HAEMOGLOBIN
DISORDERS
HAEMOGLOBINOPATHIES

BOOKLET
ONE (1)

ABOUT Beta [β] thalassaemia

about thalassaemia
about thalassaemia
about thalassaemia

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FOREWORD BY THE PRESIDENT

This booklet (number one) contains basic information about β-thalassaemia. Whether you are a carrier or a patient, or simply interested in finding out more about β-thalassaemia, we encourage you to read this booklet. Every effort has been made by the authors to include useful information regarding the disease, its inheritance, prevention and treatment.

If you need to know more details on any aspect described in this booklet, we advise you to consult your physician or national health authority. The authors of this booklet, will also be very happy to answer your questions as far as possible.

> *I hope that this booklet, which constitutes part of our educational material, will contribute significantly to TIF's efforts in spreading awareness across the world about Haemoglobin disorders, their prevention and treatment.*

TIF is greatly indebted to Dr. Androulla Eleftheriou and Dr. Michael Angastiniotis, members of TIF's Scientific Advisory Panel, for their invaluable contribution to the preparation including this one of three booklets, which aim to provide important information in a simple manner to everyone interested in learning about β-thalassaemia (booklet one), α-thalassaemia (booklet two) and sickle cell disease (booklet three).

PANOS ENGLEZOS
PRESIDENT, TIF

ABOUT THE THALASSAEMIA INTERNATIONAL FEDERATION

The Thalassaemia International Federation (TIF) was established in **1987** with the mission to promote the establishment of national control programmes for the effective prevention and appropriate clinical management of thalassaemia, in every affected country of the world. TIF is today, a Federation "umbrella", comprised of *98 national thalassaemia associations from 60 countries*, embracing hundreds of thousands of patients worldwide.

TIF has been in official relations with the World Health Organisation (WHO), since 1996, and works closely with scientific and medical professionals in this field from more than 60 countries, as well as with international and European health bodies, pharmaceutical companies and agencies and other disease orientated patients' organisations.

TIF's educational programme is one of its most important and successful activities. It includes the organisation of local, national, regional and international workshops, conferences and seminars, as well as the preparation, publication and translation of leaflets, magazines and books for health professionals, patients/ parents and the community at large, *distributed free in more than 60 countries of the world.*

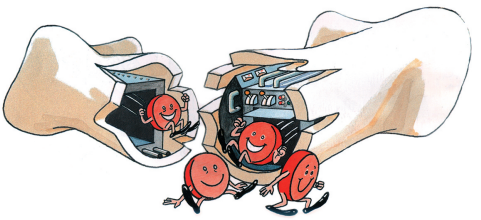
"UNITY IS OUR STRENGTH"
our Motto

"*Equal Access to quality health care for every patient with Thalassaemia across the world*"
our mission

HAEMOGLOBIN DISORDERS HAEMOGLOBINOPATHIES

BETA (β)-THALASSAEMIA (THALASSAEMIA) OR MEDITERRANEAN ANAEMIA (ANEMIA) OR COOLEY'S ANAEMIA (ANEMIA)

Introduction:



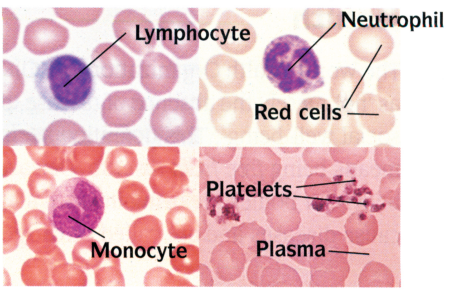
Bone Marrow

Haemoglobin disorders are a group of conditions affecting the red blood cells - an important part of the human blood - the vital fluid that brings nourishment, such as oxygen (O2), hormones, proteins, fats and carbohydrates, to the body's organs and tissues and carries away waste substances such as Carbon Dioxide (CO_2), urea and uric acid.

Blood (Whole Blood):

In adults, blood is exclusively produced in a special tissue called marrow, which is found in the central cavity of the bones (bone marrow). Blood consists of two major components:

I. the plasma, the yellow liquid, that constitutes about 55% of the volume of blood and contains water, salts and important proteins, and;



Composition of blood

II. the part that contains three types of cells microscopic building blocks, trillions of which make up the human body. The cells are:

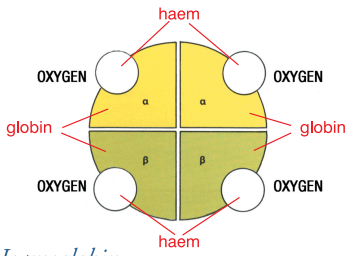
- The white cells or leucocytes
- The platelets or thrombocytes, and
- The red cells or erythrocytes

Each type of blood cell has specific functions and each contributes, in its own special way, to the well-being of the human organism, including protection against infection (white cells); limiting blood loss when a vessel is damaged (platelets) and provision of oxygen to tissues and vital organs (red cells).

Many diseases in humans are caused by abnormalities in the blood and these are categorized according to the component of the blood affected (white cell diseases, platelet diseases and red cell diseases) Red cell diseases include amongst others the hereditary Haemoglobinopathies or Haemoglobin disorders, the most severe of which are the thalassaemias [alpha (α-) and beta (β-)] and sickle cell disease, and are so called because they result from abnormalities of a special protein inside the red cells of blood called haemoglobin.

Haemoglobin:

4,500,000 – 5,000,000 red cells circulate in human blood and each one of them is packed with, 300 million molecules of Haemoglobin. Haemoglobin gives the red blood cells their oxygen carrying capacity, which is their most important function in blood. (Oxygen is essential for the growth and performance of the cells and organs of the human organism). The haemoglobin molecule itself consists of two major parts (i) the **globin** and (ii) the **haem**:



Heamoglobin

(i) The **globin** is a protein made up of smaller units, referred to as chains - the alpha (α) and the non-alpha such as Beta (β), Gamma (γ), Delta (δ), chains. The alpha (α) chains couple with beta (β) chains to make up the haemoglobin (HbA) which is the dominant one in adults, and up to 10% of the haemoglobin of the fetus. Alpha (α) chains also couple with other chains making up the haemoglobins found at various stages of human life, from conception, through fetal life to birth.

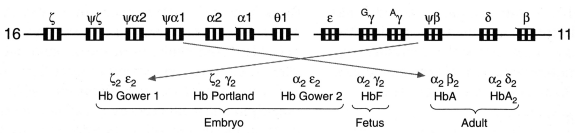


Fig. 2.11 The α- and β-globin gene clusters on chromosomes 16 and 11, respectively. In the extended α- and β-globin genes the introns are shaded dark, the 5′ and 3′ non-coding regions are hatched, and the exons are unshaded.

NOTE: The words alpha, beta, gamma, delta where met in this text will be referred to with their respective abbreviations α, β, γ, δ.

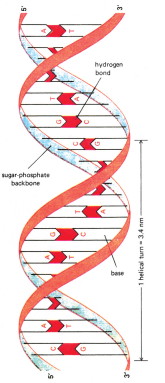
(ii) The **haem** part contains iron - a metal that is essential for the growth and normal functioning of the cells. Iron has the capacity to easily bind and lose oxygen, providing the haemoglobin molecule the capacity to carry and distribute easily oxygen to tissues and organs of the body. Adults have about 4g of iron in their body, 75% of which is used to synthesize the haemoglobin molecules of the red cells.

The level of haemoglobin found in a routine laboratory blood examination will, therefore, reflect the level of the individuals' iron.

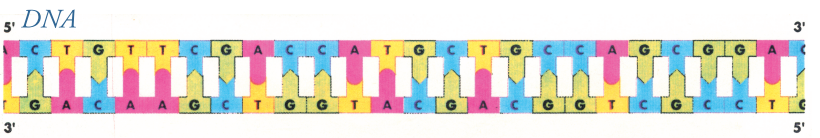
Inheritance:

Haemoglobinopathies are genetic disorders, that are passed on from parents to children according to what is referred to in biology as *"Mendelian recessive autosomal pattern of inheritance"*. i.e. all characteristics are passed on from parents to children through genes - the biological units of inheritance that provide all the information needed for controlling growth and development throughout human life. The contribution of genes from both of the parents (recessive) is essential for the inheritance of these disorders, which can affect both male and female children alike (autosomal).

Deoxyribonucleic Acid, a chemical substance often referred to by its abbreviation, DNA, constitutes the key part of genes, of which a great number are needed to carry out the many and complicated biological functions of the human organism. Genes linked together in the cell on long piles of DNA are called chromosomes, of which there are 23 pairs, half inherited from one, and half from the other, parent.



DNA DOUBLE HELIX



In the case of adult Haemoglobin, for example, the production and synthesis of its α and β chains, which constitute its major component, is controlled by genes on specific chromosomes. Four (4) α-globin genes on chromosome 16 and two (2) non-α-globin such as (β, γ and δ) genes on chromosome 11, are responsible for the production, in exactly equal numbers, of α and β chains, respectively.

Chromosomes

Any defect in a gene responsible for the production of α-chains (or as referred to in scientific terms "coding" for α-chains), may cause reduced production of these chains, resulting in α-thalassaemia carrier status. If the defect involves more genes then less α-chain is produced and the individual may be affected more significantly. Similarly, a defect in the gene coding for β-chains (the β-globin gene) may cause a reduction or total loss of β-chains. The degree of β-chain reduction will determine whether an individual is a β-thalassaemia carrier, or a patient with β-thalassaemia intermedia or major.

In contrast to the thalassaemias in which the production of a globin is affected, there are conditions in which the defect in the gene results in the production of wrong kinds of proteins - called abnormal or structural haemoglobin variants - whose structure as well as their function, are different from that of the common haemoglobin (HbA). Reference is made to their inheritance and clinical outcome in booklets 1, 2 and 3.

The major Haemoglobin disorders are:

α- chain disorders	β- chain disorders
α-thalassaemias	**Sickle cell disorders**
HbH disease	Sickle cell anaemia (HbSS)
α-thalassaemia Hydrops Fetalis	HbS/β-thalassaemia
(=Hb Bart's Hydrops Fetalis)	HbSC disease
α-chain variants	HbSD disease
	Other rare sickling disorders
	β-thalassaemias
	β-thalassaemia major
	β-thalassaemia intermedia
	HbE/β-thalassaemia
	Other rare thalassaemias

In this booklet it will be described how β-thalassaemias are passed on to children, according to their parents' genetic characteristics. In other booklets (2 and 3) the inheritance of α-thalassaemias and Sickle Cell Disorders respectively will be described.

- **Both parents with "functional" β-globin genes**
  When in both parents the β-globin genes are unaffected, or fully functional, the child will inherit two unaffected, functional β-globin genes, and all children will have common adult haemoglobin (HbA).
- **When one of the parents carries an affected β-globin gene** i.e., when he/ she is a β-thalassaemia carrier - and the other parent carries two unaffected β-globin genes, each child born to these parents has a one in two or a 50% chance of inheriting the affected β-globin gene from the carrier parent.
  (FIG 1)

One may also come across other names describing the carrier status, such as:

I. Carriers of the β-thalassaemia trait
II. Individuals heterozygous for β-thalassaemia or
III. Individuals with β-thalassaemia minor

About carriers of β-thalassaemia:

Carriers of β-thalassaemia do not have a disease. They have no physical or mental symptoms and do not require a special diet, medical advice or treatment.

- They have smaller red blood cells than other non-carrier individuals. This is because a carrier has inherited an affected β-globin gene from one parent, which, as a result makes less amount of human adult haemoglobin (HbA), or none at all. His/ her red cells thus contain less haemoglobin than usual and consequently their size is smaller and paler than non-carriers cells. Carriers, however, make up for this by producing more red cells, and in this way the blood continues to function and serve the human organism normally.

- The carrier status cannot become a disease over time. Indeed, most will be unaware that they are carriers unless specifically tested. However, some carriers may experience mild anaemia, which can be inaccurately diagnosed as iron deficiency anaemia. Laboratory tests, however, can easily differentiate between the two.

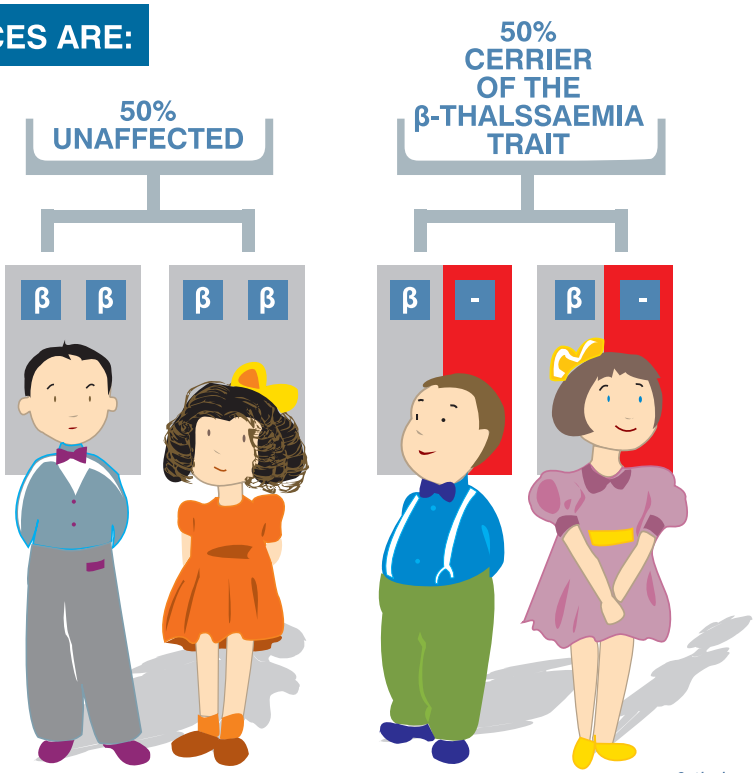
FIG1

ONE PARENT IS A CARRIER OF β-THALASSAEMIA TRAIT AND THE OTHER PARENT HAS FULLY FUNCTIONAL β-GLOBIN GENES

UNAFFECTED

β-THALASSAEMIA

CHANCES ARE:



In conclusion, carrying β-thalassaemia has no effect on health, length or quality of life.

What about pregnant women who are carriers?
Like other pregnant women, women who carry β-thalassaemia can become iron deficient and may need extra iron. The mild anaemia due to carrying β-thalassaemia can become more severe during pregnancy and a pregnant carrier may, very rarely, need a blood transfusion. The anaemia will improve after the baby is born.

Is there any treatment to stop being a carrier?
A person who is born carrying β-thalassaemia will always carry it throughout his/her life.

Can the β-thalassaemia trait be transmitted or acquired at a later stage in life?
The β-thalassaemia trait cannot be acquired or transmitted through the environment, transfusion or other means by which people become infected.

Can carriers donate blood?
Carriers may be suitable blood donors if their haemoglobin level meets the national inclusion criteria for donating blood.

What should carriers do if they are thinking of having children?
They should tell their partner that they probably carry β-thalassaemia and ask them to have a blood test carried out specifically for haemoglobin disorders.
This should be done before they start a pregnancy. If their partner is also a carrier then they should both see a specialist counselor for further information.

Is there anything else that a carrier should do?
A carrier should also let their brother or sister know about it and advise them to also have a blood test for Hb disorder.

Both parents carrying an affected β-globin gene - an "at risk" couple.

As stated above, although being a carrier of the β-thalassaemia trait has no adverse health effects, if he/she plans to make a family with another carrier, there is, with each pregnancy:

- a one in four or 25% chance that their child will have β-thalassaemia major/intermedia, the full-blown disease. β-thalassaemia intermedia/major is also known as Mediterranean Anaemia or Cooley's Anaemia and the patient may also be referred to as homozygous for β-thalassaemia.
- a one in two or 50% chance that the child will be a carrier of β-thalassaemia trait with no clinical signification and
- a one in four or 25% chance that the child will be completely unaffected.
(FIG 2)

δβ thalassaemia

In this form, both the δ genes and the β genes are not functioning, a situation partly balanced by increased production of the γ-chains.

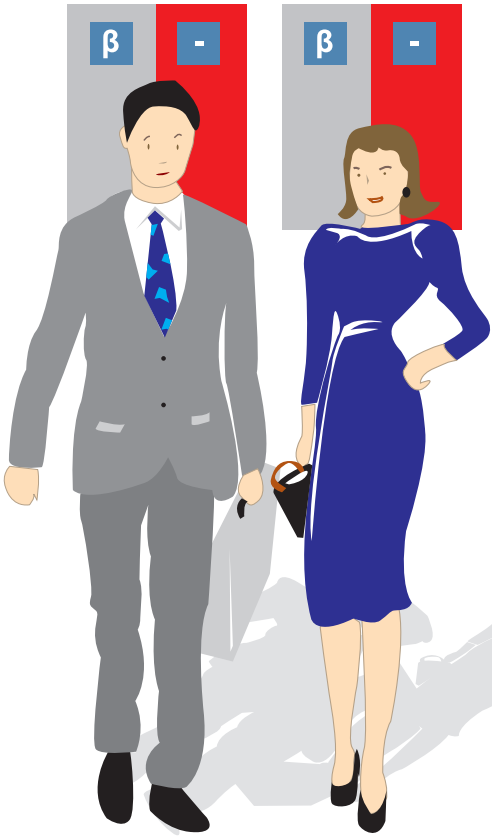
Like the β-thalassaemia carrier, the δβ carrier is healthy and needs no medical treatment, but the affected gene can be passed on from the parent to his/ her children. A child inheriting either one δβ gene from each carrier (δβ) parent or one δβ gene from one parent and one β-thalassaemia gene from the other parent, will develop a severe haemoglobin disorder, similar in its clinical outcome to β-thalassaemia major or β-thalassaemia intermedia, and will require similar clinical management.

Other "abnormal haemoglobins" and haemoglobin disorders

A number of other "abnormal" types of adult haemoglobin have been identified, which differ both in their structure and clinical outcome. These are also known as "structural haemoglobin variants", and include HbS, the haemoglobin responsible for sickle cell disease, **Haemoglobin E (HbE), Haemoglobin C (HbC), Haemoglobin D (HbD)** and **Haemoglobin Lepore (Hb Lepore)**. These are passed on from parents to their children and inherited in exactly the same way as described in this booklet for β-thalassaemia. However, only those that inherit from both parents Hb Lepore or HbS, have **clinically significant conditions that require medical care.**

FIG2

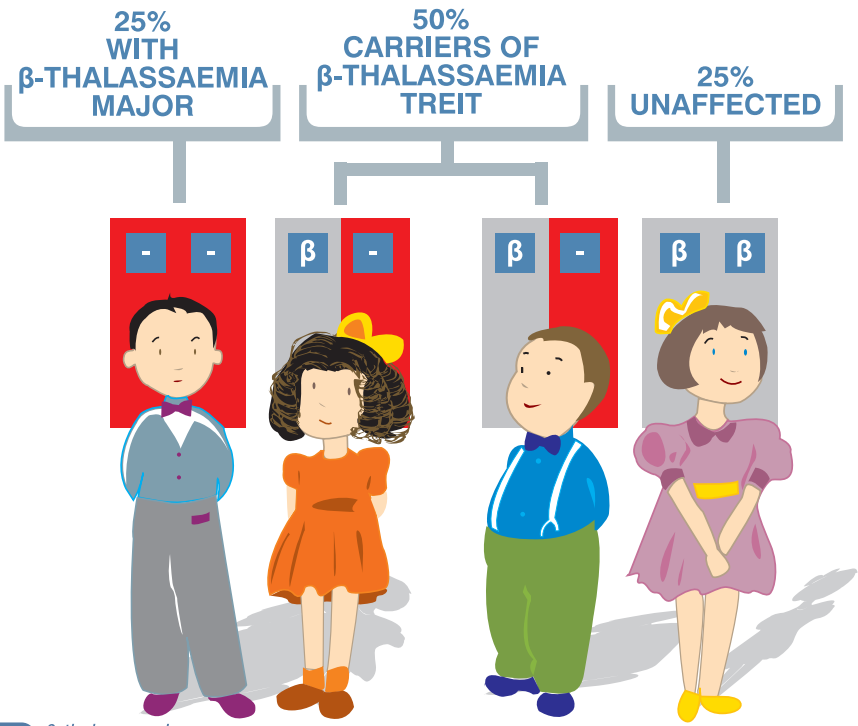
BOTH PARENTS ARE CARRIERS OF THE β-THALASSAEMIA TRIT



UNAFFECTED

β-THALASSAEMIA

CHANCES ARE:



Inheritance of the other abnormal haemoglobins (HbC, or HbD or HbE) from both parents is not related to any significant clinical outcome, and do not require any medical attention.

Inheritance, however, of the variant haemoglobins (Lepore, E or S) from one parent and β-thalassaemia from another parent results in compound haemoglobinopathies such as. Hb Lepore/β, HbE/β, and HbS/β, which are clinically significant blood disorders similar to β-thalassaemia major/intermedia and require medical care. More details associated with the "abnormal" or structural haemoglobin variants are provided below.

HbLepore/ β-thalassaemia

In this form there is a rearrangement of the β and δ genes so that an abnormal Haemoglobin is formed, called Haemoglobin Lepore. Like the β-Thalassaemia carrier, the Hb Lepore carrier is a healthy individual and needs no medical treatment. The affected gene, however, can be passed on from the parent, according to the inheritance pattern described for β-thalassaemia, to his/ her children. A child inheriting either Hb Lepore from both parents or one Hb Lepore and one β-thalassaemia trait from the other parent will develop a severe Hb disorder similar in its clinical outcome to β-thalassaemia major and will thus require similar clinical management.

HbE/ β-thalassaemia

HbE is one of the most common abnormal haemoglobins, particularly amongst people of South East Asian origin. Like the β-thalassaemia carrier, the HbE carrier is healthy and needs no medical treatment. However, the affected genes can be passed on from the parent to his/her children according to the inheritance pattern described earlier for β-thalassaemia. A child inheriting two HbE genes, one from each of his/ her parents will still be healthy and not require medical care.

HbE becomes important only when the child inherits from one parent the β-thalassaemia trait, and from the other parent, the HbE trait.

HbE/β thalassaemia is a serious disorder, the clinical symptoms of which are similar to those seen in β-thalassaemia intermedia, but which may be as severe as those seen in thalassaemia major.

(FIG 3)

FIG3

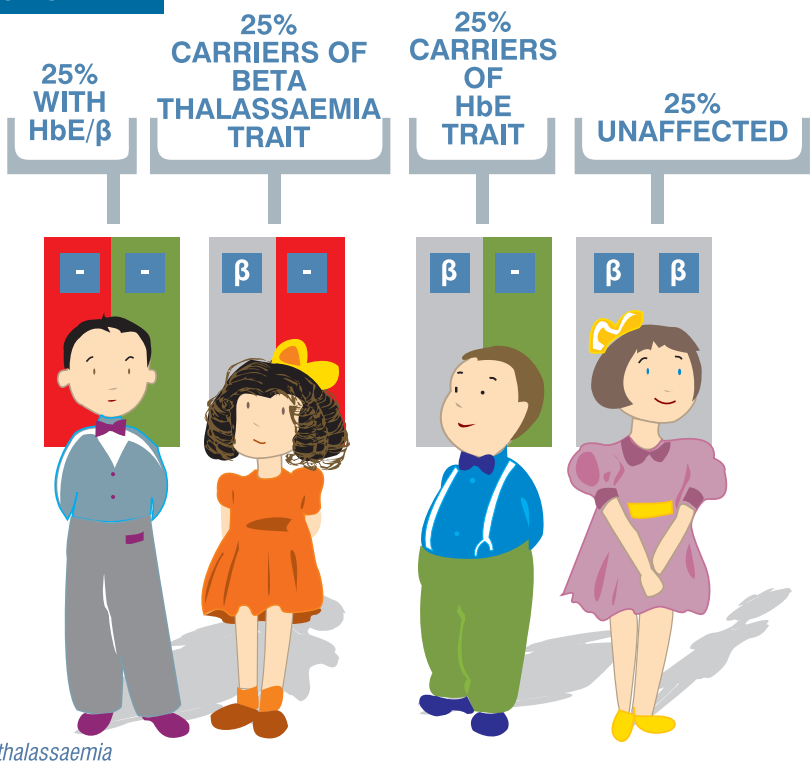
HbE AND β-THALASSAEMIA

UNAFFECTED

β-THALASSAEMIA

HbE

CHANCES ARE:



Sickle Cell disorders are different in cause and clinical outcome from β-thalassaemia and these are described in detail in Booklet 3.
Inheritance of β-thalassaemia trait from one parent and HbS trait from the other, will result in a haemoglobin disorder (HbS/β), the clinical outcome of which is similar to sickle cell disease, which is very different from β-thalassaemia major/intermedia and, consequently is different in its clinical management. (see booklet 3 for more detailed information)

How does one know whether he/she is a carrier?

In most cases, simple but specific laboratory tests can identify whether a person carries the β-thalassaemia trait or any other Haemoglobin disorder. Genetic counselling before and after the tests i.e. provision of validated, updated information, and guidance by specialists in the field, will cover important aspects of prevention, including:

- Where to be tested
- What the test results mean
- What it means to be a carrier
- What options are available to couples when both are carriers
- The nature and treatment of β-thalassaemia major.

Laboratory Testing to establish whether one is a carrier of the β-thalassaemia trait

Laboratory testing for Thalassaemia includes a routine blood test known as a Complete Blood Count (CBC), which involves measuring, parameters related to the content of haemoglobin inside the red cells and the size and volume of red blood cells referred to as Mean Corpuscular Haemoglobin (MCH), and Mean corpuscular Volume (MCV) respectively. Both of these, will be lower in individuals carrying the β-thalassaemia trait.

Red blood cells are also seen under a microscope in order to examine their size and shape. The red cells of a Thalassaemia carrier will be a paler shade of red, will be of various shapes (poikilocytosis), and will be smaller (microcytosis), compared to normal red blood cells which are a darker red in colour, round and concave in shape.

Other tests to determine the presence of the β-thalassaemia trait include a laboratory process known as haemoglobin electrophoresis,

which enables measurement of the quantity of HbA and HbA2, the main and minor components respectively of **adult haemoglobin**. Other haemoglobins present in adult red cells such, as fetal haemoglobin (HbF) and HbS, may also be measured by electrophoresis. In most cases the above tests are sufficient to determine whether an individual is a carrier.

Another way to measure the quantity of the HbA2 fraction which is always raised in β-thalassaemia carriers, but also to identify the Hb variants, ***is through a special laboratory technology called High Pressure Liquid Chromatography***, for short HPLC.* Due to its high sensitivity and specificity and very importantly its rapid daily output, it is considered today as a method of reference for confirming diagnosis of haemoglobin disorders.
Where the above tests are inconclusive and do not allow the laboratory scientists to provide a confirmed diagnosis, other more specialised tests are available, such as genetic tests i.e. tests that are based on the examination of the individual's DNA. For this test, blood is required from other members of the family for a definite diagnosis to be made.
On occasions, where iron deficiency exists, and this may obscure the diagnosis, it may be necessary just to give iron tablets to the individual and ask him/ her to come back in at least one month's time to repeat the test, after which the diagnosis may be confirmed.

Can haemoglobin disorders be prevented?

"Their choices are certainly not simple"

Carrier couples, who know of the risk for their children have, today, a number of choices. They can take steps to make sure that they have healthy children, and that affected children have the best possible care from birth. Their choices are certainly not simple. Every such couple, and every citizen in general can obtain reliable, detailed and updated information from national health authorities and patients/ parents support groups. Parents who are both carriers should know well their risk as early as possible, so that they have enough time to make the decisions that they feel are right for them.

Health service providers are responsible to:

- offer carrier testing, at high school or before or when just married, before pregnancy or as soon as the pregnancy has begun.

*Bio-Rad HPLC for example is considered by many as the Gold Standard for Hb determination.

- inform carriers, providing them with the appropriate information and advising them of the need for their partner (or husband) to also have a carrier test.

- inform carrier couples (at risk couples). Couples who are both, carriers of β-thalassaemia need to see a haemoglobinopathies specialist (or a specialist genetic counselor) who will inform them of the exact nature of the risk and what choices are available to them.

An obstetrician specializing in prenatal diagnosis may also provide more detailed information on the procedures available and the possible choices that a couple may adopt to avoid having an affected child. In addition, the potential parents must be informed on the kind of treatment/care options that medical science has available for thalassaemia patients to date, should they decide to proceed with a pregnancy, irrespective of the result of prenatal testing of the fetus.

The choices available for an "at-risk" couple - when both partners are carriers of β-thalassaemia trait

If two partners in a relationship are aware that they have the β-thalassaemia trait they may decide to marry anyway, or they may decide not to proceed with the marriage at all. Partners that are both carriers of β-thalassaemia trait and are already married, may decide:

- not to have children at all, or not to have their own children
- to adopt children
- to proceed to have children with artificial insemination with donated sperm from a non-carrier donor
- to have a child anyway and proceed with the pregnancy without finding out the status of the fetus or
- even when the fetus is diagnosed with β-thalassaemia major or other severe haemoglobin disorder, to continue with the pregnancy
- to terminate the pregnancy upon diagnosis of an affected fetus

Testing a fetus for thalassaemia syndromes and other haemoglobin disorders

There are three types of tests that can determine whether an unborn child has β-thalassaemia major or intermedia:

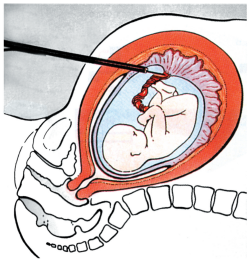
(i) **Amniocentesis:**

Amniocentesis is performed in the second trimester of pregnancy, after about 15 weeks' gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother's abdomen. A small amount of amniotic fluid, containing cells from the fetus, is withdrawn.

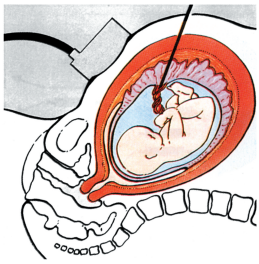
This is then analysed in the laboratory to determine whether the fetus has β-thalassaemia (Major or Intermedia).

The risks that this test pose to the mother and the fetus are not significant. There is a small risk of miscarriage, which occurs in 1:200-1:400 cases (less than 0.5%) The specialist Obstetrician, however, will be able to explain and discuss in detail all aspects of this test.

Amniocentesis



Cordocentesis



(ii) **Cordocentesis (sampling of fetal blood)**

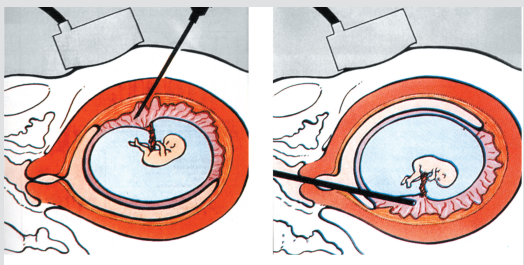
Under ultrasound guidance, a fine needle is inserted through the abdomen into the fetal umbilical cord, through which a small volume of blood is aspirated. Fetal blood is separated out and analysed in the laboratory. In skilled hands as much as 100% of pure fetal cells are obtained from the first attempt in the majority of cases. The obstetrician specialising in prenatal examination will be best able to explain and discuss with you causes of failure in obtaining pure fetal blood as well as any other potential risks, when undergoing the procedure.

Cordocentesis is performed after 18 weeks into pregnancy. The risks include miscarriage (1- 2%), blood loss, infection and leaking of amniotic fluid.

Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis which is now mainly indicated only in pregnant women who report late, in those in whom CVS

(see below) is inconclusive and when previous studies of at risk couples are not available.

(iii) Chorionic Villus Sampling (CVS)



CVS

CVS is a method of diagnosing haemoglobin disorders in the fetus and can be performed earlier than amniocentesis, at about 10-11 weeks' gestation. Using ultrasound as a guide, the specialist obstetrician removes a small sample of the chorionic villi i.e. cells that contain the same genetic information as the fetus and which will eventually form the placenta. The cells are removed either by a thin needle inserted through the mother's abdomen (transabdominal) or a thin catheter inserted through the vagina (transcervical). The cells are then analysed and a diagnosis made. There is a small risk of miscarriage (up to 2%) and an even smaller risk of infection or bleeding as compared with the previousely described procedures. There is, in addition, a very small risk of limb abnormalities, which is virtually excluded if CVS is performed after 10 weeks.

As with other prenatal diagnosis methods, information on potential risks and benefits of using this procedure are provided to the couple by the specialist obstetrician.

How is the diagnosis of the fetus made after obtaining samples using the above methods?

Amniocentesis and CVS are both based on DNA, otherwise known as genetic testing and involve identifying the genetic abnormality (mutation) present in the parents. This kind of testing constitutes the most accurate means of diagnosing inherited diseases. As with all tests, there is a possibility of laboratory error, albeit a very small one.

In the case of CVS, for example, laboratory scientists study the haemoglobin genes contained in the DNA of cells from the chorionic villi to see if the baby will be healthy, with unaffected genes, whether it will be a thalassaemia carrier or whether it will have affected

> *"Analysis of the sample usually takes about a week."*

Hb genes and have β-thalassaemia major.
Analysis of the sample usually takes about a week.
If the test shows that the baby is affected, the couple may decide to either proceed with the pregnancy, accepting that lifelong treatment will be necessary, or to end the pregnancy, as previously mentioned. However, if pregnancy termination is the choice this is done in one of two ways, depending on the stage of the pregnancy.

Termination of Pregnancy

Early terminations

Early termination can be carried out when a woman is less than 14 weeks pregnant. The couple should be given all information and their concerns and worries should be addressed by appropriate counselling. They should, for example, be informed by the Obstetrician and/ or Counsellor that termination will not reduce the woman's chance of having another baby and that each pregnancy conceived by an at-risk couple carries the same risk of producing an affected child.

In addition, it should be clearly explained that If the couple wishes to know whether any subsequent babies conceived carry thalassaemia, prenatal diagnosis will have to be carried out again, involving exactly the same procedures and with the same benefits and risks.

Late termination

The procedure for terminating a pregnancy at over 14 weeks involves inducing labour of the pregnant woman by introducing hormones (prostaglandin). The labour may last for several hours and the procedure is much more psychologically disturbing for the woman than an early termination. Late termination does not affect the woman's ability to become pregnant again, and the Obstetrician will provide all information and answer all related questions.

Other approaches

Prenatal diagnosis and the termination of pregnancy are methods that may not be acceptable to every couple at risk or to certain populations due to religious and cultural beliefs.

Unfortunately, however, prevention cannot rely on the identification of carriers alone and screening cannot be effective and successful in the absence of prenatal diagnosis and pregnancy termination. Other methods of prevention have been developed, while others are still in the research stage, both to minimise intervention and psychological stress, as well as to be more acceptable by certain populations and individual couples. **For example, analysis of fetal cells circulating in the mother's blood is a test where significant research has been focused in the last decade.** This however, has limitations and still cannot offer to date a reliable alternative to classical prenatal testing.

Pre-implantation genetic diagnosis (PGD), is another refined laboratory procedure developed in the last decade making use of in-vitro fertilisation technology to analyse cells taken from the very early embryo or to select an egg from the carrier mother an egg that is free of Hb disorders. This is then fertilized in the laboratory and is finally introduced into the womb. PGD proves more acceptable than prenatal diagnosis, particularly to those individuals opposed to the termination of pregnancy, despite the fact that the technology is still costly, and several attempts are often necessary for a successful pregnancy.

Being homozygous for β-thalassaemia or patient with β-thalassaemia major, (Mediterranean Anaemia or Cooley's Anaemia)

People with homozygous β-thalassaemia cannot make haemoglobin normally, and so cannot make normal red blood cells. Each red blood cell contains much less haemoglobin than usual, and there are far fewer of them than usual. This causes anaemia which is severe in individuals with β-thalassaemia major and can be milder in those with β-thalassaemia intermedia.

A child with β-thalassaemia major is normal at birth but develops a severe anaemia between three months and one year of age. If left untreated, affected children have a very poor quality of life and most die at a very young age. The patients with homozygous β-thalassaemia who have β-thalassaemia intermedia, which is considered in the majority of cases to be a "milder" condition than β-thalassaemia major can manage, although they still have a serious

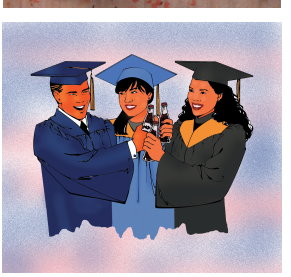
anaemia, without regular blood transfusions, at least in the early years of life. The anaemia, however, may get worse with age, and they may need to start regular blood transfusions later in childhood or in adult life. Many other medical complications, apart from serious anaemia, are seen in both β-thalassaemia major and intermedia and these need multi-disciplinary medical care.

What is the treatment for β-thalassaemia major?

The basic treatment is regular blood transfusion, usually every four weeks. Children who are transfused appropriately grow well and have a normal life. However, to live past their twenties, patiens with β-thalassaemia major, also need to start from early childhood, a specific treatment to remove the excess iron, which is released from the haemoglobin of the transfused red cells, as these, continuasly break down. Iron builds up in the body and causes overload, which can ultimately damage vital organs such as the heart, liver and endocrine glands. Iron can be removed by specific drugs called iron chelating agents that bring it out in the urine and/or the stools. The first, iron chelating agent, to be used with efficiency and safely, is desferrioxamine, or Desferal, which is injected under the skin for many hours, almost every night using a small pump. Although difficult and cumbersome, this type of treatment has proved to be a life-saving one.

The outlook is, however, steadily improving as new iron chelating agents that can be taken by mouth are increasingly available. Already, two orally taken drugs, Deferiprone (L1) and Deferasirox (Exjade) are officially registered in many countries and are in use by many thousands of patients across the world.

Children born today with Thalassaemia major are expected to live an almost normal length of life, provided that they can obtain all the treatment they need, and take it regularly, according to consensus guidelines.



Considerable research is focused on further improving medical care of Thalassaemia major through pharmaceutical substances that may ultimately lead to a reduction in the need for blood transfusion therapy and iron chelation. Cure of this disease can only be achieved to date by bone marrow transplantation (BMT). This has been shown to be successful,

provided that, a fully matched sibling (brother or sister) can be identified, the patient is in good condition clinically, and has been following regular treatment since his/ her childhood. However, only a relatively small percentage of patients (about 20%) will have a fully matched donor. Moreover, bone marrow transplantation is still an expensive procedure and its level of success relies, apart from the suitability of the donor and the clinical state of the patient, on the experience of the BMT centre.

One possible answer to the limitation with regards to finding a suitable donor, is for the parents to have another child, who is fully compatible with the living affected one. In order, however, to ensure that this new child will be a compatible donor, a special process known as Pre-implantation Genetic Diagnosis - HLA (PGD-HLA) has been developed in recent years, whereby the embryo to be implanted into the woman's womb is selected in the laboratory, not only to be free from thalassaemia, as in the PGD technology described previously, but also to have the same tissue characteristics (HLA type) as the affected living child. For achieving this, blood from the umbilical cord will be taken at birth, the cells of which may be used for transplanting the patient sibling. In other words, the "new" baby is selected from the beginning to be a perfect donor for his/ her affected brother or sister.
This is a laborious process not ethically approved by all, but which nevertheless may provide a better chance of a matched donor than BMT for curing patients with β-thalassaemia major, and other severe hereditary disorders.

The final cure for thalassaemia is also hoped to come from another scientific process called ***gene therapy.*** This is still experimental and it involves placing functional genes in the patient's cells outside of the body, in the laboratory, and then replacing them into his/ her blood-forming tissues, making them capable of producing new red cells containing normal haemoglobin. Patients very much look forward to the success of this research work which does not depend on donors but on the patient's own cells. In this context this procedure has not, therefore, the limitations encountered in BMT. It is hoped that science will soon overcome the many technical difficulties and make this dream of a cure for all a reality.

How is β-thalassaemia major diagnosed?

A child born with β-thalassaemia major will show no visible signs of the disease. Even laboratory tests may fail to diagnose

"β-thalassaemia major can be diagnosed in the first few months and before the age of 2 years."

thalassaemia, particularly if the parents have not been tested, no prenatal tests were carried out, and there is no other affected child in the family. It is possible to diagnose β-thalassaemia major at this very early age only by means of genetic tests that identify the haemoglobin genes the child has inherited from each parent.

Unfortunately, even where newborn screening programmes are established, the routine diagnostic tests used cannot identify β-thalassaemia major at such an early stage. However, screening at this stage will be of use in diagnosing the presence of a variant such as HbE or HbS.

In most cases, β-thalassaemia major can be diagnosed in the first few months and before the age of 2 years.

β-thalassaemia intermedia which in the majority of cases is a "milder" clinical condition than β-thalassaemia major can, however, remain undiagnosed for longer periods.

Methods commonly used to diagnose thalassaemia major in the laboratory

(i) **Measuring Haematological indices.** Electronic equipment - a red cell counter - assesses the size and volume of red blood cells and the amount of haemoglobin contained in them.
Thalassaemia is diagnosed where the size and volume of red blood cells and the concentration of haemoglobin inside them are significantly reduced, with haemoglobin levels of between 2-6g/dl. Some haematological indices most commonly found in patients with thalassaemia are shown below:
Mean, (Range)

Haemoglobin (Hb) g/dl 6.8 (range 3.9-9.3)
Mean Corpuscular Haemoglobin (MCH) pg 20.9 (range15-26)
Mean Cell Volume (MCV) FL 65.8 (range 57-75)
Mean Corpuscular Haemoglobin content (MCHC) g/dl 30.9 (range 26-34)

(ii) **Blood film and RBC morphology.** Observed under a microscope, the red blood cells appear paler (hypochromic) and smaller (microcytic) than normal and, very importantly, the majority have abnormal sizes and shapes - anisocytosis and poikilocytosis, which are more marked than the changes seen in the carrier.

(iii) **Analysis of haemoglobin through electrophoresis.** This is a process that separates the different proteins that make up a

haemoglobin molecule - i.e. HbA, HbA2, and HbF. A diagnosis of thalassaemia is indicated where levels of foetal haemoglobin are higher than normal and may vary between 20-90%. HbA2, which usually accounts for up to 3% of normal adult haemoglobin, may be non-existent, reduced, normal or slightly elevated.

(iv) **By Molecular methods.** These are specialised ways used to confirm or obtain more specific information in a diagnosis, using DNA investigation to identify the mutations (the genetic changes) that cause a condition - information that, in addition to confirming a diagnosis, may also provide an indication of the clinical severity of the disease.

Although the diagnosis of β-thalassaemia major is usually fairly straightforward, difficulties may arise, particularly in developing countries where the prevalence of diseases such as malaria can complicate the diagnosis.

For example, malaria can cause anaemia and splenomegaly, and although the haematological laboratory findings are quite different, it may be necessary to treat the patient with anti-malarial drugs before reassessing the patient's condition and diagnosis.
Other conditions may also cause anaemia and splenomegaly as well as raised HbF levels and a differential diagnosis is necessary with additional clinical and laboratory tests. It is very important to confirm an accurate diagnosis of thalassaemia before the initiation of treatment.

Can patients with thalassaemia major have children?

Yes, many adult patients are now married and have become parents. The possibilities of transmitting their genes include the following:

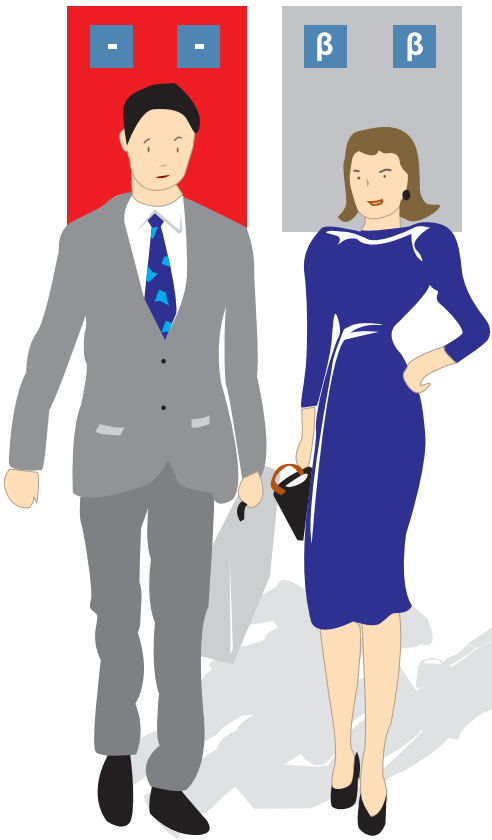
i. Children from parents, one of whom is β-thalassaemia major/ intermedia, and the other has fully functional β-globin genes (HbA) will all be healthy carriers of β-thalassaemia trait. (FIG 5)

ii. From parents where one of whom is a β-thalassaemia carrier and the other is a patient with β-thalassaemia major, one in two or 50% of their children will be carriers of β-thalassaemia trait and one in two or 50% will be patients of β-thalassaemia major. (FIG 6)

iii. When both parents are patients with β-thalassaemia major, all children will also be patients of β-thalassaemia major. (FIG 7)

FIG5

A THALASSAEMIA PATIENT AND A NON-CARRIER PARTNER



UNAFFECTED

β-THALASSAEMIA

CHANCES ARE:

ALL HEALTHY CARRIERS OF β-THALASSAEMIA TRAIT

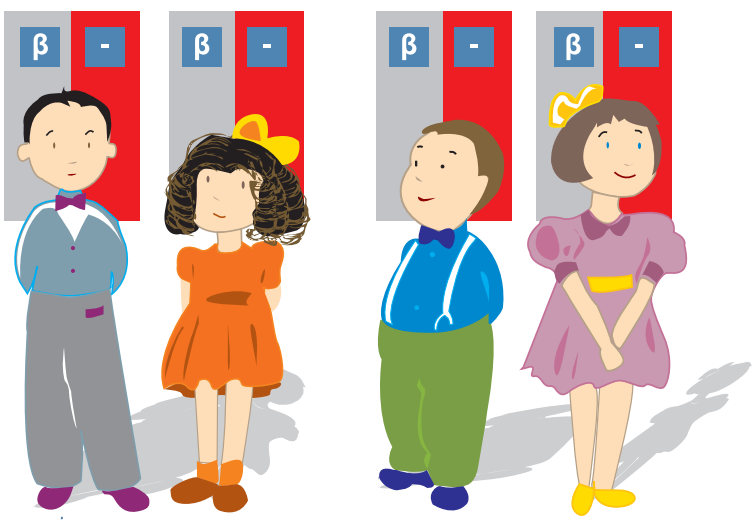
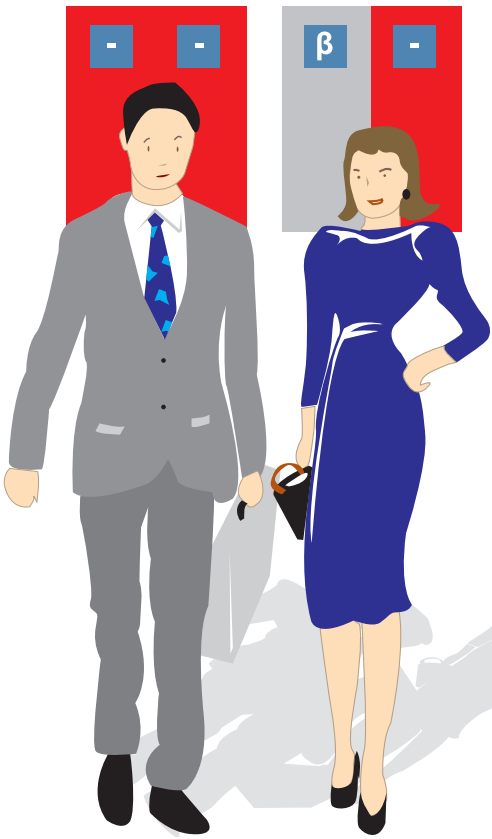


FIG6

A THALASSAEMIA PATIENT AND A CARRIER PARTNER



UNAFFECTED

β-THALASSAEMIA

CHANCES ARE:

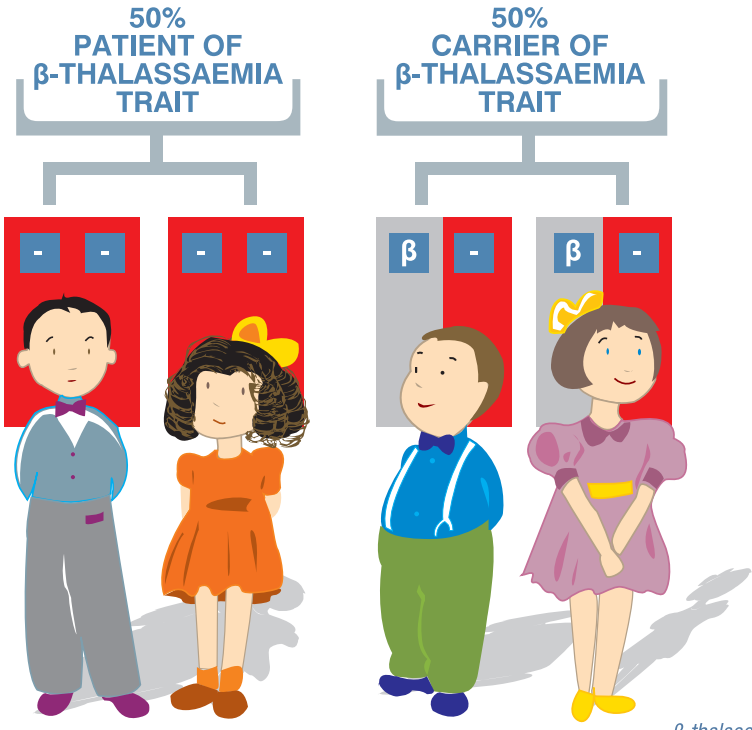


FIG7

BOTH PARENTS ARE THALASSAEMIA PATIENTS

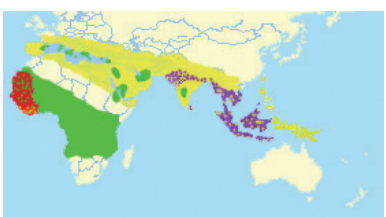
β-THALASSAEMIA

CHANCES ARE:

Where do we find β-Thalassaemia and other Hb disorders?

Thalassaemia was originally thought to be a disease limited to the Mediterranean region, hence its names Mediterranean Anaemia and Thalassaemia, a compound Greek word from thalassa, (meaning sea), and anaemia, (meaning poor or no blood). It is now known that Hb disorders occur widely throughout many parts of the world. Across southern Europe from Portugal to Spain, Italy and Greece, in a number of Eastern European countries, the Middle East through to Iran, Pakistan, India, Bangladesh, Thailand, Malaysia, Indonesia and southern China, as well as countries along the north coast of Africa and South America. Thalassaemia is particularly prevalent in areas in which malaria is or was once endemic.

Countries affected by malaria before establishment of control programmes



Map of haemoglobin disorders worldwide "Guidlines to the clinical Management of Thalassaemia " 2000

It is believed that, in these areas of the world, the human organisms underwent a slight change in their genes – a genetic adjustment, or a mutation, as called in biology. This change led to important changes in the environment of the red cells that prevented malaria parasites from growing and multiplying in them, thus giving these people a survival advantage over those in whom this genetic change did not occur. It is believed that carriers of the thalassaemia trait (α and β) as well as carriers of other Hb disorders, such as Sickle Cell, were thus better able to survive malaria than healthy individuals, so the number of carriers increased significantly over the years in malaria-endemic regions of the world as large numbers of healthy individuals died as a result of severe malaria infection.

Population migration and intermarriage between different ethnic groups has introduced thalassaemia in almost every country of the world, malaria endemic or not, including northern Europe and other countries where thalassaemia did not previously exist.

According to recent epidemiological information about 7% of the global population carries an affected haemoglobin gene, with between 300,000 and 500,000 affected children born annually. More than 80% of these are born and live in the developing part of the world. About 70% of them have sickle disorder and the rest have thalassaemia syndromes. Still, a significant number of affected children, born in developing countries, die undiagnosed or misdiagnosed, receiving sub-optimal treatment or left untreated altogether. ("World Bank 2006, report of a joint WHO - March of Dimes meeting 2006)

National control programmes are urgently needed to reduce the overall number of affected births and to improve the survival and quality of life of the patients with Hb disorders across the world.

THALASSAEMIA INTERNATIONAL FEDERATION'S PUBLICATIONS

1. "Blood Safety Kit" (1999)
   [In English]

2. "Guidelines to the clinical Management of Thalassaemia" 2000
   [Translated into 6 languages]

3. "Compliance to Iron Chelation therapy with Desferrioxamine" 2000 - Reprint 2005
   [Translated into 4 languages]

4. "About Thalassaemia" - 2003
   [Translated into 11 languages]

5. "Prevention of Thalassaemias and other Haemoglobinopathies " Volume I (2003)
   [Translated into 2 languages]

6. "Prevention of Thalassaemias and other Haemoglobinopathies" Volume II (2005)
   [Translated into English]

7. "Patients' Rights" 2007
   [In English]

8. "A guide to the establishment and promotion of non-government patients/parents' organization" 2007
   [In English]

9. Updated version of the book "Guidelines to the Clinical Management of Thalassaemia" May 2007
   [In English]

10. Children's dialogue: "Thalassaemia and Me" 2007
    [In English]

11. Booklet One: About β-thalassaemia 2007

12. Booklet Two: About α-thalassaemia 2007

13. Booklet Three: "About Sickle Cell Disease" 2007

14. TIF's Educational Folder 2007

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