be made to the local clinical genetics service prior to a pregnancy. This ensures that appropriate advice and investigations are undertaken and confirms whether or not prenatal diagnosis is possible. All couples considering pre-implantation genetic diagnosis must be referred to their local clinical genetics service.

Genetic testing is available in the UK and usually provided through specialist clinics or regional genetic centres.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.