β-Thalassemia: From Clinical Symptoms to the Management

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ABSTRACT

Thalassemia is a single gene disorder is characterised by reduction or absence of beta-globin chain. It is commomest in the Middle East, Southeast Asia, African and some Asian countries including India. Thalassemia has diverse clinical phenotypes. Thalassemia major patients present with severe anemia requiring regular blood transfusion for survival whereas Thalassemia trait is characterized by mild hypochromic, microcytic anemia with elevated HbA2 levels. The prevalence of thalassemia in India 3.3% and a high of 17% in certain communities. There are 30 million carriers and approximately 10000 children are born with the disease every year. Estimated cost for treatment is 1 lacs per child per year which is difficult to afford in developing countries. Management of thalassemics is not only traumatic to the family but also poses a tremendous socio-economic burden on the country making its control and prevention a cause of prime concern. Prenatal diagnosis, of thalassemia offers parents to make reproduction choices and therefore reduce the burden from the society.

Keywords: Thalassemia, Beta-globin, Anemia, Prenatal Diagnosis, Blood transfusions

INTRODUCTION

Beta-Thalassemia syndromes are a group of hereditary blood disorders that are characterized by reduced or absent beta globin chain synthesis, resulting in reduced hemoglobin in red blood cells (RBC), decreased RBC production and leading to anemia. Thalassaemia was not recognized as a clinical entity until 1925, when Cooley and Lee described a syndrome occurring early in life that was associated with splenomegaly and bone deformities.[1] β-thalassemia has diverse clinical phenotypes. It is one of most common autosomal recessive disorders found worldwide. Individuals with thalassemia major usually come into attention in initial two years of life where they present with severe anemia requiring regular blood transfusions for their survival. On the other hand, Thalassemia trait is characterized by mild hypochromic, microcytic anemia with elevated HbA_2 levels. Except in the rare dominant forms, heterozygous beta thalassemia results in the clinically silent carrier state. HbE/beta-thalassemia and HbC/beta-thalassemia exhibit a great range in terms of diversity of phenotypes and spectrum of severity. Estimated cost for treatment is more than 1 Lac per child per year, which is difficult to afford in developing countries. Management of thalassemics is not only traumatic to the family but also poses a tremendous socio-economic burden on the country making its control and prevention a cause of prime concern. Prenatal diagnosis therefore is a first priority to reduce the burden of the disease.

Beta-thalassemias can be classified into:

- Beta-thalassemia
  - Thalassemia major
  - Thalassemia intermedia
  - Thalassemia minor
- Beta-thalassemia with associated Hb anomalies
  - HbC/Beta-thalassemia
  - HbE/Beta-thalassemia
  - HbS/Beta-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)
- Hereditary persistence of fetal Hb and beta-thalassemia
- Autosomal dominant forms
- Beta-thalassemia associated with other manifestations
  - Beta-thalassemia-tricothiodystrophy
  - X-linked thrombocytopenia with thalassemia

Epidemiology

Its high prevalence is observed in populations in the Mediterranean, Middle-East, Transcaucasus, Central Asia, Indian subcontinent, and Far East. Consanguineous or common-ancestry marriages increase the chances of offspring inheriting disease traits, with closer consanguineous relationships at an increased risk.[2] Sociological studies indicate that they increase the couple's stability due to compatibility between the husband, the wife and the in-laws, strengthen family ties and solidarity, support the transmission of shared values and ease premarital negotiations particularly by allowing wealth and property to remain within the family. It is also relatively common in populations of African descent. The highest incidences are reported in Cyprus (14%), Sardinia (12%), and South East Asia.[3] Thalassemia is prevalent in India with an average incidence of 3.3% and a high of 17% in certain communities. Observation says, in India there are 30 million carriers and approximately 10000 children are born with the disease every year which draws its importance in India. The predominant abnormal hemoglobins i.e. hemoglobin S, D and E which occur with a frequency of 5.35% further poses tremendous burden on medical care in India (Fig. 1).

Population migration and intermarriage between different ethnic groups has introduced thalassemia in almost every country of the world, including Northern Europe where thalassemia was previously absent. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected.[4]

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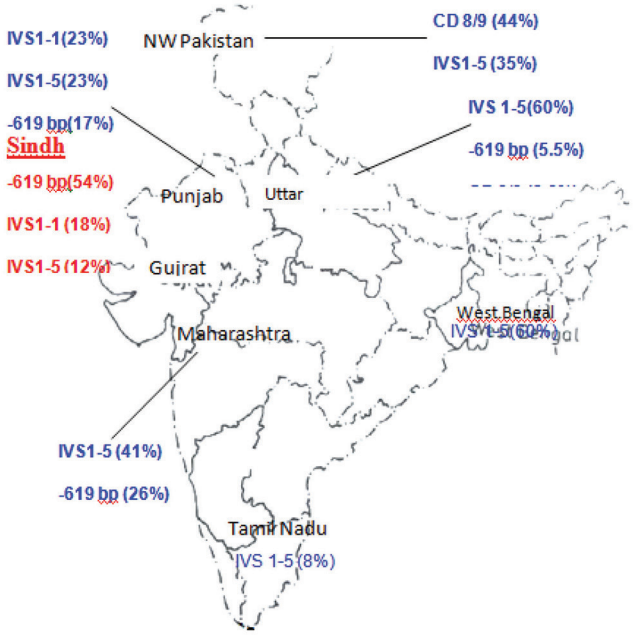

Figure-1: Distribution of mutation on Indian soil

According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world.[5]

Clinical features

Homozygotes for beta-thalassemia may develop either thalassemia major or thalassemia intermedia. Clinical presentation of thalassemia major occurs between 6 and 24 months. Failure to thrive and progressively becoming pale are initial symptoms of a β-Thalassemia major child. Feeding problems with recurrent diarrhea, irritability, fever, and abdominal enlargement due to hepatospllenomegaly occurs. Due to the lack of resources patients are untreated or poorly transfused in developing countries. There the clinical picture of thalassemia major is characterized by growth retardation, pallor, jaundice, poor musculature, genu valgum, hepatosplenomegaly, leg ulcers, extramedullary hematopoiesis, and expansion of the bone marrow resulting in skeletal changes. The skeletal changes include deformities in the long bones and typical craniofacial changes like bossing of the skull, prominent malar eminence, depression of the nose bridge, mongoloid slant of the eye and hypertrophy of the maxillae leading to exposure of upper teeth.[6] If a regular transfusion program that maintains a minimum Hb concentration of 95–105 g/L is initiated, then growth and development are normal until the age of 10–11 years.[6] After the age of 10–11 years, affected individuals are at risk of developing severe complications related to post-transfusional iron overload, depending on their compliance with chelation therapy which varies from patient to patient. Iron overload may lead to many severe complications. Complications include growth retardation and failure or delay of sexual maturation. At later stages, complications may include dilated myocardiopathy, pericarditis or rarely arrhythmias, chronic hepatitis with fibrosis and cirrhosis of liver, diabetes mellitus, hypogonadism and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands.[7] Infectious complications, including hepatitis B and C virus and HIV, relatively common in old patients. This has now become rare due to preventive measures being taken in the form of vaccination of patients (hepatitis B), mandatory blood donor screening methods being implicated (like methods based on viral nucleic acid enzymatic amplification).[8] If individuals are regularly transfused and treated with appropriate chelation, their life extends beyond age of 40 years. Cardiac disease caused by myocardial siderosis is the most important life-limiting complication of iron overload in beta-thalassemia. In fact, cardiac complications are the cause of the deaths in 71% of the patients with beta-thalassemia major.[9]

Hematological features

Patients with thalassemia major present with severe microcytic and hypochromic anemia, associated with increased number of red blood cells and low mean corpuscular volume (MCV) and mean corpuscular Hemoglobin (MCH). Peripheral blood smear shows features like microcytosis, hypochromia, anisocytosis, poikilocytosis, and nucleated red blood cells. The number of erythroblasts is related to the degree of anemia and is markedly increased after splenectomy. Hemoglobin pattern High Performance Liquid Chromatography (HPLC) reveals absence of HbA, HbF of 95–98%, and HbA_2 of 2–5%.

Present knowledge

The heterogeneous nature of β-Thalassemia is well known with more than 200 different mutations.[10] The spectrum of β-Thalassemia mutations in different world population has revealed extensive variation for both the types of mutations and their relative frequencies. Apart from such a vast molecular variability, each ethnic population has its own cluster of specific mutations.[5] In Asian Indians a subset of ten common mutations is defined.[11] In spite of having its own defined cluster of mutations, each ethnic group has a variable number of rare mutations. This number increases every time with characterization of unknown mutations that account for 2.0-4.0% of β-Thalassemia allele in each population.[11,12] These uncharacterized chromosomes need to be delineated and elaborated not only for updating the spectrum of mutations in an ethnic group but also for providing an early PND to couples at risk for β-Thalassemia.

Each mutation is in strong linkage disequilibrium with specific arrangements of restriction fragment length polymorphism (RFLP) within the β-globin gene cluster. A limited number of RFLP haplotypes of the β-globin gene cluster have been demonstrated in different ethnic groups,[13,14] so that 80 percent of the β-Thalassemia mutations are associated with only 20 different haplotypes.[15,16] These polymorphism are not only used as diagnostic tools for β-Thalassemia but they also provide information on the relative antiquity of some mutations, their spread in human population, and their unique vs. recurrent appearance in the same or different populations.[17,18] Therefore, for successful implementation of control programs of thalassemia, and to make them more cost effective, an idea about the mutation pattern and hence, genetic testing of the disease is important.

INDIA

Common mutations

A total number of about 30 different mutations have been reported in Indian population till date.[19] Among these, five

mutations namely IVS-1-5 (G-C), 619 bp deletion at the 3' end of β-globin gene, IVS-1-1 (G-T), FS mutation CD8/9 (+G) and CD41/42 (-CTTT) are the commonest. Though these are the five most common mutations found in Indian population but the frequency of each and in whole varies from study to study. A study conducted in 1984 reported eight mutations to account for 82.0% of the 44 β-Thalassemia alleles studied with three common mutations accounting for 70.0% of the cases.[20] In another report, Thein and his co-workers in 1988 showed that nine mutations account for 98.0% of the 102 β-Thalassemia alleles studied with five mutations accounting for 88.0% of the cases.[21] Then there was a study by Varawalla in 1991,[11] in which 702 unrelated β-Thalassemia carriers studied. There are now several studies that show that IVS-1-5 (G-C), IVS-1-1 (G-T), 619 bp deletion, CD 8/9 (+G) and CD41/42 (-CTTT) are the common mutations in India, present in differing frequencies among different states.[11,18,22-,25] The IVS-1-5 (G-C) transversion is the predominant mutation in all states and is common to all caste groups in India.[12,26] Its prevalence varies from 22.8-81.4% in different regions being the highest in Tamil Nadu in south-eastern area.[25] Even after five decades of independence the IVS-1-1 (G-T) mutation is observed at a high frequency among the migrants from Pakistan, and thus frequently encountered (upto 28.0%) in the states adjoining Pakistan (Punjab, Sindh and Gujarat). Likewise, the 619 bp deletion mutation is more frequently observed towards the central and northwestern part of India (Punjab, Gujarat, Haryana, UP, Rajasthan and areas adjoining Delhi), and is mostly absent from the southern states. The FS mutations, CD8/9 (+G) and CD41/42 (-CTTT) have a rather uniform distribution in different ethnic groups, with a frequency varying from 3.0-15.0%.

Less common mutations

Besides the common, the other less common mutations accounting for 4.0-6.0% of the remaining include nonsense CD15 (G-A), CD16 (-C), CD30 (G-C), -88 (C-T), Cap+1 (A-C), CD5 (-CT), IVS-1-1 (G-A). There are a few studies that have mentioned the distribution of mutations that are not so frequently found in the Indian subjects.[11,24] The CD30 (G-C) mutation first found in India from the neighboring regions of Gujarat, Sindh and Punjab, is occasionally found in almost all states with a low frequency (0.7-2.0%).

Rare mutations

The rare mutations are the most ill defined in an ethnic group. The number as well as the frequency varies. As the unknown mutations (1.0-2.0%) are being characterized in a population, the number of these mutations is going high. With more and more studies reporting the same mutation they finally join hands with the less common ones. The IVS-1, 3'-end (25 bp del) was first reported from India by Orkin in 1983.[14] Studies conducted by Garewal in 1994 demonstrate 0.7-2.0% prevalence of FS CD5 (-CT) and CD47/48 (+ATCT) in Punjab, Maharashtra and U.P while the Cap+1 (A-C) mutation has been seen to affect the U.P (1.0-3.0%) and Punjab (3.0-10.0%) populations only.[24] The FS CD88 (+T), IVS-2-837 (T-G), IVS-1-110 (G-A) mutations and IVS-2-1 (G-A) mutation from Punjab (0.7%) and Maharashtra (7.6%) have been reported.[15] The FS CD54/55 (+A), a novel mutation was discovered in one Maharashtrian native.[24] Another novel mutation at CDs 57/58 (+C) was reported in 1995 by el Kalla and Mathews. The Molecular genetic analyses of beta-thalassemia in South India by Bashyam in 2004 reveals rare mutations in the beta-globin gene.[27] These studies of mutation patterns in different communities have helped in the quick identification of beta-thalassemia mutations for prenatal diagnosis.[12]

MANAGEMENT

Transfusion

Regular transfusions are essential to correct the anemia, suppress erythropoiesis, and inhibit increased gastrointestinal absorption of iron in β-Thalassemia patients which occurs in non-transfused patients as a consequence of increased, although ineffective, erythropoiesis. Several different transfusional regimens have been proposed over the years, but the most widely accepted aims at a pre-transfusion Hb level of 9 to 10 g/dl and a post-transfusion level of 13 to 14 g/dl.[5] This prevents growth impairment, organ damage and bone deformities, allowing normal activity and quality of life.[7] Before beginning with any transfusions, it is mandatory to carry out hepatitis B vaccination and perform extensive red blood cell antigen typing, including Rh, Kell, Kidd, and Duffy and serum immunoglobulin determination, the latter of which detects individuals with IgA deficiency who need special (repeatedly washed) blood unit preparation before each transfusion. The transfusion regimen is designed to obtain a pre-transfusion Hb concentration of 95–100 g/L. Transfusions are usually given every 2–3 weeks.

Several factors should be taken into consideration before estimating the amount of blood to be transfused like weight of the patient, target increase in Hb level and hematocrit of blood unit. The amount of transfused RBC should never exceed 15 to 20 ml/kg/day and to avoid a fast increase in lood volume, RBCs should be infused at a maximum rate of 5 ml/kg/hour. Some indices should be recorded during each transfusion, such as pre- and post-transfusion Hb, amount and hematocrit of the blood unit, daily Hb fall and transfusional interval to monitor the effectiveness of transfusion therapy. These measurements enable two important parameters to be calculated: red cell requirement and iron intake.[5]

Iron overload

The most common complications related to patients on regular transfusion is iron overload. A regular transfusion regimen progressively develops clinical manifestations of iron overload which include hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hypoparathyroidism (4%), diabetes (6- 10%), liver fibrosis, and heart dysfunction (33%).[7,28] We all know that human body has no effective means for removing iron, hence, using chelators, which are also called as iron binders, are the only way which allow iron excretion through the urine and/or stool. Once the patients have had 10-20 transfusions or when their serum ferritin levels shoot above 1000ng/ml, patients should start iron chelation treatment.[5]

Deferoxamine (DFO) was the first drug made available for treatment. This is an exadetate iron chelator which needs to be administered parenterally as a subcutaneous infusion via a portable pump of 8-12 hours for 5-7 days per week. Recommended dosage depends on the individual's age and the serum ferritin concentration. However, the average dosage for children and adults is 20-40 mg/kg body weight and 30-50 mg/

kg body weight.[5,7] About 40% of iron gets excreted in feces and urine with DFO. DFO therapy prevents the secondary effects of iron overload, resulting in a consistent decrease in morbidity and mortality.[7] But it is also associated with adverse effects like local reactions at the site of infusion, such as pain, swelling, induration, erythema, burning, pruritus, wheals and rash, occasionally accompanied by fever, chills and malaise. The major drawback of DFO chelation therapy is low compliance resulting from complications of administration.[5]

Two other chelators have been introduced into clinical use: *deferiprone* (DFP) and *deferasirox*.

DFP, which is also known as the orphan drug, is an orally active iron chelator. Studies have shown that this is as effective as DFO at doses of 75-100 mg/kg/day.[29] However, DFP therapy too is also associated with some side-effects which include neutropenia, agranulocytosis, arthropathy, and gastrointestinal so, this requires close monitoring. Deferasirox has become recently available for clinical use for thalassemia patients. It is effective in both adults and children and has a defined safety profile that is clinically manageable with appropriate monitoring. Gastrointestinal disorders, skin rash, and a mild, non-progressive increase in serum creatinine concentration are some most common treatment-related adverse events.[29]

Follow-up

A regular follow-up is necessary to monitor the effectiveness of transfusion and chelation therapy. This includes the following:

1. Physical examination of patient every month by a physician who is familiar with the disease.
2. Assessment of liver function tests (serum concentration of alanine transaminase) every 2 months without failure.
3. Every 3 months, serum ferritin concentration determination.
4. For pediatric patients, assessment of growth and development every 6 months

Yearly assessment includes:

1. Ophthalmologic and audiologic examinations.
2. Complete cardiac and thyroid evaluation
3. Evaluation of endocrine pancreas, parathyroid, adrenal, and pituitary function (usually after 10 years).
4. Liver ultrasound evaluation, determination of serum alpha-fetoprotein concentration in adults with hepatitis C and iron overload for early detection of hepatocarcinoma.
5. In adults for accessing osteoporosis, bone densitometry.

Apart from the above said, assessment for liver and heart iron with MRI should be recommended after 10 years of age and also repeated according to the severity of iron overload, transfusion, and chelation regimes.[30]

CONCLUSION

An estimated cost for treating major thalassemia disease is about US $ 3200 per child per year, which is beyond the reach of the majority of families. Management of thalassemics is not only traumatic to the family but also poses a tremendous socio-economic burden on the country making its control and prevention a cause of prime concern. Prevention of the birth of an affected fetus is, therefore, a first priority to reduce the burden of the disease.

Prevention encompasses carrier screening, genetic counseling along with prenatal diagnosis (PND) and abortion of affected fetus. This approach is cost-effective and is proving remarkably successful in reducing the frequency of thalassemia in many countries. For an effective and rapid prenatal diagnosis/genetic counseling, knowledge of the spectrum and distribution of β-Thalassemia mutations in a given population is a prerequisite.

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