Special Correspondence

[We are publishing this Special Correspondence to commemotare World Thalassaemia Day on 8th May]

Thalassaemia

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The thalassaemia are the commonest monogenic disease in human resulting from quantitative defects of globin moiety of haemoglobin. First described by Cooley and Lee in 1925 as a severe form of anaemia presenting with splenomegaly and bone disease. Whipple, a pathologist coined the term thalassic anaemia, later changed to Thalassaemia from Thalassa or 'the sea', because initially all the patients described, were around the Mediterranean sea. Inherited mostly in recessive manner, the homozygous condition ,the severest form called thalassaemia major, the heterozygous condition termed thalassaemia minor and thalassaemia intermedia which is neither too severe to call it major or not to mild to call it minor. The high frequency of inherited haemoglobin variants in certain regions reflects their heterozygote resistance to Plasmodium falciparum malaria. Heterozygosity for α-thalassaemia, β-thalassaemia and haemoglobin E confer protection against this severe form of malaria. Thalassaemia in its different genetic subtypes mostly prevalent in sub-Saharan Africa, through the Mediterranean region and Middle East, to the Indian subcontinent and east and southeast Asia ie, low-income and middle-income countries bear more than 90% burden of the disease. . Gene drift and founder effects are other reasons that thalassemia are most frequent in these areas. The number of patients with these diseases is expected to increase in the coming years as infant mortality from infectious and nutritional causes declines in many regions of the world.

Magnitude of the Problem :

An estimated 7% of the world population carry an abnormal haemoglobin gene, while about 300,000-500,000 are born annually with significant haemoglobin disorders. They consist of two major groups – Thalassemia and Sickle cell syndromes. Sickle cell syndromes are more frequent and constitute 70% of affected births world-wide, the rest are due to thalassemia. The average prevalence of b thalassemia carriers is 3-4% ie, 35 to 45 million carriers out of 1.21 billion people including around 8% of tribal groups according to the Census of India 2011. India has the largest number of children with Thalassemia major in the world – about 1 to 1.5 lakhs and almost 42 million carriers of β (beta) thalassemia trait. About 10,000 - 15,000 babies with thalassemia major are born every year.

Pathophysiology :

Haemoglobin is a globular molecule made up of four subunits. Each subunit contains a heme, an iron-containing porphyrin derivative, conjugated to a polypeptide, globin. Haemoglobin synthesis is controlled by two multigene clusters on chromosome 16 (encoding the α-like globins) and on chromosome 11 (encoding the β-like globins).The genes are arranged in the order that they are expressed during development to produce different haemoglobin tetramers during embryonic, foetal, and adult life. Within the β-globin gene cluster, the ε-gene is expressed only in early embryos and downstream from this gene are two γ-genes, producing foetal haemoglobin (Hb F,$\alpha_2\gamma_2$)—the haemoglobin form that predominates throughout most of gestation. The δ-gene product forms a minor haemoglobin component, Hb A2 ($\alpha_2\delta_2$), which is useful in the diagnosis of the thalassaemias. The β-gene product combines with α-globin to form Hb A ($\alpha_2\beta_2$), the major haemoglobin component of adult red blood cells. During the first month of gestation, embryonic haemoglobins $\zeta_2\varepsilon_2$, $\alpha_2\varepsilon_2$ and $\zeta\gamma_2$ are formed in erythroid cells located primarily in the yolk sac. During the remainder of fetal life, the sites of erythropoiesis gradually shift from the liver and spleen to the bone marrow, with red blood cells mainly containing Hb F ($\alpha_2\gamma_2$). A switch from foetal Hb to adult Hb expression begins in third trimester and completes by the time the baby reaches 6 months of age. After this time over 95% of the haemoglobin in normal red blood cells is adult Hb A ($\alpha_2\beta_2$) with the remaining haemoglobin consisting of two minor components, Hb A2 and Hb F.

Defects at the molecular level in the α-globin or

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β-globin gene clusters form the basis of defective haemoglobin synthesis and the various inherited forms of α-thalassaemias or β-thalassaemias. The type and severity of these clinical forms can also rely on additional and independent intrinsic and extrinsic factors; primary ,secondary and tertiary modifiers. Structural haemoglobin variants like haemoglobin S, C, and E can co-inherit with β thalassaemia thereby producing S/β, C/β and E-β thalassaemias with variable clinical courses.

β-Thalassaemia :

usually present as minor or trait, major and intermedia depending on α-globin or β-globin chain imbalance, severity of anaemia and clinical picture at presentation. Over 300 mutations in the β-globin gene ranging from silent mutations (silent β), to mild mutations that cause a relative reduction in β-globin chain production (β+), to severe mutations with complete absence of β-globin chain synthesis (βo), with deletions of the gene being uncommon.

β-major patients usually presents earlier, approximately 6 months to 2 years of age because á homotetramers in -β thalassemia are more unstable than -β–homotetramers in α-thalassemia and therefore precipitate earlier in the RBC life span, causing marked RBC damage and severe haemolysis associated with ineffective erythropoiesis (IE) and extramedullary haemolysis. Usually major phenotype denotes the homozygous or compound heterozygous forms of the disease, which are characterized by severe anaemia (range, 1-7 g/dL of Hb), haemolysis and massive IE. Presents with severe anaemia characterized by severe pallor, jaundice or growth retardation, accompanied by poor feeding, irritability, decreased activity and/or increased somnolence. Hepatosplenomegaly and In severe thalassemia, IE results in expanded marrow cavities that impinge on normal bone and cause distortion of the cranium, (hair- on- end appearances as seen in skull-x ray) and of facial and long bones. IE, chronic anaemia and hypoxia leads to increased iron absorption from gastrointestinal tract. Transfusion for severe pallor also leads to cumulative iron accumulation (1 unit PRBC contains approximately 225 mg of iron). When serum transferrin saturation exceeds 70%, free iron species, eg, labile plasma iron and pool in RBC increases. These iron species are mainly responsible for generating reactive oxygen species through Fenton's Reaction with eventual tissue damage, organ dysfunction, and death.

β-Thalassaemia minor (trait or carrier) represents the heterozygous inheritance of a β-thalassaemia mutation, with patients often having clinically-asymptomatic-microcytic anaemia requiring no transfusion but genetic counselling. Patients with β-thalassaemia intermedia (TI) can present later in life with mild-to-moderate anaemia and variable transfusion requirements.

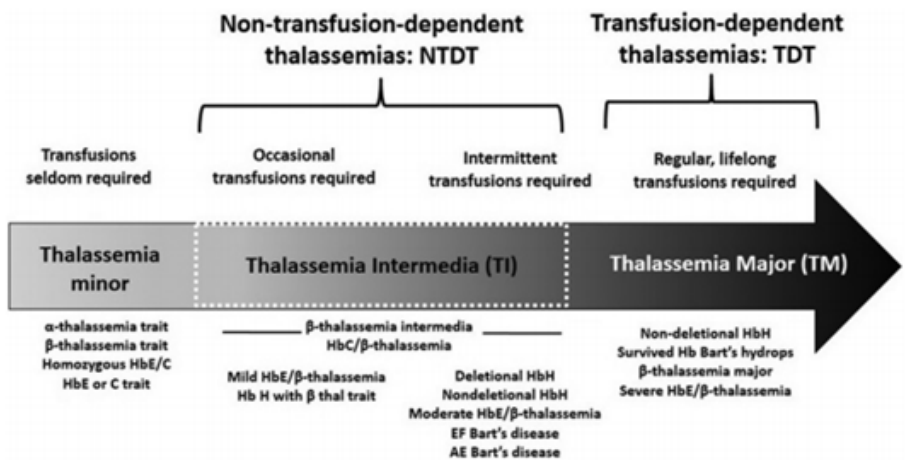
Approximately 10% patients have thalassaemia intermedia phenotypically. Genotypically TI patients may have homozygous or compound heterozygous βo or β+ thalassaemia, homozygous δβ thalassaemia. Concurrent α gene deletion, mutation or triplication or γ mutation may be present with β mutations. Moderate haemolytic anaemia with Hb levels around 7 g/dL without transfusion support is the usual presentation . In TI patients, the clinical phenotypes vary from those with -thalassemia minor to transfusion dependent -thalassemia major (TM). TI patients when require more than 8 units of PRBC annually considered as Major phenotype.

TI patients presents typically at 2-4 years of age, with anaemia, hyperbilirubinemia and hepato-splenomegaly. They have better growth, development, and sexual maturation than TM patients and they typically live longer. The majority of the patients will require episodic transfusions at some point in their lives or when haemolytic or aplastic crises associated with acute infections, folate deficiency, hypersplenism or pregnancy occur. In spite of maintaining Hb more than 7 gm/dl, facial cosmetic defects with depressed nasal bridge and mild malar prominences are usually present. As patients grow older massive splenomegaly with hypersplenism with cytopenia in single or in combination usually occur warranting regular transfusion for improving spleen size and functions and sometimes splenectomy.

In 2012, the new terminology for a clinical classification of thalassemia (TDT and NTDT) was proposed and then adopted by the **Thalassemia International Federation** in their recent guidelines and publications:

α-thalassaemia :

α-Thalassaemia has two main forms, αo-thalassaemia and α+ -thalassaemia and their classifications depend on whether one or both of the linked α-globin genes are deleted or reduced in activity by mutation. The two common forms of α+ -thalassaemia are designated $-\alpha^{3,7}$ and $-\alpha^{4,2}$ to describe the lengths of the underlying deletions. α+ -Thalassaemia result from point mutations, the most common being caused by the chain-termination mutant haemoglobin Constant Spring, designated αCSα. They in heterozygous state are silent and in homozygous state usually present with mild



hypochromic anaemia.

The compound heterozygous states for α+ -thalassaemia and αο -thalassaemia, –α/— or αCSα/—, result in a large excess of β-chain production with the formation of β4 tetramers, known as haemoglobin H. These β4 tetramers are a highly unstable variant of the β-chain and precipitate in RBC causing haemoglobin H disease, characterised by variably severe haemolysis and consequent anaemia. The homozygous state for αο -thalassaemia, —/—, results in the production of tetramers of γ-chains (γ4) known as haemoglobin Bart's. This homozygous state of αο -thalassaemia is associated with a condition called haemoglobin Bart's Hydrops fetalis, which is usually characterised by death in utero or just after birth. Rarer causes of α-thalassaemia include deletions or mutations of regulatory mutations involving the α-globin gene cluster.

Another group of α-thalassaemias that, unlike those described above, occur in no particular ethnic groups: α-thalassaemia and mental retardation; ATR-16 syndrome and ATRX syndrome. Mutation of this ATRX gene sometimes seen predominantly in male patients with mild HbH disease associated with myelodysplastic syndrome.

α-thalassemia usually suspected based on factors, such as a family history of anaemia and geographic and ethnic background where α-thalassemia is common. The diagnosis is suspected in the presence of microcytic hypochromic anaemia not because of iron deficiency, with normal HbA2 levels in Hb electrophoresis. Silent carriers of α-thalassemia and/or α-thalassemia trait are in general clinically asymptomatic and may present with either normal blood count and morphology or with mild microcytic hypochromic anaemia.

Screening and Diagnosis of Thalassemia :

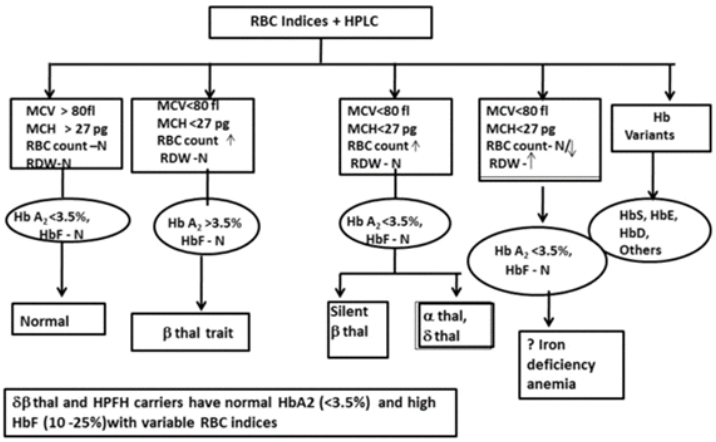
The screening and diagnosis for thalassemia can be divided into 2 levels—population and individual—in which different approaches have been implemented due to different objectives of screening.

Screening Tests for Thalassemia Carriers in a Population Based Approach :

The main purpose of screening for thalassemia carrier status is to identify couples at risk of having offspring with severe thalassemia diseases, such as β-TM, Hb E/β thalassemia, and Hb Bart's hydrops fetalis as the first part of a prevention and control program for thalassemia syndromes.

Diagnosis of Thalassaemia :

(1) Peripheral blood smear : Typical RBC morphology in thalassemia disease shows microcytosis, hypochromia, anisocytosis (variation in cell size) and poikilocytosis (variation in shape). Anisopoikilocytosis results from various abnormal RBC morphology including schistocytes, microspherocytes, target cells, polychromasia, and nucleated RBCs (erythroblasts). nRBC increase proportionately with degree of anaemia and markedly after splenectomy. A



Courtesy : R. Colah et al. / Pediatric Hematology Oncology Journal 2 (2017) 79-84.

characteristic finding is the presence of severe hypochromic, wrinkled and folded cells (leptocytes) containing irregular inclusion bodies of precipitated α-globin chains.

(2) Haemoglobin analysis : Several platforms available for Hb analysis including Hb electrophoresis using cellulose acetate membrane (at pH 8.6), acid agarose (at pH 6.0) or citrate agar gel, isoelectric focusing, low-performance liquid chromatography, high performance liquid chromatography (HPLC) and capillary electrophoresis.

HPLC provides an automated system with a good resolution to discriminate different Hb species. HPLC has been widely adopted worldwide and standard library of Hb variants help making presumptive diagnosis of thalassemia and Hb variants. However, HPLC has a limitation in detecting and quantifying the % of Hb Bart's and Hb H based on their widely used b-thal short program; In addition, it could not separate Hb A2 from Hb E; therefore, these 2 Hb species are eluted into the same retention time and the interpretation of Hb E traits and homozygous Hb E are based on the summation of both Hb E and Hb A2 percentages. Recently introduced a new capillary electrophoresis platform can overcome these problems. Hb E can be separated from Hb A2, and thus can distinguish between homozygous Hb E and Hb E/b-thalassemia.Also detection and quantification for Hb Bart's, Hb H, Hb CS, and Hb Q-Thailand (combined deletion and point mutation on the same allele) for both disease conditions and heterozygotes can be done.

(3) DNA or molecular analysis : These are the most definitive diagnostic modalities. Mutation-specific detection and genome scanning are the two main categories commonly used. Molecular techniques used commonly to detect known mutations, are GAP-PCR using conventional or real-time detection (for gene deletions or insertions), allele-related mutations specific PCR, reverse dot blot hybridization or array-based detection, mismatched-PCR restriction fragment length polymorphism and analyses of a high-resolution melting curve (for point or small nucleotide changes). Although cost effective it cannot detect unknown or rare variations, which might not be included into the panels. Genome scanning (by denaturing gradient gel electrophoresis, denaturing HPLC or single strand conformation polymorphism) and direct sequencing of the whole globin genes would be useful in such situations. Molecular analysis are required only in selective cases but they are very much useful in predicting clinical severity and play important role in thalassaemia control and prevention programme because the mutation data would be required for genetic counseling, genetic risk calculation in the offspring and prenatal and preimplantation genetic diagnosis.

Treatment of Thalassaemia :

Ineffective erythropoiesis, chronic haemolytic anaemia, compensatory hemopoietic expansion, hypercoagulability, and increased intestinal iron absorption are the hallmarks of thalassemias due to the a/b globin chain imbalance and are responsible for several clinical complications.

Thalassaemia Intermedia :

As mentioned previously they are of two clinical types: Non Transfusion Dependent (NTDT) and Transfusion Dependent(TDT). NTDT Patients require episodic transfusions In situations of stress eg, pubertal growth spurt, pregnancy etc. TDT patients are phenotypically like Thalassaemia Major requiring regular transfusions. Although NTDT patients do not get regular transfusions, due to presence of age related chronic anaemia they absorb gastrointestinal iron and iron overload is a recognised complication in them. Serum ferritin to be estimated although above 500µg/L they are not good indicator of iron overload. To overcome this, liver iron concentration (LIC) by liver biopsy(rarely done now-a days due to its invasiveness) or by the more recently applied non-invasive T2* magnetic resonance imaging (MRI) beginning in late childhood or early adolescence should be done.

Extramedullary haematopoiesis, hepatic fibrosis, hypercoagulability, pulmonary hypertension, bone diseases, leg ulcers and cardiac dysfunctions are seen in greater frequencies in comparison to major patients. So these are to be monitored accordingly.

Thalassaemia Major -Treatment Strategies :

Clinical manifestations appear in infancy and include severe anaemia characterized by severe pallor, jaundice or failure to thrive, accompanied by poor feeding, irritability, decreased activity and/or increased somnolence. Hepatosplenomegaly and haemolytic facies. Depending on clinical presentation and laboratory reports decision for initiating transfusion is taken. Poor growth, facial or bone abnormalities and Hb <7 gm/dl are indicator for starting transfusion. Folic acid deficiency and acute febrile illness, blood loss or coinheritance of G-6PD deficiency, need to be addressed before and simultaneously with transfusion therapy. Before first transfusion, patient's RBC should be typed for Rh, ABO antigen and if possible extended panel antibody screening to be done. Parents and First degree relatives should not be donors. Vaccination

against Hepatitis B should be given. For minimising transfusion reactions leucodepleted RBC are preferred, sometimes with bedside leucofilters.

If cardiac failure present then smaller aliquots of RBCs (5 mL/kg) should be administered to prevent volume overload until the Hb level is gradually increased to 9 g/dL. Once a pretransfusion Hb level 9-10 g/dL is achieved, transfusions are administered monthly in infancy and subsequently at 2- to 4-week intervals. In clinically stable patients, 8-15 mL RBCs per kg of body weight can be infused over a span of 1-2 hours at each transfusion event. A record of weight, the amount of blood transfused at each visit and the pretransfusion Hb level is needed to calculate the annual transfusion requirement so that hypersplenism can be diagnosed and decision regarding splenectomy can be taken.

Clinical Complications and Management :

Iron Overload and iron chelation — In TM and TI patients, the rate of transfusional and GI tract iron accumulation is generally 0.3-0.6 mg/kg per day. Ineffective erythropoiesis, haemolysis and severe pallor down-regulate the synthesis of **hepcidin**, a protein that controls iron absorption from the GI tract and increases release of recycled iron from macrophages resulting in increased iron absorption from gut. So Iron overload is an evitable complication in thalassaemia and responsible for many of the clinical complications. Appropriate treatment for combating this iron overload is very important.

3 major classes of iron chelators: hexadentate (deferoxamine [DFO], in which 1 atom of iron is bound to 1 DFO molecule; bidentate (deferiprone, L1 [DFP]), in which1 atom of iron is bound to 3 DFP molecules; and tridentate (deferasirox [DFX], in which 1 atom of iron is bound to 2 DFX molecules presently available.

DFO, with its very short half-life of 8-10 minutes, requires intravenous or subcutaneous parenteral administration. Maintaining normal ascorbic acid levels optimizes DFO iron excretion. The starting dose is 30-40 mg/kg per day for daily use 5-7 days each week in regularly transfused patients. Chelation generally begins between 2 and 4 years of age, after 20-25 RBC units are transfused, with a serum ferritin level 1000 g/dL and an LIC 3 mg Fe/g dry weight. Depending on the efficiency of chelation dose can be gradually escalated to 50 mg/kg and subsequently to 60 mg/kg in adolescents and adults. Before starting and thereafter annually fundal examination and audiometry should be done to avoid ocular and auditory toxicities. **DFP (L1)** is a synthetic compound, absorbed by the GI tract with plasma half-life of 1.5-4 hours. The recommended daily dose is 75 mg/kg per day, which can be increased to 100 mg/kg per day, given orally in 3 divided doses with meals. It removes intracellular iron, and also iron from the heart, improving cardiac function, and preventing iron-induced cardiac disease. The sequential combination of DFP and DFO has an additive chelating effect. The "shuttle hypothesis" suggests that intracellular iron chelated by DFP may be transferred to DFO, a stronger chelator, in the plasma. Subsequently, DFP may renter cells to bind with more iron, inducing greater iron excretion. Agranulocytosis (1%) is a potential risk factor; Weekly blood count monitoring is mandatory for avoiding this.

DFX (Deferasirox), most recently approved (2005) oral iron chelator, highly bioavailable that is absorbed in the GI tract. Because of its relatively long half-life of 12-18 hours, it is prescribed once a day and to be taken in empty stomach. Daily use of a single oral dose of 20-30 mg/kg per day. DFX is also effective in the removal of cardiac iron in hyper transfused rats and TM patients with abnormal MRI T2* cardiac iron. combination of DFX with DFO results in additive iron excretion.

Serum ferritin and creatinine levels and liver function should be monitored closely. Withholding or discontinuation of DFX may be required in cases of unexplained transaminase elevation or progressive increase in serum creatinine or progressive GI symptomatology. In pregnancy who require iron chelation it is recommended to delay chelation until the second trimester and to use subcutaneous DFO. DFX is not approved for use during pregnancy.

Cardiac Complications :

Primary cause of mortality in TDT and to a lesser extent morbidity in patients with NTDT. Cardiac iron deposition occurs mainly in the ventricle, more in the epicardium. Free labile iron interacts with calcium channels and leads to impaired myocardial contractility.

In NTDT, Cardiac iron overload may also affect the conduction system of heart and responsible for conduction delays and heart block. Supraventricular arrythmia particularly atrial fibrillation can be symptomatic requiring prophylactic drug treatment (often with beta-blockers). In uncontrolled or persistent AF, antiarrhythmic therapy and rhythm control with amiodarone and in refractory cases Catheter ablation may be required. Anticoagulation is generally recommended in the presence of AF, heart failure or if the medical history is positive for stroke. Long-term amiodarone therapy may cause hypothyroidism; therapy can often be terminated after 6 to 12 months. MRI T2* is a good tool for arrhythmia prediction.

Cardiac function to be monitored annually beginning at 7 or 8 years of age by ECG, echo, 24-hour Holter monitor and recently by cardiac T2* MRI, which can detect preclinical cardiac iron accumulation. Benign pericarditis, possibly caused by viral and mycoplasmal organisms, bacterial or fungal infections or associated with the engraftment syndrome in post transplantation thalassaemic patients. Pericarditis managed with bed rest and aspirin. Steroids may be helpful with engraftment syndrome and iron chelation with hemosiderosis.

Liver Disease :

Liver is involved in several ways: Transfusion related viral hepatitis with HCV & HBV, secondary haemochromatosis, as a site of extramedullary haematopoiesis and drug induced hepatitis (eg, DFX). In thalassemia patients HBsAg postivity ranges from 0.3% to 5.7% with a higher prevalence of chronic HBV infection in Asia and Southeast Asia countries; Anti HCV antibodies detected in 4.4% to 85.4% of patients In single or concomitant presence of more than one risk factor in a particular patient cause progression of liver fibrosis at an accelerated rate. Chronic liver disease complicated by cirrhosis and ultimately Hepatocellular Carcinoma (HCC), an increasing presentation due to prolonged survival. But assessment of liver fibrosis by noninvasive transient elastography(TE), availability of MRI T2* and good iron chelator as well as effective antiviral drugs and close monitoring can check these hindrances.

Managing Endocrinopathies :

Endocrine complications are very common in thalassaemia patients particularly who are inappropriately iron chelated. The anterior pituitary gland is vulnerable to iron related free radical damage. TDT patients are more prevalent for endocrine complications than NTDT patients. Hypogonadotropic hypogonadism (HH) is the most frequent endocrinopathy encountered ranging from less than 50% to 100%. Iron-induced damage to the hypothalamic pituitary axis can cause delayed pubertal growth and sexual development. Therefore, annual endocrine evaluations are recommended, including measures of pancreatic, thyroid, parathyroid, gonadal function and bone health with nutritional counselling.

Tanner staging should be performed every 6 months in the prepubescent child. For assessment of skeletal maturation annual bone age films and for early detection of growth failure and sexual development monitoring for luteinizing hormone, follicular stimulating hormone, insulin-like growth factor and insulin-like growth factor binding protein-3 from 8-10 years of age should be done. If pubertal changes have not developed by 13 years of age in females, or 16 years of age in males, the use of GnRH and gonadal steroids may be necessary.

Glucose intolerance and Diabetes mellitus can be seen in 20% to 30% of adult patients with β-thalassemia. Starting at 8-10 years of age, annual GTT for the early detection of insulin resistance is recommended to identify prediabetic or diabetic states who may be benefitted from metformin or insulin treatment. For assessment of glycaemic status in these patients fructosamine test is preferred over HbA1C estimation because of alteration of Hb balance.

Bone Disease :

Osteopenia and osteoporosis and increased risk of fractures are almost universal complications of patients with thalassemia, involving both TDT and NTDT, can be more severe in patients with NTDT. Endocrinopathies, iron related toxicities on osteoblasts, chelating agent toxicity (DFO) and Vit D deficiency are some of the contributing factors. Bone Mineral Density (BMD) measured with bone densitometry and calculating Trabecular Bone Score (TBS) by reanalysing spine densitometric images and converting them into a numeric value provides information regarding bone structure. The current treatment of patients with bone disease includes vitamin D and Ca supplementation and bisphosphonates therapy. Recently also denosumab (RANKL inhibitor) and anabolic teriparatide have been introduced for treating osteoporosis in these patients. Also maintenance of optimal Hb level, treatment of concurrent endocrinopathies and promotion of physical activity and smoking cessation are also integral part of the management of bone diseases.

Hypercoagulability :

Thalassaemia patients particularly NTDT and splenectomised ones are prone for hypercoagulability. Low levels of protein C and protein S as well as thrombocytosis and platelet activation, damaged RBC, endothelial injury are contributing factors. Both venous and arterial events, including infrequent thrombotic events in the brain,(5-9%) have been reported. The prevalence of thrombotic events can reach up to 20% in patients with NTDT compared with less than 1% in patients with TDT.

Pulmonary Hypertension(PH) defined as an increase in mean PAP of 25 mm Hg or greater is one of the most significant cardiovascular finding and the main cause of heart failure in NTDT. Endothelial dysfunction, NO depletion following chronic

haemolysis, increased vascular tone, inflammation, hypercoagulability and finally vascular remodelling are underlying pathophysiology. The use of prophylactic antithrombotic therapy for high-risk NTDT patients during surgery, immobilization, and pregnancy, should be considered, as should the use of antiplatelet aggregating agents for patients with thrombocytosis. For PH no prospective RCT in patients affected by NTDT are available for guiding the treatment. Sildenafil citrate, a potent inhibitor of cGMP–specific phosphodiesterase-5, Bosentan, an endothelin receptor antagonist, and epoprostenol, a prostacyclin analogue have shown promising results. However, until now, there are no recommendations regarding if, when or for whom prophylactic antithrombotic treatment is indicated.

Other Complications :

Ineffective erythropoiesis, the hallmark of untreated thalassemia, may cause the expansion of the hematopoietic tissue leading to Extramedullary Haematopoietic (EMH) masses. This is more common in patients with NTDT in whom the reported prevalence is around 20% compared with less than 1% in patients with TDT. Although any body sites may be involved the paraspinal involvement, (11% to 15%) may cause spinal cord compression and paraparesis, which is to be treated on emergency basis Transfusions, hydroxyurea and in some instances, radiation are the management approach to control extramedullary hematopoietic masses.

Cholelithiasis, leg ulcers are among some other complications not infrequently encountered.

Role of Splenectomy :

The therapeutic rationale for splenectomy, particularly in patients with growth retardation and poor health, is to protect against the development of EM haematopoiesis by improving the Hb level, decreasing the transfusion requirement and iron overload. Presently splenectomy done in case of Increased pRBC transfusion requirement > than 200 to 220 mL RBCs/kg per year with a haematocrit of 70%. Hypersplenism ,massive splenomegaly interfering with daily life activities are other indications. Laparoscopic (preferred) or open splenectomy usually done.

Splenectomy should be avoided in less than 5 years of age and should be vaccinated against H influenzae, Pneumococcus, meningococcus as spleen is the site for production of properdin and tuftsin, opsonins responsible for opsonisation of encapsulated bacterias and oral penicillins following splenectomy.

Prevention :

Prenatal diagnosis — Prevention of severe β or α thalassemia births by prenatal diagnosis by CVS (9-12 weeks) or amniocentesis (14-16 weeks) with termination of pregnancies is important way in reducing thalassaemia burden. Acceptance of prenatal diagnosis and termination of affected foetuses are dependent on the early identification of couples at risk, culturally sensitive genetic counselling, the cost, and religious beliefs and it is one of the most difficult ways in addressing the disease.

Cure :

Hematopoietic SCT — allogeneic SCT is the only curative strategy available. Donor selection is of utmost importance; The best results obtained with HLA-matched siblings. Matched unrelated donor or Cord blood are other options. Several risk factors, including hepatomegaly > 2 cm, portal fibrosis and inadequate iron chelation therapy, that can influence the outcome of SCT. Patients are typically classified into 3 risk groups: class 1, those with no risk factors; class 2, those with 1 or 2 risk factors; and class 3, those with all risk factors.

Upcoming Therapies:

Foetal Hb inducing agents- Hydroxyurea, metformin beneficial in reducing transfusion requirement by increasing HbF and total Hb. Foetal globin reactivation by BCL11a inhibitor, Ineffective Erythropoiesis Signalling Modulators (Luspatercept (ACE- 536) and sotatercept (ACE-011) by interfering with signalling molecules in the TGF-β family, such as BMP4, GDF11, and GDF15 showed promising results. Jak2 inhibitor, ruxolitinib and hepcidin mimetics (LJPC-401) are undergoing trial which may in future emerge as promising agents.

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