

Alpha Thalassaemia : An Emerging Health Care Problem



Dr Debbie Clark
Haematologist

Mutations of the alpha globin genes are among the most common genetic defects in humankind.

Although commonest in Asian communities, they are found worldwide. Generally these mutations are found in fewer than 10% of affected populations, but there are a few areas of the world where the alpha thalassaemia gene is commoner than the normal gene. However, with the relative lack of reliable diagnostic tests for the alpha thalassaemias in comparison with the beta thalassaemias, these abnormalities have tended to be neglected.

Why do we need to identify alpha thalassaemia carriers?

If two parents are carriers of alpha thalassaemia, they may have a risk as high as one in four of a pregnancy affected by Hydrops Fetalis.

Thalassaemic Hydrops Fetalis is, with very rare exceptions, an inevitably fatal disorder. Affected babies usually die in late pregnancy or immediately after delivery. There is also an enormously increased incidence of maternal complications in these pregnancies: it has been estimated that without medical care, half these women would die as a result of their pregnancy. An unusually large placenta is an important causative factor. There is a high incidence of pre-eclampsia, antepartum and postpartum haemorrhage and other complications.

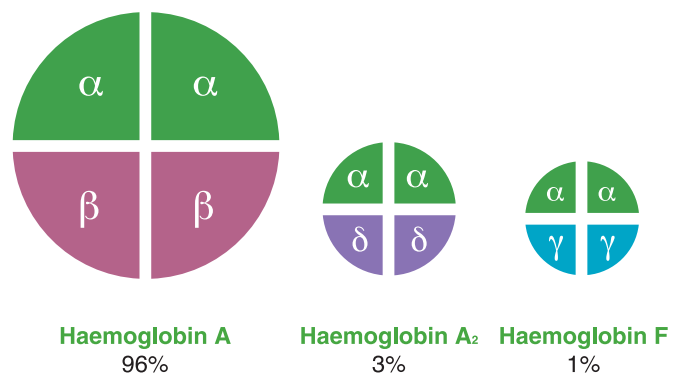
The prevention of Hydrops Fetalis, with its accompanying severe physical risks to the mother and emotional strain on both parents, is the major reason behind the need to detect alpha thalassaemia carriers of childbearing age. For obvious reasons, it is preferable to detect carriers before conception occurs, and give the couple time for genetic counselling and consideration of their options.

The level of risk of a Hydrops Fetalis child depends on the exact nature of the DNA defect in the parents. One particularly common South East Asian deletion, for example, will result in a one in four risk for each pregnancy. Homozygosity for this particular defect is the commonest cause of thalassaemic Hydrops Fetalis.

What is the difference between alpha and beta thalassaemia traits?

The haemoglobin molecule consists of the haem part which carries oxygen to the tissues, and four supporting globin chains forming a tetramer. Thalassaemias occur when a genetic defect results in a reduced production of one type of chain. **The terms alpha and beta thalassaemia therefore refer to a reduced or absent production of alpha or beta globin chains respectively.** Both alpha and beta thalassaemia traits result in red cell microcytosis and the two conditions are not readily distinguishable by blood film examination.

In the normal adult the major haemoglobin present is haemoglobin A, but small amounts of haemoglobins A₂ and F are also present. As can be seen from the diagram, all these types of haemoglobin contain alpha chains, but only haemoglobin A contains beta chains. Thalassaemic Hydrops Fetalis, often known as Haemoglobin Barts Hydrops Fetalis, is lethal because such individuals cannot produce any alpha chains, and all postnatal haemoglobins require alpha chains. The name haemoglobin Barts arises from the presence of tetramers of gamma globin chains which form in the absence of alpha chains to pair with, but which are incapable of proper oxygen delivery to the tissues. The fetus manages to survive to a late stage of pregnancy only because some embryonic haemoglobins do not rely on alpha chain production.

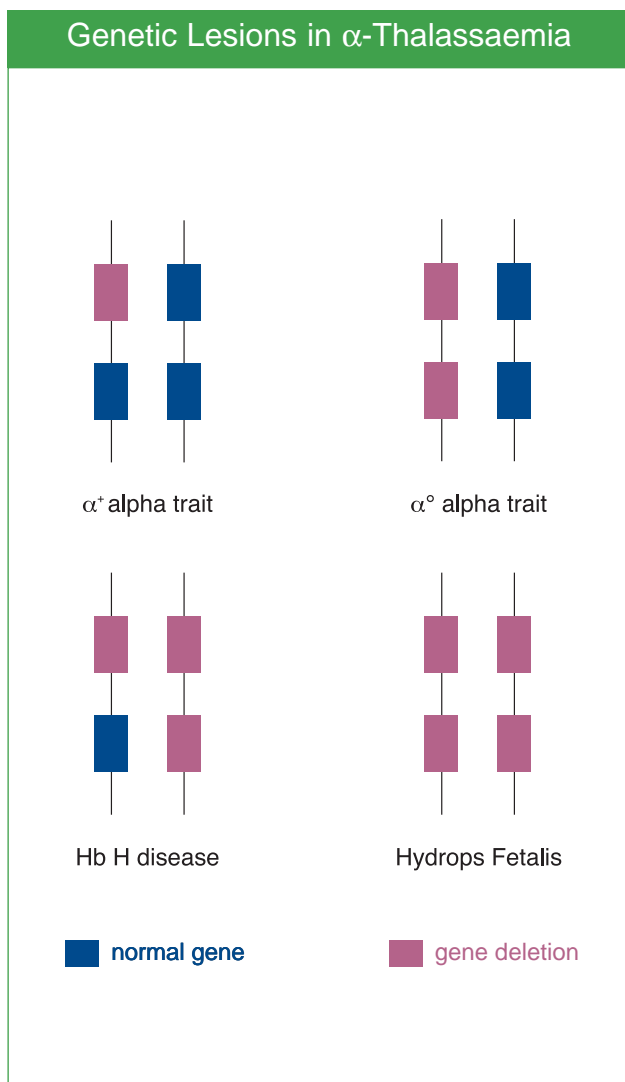


Haemoglobins present in normal adult blood

How is alpha thalassaemia inherited?

The inheritance of alpha thalassaemia is a little more complicated than for beta thalassaemia. Beta globin chain production is controlled by two genes, one from each parent, so that affected individuals are limited to the effects of either one or two abnormal genes. However, **alpha globin chain production is under the control of four genes.** This results in a more variable genotype, as can be seen from the diagram.

Alpha Thalassaemia : An Emerging Health Care Problem



Alpha thalassaemia trait (alpha thalassaemia minor)

This is the result of the deletion of **one or two alpha globin genes**. Most patients have a low normal or mildly reduced haemoglobin level, with a mild to moderate microcytosis. Those with only one gene deletion may show only slight microcytosis or be haematologically normal.

Haemoglobin H disease

This is the result of a **three gene abnormality**. Many patients are asymptomatic and are discovered only as a result of routine blood testing. They tend to have a mild to moderate anaemia and a marked microcytosis, but only a minority require transfusion. Diagnosis is relatively easy, as haemoglobin H (tetramers of 'spare' beta chains) is readily detected. Most haematologists would suggest specialist referral for these patients as some may develop clinical problems during their lifetime.

Hydrops Fetalis

This is the **absence of all four alpha globin genes** resulting, with rare exceptions, in perinatal death. It occurs when each parent carries a two gene deletion on one chromosome, with a one in four risk for each pregnancy.

Is alpha thalassaemia trait more difficult to identify than beta thalassaemia trait?

The answer to this question is yes, it is sometimes more difficult to identify carriers of alpha thalassaemia.

If microcytosis is present in a well person with no evidence of iron deficiency, a thalassaemia trait should be considered. This applies particularly to individuals with Mediterranean or Asian ancestry, but anyone in Australia who presents with these features may be at risk of being a carrier.

Conventional screening for the presence of thalassaemia trait is performed in response to a request for a thalassaemia or haemoglobinopathy screen, or haemoglobin EPG. In our laboratory this will result in the measurement of **haemoglobin A2 and haemoglobin F levels, and a screen for the major haemoglobin variants, such as haemoglobin S, haemoglobin E, etc.** We also examine a specially stained blood film for the presence of haemoglobin H bodies.

It is this latter test alone which will identify alpha thalassaemia trait, as the levels of HbA2 and HbF are normal in this condition. The difficulty lies in the fact that it is a test with a **high false negative rate**, as haemoglobin H bodies may be very infrequent. A patient with an unexplained microcytosis who has normal HbA2 and HbF levels and is negative for HbH bodies is in fact quite likely to have alpha thalassaemia trait, despite the negative screen. Indeed, it should be assumed that alpha thalassaemia trait is the most likely explanation in these circumstances. Note also that rare forms of beta thalassaemia trait can also give rise to this constellation of findings. For such patients, modern methods employing molecular technology can determine the presence of a genetic defect of haemoglobin production.

It is important, therefore, in a patient of childbearing age who has a possible but unconfirmed carrier status for thalassaemia trait, to test the partner. If the partner is also a possible carrier, then the couple should have genetic counselling and molecular testing to determine the risk to future pregnancies.

Alpha Thalassaemia : An Emerging Health Care Problem

My patient has microcytosis, a normal ferritin, and a negative thalassaemia screen. What do I do next?

This will depend on the age of the patient. Bearing in mind that a possible explanation for the findings is the presence of an alpha thalassaemia trait, the main concern is whether or not **the individual is likely to have children in the future**. If so, it is **essential that the partner is tested**, and appropriate steps taken, including **molecular testing and genetic counselling** if necessary. If the patient is already pregnant, urgent referral for molecular testing and counselling may be required.

If the patient is beyond childbearing age, then the condition is of little importance to the individual but **descendants of childbearing age** should be tested.

If the patient is a child, molecular diagnosis and, of course, genetic counselling, can be deferred until early adulthood. However, the presence of a thalassaemia trait in a child implies the presence of thalassaemia trait in at least one parent. This may be important if the parents may go on to have further children, and in these circumstances **both parents should be tested**.

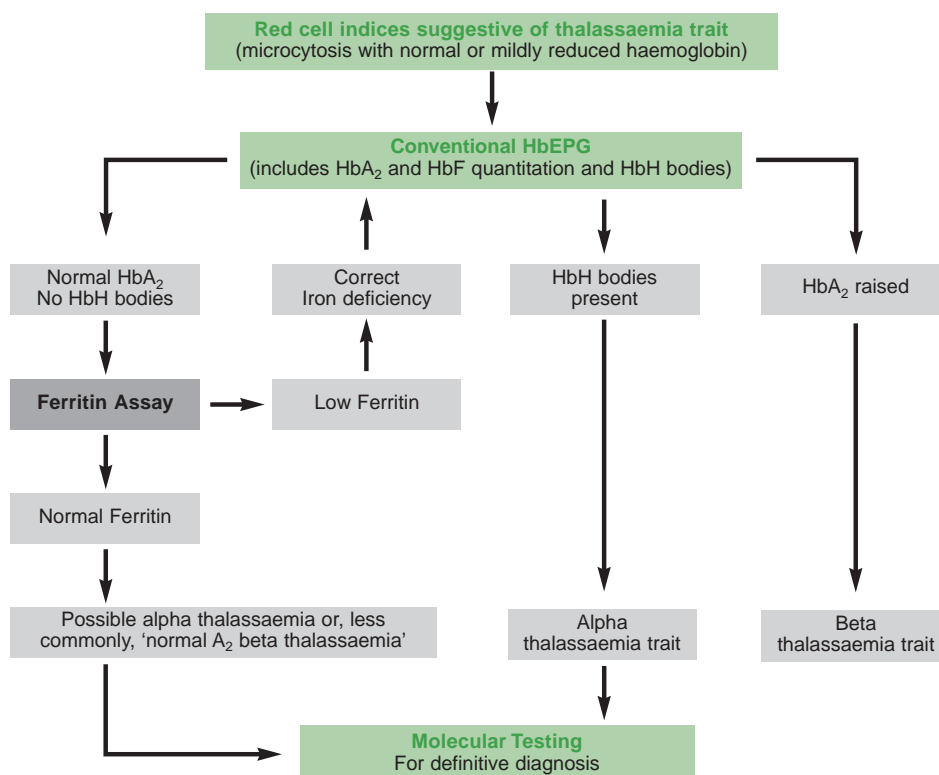
The future of thalassaemia screening

Alpha thalassaemia trait is an underdiagnosed condition in most countries and is easily missed. Yet the risk of Hydrops Fetalis to parents who are carriers is both **predictable and preventable**. Its recognition and importance to those of childbearing age is an increasing public health challenge to most societies around the world, including Australia.

Currently, relevant **Medicare rebateable screening tests consist of the full blood count, ferritin, and HbEPG**. There is no Medicare item number for molecular testing. Where this is felt necessary, genetic counselling and molecular testing for couples is available at specialist centres at large teaching hospitals.

Molecular testing now available at Douglass Hanly Moir Pathology is listed on the back page of this edition of the Doctors' Newsletter.

Flow Chart for the Diagnosis of Alpha Thalassaemia Trait



For any enquiries, please contact Dr Debbie Clark, Haematologist on 98 555 472