PAINFUL THALASSEMIA : A REVIEW

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Introduction

The term Thalassemia is a disorder, mainly prevalent among Mediterranean people, and was responsible for its naming. 'Thalassa' is a Greek word for the 'Sea', and 'Haema' is for 'blood'. It was first identified by Cooley and Lee (1925), hence named 'Cooley' s Anaemia'.Thalassemia is an inherited blood disorder, passed down through generations through genes. The disorder is a result of the failure of formation of haemoglobin in red blood cells and consequently is causing anaemia (Forget and Cohen, 2005). Normally, red blood cells survive for 120 days but inThalassemia, red blood cell survival is reduced.Thalassemia is actually an inherited autosomal co-dominant disorder. In this, the genetic defect results in reduced rate of synthesis of one of the globin chains that make up of haemoglobin. The most clinically relevant are alpha (á) and beta (â) thalassemias, which are caused by mutation in globin gene cluster. These defects include mutations usually have geographic and ethnic distribution.

The normal adult haemoglobin molecule is made up of two parts – 'heme' and 'globin'. 'Heme' is a porphyrin containing iron and 'Globin' is made up of four polypeptide chains of two types – Alpha (á) and Beta (â). Thus, each globin molecule is made up of two alpha and two beta chains. This haemoglobin is called haemoglobin A (Hb A) because this forms the major part of haemoglobin found in adults. In adults, there is another small fraction of haemoglobin called haemoglobin A_2 (HbA_2), the globin portion of which is made up of two á and two delta (ä) chains (Shah, A., 2004).

The â – globin chain of Hb A and ä-globin chain of HbA_2 differ only by ten amino acids in the sequence. Normally the concentration of HbA_2 is less than 3.5 per cent of the total Hb. During fetal life, the major portion of Hb is fetal haemoglobin (Hb F). The globin of which is made up of two á chains and two gamma (ã) chains. The concentration of HbF falls after birth and in adults

HbF is less than 2-3 per cent of total haemoglobin (Shah, A., 2004 and Sarnaik, 2005). In fact the type of haemoglobin varies during the foetal life and that of the adult. There is a genetic regulation that during the foetal life HbF is synthesised and among adults HbA replaces HbF.

The thalassemia syndromes are heterogenous group of inherited anemias characterised by defects in the synthesis of one or more of the globin chains (Weatherall and Clegg, 1981).

- Production of structurally normal, but decreased amounts of globin chains – the thalassemias (Sarnaik, 2005).
- Production of structurally abnormal globin chains – e.g. Hb S, Hb C, and Hb E (Sarnaik, 2005).
- Failure to switch globin chain synthesis (Sarnaik, 2005).

The thalassemias are classified according to the affected chain of the haemoglobin molecules. The á-globin chain is affected in á-thalassemia and in â-thalassemia, the production of â-globin is affected. The á-globin gene cluster is located very close to the telomere of the short arm of chromosome number 16 whereas â-globin gene cluster has locus on the distal end of the short arm of chromosome number 11 (Antonarakis *et al.*, 1982; Turn *et al.*, 1985; Wilkie *et al.*, 1991). Thus in a normal person with two copies of each chromosome, there are two loci encoding the â chain, and four loci encoding the á-chain. As â-globin chains are encoded by single gene on chromosome 11; á-globin chains are encoded by two closely linked genes on chromosome 16 (Low, 2005).

Types

The various types of thalassemia have specific names related to the severity of the disorder. Both alpha and beta thalassemias are of major thalassemia and minor thalassemia type. Thalassemia minor occurs if one receives the defective gene from either mother or father only. Thalassemia minor is asymptomatic and hence this condition is called as carrier. If an individual inherit the defective genes from both parents then thalassemia major develops.

Alpha Thalassemia

Alpha thalassemia involves the genes HBA_1 and HBA_2 inherited in a Mendelian recessive fashion. It is also connected to the deletion in the short arm (p) of the 16th chromosome (OMIM). This results in decreased á- globin production, therefore, fewer alpha globin chains are produced, resulting in an excess of â-chains in adults and excess of ã-chains in newborns. The excess of â-chains form unstable tetramers (HbH of â-chains) which have abnormal oxygen dissociation curves i.e., reduced capacity to carry oxygen.

Homozygote á°(alpha Zero) thalassemias, where there is lots of $ã_4$ chains but no á-globin at all (Hb Bart's), often results in still birth (Steensma et al., 2005).

- In á -thalassemia silent carrier, one of the four á loci is affected.
- In á -thalassemia minor, two of the four á loci are affected. It is also called á -thalassemia trait.
- When three loci are affected, the haemoglobin-H (HbH) disease occurs. This

disease rises from interaction of á + and á° determinants and patient have moderate anemia.

- á -thalassemia major develops when all four loci are affected. It is also called hydrops fetalis or Hb Bart's disease in which fetus cannot survive and mostly dead at birth (Low,2005; Higgs, 1993; and NHLBI, 2008).

Beta Thalassemia

â - thalassemia occurs when a defected gene affects the production of beta-globin chain of the haemoglobin protein, due to mutations in the HBB gene on chromosome 11, (OMIM) also inherited in an autosomal recessive fashion. The severity of the disease depends on the nature of the mutation. Mutations are characterised as $â^0$ (beta zero) if they prevent any formation of â chains; they are characterised as â+ (beta positive) if they allow some â chain formation to occur. In either case, there is a relative excess of á -chains, but these do not form tetramer. They bind to the red blood cell membranes, producing membranes damage, and at high concentrations they form toxic aggregates (NHLBI, 2008).

In â -thalassemia minor, only one â -globin allele bears a mutation. It is also called â -thalassemia trait. This is a mild microcytic anemia. In most cases â -thalassemia minor is asymptomatic, and many affected people are unaware of the disorder. The patient will have an increased fraction of HbA_2 (→2.5 per cent) and a decreased fraction of HbA (←97.5 per cent).

In â -thalassemia major, both of the â -chains are affected and results in severe microcytic, hypochromic anemia, which lead to death before age twenty if not treated properly and in time (Weatherall, 1967 and Thein, 1993).

â -Thalassemia Intermedia: It is a condition intermediate between the major and minor forms. Affected individuals can often have moderate type of anemia, and individuals can manage a normal life but may need occasional blood transfusions, for examples at times of illness or pregnancy, depending on the severity of the case (Low, 2005).

Delta Thalassemia

Similar to that of á and â (globin) chains being present in haemoglobin, about 3 per cent of adult haemoglobin is made up of alpha and delta (ä) chains. Just as with beta thalassemia, mutations can occur which affect the ability of this gene to produce delta-chains. A mutation that prevents formation of any delta chain, termed as delta zero (ä°) mutation (Low, 2005).

- When an individual inherits two delta zero mutations, no HbA_2 ($á_2ä_2$) can be formed.
- Individuals who inherit only one delta thalassemia mutation gene, will have a decreased HbA_2.

  Thalassemia can co-exist with some other haemoglobin opathies or haemoglobin variants (Debaun and Vichinsky, 2007). The most common of these are as follows:
- HbE/thalassemia; common in Combodia, Thailand and parts of India; clinically similar to â -thalassemia major or thalassemia intermedia (Fucharoen *et al.*, 2000).
- HbS/thalassemia; common in African and Mediterranean populations; clinically similar to sickle cell anemia.

- HbC/thalassemia; common in Mediterranean and African populations; HbC/â^{0}-thalassemia causes a moderately severe hemolytic anemia with splenomegaly; HbC/â$^{+}$ thalassemia produces a milder disease (Low, 2005; Angastiniotis and Modell, 1998).

Prevalence

Thalassemias are common autosomal recessive disorders especially in populations of Mediterranean, Middle Eastern and Far Eastern descent. Relatively high incidence is also observed in people of Asian Indian origin but the incidence is more limited in those of African descent (Cao *et al.,* 1997). In India the majority of â -thalassemia carriers were migrants from Pakistan and their pattern of mutations differed from the subjects of Punjab, Haryana and Uttar Pradesh (Verma *et al.*, 1997). Region-wise and Caste-wise analysis showed the highest prevalence of á -thalassemia among the Punjabi population originating from Northern region of India (Nadkarni *et al.*, 2008).

Signs and Symptoms

The most severe form of á -thalassemia major causes still at birth i.e., death of the unborn baby during last trimester of pregnancy. Children born with thalassemia major are normal at birth, but develop severe anemia during the first year of life. Other symptoms can include as follows:

Spleen enlargement

The spleen is an organ that helps your body to fight with infections and remove unwanted material. When a person has thalassemia, the spleen has to work very hard. As a result, the spleen becomes larger than normal.

Growth failure

The child becomes weak and lethargic with poor appetite, height, weight and the overall development is abnormal.

Bone deformities

Specially in case of bone marrow expansion, an attempt to compensate for excessive ineffective erythropoesis causes marked skeletal deformities with frontal bossing, cheek bone and jaw protrudes. Also distortion of ribs vertebrae and pathological fracture of long bones can be seen in thalassemic patients.

- Paleness and restlessness accompanied with symptoms of Jaundice
- Headache
- Fatigue
- Also the shortness of breath occurs.

Thalassemia minor is generally asymptomatic.

Clinical Complications

Heart and Liver Diseases

Cardiac complications remain the most important in determining the survival of â -thalassemia major patients (Brittenham *et al.*, 1994 and Piga *et al.*, 1997). Myocarditis, pulmonary hypertension can be related to iron overload in adult patients. Cardiac disease causes death in developed countries as a result of non-compliance to

desferoxamine from the third decade of life. With the emergence of advanced cardiac magnetic resonance imaging technique, the early diagnosis can be possible and survival of patients can be improved (Wonke, 2001).

- Blood of â – thalassemia patients remain chronic hyper-coaguable state with increase incidence of thromboembolic episodes. It is common in thalassemia intermedia patients. Patients had high plasma levels of markers of coagulation and fibrinolysis activation. Also their erythroid precursors had an enhanced capacity to generate thrombin (Cappellini *et al.*, 2000; Panigrahi and Agarwal, 2007).

Infections

Thalassemic patients have an increased risk of infections because of splenectomy, iron load and blood borne infections, particularly viral. Bacterial infection mainly *Yersinia enterocolitica* infection is suspected with other clincial symptoms (Adamkiewicz *et al.*, 1998). The blood borne viral infections, particularly Hepatitis B and C and more recently HIV have relatively high frequency in transfusion dependent â -thalassemia patients (Shad and McHutchinson, 2001).

Endocrine dysfunctions

- Delayed Puberty and defective functions of gonads or failure of whole hypothalamic pituitary gonadal axis (Beshlawy *et al.*, 2007).
- Diabetes Mellitus is also relatively common complication in patients who have been inadequately iron chelated (Chern *et al.*, 2001; Dmochowski *et al.*, 1993; Ladis *et al.*, 1998).
- â - thalassemic patients also deals with fertility problems. Most of patients in their second and third decade of life apparently well feeling, are asking for help with fertility related problems (Skordis *et al.*, 1998).
- Osteoporosis represents an important cause of morbidity in adult patients with thalassemia major. The pathogenesis of osteoporosis in thalassemia major is multifactorial and includes bone marrow expansion, endocrine dysfunction and iron overload. In this, the diminished osteoblast function is accompanied by a comparable or even greater increase in osteoclast activity (Voskaridou and Terpos, 2004).

Psychological Problems

Due to growth failure and other complications, thalassemic patients oftenly seem to be emotionally disturbed. Also some of the patients reported with X-linked alpha thalassemia/mental retardation Syndrome (ATR-X). It is a syndromic form of X-linked mental retardation. The ATR-X syndrome accompanied by severe psychomotor retardation, minor facial anomalies, genital abnormalities and an unusual form of á-thalassemia (Gibbons *et al.*, 1995; Wada *et al.*, 2005; McPherson *et al.*, 1995). Depression regarding the future, Illness and finances can also be seen in thalassemic patients (Shaligram *et al.*, 2007).

Sociological Problems

Sociological problems also occur with psychological problems in thalassemic patients.

The problems like failure in adjustment with family and friends are occurred due to abnormal growth and body image especially during adolescence. Economic burden may be arise due to poor family conditions and low educational status. Thalassemic individuals have to deal with problems of fertility and reproducibility, so marital life, of Thalassemic individuals get miserable (Anastasopoulos, 1996; Palma *et al.*, 1998; Khurana *et al.*, 2006 and Ratip *et al.*, 2003).

Diagnosis

- At the diagnosis protocol includes spleen enlargement.
- Complete Blood Analysis—A complete blood analysis of the thalassemic individual should be done to check the following abnormalities which can occur in red blood cells:
- A. Red blood cells appear small and abnormally shaped when looked under microscope
- B. Haemoglobin level can be decreased
- C. A Complete Blood Count (CBC) reveals mild anemia.
- D. Platelet count can also be lower down.

Electrophoresis: A larger number of haemoglobins are identified by electrophoresis. System is very convenient, can be adopted for identification of other haemoglobin (Hb) variants like HbF, HbD, HbE, HbS etc. and for globin chain analysis. With this, the elevated level of HbA_2 can be detected (Sachdeva *et al.*, 2002).

Polymerase Chain Reaction (PCR): A reliable, single-tube multiplex PCR assay have developed for the 6 most frequently observed determinants of á -thalassemia. The assay allows simple, high throughout genetic counselling or screening for the common hematological disorders (Chong *et al.*, 2000).

High Performance Liquid Chromatography (HPLC): It is convenient , efficient, reproducible and cost-effective method for screening and diagnosis of thalassemia (Precisely HbA_2 and HbF) and other haemoglobinopathies like, HbF, HbA_2 HbD, HbE, Hbs and á -thalassemia. With the help of HPLC technique percentage of variants present in the blood can be detected very easily.A test called Mutational Analysis can help to detect á -thalassemia that cannot be detected with haemoglobin electrophoresis.

Treatment and Medication

Thalassemia minor do not require any specific treatment. In Thalassemia major, patients require treatment like regular 'Blood Transfusions' when the haemoglobin level lower down than 8 g. To maintain the Hb level above 10g is the mainstay of treatment. Since the deficiency in thalassemia is that of red cells, only packed red cells and not whole blood should be transfused. Blood transfusions are usually require in every 2-5 weeks, to maintain the pre-transfusion Hb level above 9-10.5g/dl. The decision to initiate life-long transfusion therapy should be based on a definitive diagnosis of severe thalassemia, taking into account the molecular defects, the severity of anemia on repeated measurement, the level of ineffective erythropoiesis and clinical criteria such as failure to thrive or bone changes. (Shah, A., 2007).

Splenectomy is indicated when hypersplenism sets in, as indicated by increase in the transfusion

requirements. Splenectomy may also be done if massive enlargement of the spleen produces intolerable discomfort. It increases the risk of serious infections and hence should be avoided till 6 years of age (Viens *et al.*, 1998).

Chelation Therapy: Iron overload is an inevitable and serious complication of long-term blood transfusion therapy which requires adequate treatment in order to prevent early death mainly from iron induced Cardiac disease. It has been clearly shown that optimal Chelation therapy extends complication-free survival (Brittenham *et al.*, 1994; Anderson *et al.*, 2002; Piga *et al.*, 2003).

Stem cell transplantation: It may be called as bone-marrow transplantation which can cure â -thalassemia major. In this, affected children can received a transplantation from a family donor or HLA identical sibling donor (Orofino *et al.*, 2003). Allogenic haematopoietic stem cell transplantation is the only cure for the patients with haemoglobinopathies. Results of transplants have steadily improved over the last few decades due to effective control of transplant-related complications and development of new preparative regimens (Gaziev and Lucarelli, 2003; Piga *et al.,* 1997; Lucarelli *et al.*, 2002).

Gene Therapy or Genetic Engineering: Gene therapy is being tried by replacing the defective gene with normal functional gene. The concept of introducing genes into human cells for therapeutic purposes developed nearly 50 years ago as diseases due to defects in specific genes were recognised. The Hb disorders, an early target for gene therapy, have proved particularly challenging. Although ongoing research is yielding new information that may ultimately lead to successful clinical trials (Nienhuis, 2008).

Prevention

The most important concern of the thalassemia eradication programme should be its prevention.

Programmes of prospective Carrier screening and genetic counselling of â -thalassemia among couples planning marriage, pre-conception, or during early pregnancy are ongoing in several at risk populations. Carrier detection is carried out by haematological analysis followed by mutation detection by DNA analysis. The pregnant women can be screened using the single tube osmotic fragility test and prenatal diagnosis can accomplished by mutation analysis on PCR amplified DNA from chorionic villi. These programmes have been very effective due to education programmes, because awareness generation is still a primary requisite to make women register early at antenatal clinics and bring their spouses for screening when required (Cao *et al.*, 2002; Colah *et al.*, 2008).

Conclusion

Management of â -thalassemia is very expensive, arduous and painful as frequent blood transfusions are required, with possible risk of blood transmitted infections. Iron overloading in liver, heart and endocrine glands results, leading to their dysfunction, requiring expensive chelating agents for its removal. It is, therefore, necessary to prevent the birth of affected children by prenatal diagnosis, to reduce the socio-economic pressure on the family and burden of the disease on community. So, screening, genetic counselling , awareness and prenatal diagnosis are essential to control this dreaded and painful genetic disorder.

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