Jharna Bhattacharyya

Thalassemia

Thalassemias are forms of inherited autosomal recessive blood disorders that originated in the Mediterranean region. In thalassemia, the disorder is caused by the weakening and destruction of red blood cells. Thalassemia is caused by variant or missing genes that affect how the body makes hemoglobin. Hemoglobin is protein in the red blood cells that carries oxygen. People with thalassemia make less hemoglobin and have fewer circulating red blood cells than normal, which results in mild or severe anemia. Thalassemia will be present as microcytic anemia. This disease can cause significant complications, including iron overload, bone deformities and cardiocascular illness. This same disease may confer a degree of protection against malaria, which is or was prevalent in the regions where the trait is common. This selective survival advantage of carriers may be responsible for perpetuating the mutation in populations. In that respect, the various thalassemias resemble another genetic disorder affecting hemoglobin, sickle-cell disease.

Signs and symptoms

- **Iron overload**: People with thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver and endocrine system, which includes glands that produce hormones that regulate processes throughout the body. The damage is characterized by excessive deposit of iron. Without adequate iron Chelation therapy almost all patients with beta-thalassemia will accumulate potentially fatal iron levels.
- **Infection:** People with thalassemia have an increased risk of infection. This is true if the spleen has been removed.
- **Bone deformities:** Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Sometimes bones become thin and brittle, increasing the risk of broken bones.
- **Enlarged spleen:** The spleen aids in fisting infection and filters unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of large number of red blood cells and the task of removing these cells causes the spleen to enlarge. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Enlargement of the spleen make necessitate its removal.
- **Slowed growth rates:** Anaemia can cause a child's growth to slow. Puberty also may be delayed in children with thalassemia.
- **Heart problems:** Such as congestive heart failure and abnormal heart rhythms may be associated with severe thalassemia

Causes

Thalassemia has an autosomal recessive pattern of inheritance. Both alpha and beta-thalassemias are often inherited in an autosomal recessive manner, although this is not always the case. For the autosomal recessive forms of the disease, both parents must be carriers in order for a child to be affected. If both parents carry a hemoglobinopathy trait, there is a 25% risk with each pregnancy for an affected child. Genetic counseling and genetic testing is recommended for families that carry a thalassemia trait. There are an estimated 60-80 million people in the world carrying the beta thalassemia trait. This is a rough estimate; the actual number of those thalassemia major is unknown due to the prevalence of thalassemia in less developed countries. Countries such as Nepal, Bangladesh and Pakistan are seeing a large increase of thalassemia patients due to lack of genetic counselling and screening. There is growing concern that thalassemia may become a very serious problem in the next 50 years, one that will burden the world's blood bank supplies and the health system in general. There are an estimated 1001 people living with thalassemia major in the United States and an unknown number of carriers.

Pathophysiology

Normally, the majority of adult hemoglobin (HBA) is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. In thalassemia patients have defects in either the α or β glo-

bin chains causing production of abnormal red blood cells (in sickle-cell disease, the mutation is specific to β globin). The thalassemias are classified according to which chain of the hemoglobin molecule is affected. In α thalassemias, production of the α globin is affected, while in β thalassemia production of the β chain is affected. The β globin chains are encoded by a single gene on chromosome II, α globin chains are encoded by two closely linked genes of chromosomes 16. Thus in a normal person with two copies of each chromosome, there are two loci encoding the β chain and four loci encoding the α chain. Deletion of one of the α loci has a high prevalence in people of African or Asian descent, making them more likely to develop α thalassemias. B thalassemias are not only common in Africans, but also in Greeks and Italians.

- **Alpha (α) thalassemias:** The α thalassemias involve the genes HBA1 and HBA2, inherited in a Mendelian recessive fashion. There are two gene loci and so four alleles. It is also connected to the deletion of the 16p chromosome. α thalassemias result in decreased α-globin production, therefore fewer α-globin chains are produced, resulting in an excess of β-chains in adults and excess of α-chains in newborns. The excess β chains form unstable tetramers, which have abnormal oxygen dissociation curves.
- **Beta (β) thalassemia:** β thalassemias are due to mutation in the HBB gene on chromosomes II, also inherited in an autosomal-recessive fashion. The severity of the disease depends on the nature of the mutation. Mutations are characterized as either β° or β thalassemia major if they prevent any formation of β chains, the most severe form of β thalassemia, as either β^{+} or β thalassemia intermedia if they allow some β chain formation to occur, or as β thalassemia minor if only one of the two β globin alleles contains a mutation, so that β chain production is not terribly compromised and patients may be asymptomatic.
- **Delta (δ)** thalassemia: As well as α and β chains present in hemoglobin, about 3% of adult hemoglobin is made of α and δ chains. Just as with β thalassemia, mutations that affect the ability of this gene to produce δ chains can occur.

Management

Mild thalassemia people with thalassemia traits do not require medical or follow-up care after the initial diagnosis is made. People with β thalassemia trait should be warned that their condition can be misdiagnosed as the more common iron deficiency anemia. They should avoid routine use of iron supplements, yet iron deficiency can develop during pregnancy or from chronic bleeding. Counseling is indicated in all persons with genetic disorders, especially when the family is at risk of a severe form of disease that may be prevented. People with severe thalassemia require medical treatment. A blood transfusion regimen was the first measure effective in prolonging life.

Medications

Multiple blood transfusions can result in iron overload. The iron overload related to thalassemia may be treated via Chelation therapy with the medications deferoxamine, deferiprone or deferasirox. These treatments have resulted in improved life expectancy in those with thalassemia major.

Deferoxamine is only effective via daily injections which make its long-term use more difficult. It has the benefit of being inexpensive and decent long term safety. Adverse effects are primary skin reactions around the injection site and hearing loss.

Deferasirox has the benefit of being an oral medication. Common side-effects include: nausea, vomiting and diarrhoea. It is not suitable in those with significant cardiac issues related to iron overload. The cost is also significant.

Deferiprone is given as an oral medication. Nausea, vomiting and diarrhoea are irrelatively common with its use. Available in Europe as of 2010 but not available in North America. It appears to be most effective agent when the heart is significantly involved.

Carrier detection: A screening policy exists in Cyprus to reduce the incidence of thalassemia which since the programme's implementation in the 1970s has reduced the number of children born with the hereditary blood disease from 1 out of every 158 births to almost zero.

In Iran as a pre-martial screening, the man's red cell indices are checked first, if he has microcytosis, the woman is tested. When both are microcytic their hemoglobin A2 concentrations are measured. If both have a concentration above 3.5% they are referred to the local designated health post for genetic counseling.

Bone-marrow transplant

Bone marrow transplantation may offer the possibility of a cure in young people who have an HLA-matched donor. Success rates have been in the 80-90% range. Mortality from the procedure is about 3%. If the person does not have an HLA-matched compatible donor such as the first curative method requires, there is another curative method called Bone Marrow Transplantation (BMT) from haplo-identical mother to child (mismatched donor), in which the donor is the mother. The results obtained by Pietro Sodani are

- ✓ Thalassemia-free survival rate 70%
- ✓ Rejection 23% and
- ✓ Mortality 7%

The best results are with very young patients.

Epidemiology

β thalassemia is particularly prevalent among Mediterranean peoples. Globally in 2010 it resulted in about 18,000 deaths. In Europe, the highest concentrations of the disease are found in Greece, coastal regions in Turkey, in parts of Italy. The major Mediterranean islands such as Sicily, Sardinia, Malta, Corsica, Cyprus and Crete are heavily affected in particular. People from West Asia and North Africa also have high rates of thalassemia. Far from the Mediterranean, South Asians are also affected with the world's highest concentration of carriers (16% of the population) being in the Maldives. Nowadays it is found in populations living in Africa, the Americas and also in Tharu people in the Terai region of Nepal and India. The Maldives has the highest incidence of thalassemia in the world with a carrier rate of 18% of the population. The estimated prevalence is 16% in the people from Cyprus, 1% in Thailand, and 3-8% in populations from Bangladesh, China, India, Malaysia and Pakistan. Thalassemias also occur in descendants of people from Latin America and Mediterranean countries.

Jharna Bhattacharyya
Retired Scientist , IICB, Kolkata
Phone: 2668 5540