Alpha-thalassaemia

Key facts

- Thalassaemias are a group of genetically-inherited conditions of haemoglobin, characterised by a reduced synthesis (production) of a globin chain. The most common of these is a reduction in the alpha (alpha-thalassaemia) or beta (beta-thalassaemia) globin chain of the haemoglobin molecule.
- Alpha-thalassaemia is considered an autosomal recessive disorder, but inheritance is complex because the alpha globin chain production is controlled by two genes: *HBA1* and *HBA2*.
- There are two clinically significant forms of alpha-thalassaemia. The more severe type is known as haemoglobin Bart's hydrops fetalis (Hb Bart's), or alpha-thalassaemia major; the milder form is called haemoglobin H disease (HbH).
- The majority of patients with HbH disease are well, and do not require medical treatment. Some may present in early childhood, but the majority are diagnosed in adulthood, for example, as part of routine screening during pregnancy.
- Hb Bart's is a fatal disease, and is incompatible with extra uterine life.
- Alpha-thalassaemia is most prevalent in sub-Saharan Africa, south and south-east Asia, the Middle East and regions of the Mediterranean, such as Cyprus.
- Being a carrier of alpha-thalassaemia is thought to grant some protection against malaria.
- Testing for alpha-thalassaemia is available across the UK and can be provided by the GP, at a local sickle cell and thalassaemia centre or via referral to a regional genetics centre.
- Antenatal screening for thalassaemia is available throughout the UK (except in Northern Ireland), and is part of the national antenatal screening programme.

Clinical features

- Hb Bart's and HbH disease need to be considered independently, as their clinical manifestations differ.
- Hb Bart's presents during fetal life. The majority of these babies are born prematurely as a stillbirth, or die soon after birth commonly during the second trimester of pregnancy.
- Those with HbH disease survive fetal life. The condition usually causes a mild to moderate haemolytic anaemia, which may or may not require medical intervention. Cases can be severe - usually during an acute illness or increased metabolic exacerbation, such as during pregnancy.

Diagnosis

- The diagnosis depends on measuring red blood cell (RBC) indices, examining a peripheral blood film, detecting RBC inclusion bodies, and qualitative and quantitative haemoglobin analysis. Haemoglobin electrophoresis will show a decreased level of alpha globin.
- DNA testing (see below) may be useful in confirming the diagnosis, and for predicting the clinical phenotype and/or risk to an individual's or couple's offspring.
- The results are complex and need expert interpretation by an experienced laboratory scientist, haematologist, haematology clinical scientist, experienced haemoglobinopathy specialist nurse or genetic counsellor.

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 chains produced.
- An individual inherits two alpha globin genes from each parent and has a total of four alpha globin genes (α α/ α α) to produce the required amount of alpha chains.
- Many disease-causing variants have been identified in the alpha globin genes. However, more than 90% of cases are caused by globin gene deletions involving one or more of the alpha globin genes - ranging from the least significant one gene deletion (- α/ α α), to the most serious four gene deletion, which causes Hb Bart's (- - / - -).
- There are two genetically important alpha-thalassaemia carrier states: alpha plus (α - / α -), which occurs in sub-Saharan Africa, the Middle and Far East and the Mediterranean, and the alpha zero thalassaemia (- - / α α) which is seen mostly in the Far East, especially China and Vietnam.
- A couple who both have alpha zero thalassaemia (- - / α α) have a 25% (one-in-four) chance, in every pregnancy, of having a child with Hb Bart's (- - / - -).
- HbH disease occurs when there is a genetic mutation in three of the four alpha globin genes (- - / - α).
- Due to the complexity of alpha-thalassaemia, referral to a specialist counsellor is recommended.

Genetic testing

- Genetic testing can be used to:
  - » identify the gene variant in the alpha globin genes in someone suspected of having alpha-thalassaemia;
  - » provide information about the genetic status of the relatives of someone identified with alpha-thalassaemia following 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 or specialist haemoglobinopathy service prior to conception of a pregnancy or as early as possible in a pregnancy. This ensures that appropriate advice and investigations are undertaken, and confirms whether an individual or couple are at risk of having an affected fetus and whether prenatal diagnosis is possible.
- All couples considering pre-implantation genetic diagnosis must be referred to their local clinical genetics or haemoglobinopathy service.
- Genetic testing is available across the UK, and referral can be arranged by the GP, specialist haemoglobinopathy centres or via regional genetic centres.

Clinical management

- No treatment is known to be effective for Hb Bart's. Although intrauterine transfusions and haematopoietic stem cell transplantations have been performed experimentally, the outcome does not make this a particularly viable option.
- Pre-eclampsia is common in pregnancies carrying a fetus with Hb Bart's, and should be managed appropriately. Preeclampsia poses a serious risk to the woman's health and, in serious cases, can be fatal.
- Most patients with HbH disease are well, but will need a haematological evaluation every 6 to 12 months. Occasional red blood cell transfusions may be required, particularly during febrile illnesses

when a haemolytic crisis is more likely. If long term transfusion is given, the individual may need adjunct therapies.

- Regular outpatient management from birth, and throughout adulthood, is crucial to ensure adequate monitoring and management of those with HbH disease.

Direction to further reading, guidelines and patient groups

- For detailed and comprehensive guidance in the management of thalassaemia, a document from the United Kingdom Thalassaemia Society is available to view and download.
- Information on the UK screening programme can be found here
- For sources of further support and information, contact the national voluntary organisation:

  United Kingdom Thalassaemia Society
  19 The Broadway
  Southgate
  London N14 6PH
  Tel: 020 8882 0011
  Website: http://www.ukts.org

This information is intended for educational use and was current in March 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Brent Sickle Cell & Thalassaemia Centre, London North West University Healthcare NHS Trust.