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Mini Review

Overview of the Thalassemia

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Abstract

Thalassemia is an inherited blood disorder that affects the body's ability to produce hemoglobin and red blood cells. A person with thalassemia will have increased number of the red blood cells and also hemoglobin, and the red blood cells may be too small. The impact of disease can range from mild to severe and life-threatening. About 100,000 newborns are born each year with severe thalassemia. It is most commonly found in the Mediterranean, South Asia and Africa. A person with thalassemia has a normal life expectancy. However, cardiac complications arising from beta thalassemia major can make this condition fatal before the age of 30. With the introduction of stem cell transplantation from a related donor, a bright future has been opened for children with thalassemia in the Republic of North Macedonia.

Keywords: *Hemoglobin Disorders; Thalassemia; Transfusion-Dependent Thalassemia (TDT)*

Diagnostics

The most reliable way to diagnose thalassemia of any form is molecular diagnosis, which allows the diagnosis to be made from an early age. All this is made possible by modern methods of molecular genetics, such as analyzes based on PCR methodology (ARMS and ASO hybridization), DGGE, SSCP and sequencing [1].

The ICGIB conducts several protein and molecular analyzes to diagnose hereditary anemia:

- Protein analysis: HPLC analysis - qualitative and quantitative determination of normal and abnormal hemoglobin - DE-52 Colon chromatography - determination of HbA2 value.
- Alkaline denaturation: Determination of HbF - Starch gel - Detection of normal and abnormal hemoglobins - Osmotic resistance of erythrocytes - Tests to determine hemoglobin stability.
- Molecular analysis: SNaPshot analysis lead to β thalassemia and are most common in our country (c.93-21G> A, c.92 + 1G> A, c.92 + 6T> C, c.316-106C> G, c.118C> T, c .17_18delCT, c.19G> A, c.25_26delAA).

Specific PCR method for detection of Hb Lepore. - MLPA analysis (Multiplex Ligation-dependent probe amplification) - detection of large deletions and duplications in the α and β genes. - Sequencing of α and β genes - detection of rare mutations responsible for α and β thalassemia. - Sequencing of other globin genes and analysis for their expression is performed as needed [2].

Prenatal diagnostics

Monitoring of genetic markers in the family enables prenatal diagnosis of this disease and reduction of the number of patients with severe forms of thalassemia. Significant progress in thalassemia prevention has been made with the development of recombinant DNA technology. These methods enable the characterization of molecular defects in thalassemia homozygotes and heterozygotes and early prenatal diagnosis in couples at risk of giving birth to a sick child [3]. The diagnosis can be confirmed by biosynthetic tests that show a deficiency in β-globin synthesis, or by molecular tests that will determine the correct gene defect.

Therapy

The therapy of thalassemia is limited in scope and the treatment of thalassemia is only of an assisted nature. In addition, treatment may include splenectomy (removal of the spleen), a procedure that is indicated in patients with marked erythrocyte sequestration and may alleviate the clinical symptoms and signs of the disease. Iron chelation therapy can also be used, which is a mandatory procedure. This is achieved by subcutaneous administration of deferoxamine. Unlike severe forms, mild forms of thalassemia do not need to be treated.

The excess chains are unstable and precipitate on the erythrocyte membrane (Heinz bodies, also known as Heinz-Ehrlich bodies), damaging the cell and shortening its lifespan. Patients are treated with Desferal, Ferriprox and Exjade, preparations designed to cure excess iron in the body. In a small number of patients, iron supplements have been administered, such as Feroglobin, a specially formulated pharmaceutical product with moderate but effective levels of iron, vitamins and co-factors, which helps treat the symptoms of anemia. The preparation Tot`hema serves the same purpose, i.e. it is administered to reduce the iron deficiency in anemias, regardless of their origin. Hearing loss may occur due to taking Deferasirox during long time [4].

Curative therapies such as bone marrow transplantation and gene therapy are becoming available in Western countries. In addition, the role of programs to support patients and their families, which prevent psychosocial consequences, is important. Efforts are being made in developing countries to provide safe blood transfusions (virus filtration and control) and chelation. As a result of this condition, a large number of thalassemia patients die during childhood and adolescence [5].

In November 2018, at the Department for Hematology, within the University State Hospital Mother Theresa, on the November 2018 the first unrelated transplantation of hematopoietic stem cells was performed in the Republic of Northern Macedonia. It is one of the most modern and most complex biological interventions that treat the most severe hematological diseases without surgery. This opened the possibility for treatment of patients with thalassemia Beta major in our country. Macedonian public health entered the map of world and European medical centers for the treatment of the most serious blood diseases. The Macedonian Bone Marrow Donor Registry was established within the Institute of Immunobiology and Human Genetics, within the Faculty of Medicine and is a member of the World Marrow Donor Association.

Regarding the research and monitoring of hemoglobinopathies in the Republic of Northern Macedonia, an important place has ICGIB - Research Center for Genetic Engineering and Biotechnology “Georgi D. Efremov” MANU, in Skopje.

The National Reference Laboratory for Hemoglobinopathies, was established in 1970, functions within ICGIB, where during the past 40 years more than 30,000 individuals from our country have been examined [6]. Hydroxyurea Hydroxyurea is used to increase fetal hemoglobin production. Success is variable [7]. Butyrate analogues are newer preparations that are still in clinical trials [8].

Recently, gene therapy with autologous CD34 + cells transduced with the BB305 vector has been used in more developed countries around the world to treat patients with transfusion-dependent beta thalassemia [9].

Clinical picture

Anemia stimulates increased production of erythropoietin, leading to marked erythroid proliferation. Expanded erythroid mass results in osteoporosis and a risk of pathological fractures. Characteristic deformities of the skull and facial bones, maxillary protrusion, and extra-medullary haematopoiesis are also present. In regularly transfused children (at 3 - 4 weeks) the hemoglobin level can be maintained above 10 g/dl, allowing relatively normal growth and development. However, the large amount of iron that is ingested through transfusions and the excessive absorption of iron from the gastrointestinal tract (which occurs as a physiological response to anemia) leads to excessive accumulation of iron in the tissues, i.e. to secondary hemochromatosis. The liver, endocrine glands and especially the heart are the organs that are most damaged by iron overload [10]. Tablets Exjade are also used in the treatment of thalassaemias, which are oral iron chelator and are taken once a day [11]. In the literature one case study gives a report of a cardiopulmonary bypass procedure required in the case of patient with thalassemia [12].

After the age of 15, additional complications such as diabetes mellitus, hypothyroidism and, less commonly, hypoparathyroidism occur. Splenomegaly is a common finding and often leads to hypersplenism manifested by increased need for transfusions, leukopenia and thrombocytopenia. In these cases, splenectomy is performed, which due to the increased postoperative risk of sepsis with encapsular microorganisms is not practiced before the age of 4 years [13]. The splenomegaly is one of the most common and major complications in patients with β-thalassemia major, often suggesting removal of the spleen to improve the patient's health [13].

The prognosis is improved by the use of the iron chelator deferoxamine which removes excess iron. the starting of the use of deferoxamine in early childhood have impact on overall survival in patient with β-thalassemia and significantly slows down the occurrence of heart disease, diabetes mellitus, arthritis and hypogonadotropic hypogonadism [14].

Conclusion

The recent development of both oral iron chelators deferiprone and deferaxirox has offered new options for preventing and treating excess iron in hemoglobinopathy as well as in other transfusion-dependent anemias.

I hope that in the near future, with the increasing use of bone marrow transplantation from an early age will result to the reduction of the complications of iron overload, prolong life of the children with thalassemia and also significant improvement in the quality of life of the patients with beta thalassemia major.

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