CRACKING THE CODE: UNDERSTANDING THE GENETIC CONNECTION TO THALASSEMIA

BY MALKI EPASINGHE

The World Thalassemia Day falls on 8 May . This day is observed globally to raise awareness about thalassemia and the importance of early diagnosis, genetic counselling, and treatment. In this article, we aim to contribute to this effort by shedding light on the genetic connections of thalassemia and how individuals can make informed decisions to prevent the disease.

This article was written based on an interview with Professor Sachith Mettananda a highly respected researcher, consultant paediatrician, and professor of paediatrics at the University of Kelaniya in Sri Lanka. He has made significant contributions to the fields of molecular biology, haematology, and paediatrics, particularly in the area of thalassemia research. Professor Mettananda's current research projects focus on understanding the genetic basis of thalassemia and developing new treatments for the disease.

He shared his insights on the genetic connections of thalassemia. He explained how mutations in specific genes cause thalassemia and how individuals can prevent the disease by carefully choosing their life partners.

What is thalassemia? How are genes connected with this disease?

A: Thalassemia is a problem with the haemoglobin molecule. Haemoglobin is the component in the red blood cells that carries oxygen. The adult haemoglobin molecule, has four globin proteins. Two of them are alpha-globin proteins whereas the other two are beta-globins. What happens in thalassemia is that the production of this beta-globin is grossly impaired.

Similar to all proteins in the human body, the beta-globin protein is produced by a gene. In beta thalassemia, there's a mutation in those beta-globin genes. Humans have two beta-globin genes in all our cells. We inherit half of our genes from our mother and the other half from our father. Of the two copies of the beta-globin genes in each cell, one is inherited from the father and the other from the mother. When there are mutations in both copies of the beta-globin gene it results in thalassemia.

So, thalassemia is a genetic disease. That's because it's caused by a problem in your beta-globin genes. When both your beta-globin genes are not working, you don't have any beta-globin. You have very low haemoglobin and red cells get destroyed inside the body. When the red cells get destroyed, the hemoglobin drops drastically. A normal person has a haemoglobin level of 11 - 15 g/dL. A thalassemia patient's haemoglobin level can drop to 2 or 3 g/dL, which can be fatal if they are not treated.

How is thalassemia passed from one person to another, is it only inherited from parents?

A: Yes. It is very rare for these mutations to happen later on. The vast majority, almost every child with thalassemia inherits the mutated genes from their parents. Their parents are referred to as thalassemia carriers.

If you take the mother, she will have one abnormal beta-globin gene and one normal gene. And the father too will have one abnormal gene and one normal gene. The father and mother will transmit one of their genes to their children. So, when the mother and father transmit the defective gene to their child, he or she will get the disease.

To clarify this a bit more, both the father and the mother have two beta-globin genes. When parents produce children, one of the genes from the mother and the father will go to the child. Four scenarios arise here. Both parents might transmit the normal gene to the child and the child would be perfectly normal. There are two chances that one parent might transmit the normal gene and the other might transmit the mutated gene. Then the child also will be carriers like the parents. If each parent passes the mutated gene to their child, then the child will get thalassemia. So, there's and

Dr. Sachith Mettananda

25% (1 in 4) chance with each pregnancy to have a child with thalassemia,if both parents are thalassemia carriers.

Is it possible to detect whether a child has thalassemia before they are born?

A: Yes, it can be checked in the foetus stage. Doctors can take some tissue samples from the foetus and see if the mutations are there and it can be detected if they have thalassemia. But this test is not widely available in this country.

It is said that marriage between close relatives leads to producing children with thalassemia. What is the science behind this?

A: Every person has some kind of mutated genes in their bodies, even though they look perfectly normal. When you are a close relative, it is likely that the mutated genes that you have are same as the mutated genes that your relative has, because the genes are quite similar. The likelihood of both having a mutated beta-globin gene is higher when you are a close relative.

Is thalassemia curable? What kinds of treatments are given for thalassemia?

A: Yes, thalassemia is curable. But the cure is not widely available and not available to all patients, even in developed countries.

There are two ways of curing thalassemia. One is the traditional bone marrow transplantation. Haemoglobin is produced in red blood cells, and red blood cells are produced in bone marrow, which are found within our bones. It is the factory that produces red blood cells. In the patients with thalassemia, the factory is perfectly normal, but the gene is defective. So, the cells that are produced have low haemoglobin. By bone marrow transplant, you destroy the bone marrow of a patient with thalassemia by radiation or chemotherapy. Then, you transplant bone marrow cells from another donor, who does not have thalassemia. But there are problems with this. The most important thing is that your body may reject the transplanted bone marrow and it may fight against your body. To avoid that from happening, it should be suppressed. For that, some drugs will be needed. Still, there's a chance it might be rejected. And there's some possibility that the transplant itself could be fatal. But if the transplant and the suppressing are successful, you are cured. But this kind of treatment is quite costly. The only place this is done in Sri Lanka free of charge is the Lady Ridgeway Hospital. It is also available in a few private hospitals but at a very high cost. Even if you can afford it, finding a suitable donor is difficult. A donor must ideally match with you, for your body to accept that person's bone marrow.

The other cure is gene therapy. It is still in the research stage. Gene therapy is something that can be done for any genetic disease. What is done by gene therapy is we correct the gene. In thalassemia patients, the mutated beta-globin gene is corrected. This method also has problems. The main thing is it is extremely costly. And the next thing is, although you correct the gene, it might not work properly. This is not available in Sri Lanka even at the research level. However, I must mention that the University of Kelaniya is conducting research on gene therapy for thalassemia, in collaboration with Oxford University.

There are about 2,000 thalassemia patients in the country. Only about 100 patients have been cured by bone marrow transplant so far. All the other patients are getting monthly blood transfusions. To do that, the patient has to spend a day at the hospital once a month. When blood is given externally, the iron level in the body increases. So, some medication also has to be given to these patients to reduce the amount of iron in the body. This is how the thalassemia patients are treated.

What is the lifespan of a thalassemia patient who receives monthly blood transfusions?

A: If you asked me that question twenty years ago, the answer would be probably maximum 12-13 years. But now, the treatments have advanced. We have very good iron removing medications.

I'd say a majority would live beyond 20 years. It's very rare in Sri Lanka for a patient with severe thalassemia to live beyond 45-50 years. In Western countries they usually live beyond 60 years because the treatments are advanced. In Sri Lanka there are many people who live with thalassemia beyond 30-40 years, even get pregnant, have children and live almost a normal life.

If a thalassemia patient has a child, will this disease pass on to them?

A: Both beta-globin genes of a patient with thalassemia are defective. So, that person will invariably transmit a diseased gene to his/her child. But if this person marries a perfectly normal person, who's not a thalassemia carrier, that person will transmit a normal gene to all their children. So, all their children will have one defective gene and one normal gene. All of them will be thalassemia carriers, but none of them will have the thalassemia disease. If you choose your partner wisely, your children will be normal, and be only thalassemia carriers.

What message would you like to pass on to the general public regarding thalassemia?

A: I think the public should be well aware of the burden of the disease. It takes a huge cost to treat and manage a thalassemia patient. Fortunately, all the treatments are provided free of charge in this country.

The second thing is that, if you are careful enough you can prevent having a child with thalassemia. Having a child with thalassemia is difficult and challenging.

But if you select your life partner carefully, whether you are a carrier or not, then you can avoid having a child with thalassemia. A test is available free of charge in many hospitals in Sri Lanka such as the Medical Research Institute, and Thalassemia Units at Ragama, Kurunegala, Kandy, and Anuradhapura. You can just walk into these hospitals and get yourself checked to find out whether you are a thalassemia carrier or not.

This has to be done just once in your lifetime. It is ideal if you do it before marriage. Three percent of the population in Sri Lanka are thalassemia carriers. So, it's important to get ourselves tested before we find a life partner. That is the best way in this country to prevent this disease.

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