Neonatal sickle cell disease and thalassaemia

This article describes the diagnosis and management of sickle cell disease and thalassaemia in fetal and infant life. It includes details of the basic pathophysiology of the conditions. It also discusses the recent developments in neonatal and antenatal screening and the provision of care for infants with sickle cell disease.

David C Rees
FRCP, FRCPath
Senior Lecturer/Honorary Consultant in Paediatric Haematology
King's College Hospital NHS Trust, London
david.rees@kingsch.nhs.uk

The NHS Sickle Cell and Thalassaemia Screening Programme was set up in England in 2001 following Government commitment in the NHS Plan (2000).

For more information:
www.sickleandthal.org.uk
Tel: 020 7848 6634
Fax: 020 7848 6620
Email: haemscreening@kcl.ac.uk

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Key points

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1. All newborn babies born in England are now screened for sickle cell disease using heelprick blood spots.
2. Sickle cell disease and severe beta thalassaemia do not cause symptoms in fetal life, and are very unlikely to cause illness before three months of life.
3. All babies with sickle cell disease should start penicillin prophylaxis at 2-3 months of life.
4. All infants with sickle cell disease and significant thalassaemia should be cared for by paediatricians with an interest in the condition and in conjunction with a recognised specialist centre.

Sickle cell disease and thalassaemia are very different diseases. However, they are linked by the fact that they are both due to mutations of the globin genes, both are more common in people whose families originate from countries where malaria is or was common, and the diagnostic tests are similar, involving analysis and quantitation of the different types of haemoglobin[1]. Both are also typically inherited as autosomal recessive diseases, and are cared for by the same nursing and medical staff. However, the diseases have different clinical manifestations, and sometimes suffer from being grouped together and considered as a single condition.

Sickle cell disease results from the inheritance of two mutated beta globin chains which produce abnormal proteins. To have sickle cell disease, at least one of these mutations must be that producing haemoglobin S (HbS), an abnormal form of adult haemoglobin, in which the sixth codon of the beta globin gene is mutated, leading to the beta globin protein having the amino acid valine at position 6 rather than glutamic acid. Thalassaemia results from a quantitative decrease in the production of either alpha or beta globin chains, although the globin chain proteins themselves are normal.

Thalassaemia can result from more than 400 different mutations in the alpha and beta globin genes, although the pathophysiology results from a relative deficiency of either the alpha or beta globin chains irrespective of the mutation.

Pathophysiology of sickle cell disease

Sickle cell disease was the first condition in which a change in protein sequence was linked directly to a wide range of clinical manifestations. The deoxygenated HbS molecule tends to form long polymers which distort and damage the red cell. This results in the red cell becoming more rigid and more likely to block small blood vessels[2]. Once such a blockage begins to occur then blood passing through the narrow or blocked blood vessel is rapidly deoxygenated resulting in further HbS polymerisation and worsening vaso-occlusion. The damage to the red cell is initially reversible if the cell is re-oxygenated. However, if this happens repeatedly, the red cell becomes irreversibly damaged and adopts the permanently abnormal, sickle shape which is characteristic of the condition (**FIGURE 1**). Although vaso-occlusion remains the most important pathological process, it has been increasingly recognised that a number of other processes contribute to the pathophysiology. Significant amounts of haemoglobin are released freely into the plasma. This free haemoglobin binds avidly to nitric oxide resulting in a functional deficiency[3]. This is thought to contribute to a number of the chronic endothelial problems associated with sickle cell disease, particularly pulmonary hypertension. There is also evidence of abnormal expression of adhesion molecules by both white cells and platelets. Although people with sickle cell disease are anaemic, with an average haemoglobin level of about 7.0 g/dL, there are relatively few complications directly related to this anaemia as the sickle haemoglobin releases oxygen more easily, and the body adapts to the chronic anaemia.

Pathophysiology of thalassaemia

Thalassaemias are divided into alpha (α) and beta (β) thalassaemia, depending on which globin chain is deficient. The

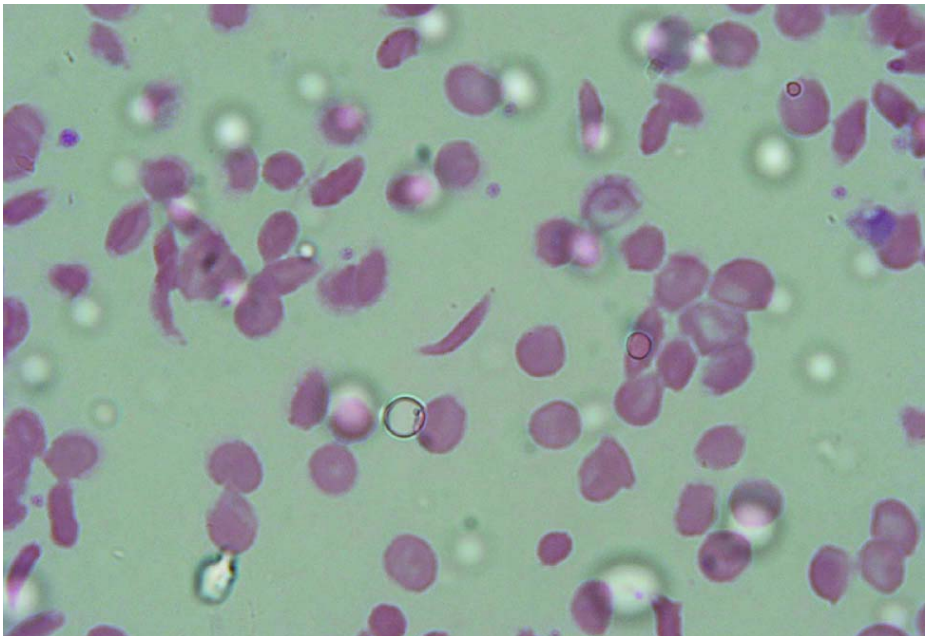

FIGURE 1 Slide of red blood cells showing the presence of sickle-shaped red blood cells.

Region	HbS	β thalassaemia	α^0 thalassaemia	α^+ thalassaemia	Annual births (thousands)
Africa	10	1	0	5	230
Americas	1.4	0.8	0	5	5
Asia	0.6	1.7	0.4	5	120
Europe	0.12	1.1	0.05	3	1.6
Oceania	0	1.8	0	20	0.2

TABLE 1 Per cent of individuals in each WHO health region carrying the major haemoglobinopathies. Figures for β thalassaemia include HbE. The last column shows the annual number of births of babies with significant clinical problems related to haemoglobinopathies in each region.

majority of problems result from the excess of the unaffected globin chain rather than the deficiency of the mutated chain. The excess globin chains are chemically reactive and typically bind to the red cell membrane and damage the red cell. This results in ineffective erythropoiesis in which the developing red cells are destroyed in the bone marrow before they are released into the circulation. The resulting anaemia causes increased levels of erythropoietin and massive expansion of erythropoiesis which causes the typical bony expansion seen in undertransfused children with thalassaemia.

Epidemiology of sickle cell disease and thalassaemia

It has been recognised for many years that many inherited red cell abnormalities are far more common in countries where malaria occurs. Sickle cell disease is most prevalent in West Africa, but occurs throughout Sub-Saharan Africa at a fairly high prevalence. It is also prevalent in North Africa, the Middle East and parts of southern Europe[4] (**TABLE 1**). Beta thalassaemia has a wider geographical distribution, occurring throughout Africa, Southern Asia and South-East Asia[1]. It is relatively less common in African populations, and the mutations which occur tend to be milder ones resulting in less severe disease. Mild alpha thalassaemia (alpha$^+$ thalassaemia) is the commonest single gene disorder in the world, with about 5% of the world's population being affected. It is common throughout Africa and Asia, reaching very high prevalences in parts of South East Asia such as Papua New Guinea. Severe alpha thalassaemia (alpha^0 thalassaemia) has a limited distribution, occurring at significant frequencies only in South-East Asia and the Eastern Mediterranean, including Turkey, Cyprus and Greece[1]. Many observations suggest that the carrier state for abnormal haemoglobins is protective against death or serious complications from infections with malaria. Good evidence for this has only really been gathered for the sickle mutation, but there is a significant amount of epidemiological and *in vitro* data suggesting that haemoglobin polymorphisms are common because of relative protection against malaria. These conditions are increasingly common in developed countries because of population movements. The traditional ethnic distribution has also become blurred in many areas due to the increasing number of people with mixed ethnic backgrounds[5].

In England it is thought that there are approximately 12,000 people with sickle cell disease, and about 10,000 of these live in London. Although sickle cell disease is predominantly an urban disease in the UK, this is gradually changing as patients move to previously low prevalence areas. For example, neonatal screening has recently highlighted a significant number of babies with sickle cell disease being born in Essex. Beta thalassaemia has a similarly urban distribution in the UK, although it is less centred on London. There are thought to be about 700 individuals with significant thalassaemia in the UK. Initially, the majority of patients were of Cypriot or Greek origin, although there are now increasing numbers of babies born to families of Southern Asian origin. Severe alpha thalassaemia is rare in the UK, mainly because there are relatively few people present from areas where alpha^0 thalassaemia was common.

Based on studies in Jamaica, the median survival for patients with sickle cell anaemia is 53 years for men and 58 for women[4]. Median survival for those with transfusion dependent thalassaemia is improving, with more than 90% children born in the 1980s surviving until the age of 20[1].

Fetal manifestations of sickle cell disease and thalassaemia

In the second and third trimester of pregnancy, the predominant haemoglobin in the fetus is haemoglobin F (HbF), which consists of two alpha globin chains and two gamma globin chains. At birth, the haemoglobin typically consists of 90% HbF with about 10% haemoglobin A (HbA). A gradual switch occurs with the level of gamma chain production decreasing and the level of beta chain production increasing, such that the HbF level gradually falls over the first year of life and the HbA (or HbS) level correspondingly

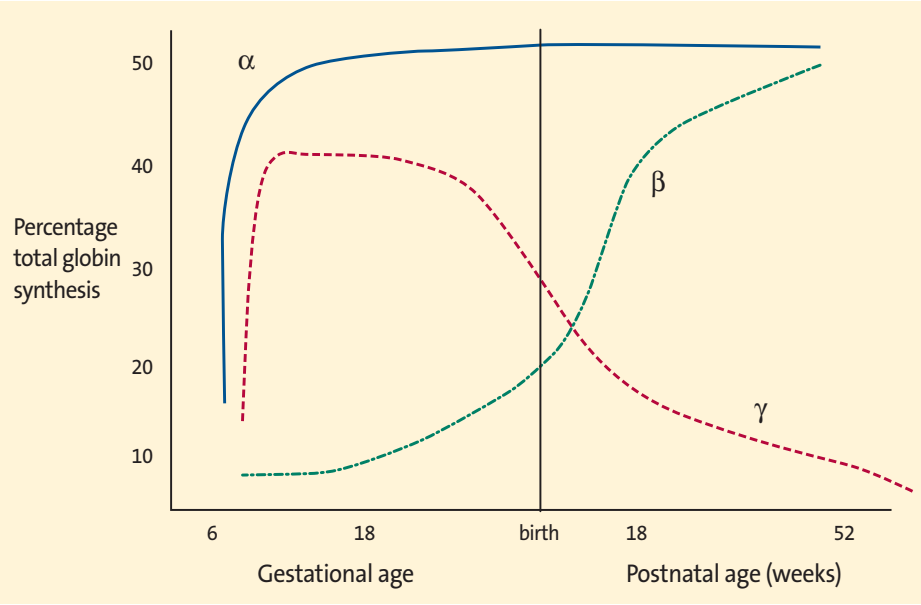

FIGURE 2 Globin chain synthesis in fetal and infant life, illustrating the switch between γ and β chain synthesis which occurs at birth. Embryonal globin chains (ζ and ε) occur up until 8 weeks of fetal life and are not shown.

increases (**FIGURE 2**).

At one year of age, a child typically has about 95% HbA (the normal adult haemoglobin) 2-3% HbF, and a small amount of the minor adult haemoglobin, haemoglobin A_2. As the beta globin chain is only expressed to a small extent in fetal life, mutations of the beta globin gene are asymptomatic until a few months after delivery. There is no evidence of any increase in the risk of fetal or maternal mortality or morbidity if the fetus has either sickle cell anaemia or significant forms of beta thalassaemia. These conditions typically only become manifest after 2-3 months of life at the earliest.

Alpha globin however is used for fetal haemoglobin, and is fully expressed in the second and third trimester; aberrations in alpha globin can therefore result in significant fetal problems. If the fetus inherits no functional alpha globin genes, this causes a condition known as haemoglobin Bart's Hydrops Fetalis, which is generally incompatible with life.

Embryonic haemoglobins are present for most of the first trimester, and these do not contain alpha globin. However, anaemia typically starts to develop by 12 weeks of age and progresses throughout the second trimester, with the development of hydrops and heart failure. Typically the pregnancy is lost around the 20th week. Occasionally fetal anaemia has been detected early in pregnancy, and intrauterine blood transfusions have been given. This has resulted in a few children surviving to birth, although the majority of these were born with significant handicap. It is not clear whether this results from significant intrauterine anaemia despite the blood transfusions, or is possibly related to the large deletions of chromosome 16 which cause severe forms of alpha thalassaemia and also remove other important genes[6].

Neonatal manifestations of sickle cell disease

A full term baby with sickle cell disease typically has about 10% HbS in the blood with 90% HbF. Newborn babies therefore do not get symptoms of sickle cell disease, and are not anaemic at birth. If significant anaemia is discovered, then it is important to look for other causes. At birth the HbF production is gradually switched off, and HbS production increased. By the age of three months, typically more than 50% of the haemoglobin is HbS, and it is possible to get symptoms, although it is unusual to have significant problems before the age of six months. After twelve months, most of the switch between fetal and adult haemoglobin synthesis has occurred, with 80-90% HbS being present and symptoms become more likely[7].

Neonatal manifestations of beta thalassaemia

As for sickle cell disease, the beta globin gene is expressed to a very limited extent in the neonatal period. Children with severe beta thalassaemia, therefore, do not usually show any significant signs neonatally.

Manifestations of alpha thalassaemia in the neonatal period

As discussed previously, alpha globin forms an important component of HbF and so significant forms of alpha thalassaemia can present neonatally. If there are no functional alpha globin genes this is nearly always incompatible with life. If there is one functional alpha globin gene, haemoglobin H (HbH) disease occurs, which is usually a fairly mild haemolytic anaemia associated with moderate anaemia and splenomegaly. This may present neonatally, and rarely severe forms of Hb H disease can cause significant neonatal anaemia and hyperbilirubinaemia. If the parents are from the Eastern Mediterranean or South-East Asia, then this should be considered in the differential diagnosis of fetal anaemia. Milder forms of alpha thalassaemia, where there are two or three functional alpha globin genes, result in no significant clinical symptoms in either neonatal or later life. However, these can show neonatally as increased levels of haemoglobin Bart's, which consists of four gamma globin chains.

Manifestations of sickle cell disease in infancy

The characteristic earliest symptom of sickle cell disease is dactylitis (hand-foot syndrome) resulting in painful swelling of one or both hands or feet[7]. This typically occurs at around six months of age, although 80% of children are symptom-free in the first year of life. It may be noticed that a hand or foot is swollen, and sometimes it is thought that the infant may have been injured in some way. Children are sometimes brought to hospital with this symptom, and it is important that medical staff are aware of the possibility that this could be a presenting sign of sickle cell disease. Treatment typically involves simple analgesia, and the pain and swelling usually subsides within 3-5 days. However, more severe episodes can require admission to hospital for parenteral analgesia.

It has been known for sometime that children with sickle cell disease have an increased susceptibility to certain infections, particularly with pneumococcus and other capsulated bacteria, such as haemophilus and meningococcus. The risk of infection with pneumococcus for an infant with sickle cell disease seems to be increased about 300 fold compared with a

child without sickle cell disease. This can result in severe illness, and death from overwhelming pneumococcal infection.

Several randomised trials have demonstrated that starting prophylaxis with penicillin within 2-3 months of life greatly reduces the increased risk of death from overwhelming pneumococcal infection[8], and in developed countries this is combined with vaccination with the conjugated anti-pneumococcal vaccine. Despite penicillin prophylaxis and immunisation, children under the age of two with sickle cell disease continue to be vulnerable to infection. In general, infants with sickle cell disease with temperatures greater than 38°C for more than four hours, require treatment with intravenous antibiotics which usually means being admitted to hospital. Other significant manifestations in infancy include the development of acute life-threatening anaemia which can be secondary to rapid enlargement of the spleen (splenic sequestration) or parvovirus B19 infection resulting in temporary erythroid hypoplasia. It is important to be aware that in infants, serious manifestations of sickle cell disease often do not involve obvious pain and it is important to consider the possibility of either severe anaemia or septicaemia in children with sickle cell disease who are unwell. Despite the increased risk of significant illness, the majority of infants with sickle cell disease are symptom-free, and on average suffer one significant complication each year.

Manifestations of beta thalassaemia infancy

Severe beta thalassaemia usually results in significant anaemia within the first six months of life. If a diagnosis has not been made already, this normally manifests as failure to thrive, poor feeding, jaundice, pallor or hepatosplenomegaly. The age at which the first blood transfusion occurs is variable, but typically occurs between 6-12 months for infants who go on to be transfusion dependent. The decision as to when to start blood transfusions can be difficult, and is based primarily on clinical assessment of the child's health and growth, rather than any laboratory measurement. Significant splenomegaly or the development of bony abnormalities can also be an indication for starting regular blood transfusion. Once the decision has been taken to start blood transfusions, these are typically continued on a monthly basis with the aim of maintaining the pre-transfusion haemoglobin levels between 9.5-10.0 g/dL.

In young children this may involve the insertion of a portacath or other central venous access device. Children should be routinely vaccinated against hepatitis B. After approximately one year of regular blood transfusion, significant iron overload develops and the need for iron chelation therapy has to be addressed. This is ideally delayed until the child is more than three years old, as there is some evidence that desferrioxamine impairs skeletal development, particularly if used in very young children. However, most children have received more than 10 transfusions by the age of two, and low dose iron chelation therapy is often started in the second or third year. Iron chelation has traditionally involved the use of desferrioxamine which can only be administered subcutaneously, although more recently an oral iron chelator, deferasirox, has been licensed for use in children with transfusion-dependent iron overload in the UK[9].

Manifestations of alpha thalassaemia in infants

As discussed earlier, significant forms of alpha thalassaemia either result in fetal or perinatal death, or a mild and typically asymptomatic form of anaemia called HbH disease. Alpha thalassaemia is one possible explanation for splenomegaly and anaemia found in infancy, and should be considered in families with a history of alpha thalassaemia or an appropriate ethnic origin.

Antenatal screening for sickle cell disease and thalassaemia

Sickle cell disease, alpha thalassaemia and beta thalassaemia are all typically inherited in autosomal recessive fashion. The carrier state can be detected by relatively simple blood tests and as such it is possible to identify couples at risk of conceiving a baby with a significant haemoglobinopathy. Antenatal haemoglobinopathy screening has been offered to couples in a fairly patchy and *ad hoc* way for many years. However following the NHS plan in 2000, the NHS Sickle Cell and Thalassaemia Screening Programme, directed by Dr Allison Streetly was established. This has led to the development of more systematic antenatal screening across England. In areas with a high prevalence of populations at risk of sickle cell disease or thalassaemia, it is recommended that all pregnant women are screened for the possibility that they could carry one of these conditions, using a full blood count and haemoglobin analysis, which is typically performed using high performance liquid chromatography. If a woman is found to carry one of these conditions, then her partner can be tested and it is then possible to counsel the couple regarding the risk of their baby being affected. This approach is adopted in the majority of large towns and cities in England.

In more rural areas, the prevalence of globin gene mutation is very low, and a slightly different approach is used. All women who become pregnant have full blood counts to detect the possibility of thalassaemia, although specific haemoglobin testing for sickle cell disease is only performed if the woman or her family seem to originate from an area where there is a high prevalence of the condition. In practice, this means that any woman whose family are all of Northern European origin does not need specific testing for haemoglobinopathy. If the woman or any of her known family are thought to come from a high prevalence area, then laboratory testing for sickle cell disease and other haemoglobin problems is performed as in high prevalence areas. The aim of this approach is to identify couples at risk of conceiving a baby with significant haemoglobinopathy early in pregnancy, to allow the couple to be given informed choice. This can involve invasive prenatal diagnosis and possible termination of an affected pregnancy if this is appropriate[11]. Current figures suggest that approximately 10% of at risk couples take up invasive prenatal diagnosis at the moment. Some at risk couples are not identified at an early stage during their pregnancy, making prenatal diagnosis impossible or at least a less attractive option.

Nenonatal screening and diagnosis of sickle cell disease

For the last year all babies born in England are tested for sickle cell disease, using the neonatal blood spot taken at 5-7 days, which is also tested for phenylketonuria and hypothyroidism. This universal testing occurs in centralised neonatal screening laboratories across England and has

replaced the previous patchy and less reliable screening which was performed in a number of different ways depending on location. The laboratory testing seems to be sensitive and specific, although it cannot be performed if the infant has received a blood transfusion before the blood spot is taken. It is currently recommended that a blood spot is taken before a baby is transfused and that this is kept and sent to the screening laboratory with the spots taken at 5-7 days.

Neonatal screening has already lead to the identification of significant numbers of babies with sickle cell disease in areas which did not previously screen, such as Essex. The justification for universal neonatal screening for sickle cell disease comes from the randomised control trial showing that the early administration of penicillin results in a significant reduction of mortality[8]. Babies identified as having possible sickle cell disease should be referred to the local paediatrician with an interest in the condition, and shared-care arrangements should be established with one of the Paediatric Sickle Cell Centres, as outlined in the recent standards of care document[10].

Neonatal screening picks up many cases of severe beta thalassaemia, although this is not the primary purpose of the screening programme, and some cases are missed due to the presence of HbA at birth. Patients with possible severe thalassaemia should be referred as for sickle cell disease[9]. Neonatal sickle cell screening also identifies a number of other haemoglobin variants, many of which are not of any particular clinical significance. It is currently unclear how these unidentified haemoglobin variants should be dealt with. It is likely that they will be asymptomatic, although occasional variants can result in significant anaemia, polycythaemia or methaemoglobinaemia. Practice currently varies across England as to how these are dealt with and whether parents are informed or further testing occurs. The formal arrangements for screening and follow-up care of children with haemoglobinopathies have been established in England, with a similar system being adopted in Wales. Both sickle cell disease and thalassaemia are rare in Scotland and Northern Ireland, although the incidence is likely to increase and formal screening and management practices may need to be established.

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