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Navigating the Course of "Sea of Blood" a Preface

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Hemoglobinopathies comprise a very large number of genetic biochemical/ physiological entities, most of which are academic curiosities whose major effect on medicine is to add to the surfeit of useless scientific information. However, several of these conditions (e.g., sickle cell anemia, hemoglobin SC disease, and some thalassemias) are common major life-threatening diseases.

The thalassemias are various inherited disorders of hemoglobin (Hb) synthesis. Their clinical severity varies widely, ranging from asymptomatic forms to severe or even fatal entities. The term "Thalassemia" or "Mediterranean anemia," was introduced by Whipple, to reflect the original geographic home of the target population ("thalassa" is the classical Greek name for the Mediterranean Sea). Over the years, it has become clear that the condition can be found in any part of the world and in any group especially Africans, African-Americans, Arabs, Indians, and Southeast Asians.

The type of thalassemia usually carries the name of the underproduced chain(s). The reduction varies from a slight decrease to complete absence of production. For example, when beta chains are produced at a lower rate, the thalassemia is termed beta+, whereas beta-0 thalassemia indicates a complete absence of production of beta chains from the involved allele. β-thalassemia heterozygosity habitually manifests a typical hematologic, hemoglobin and globin synthesis picture, namely an increased RBC count, a reduced hemoglobin level, reduced MCV and MCH, altered erythrocyte morphology, increased HbA2 level, imbalance in globin synthesis with the α/β ratio greater than 1.

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In more severe homozygous forms, same pathophysiology applies but with significant exaggeration. The excess of free alpha chains brought about by the deficiency of beta chains causes destruction of the RBC precursors in the bone marrow (ie, ineffective erythropoiesis). In addition, the surviving cells arriving in the peripheral blood with intracellular inclusion bodies (excess chains) are subject to hemolysis. This means that both hemolysis and ineffective erythropoiesis cause anemia in the patient with beta thalassemia. The ability of some red cells to maintain the production of gamma chains, which are capable of pairing with some of the excessive alpha chains to produce Hb F, is advantageous. Binding some of the excess alpha chains undoubtedly reduces the symptoms of the disease.

Furthermore, increased production of Hb F in response to severe anemia adds another mechanism to protect the RBCs in patients with beta thalassemia. The elevated Hb F increases oxygen affinity leading to hypoxia, which, together with the profound anemia, stimulates the production of erythropoietin. As a result, severe expansion of the ineffective erythroid mass leads to severe bone expansion and deformities. Both iron absorption and metabolic rate increase, adding more symptoms to the clinical and laboratory manifestations of the disease.

It is an established fact that in India 10,000 children are born with the disease every year, which spells the reason of its importance in our country. We are aware about the molecular basis of the disease, its epidemiology, its implication and its treatment. The disease due to a genetic predisposition does not have a permanent cure but only a prevention and management regime. The available remedies for managing thalassemics are lifelong blood transfusion supplemented with adequate chelation therapy, Bone marrow transplant, and the much talked gene therapy.

There is no doubt that the introduction of adequate transfusion regimens together with intensive iron chelation has dramatically improved the outlook for children with thalassemia but it has its own limitations. Care has to be taken to assure that blood is free of various infectious agents to prevent further complications and to transfuse the minimum amount of blood required to assure growth and good quality of life, thus minimizing the possible iron load (and cost).

Desferrioxamine remains the treatment of choice for iron overload. Although it has a number of serious well recognized side effects, the principal problem associated with desferrioxamine is poor compliance. New approaches to improving compliance include 'tailored' chelation regimens based on accurate non-invasive assessment of liver and cardiac iron, for example by MRI, intensive intravenous desferrioxamine, home delivery of disposable infusors, the use of the oral chelator deferiprone (L1) alone or in combination with desferrioxamine and intensive home support programmes.

Agents that are capable of reactivating the γ-globin gene like Hydroxyurea, erythropoietin, butyrate derivatives and hemin are also in use to cure thalassemia. Antioxidant like Rutin is also seen to have a beneficial effect.

Bone marrow transplant though is proving successful but can be performed in patients who are Transfusion-dependent thalassaemia major, Age <16 years and have a HLA-identical sibling donor or HLA-identical non-siblings family member.

All of these curative therapies are costly and with their own limitations. In terms of cost of ideal maintenance of these children it comes to around a staggering 150 crores / annum. In a developing country like India this is an enormous sum and poses a tremendous burden on both economic and medical resources. The prevention on the other hand includes antenatal genetic testing, which may be applied in a variety of clinical situations, including preconception counseling, prenatal diagnosis and postnatal determination of genetic predisposition to disease. Genetic testing not only leads to a more accurate prognosis but also minimizes the social, psychological and economical burden imposed on the family and the country on birth of a thalassemic child. Genetic testing depends on the knowledge of the spectrum of β-thal mutations in a population. β-thalassemia is heterogeneous with more than 200 different mutations reported World wide. Apart from such a vast molecular variability, each ethnic population has its own cluster of specific mutations making carrier screening easier. In Asian Indians a total of 30 mutations with five common, ten less common and a variable number of rare mutations are defined.

Mutation identification is achieved by screening first for the expected known mutations, using one or more PCR-based techniques such as gel electrophoresis, restriction endonuclease analysis, allele-specific probe hybridization and allele-specific primer amplification. In the few cases where these techniques fail to reveal the genetic defect, characterization may be achieved by the application of non-specific detection methods such as denaturing gradient gel electrophoresis (DGGE), heteroduplex analysis, single-stranded conformational polymorphism analysis (SSCP) and direct sequencing of amplified DNA

Thus a clear cut definition of β -thalassemia mutations and careful analysis of clinical, hematological, genetic and molecular data of the prospective parents is required in genetic counseling and PND and thus in eradication of the disease

Centers carrying out prenatal diagnosis in India are Sir Ganga Ram hospital, Preeti Tuli Thalassemia Centre and AIIMS in New Delhi; Bai jerbai Wadia hospital for children , I IM in Mumbai; CMC in Vellore; CDFD in Hyderabad; BJ Medical college in Pune; Vivekanand Institute of Medical sciences in Calcutta and SGPGIMS in Lucknow.

Though PND has given a new dimension to thalassemia prevention but the social, psychological and ethical issues stemming from pregnancy studies and the social stigma has reduced its effectiveness.