Thalassemia: Detection, Management, Prevention & Curative Treatment

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Thalassemia syndromes are inherited genetic diseases caused by mutation of alpha or beta globin genes, which result in abnormal hemoglobin synthesis. The patho-physiologic mechanisms can be divided into decreased production of particular types of hemoglobin (Thalassemias) and production of abnormal structure of hemoglobin types (Hemoglobinopathies). These lead to not only abnormal morphologic of erythrocytes (red blood cells), but also shorten life span of erythrocytes due to increased in vivo fragility and extra-vascular red cell destruction (hemolysis) along with ineffective erythropoiesis (bizarre, dysfunctional marrow production). Thalassemia gene is an autosomal inheritance, which implies that both parents of the affected child must have a silent carrier state, so called thalassemia trait or heterozygote, while they are both asymptomatic.

Thalassemias could be classified based on genotypic diagnosis into 2 groups: alpha-thalassemia and beta-thalassemia, while phenotypic diagnoses are various manifestations of hemolytic anemia from very severe to very mild. Thus, they could be categorized based on clinical degree of severities as thalassemia major, intermedia, and minor. Proper treatment and care for each patient should be determined according to clinical setting.

Detection

Thalassemias (and other abnormal hemoglobin disorders) are among the most common genetic impairments around the world. They are more prevalent in people living in South-East Asia, South Asia, Middle East, and Mediteranean regions. The affected persons have variousdegrees of anemia (low red blood cell values) and enlarged liver and spleen, depending on the type of genetic defects in red blood cells' hemoglobin production.

Sickle cell diseases are among the most common hemoglobinopathies in the world, though they are not prevalent among Southeast Asians. Many affected people are of African descent, with the majority living in Africa, the Middle East, Mediterranean regions, and North America. Children affected with the disease have not only clinical manifestation like thalassemia syndromes, but also risk of painful vasoocclusive crisis due to intermittent clumping of crescent-shaped red blood cells (sickle cells) and subsequent occlusion in small blood vessels. Circulatory blood flow would be blocked. It can cause agonizing pain, serious infections and end organ damage.

Common thalassemia diseases in Thailand (and other countries in South-East Asia) consist of:

1. Homozygous alpha-thalassemia 1 (hemoglobin Bart's hydrops fetalis). This is the most severe form of the disease. The affected fetus could result in stillbirth and its pregnant mother may have a high risk of fatal toxemia.
2. Homozygous beta-thalassemia. Children affected with this form of the disease show no abnormality at birth but become progressively anemic after six months of age or usually within the first year of life. Without appropriate care and management such as regular blood transfusions, the child will undergo growth retardation, increased liver and spleen size, and facial bony deformities known as "thalassemic facies." Most thalassemia patients are classified as thalassemia major. Only a few cases will manifest thalassemia intermedia. Without proper treatment and care, the patients will likely have a shortened life expectancy.
3. Beta-thalassemia/hemoglobin E disease. This form of the disease represents a clinical spectrum that ranges from severe chronic hemolytic anemia that needs transfusion support to mild anemia that is non-transfusion dependent. Some patients will exhibit thalassemia major, while others will manifest symptoms of thalassemia intermedia. To determine which phenotypic applies to the patient the diagnosis must be performed by clinical presentation on case by case basis.
4. Hemoglobin H disease (alpha-thalassemia 1/alpha-thalassemia 2). In this form of the disease, the child will usually have mild to moderate hemolytic anemia with an enlarged liver and spleen. This group of the disease is considered to be thalassemia intermedia. The patients generally have a baseline hemoglobin level below the normal range but over 7.0 grams per deciliter. They may not require regular blood transfusions. The main problematic issue is acute hemolysis crisis on top of chronic anemia when patients develop illness or high fever. Occasional rescuing blood transfusion may be essential at the time of crisis to avoid heart failure or hypoxic brain damage.
5. Hemoglobin H Constant Spring (alpha-thalassemia 1/hemoglobin Constant Spring). This is another variant of hemoglobin H disease but in the same category as thalassemia intermedia. The prominent physical finding is an enlarged spleen greater than commonly seen with hemoglobin H disease. The patients usually have lower baseline hemoglobin content and are slightly more transfusion dependent than when they have acute hemolytic crisis. However, they can live as well as normal people and have near normal life expectancy.
6. Homozygous hemoglobin E. This disease is usually classified as thalassemia minor because of its slight anemia without enlargement of the liver and spleen. The patients are often performing normally and have a normal life span.
7. Other less common thalassemias include AEBart's disease, EFBart's disease, homozygous hemoglobin Constant Spring (CS), etc. These usually manifest as mild to moderate hemolytic anemia. Treatment would be adjusted by clinical severities on a patient case by case basis.

People who have any type of genetic heterozygote state will be judged as carriers or in the category of thalassemia minor. They may have some abnormal red cells indices and slightly low normal hemoglobin levels, but should not have any anemia symptoms. They do not encounter hemolysis problems, and no specific treatment is needed. Meanwhile, the important role of genetic counseling will be involved when two correspond-gene carriers are going to have a baby.

Diagnosis

Patients usually present symptoms of anemia, jaundice, and enlarged liver and spleen, Erythrocytes (red blood cells) of thalassemia patients mostly reveals microscopically as hypochromia, microcytes, anisocytosis, poikilocytes, and polychromasia. In terms of abnormal red cell indices, thalassemia erythrocytes show characteristics as low MCV, low MCH, low MCHC, but high RDW. In addition, for diagnosis of hemoglobin H disease, inclusion body test could find a positive result.

In order to make a clear diagnosis of individual status, the essential laboratory blood tests for hemoglobin analysis will be performed, including hemoglobin electrophoresis or currently updated technique of automated high performance liquid chromatography (HPLC). It is advisable that suspicious, anemic children should have these special blood tests performed prior to receiving their first transfusion, or at least 3 months after last time of blood transfusion. In some cases requiring definite genotypes to be identified, blood tests for molecular assessment at particular globin genes can be conducted any times, regardless timing of blood transfusion.

Treatment & Management

In several modern tertiary-care medical centers worldwide Thalassemia Clinic is usually established to to provide advice, treatment and care for children and adults suffering from anemia due to thalassemia diseases by experienced hematology specialist. The health services and facilities will be comprehensive and accommodated for individual patients.

Guidelines for management for each severity group of thalassemias are as following

Severe beta-thalassemia diseases with a baseline hemoglobin lower than 7.0 grams per deciliter or hematocrit less than 20%, can receive the following forms of treatment:

- Allogeneic hematopoietic stem cell transplantation. This can potentially cure the disease but an appropriate HLA-matched donor is required. There are also some possible complications during and after transplant process, but most cases can be reversible or resolved.
- High or Hypertransfusion regularly together with adequate iron chelation therapy. This approach is affordable and suitable for compliant patients and parents. The patient will have normal growth and height, no facial deformity, and possibly a normal sized liver and spleen. This strategy of management is mandatory for the safety and successful outcome of patients following stem cell transplantation.
- Low transfusion, occasional and supportive as needed. Iron chelation and/or splenectomy may be indicated. This approach is suitable for poor compliant patients and parents.

Moderately severe thalassemia diseases with baseline hemoglobin about 7-9 grams per deciliter or hematocrit about 20-27%, can receive the following forms of treatment:

- High transfusion together with adequate iron chelation therapy in some selected cases.
- Low transfusion occasionally when acute hemolysis crisis occurs. Splenectomy is indicated in some cases.

Mild thalassemia diseases in which the baseline hemoglobin is over 9 grams per deciliter or hematocrit more than 27% may receive transfusions only in the event of acute hemolysis crisis. Basic treatment consists of daily oral folic acid intake.

Asymptomatic or thalassemia trait or carrier, do not require regular follow up or medication. Only genetic counseling is offered when indicated.

• Blood transfusion therapy

Regular blood transfusion program must be provided for those suffering anemia problem from severe beta-thalassemia diseases, using good-quality, safe, contamination -free, pathogens screened blood components complying with standard guidelines of universal precaution by the National Blood Centre, Thai Red Cross Society and International Blood Banks. Occasional blood transfusion regimen must also be provided for those with acute crisis of hemolytic anemia due to underlying thalassemia intermedia. Nursing staffs must be high experiences in taking good care for patients receiving blood transfusion.

• Iron chelation therapy.

Each packed-red-cell blood unit contains a certain amount of iron. When a blood transfusion is given to a patient repeatedly, the iron compound will gradually deposit in his/her body tissue. Everyone has a a limit of excreting excessive iron. In patients who receive numerous blood transfusions, an accumulated toxic iron overload will develop. This leads to vital organ damage, affecting the liver, heart, pancreas, and many endocrine glands. To combat with this problem, the patient must be treated with ironchelating medications.

Chelation therapy should begin after 12 to 15 blood transfusions or within 1 8 months of frequent transfusions. This correlates with a serum ferritin level over 1,000 nanograms per milliliter. Liver iron concentration (LIC) which is measured by liver biopsy is the best measure of total iron loading. However this invasive liver procedure may not be routinely performed because of patient's discomfort. In cases where it is performed, LIC should be more than 3,000 micrograms per gram dry weight before beginning chelation. The methods may be subcutaneous or intravenous infusion of desferioxamine, oral intake of deferiprone, or intake of modern drugs such as desferasirox, etc. Responsible hematologist will assess and determine which ones are suitable to be used in patient on case by case basis.

• Supportive treatment and care.

On progression of disease in patients who did not get appropriate and sufficient treatment, several complications can occur. Patients must be aware of potential problems, such as increased size of spleen, congestive heart failure, increased tendency of clot formation inside blood vessels, increased susceptibility to infection from certain microorganisms, growth failure, endocrine dysfunction, delayed physical and sexual maturity, etc., so they may be treated early. For those who have had trouble from adverse manifestations, a holistic approach and treatment must be provided in order to relieve or even solve the problems.

• Prevention of complications and treatment.

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Prevention of new birth of thalassemia baby

• Genetic counseling.

Thalassemias (and abnormal hemoglobin genes) can be inherited from symptom-free parents, if both of parents are correspond-gene carriers. Definite diagnosis is the key for relevant counseling to parents and couples at risk. Hematologists and physicians who have expertise in thalassemia issues will identify thalassemia-carrier couples at risk, and provide counseling regarding their chance of having an affected child. Based on individual genetic markers, potential parents may need to decide if they should have a baby or keep contraception until pre-natal evaluation is planned. The physician team can also coordinate with an obstetrician team for assessment of fetus-in-utero of a pregnant woman who is carrying a risk of giving birth to a severe-thalassemia baby.

The modern method to identify the fetus-in-utero before birth is so-called pre-natal diagnosis (PND). Indication for couples who require PND procedures in pregnant women are as following

1. Both are alpha-thalassemia 1 carriers.
2. Both are beta-thalassemia carriers.
3. One is beta-thalassemia carrier, while the other is a hemoglobin E carrier, or homozygous hemoglobin E.

The PND procedures can be performed under ultrasonogram as early as in the late first trimester with the chorionic villi sampling (CVS) technique by an experienced, specialized obstetrician, or it can be conducted later in the second trimester with an amniocentesis technique. In some cases, the diagnosis can be performed with cordocentesis (in utero cord blood sampling) by a specialized obstetrician. Early detection provides for a more comfortable termination of the fetus if this outcome is desired.

New technologies for in-vitro fertilization (IVF) together with pre-implantation genetic diagnosis (PGD) tests and subsequent embryo transfer to the maternal uterus have been increasingly recognized as the alternative method to achieve non-genetic-defective fetus. It may be a solution for parents to have a healthy, non-thalassemia-diseased child. In addition, if the IVF team can identify an HLA-matched, non-affected embryo, it will be beneficial for parents who have previous children with thalassemia major and needing an HLA-matched sibling's cord blood transplantation to cure the disease.

Curative treatment

• Bone Marrow Transplantation (or Hematopoietic Stem Cell Transplantation).

This modern procedure has been the only accepted method worldwide to cure beta-thalassemia diseases by means of allograft transplantation. In this procedure, the patient requires a hematopoietic stem cell donation from an HLA-matched healthy donor, possibly from a sibling or unrelated suitable volunteers. The patient's blood, as well as that of the potential donor, will be tested for typing and matching. In the case of lacking an HLA-identical sibling, the patient will be registered to search for an appropriate unrelated donor through standard volunteer donor registries and public cord blood banks. Sources of donor's stem cells may be achieved from their bone marrow, peripheral blood, or umbilical cord blood.

Due to the sophisticated scheme of patient care, high risk of complications and high expense of treatment, indications for eligible candidates for undergoing stem cell transplantation are as follows:

1. Transfusion-dependent or severe hemolytic anemic beta-thalassemia diseases.
2. Available HLA-matched, non-affected, stem cell donors. The chance of a same-parent sibling having an HLA-match with a patient is about 1 out of 4, or 25%. The chance of a volunteer unrelated donor having an HLA-match is about 1:10,000 to 1:100,000.
3. Financial status. The cost of allogeneic hematopoietic stem cell transplantation for thalassemia children varies from 700,000 to 1,500,000 Thai Baht, depending on individual body weight and sources of donor stem cells.

Estimated disease-free survival rates of patients after transplantion varies from about 75% to 92%, depending on the experience of each institute team. From the patient's perspective, the better treatment outcomes are associated with younger patients, lower number of blood transfusion units, preferred use of leuko-depleted (leukocyte-filtered) packed red cells, absence of enlarged of liver and spleen, and regular adequate iron chelation to avoid liver fibrosis and myocardium damage. In terms of donors, better outcome are related with higher degree of completely compatible HLA alleles between donors and patients (recipients), and adequacy of stem cell dose to the patient's body weight. HLA-matched sibling stem cell transplantations achieve more successful disease-free long-term survival and less post-transplant complications than HLA-mismatched, unrelated donor transplants.

Allogeneic bone marrow transplantation is the complex scheme of therapy and integration of medical sciences and technology. Bangkok Hospital Medical Center offers this well-organized comprehensive program as a

specialized, aerosol-filtration equipped, isolation units setting for particular group of patients who have full-filled indication for undergoing transplantations. The institute has experienced a considerable number of successful bone marrow and cord blood stem cell transplants for thalassemia children and young adults. The details regarding this curative therapy will be informed, discussed, and explained by relevant bone marrow transplant physicians on patient case by case basis.

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Questions of Thalassemia

Q1. We are a Thai married couple who plan to have a baby soon. What should we do in order to make certain that our baby will not have thalassemia disease?

Q2. We are a married couple. Our hemoglobin typing results both showed normal types but the counseling clinicians requested us further for molecular genetic analysis of alpha-globin genes. Why is it needed to do so?

Q3. Our one-year-old child was recently diagnoses with beta-thalassemia disease. She has marked anemia and an enlarged spleen. How can we help her? Is there a cure?

Q4. Our 14-year-old son has been diagnosed with hemoglobin H disease since he was 4 years old. He had high fever and received a blood transfusion twice last month. He had never received any transfusion before. He has a slightly palpable spleen. Does he need bone marrow transplantation?

Q5. I just learned that I have a hemoglobin E trait from a blood checkup. What I need to do? Do I need to take oral folic acid?

Answers of Thalassemia

Answer 1: Even though you both are healthy, with no anemia symptom, you should have your blood checked for hemoglobin electrophoresis, also known as hemoglobin typing test. If you both are the correspond-gene carrier which can lead to some severe types of thalassemia, the chance that your baby will have the disease is about 25%. In this case, the counseling clinicians will advise you to perform genetic testing of your offspring during its either pre-natal or pre-implantation period. If just only one of you has the carrier gene, there will be no chance of your offspring having the disease.

Answer 2: Since alpha-thalassemia-1 genes are quite common among south-east Asian people but the defects are usually presented as normal types by hemoglobin electrophoresis test, some couples at risk may miss the opportunity to prevent their baby from being affected by homozygous alpha-thalassemia-1 genes, which consequently may lead to fatal hemoglobin Bart's hydrop fetalis. So when the consultant clinicians discovers a low mean cellular volume or low percentage of hemoglobin A2 despite normal hemoglobin types, they will suggest that you undergo further blood testing for molecular genetic analysis of alpha-globin genes.

Answer 3: A child with beta-thalassemia can survive and grow relatively well by receiving adequate, regular blood transfusions. With this approach she will not develop anemia, facial deformities, growth retardation, and her spleen size will subside soon. That said, if she requires more than ten packed red cell transfusions, her body iron will accumulate and become overloaded and then she will need adequate, proper iron chelation treatment. If the patient is fortunate to have an available HLA-matched, non-affected, healthy sibling, then she can be an eligible candidate for undergoing allogeneic bone marrow transplantation which offers a high hope of cure from her disease.

Answer 4: According to the clinical status, your son is classified as a thalassemia intermedia patient. Basically, thalassemia intermedia status does not require allogeneic bone marrow transplantation because the course of the disease is not as severe. Only some episodes of acute hemolytic anemia occur that require occasional blood transfusions. In lieu of the high risk and high cost of marrow transplantation, your son should not be considered to undergo the treatment. However, taking daily folate is recommended.

Answer 5: You should carry on as usual. You have no increased risk anemia or any destruction of your red blood cells. You will be doing fine with normal life expectancy. Folic acid tablet intake is unnecessary for any carriers of thalassemia or hemoglobinopathy state, like you. Anyhow, one essential issue is, if you have a couple, to check his/her blood for hemoglobin electrophoresis. If he/she has beta-thalassemia trait, there is a possibility of 25% that your offspring will have beta-thalassemia/hemoglobin E disease. If so you will need a consultation regarding genetic diagnosis for your baby.