e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

BETA-THALASSEMIA

Janya Gehlot*1

*1Grade 11 Student, Bodhi International School, Jodhpur, Rajasthan, India.

DOI: https://www.doi.org/10.56726/IRJMETS45989

ABSTRACT

Beta-thalassemia is a group of hereditary blood disorders caused by mutations in the beta-globin gene, leading to abnormal synthesis of beta chains of haemoglobin. This results in a wide range of clinical presentations, from severe anaemia to asymptomatic individuals. The annual incidence of symptomatic cases is estimated at 1 in 100,000 worldwide. It is an autosomal recessive condition, although dominant mutations are rare. Three main phenotypes include thalassemia major, thalassemia intermedia, and thalassemia minor. Thalassemia major typically presents in early childhood with severe anaemia, requiring regular blood transfusions. Prolonged transfusion therapy leads to iron overload-related complications affecting various organs and endocrine systems. Thalassemia intermedia appears later in life with moderate anaemia, often without the need for regular transfusions. Complications involve erythroid marrow hypertrophy, extramedullary haematopoiesis, and other health issues. Thalassemia minor is usually asymptomatic, though some individuals may have mild anaemia. Diagnosis relies on hematologic and molecular genetic testing, with genetic counselling and prenatal diagnosis available. Treatment for thalassemia major includes transfusions, iron chelation, and addressing iron-related complications. Bone marrow or stem cell transplantation is the only definitive cure. Thalassemia intermedia management may involve splenectomy, folic acid supplementation, and addressing complications. Emerging therapies like HbF inducers and gene therapy offer promising results.

I. INTRODUCTION

Beta-thalassemia are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of haemoglobin resulting in variable phenotypes ranging from severe anaemia to clinically asymptomatic individuals. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world. Beta-thalassemia is caused by point mutations or, more rarely, deletions in the beta-globin gene on chromosome 11, leading to reduced (beta+) or absent (beta0) synthesis of the beta chains of haemoglobin (Hb). Transmission is autosomal recessive; however, dominant mutations have also been reported. Three main phenotypes have been described: thalassemia major, thalassemia intermedia, and thalassemia minor. Individuals with thalassemia major are usually present within the first two years of life with severe anaemia, requiring regular red blood cell (RBC) transfusions. Regular transfusion therapy leads to iron overload-related complications including endocrine complications (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated myocardiopathy, liver fibrosis, and cirrhosis). Patients with thalassemia intermedia present later in life with moderate anaemia and do not require regular transfusions. The main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary haematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Thalassemia minor is clinically asymptomatic but some subjects may have moderate anaemia. Diagnosis of thalassemia is based on hematologic and molecular genetic testing. Genetic counselling is recommended and prenatal diagnosis may be offered. Treatment of thalassemia major includes regular RBC transfusions, iron chelation, and management of secondary complications of iron overload and in some cases splenectomy. Bone marrow transplantation /stem cell transplant remains the only definitive cure currently available. Individuals with thalassemia intermedia may require splenectomy, folic acid supplementation, treatment of extramedullary erythropoietic masses and leg ulcers, and prevention and therapy of thromboembolic events. Novel therapies like HbF inducers and gene therapy have shown promising results in clinical trials and can prove to be the future. The importance of education and awareness about the disease in the community, implementation of screening programs to identify carriers, facilities for prenatal

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

testing, and genetic counselling are all important parts of the strategy to decrease the disease burden in the community.

II. METHODOLOGY

A comprehensive electronic search for relevant articles on beta thalassemia was conducted and researched material was then analysed to present a review article.

III. BETA-THALASSEMIA AND IT'S TYPES

Beta-thalassemia are a group of hereditary blood disorders characterized by reduced or absent betaglobal chain synthesis resulting in reduced haemoglobin in RBC (Red Blood Cell), decreased RBC production and anaemia [15]. Most thalassemia is inherited as autosomal recessive traits [9]. Beta thalassemia can be classified into

1. Beta thalassemia:

- Thalassemia major -also known as Cooley's anaemia or Mediterranean anaemia - subjects with thalassemia major are homozygotes or compound heterozygotes for beta^0 or beta$^+$ genes [4].
- Thalassemia intermedia - subjects with thalassemia intermedia are mostly homozygotes or compound heterozygotes [4].
- Thalassemia minor also known as beta thalassemia carrier or beta thalassemia trait- subjects with thalassemia minor are mostly heterozygotes [4].
- Dominant beta thalassemia – subjects have clinically detectable thalassemia phenotype in the heterozygote and are in contrast with the classical recessive forms of beta-thalassemia, which lead to a reduced production of normal beta globin chains, some rare mutations result in the synthesis of extremely unstable beta globin variants which precipitate in erythroid precursors causing ineffective erythropoiesis [4].

2. 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) [4].

3. Hereditary persistence of fetal Hb and Thalassemia

4. Autosomal dominant forms

5. Beta thalassemia associated with other manifestations

- Beta-thalassemia trichothiodystrophy
- X-linked thrombocytopenia with thalassemia [4].

IV. ETIOPATHOGENESIS

Beta-thalassemia are caused by point mutations or, more rarely, deletions in the beta globin gene on chromosome 11, leading to reduced (beta$^+$) or absent (beta^0) synthesis of the beta chains of haemoglobin (Hb). Transmission is autosomal recessive; however, dominant mutations have also been reported. More than 200-point mutations have been so far reported; in functionally importantregions of the beta globin gene (HBB gene) [15].

The reduced amount (beta$^+$) or absence (beta^0) of beta globin chains result in a relative excess of unbound alpha globin chains that precipitate in erythroid precursors leading to their premature death and hence ineffective erythropoiesis. The degree of globin chain reduction is determined by the nature of the mutation [9,15].

Peripheral haemolysis contributing to anaemia is less prominent in thalassemia major than in thalassemia intermedia, and occurs when insoluble alpha globin chains induce membrane damage to the peripheral erythrocytes. Anaemia stimulates the production of erythropoietin with consequent intensive but ineffective expansion of the bone marrow (up 25 to 30 times normal), which in turn causes the bone deformities. Prolonged and severe anaemia and increased erythropoietic drive also result in hepatosplenomegaly and extramedullary erythropoiesis [15].

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

V. HEREDITARY TRANSMISSION

Beta thalassemia is inherited in an autosomal recessive pattern. The parents of an affected child are obligate heterozygotes and carry a single copy of a disease-causing beta globin gene mutation. If an individual receives one normal gene and one abnormal gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk for two carrier parents to both pass the abnormal gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier, like the parents, is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females [6].

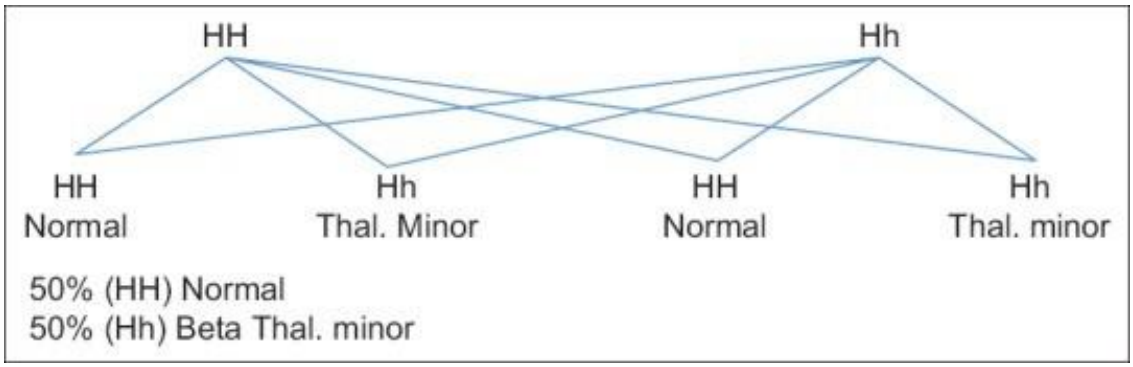

Figure 1 [6].

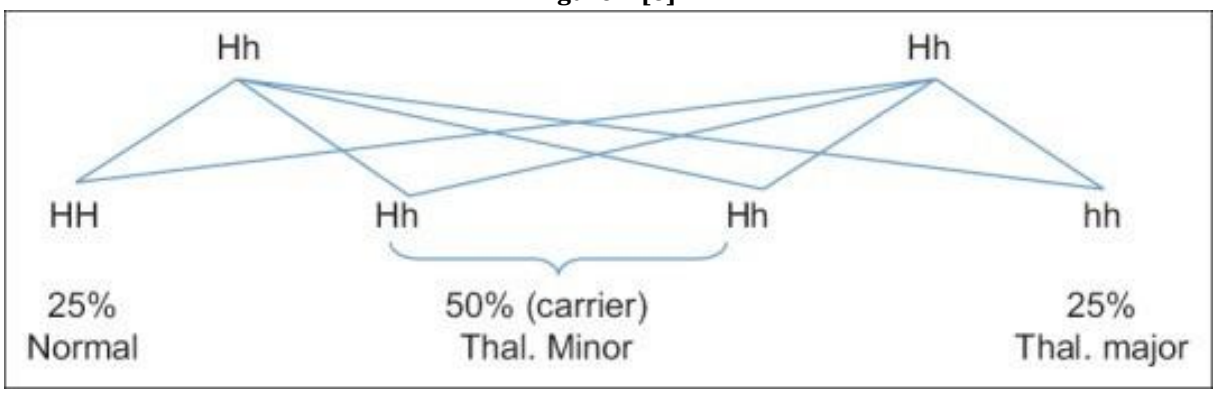

Figure 2 [6].

VI. EPIDIMIOLOGY

Beta-thalassemia is one of the most common autosomal recessive disorders in the world and is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia. The high gene frequency of beta-thalassemia in these regions is most likely related to the selective pressure from Plasmodium falciparum malaria. 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 [14,15].

It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of beta-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world [13]. In India, the average prevalence of beta thalassemia carriers is 3–4% which translates to 35 to 45 million carriers, according to the Census of India 2011 [16].

VII. NOMENCLATURE/GENOTYPE AND PHENOTYPE

Beta Thalassemia Nomenclature -This is a simplified example of the various genotypes which can lead to the

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

various clinical phenotypes seen in beta thalassemia [5].

Beta thalassemia trait-` occurs when one beta gene is non-functional or encodes a mutation resulting in a reduced rate of beta chain synthesis.

It is characterised by a mild hypochromic, microcytic anaemia. Patients are usually asymptomatic. The red blood cell count is usually higher than expected for the degree of anaemia; this is a result of ineffective erythropoiesis. Patients with beta thalassaemia traithave an increased Hb A2 on haemoglobin electrophoresis.

However, care must be taken in interpreting the results when there is a concurrent iron deficiency, as iron deficiency lowers the Hb A2 fraction [5].

Beta thalassemia intermedia- the difference between beta thalassaemia intermedia and major is transfusion-dependence. Patients with beta thalassaemia intermedia (non-transfusion- dependent thalassemia, NTDT), have a moderate anaemia withhepatosplenomegaly. There is ongoing haemolysis, and they may have features of extra-medullary haematopoiesis. They can become iron overloaded [5].

Beta thalassaemia major- patients are transfusion dependent because of the severe or absent beta chain production. They have characteristic facies which results from expansion of the bone marrow in childhood. They have a severe anaemia and die in childhood if a transfusion programme is not initiated. They are susceptible to iron overload and its consequences [5].

VIII. SIGNS AND SYMPTOMS

BETA-THALASSEMIA MAJOR- Affected infants exhibit symptoms within the first two years of life, often between 3 and 6 months after birth. They present with severe microcytic anaemia, mild jaundice,poor appetite, failure to thrive, a swollen abdomen because of hepatosplenomegaly and multiple infections [11]. Splenomegaly may lead to hypersplenism (Beta thalassemia major can cause the bone marrow to expands because it is trying to compensatefor chronic anaemia. This abnormal expansion causes bones to becomethinner, wider and brittle. Affected bones may grow abnormally (bone deformities), particularly the long bones of the arms and legs and certain bones of the face. When facial bones are affected it can result indistinctive facial features including an abnormally prominent forehead(frontal bossing), full cheek bones (prominent malar eminence), a depressed bridge of the nose, and overgrowth (hypertrophy) of the upper jaw (maxillae), exposing the upper teeth. The affected bones have an increased fracture risk, particularly the long bones of the armsand legs. Some individuals may develop 'knock knees' (genu valgum), a condition in which the legs bend inward so that when a person is standing the knees will touch even if the ankles and feet are not [11].

Even when treated, complications may develop, specifically thebuild up of iron in the body (iron overload). Iron overload results from the blood transfusions required to treat individuals with beta thalassemia major. In addition, affected individuals experience greater iron absorption from the gastrointestinal tract, which contributes to iron overload (although this primarilyoccurs in untreated individuals). Iron overload can cause tissue damage and impaired function of affected organs such as the heart, liver and endocrine glands. Iron overload can damage the heart causing abnormal heart rhythms, inflammation of themembrane (pericardium) that lines the heart (pericarditis), enlargement of the heart and disease of the heart muscle (dilated cardiomyopathy). Heart involvement can progress to life-threatening complications such as heart failure. Liver involvement can cause scarring and inflammation of the liver (cirrhosis) and high pressure of the main liver vein (portal hypertension). Endocrine gland involvement can cause insufficiency of certain glands such as the thyroid (hypothyroidism) and, in rare cases, diabetes mellitus. Iron overload can also be associated with growth retardation and the failure or delay of sexual maturation [11].

Additional symptoms that may occur include masses that form because of blood cell production outside of the bone marrow (extramedullary haematopoiesis). These masses primarily form in the spleen, liver, lymph nodes, chest, and spine and can potentially cause compression of nearby structures and a variety of symptoms. Affected individuals may develop leg ulcers, an increased risk of developing blood clots within a vein(venous thrombosis) and decreased bone mineralization resulting in brittle bones that are prone to fracture (osteoporosis)[11].

BETA-THALASSEMIA INTERMEDIA- Thalassemia intermedia presents at a later age with similar but milder clinical findings. Carriers are usually asymptomatic, but sometimes may have mild anaemia. Individuals

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

diagnosed with beta thalassemia intermedia have a widely varied expression of the disorder. Moderately severe anaemia is common and affected individuals may require periodic blood transfusions. Each individual case is unique. Common symptoms include pallor, jaundice, leg ulcers, gallstones (cholelithiasis), and abnormal enlargement of the liver and spleen. Moderate to severe skeletal malformations (as described in beta thalassemia major) mayalso occur [11].

DOMINANT BETA THALASSEMIA- It is an extremely rare form in whichindividuals who have one mutated HBB gene develop certain symptoms associated with beta thalassemia. Affected individuals may develop mild to moderate anaemia, jaundice, and an abnormally enlarged spleen (splenomegaly) [11].

IX. BETA THALASSEMIA WORKUP

- **Laboratory STUDIES**

1) CBC and PBF-RBC indices show microcytic anaemia. Thalassemiamajor is characterized by reduced Hb level (<7 g/dl), mean corpuscular volume (MCV) > 50 < 70 Xl and mean corpuscular Hb (MCH) > 12< 20 pg. Thalassemia intermedia is characterized by Hb level between 7 and 10 g/dl, MCV between 50 and 80 Xl and MCH between 16 and 24 pg. Thalassemia minor is characterized by reduced MCV and MCH, with increased Hb A^2 level. Reticulocyte count is elevated to 5–8% and leucocytosis is usually present. Platelet count is usually normal, unless the spleen is markedly enlarged. Peripheral blood film examination reveals nucleated RBCsand occasional immature leukocytes[15,4].

2) Haemoglobin electrophoresis. -Qualitative and quantitative Hb analysis (by cellulose acetate electrophoresis and DE-52 microchromatography or HPLC) identifies the amount and type of Hbpresent. The Hb pattern in beta-thalassemia varies according to beta- thalassemia type. In $beta^0$ thalassemia, homozygotes HbA is absent and HbF constitutes the 92-95% of the total Hb. In $beta^+$ thalassemia homozygotes and $beta^+/beta^0$ genetic compounds HbA levels are between 10 and 30% and HbF between 70-90%. HbA2 is variable in beta thalassemia homozygotes and it is enhanced in beta thalassemia minor. Hb electrophoresis and HPLC also detect other hemoglobinopathies (S,C, E, OArab, Lepore) that may interact with beta-thalassemia [15,4].

3) Molecular genetic analysis-The prevalence of a limited number of mutations in each population has greatly facilitated molecular genetic testing. Commonly occurring mutations of the beta globin gene are detected by PCR-based procedures [30]. The most commonly used methods are reverse dot blot analysis or primer-specific amplification, with a set ofprobes or primers complementary to the most common mutations in the population from which the affected individual originated. If targeted mutation analysis fails to detect the mutation, beta globingene sequence analysis can be used to detect mutations in the beta globin gene [15,4].

4) Prenatal diagnosis- It is possible through analysis of DNA obtained through chorionic villi sampling at 8–10 weeks' foetal gestation or by amniocentesis at 14–20 weeks' gestation. In most laboratories, the DNA is amplified using the PCR assay test and then is analysed for the presence of the thalassemia mutation using a panel of oligonucleotide probes corresponding to known thalassemia mutations. Prenatal diagnosis may be performed noninvasively, with the use of maternal blood samples to isolate either foetal cells or foetal DNA for analysis (NIPT) [4].

X. MANAGEMENT OF BETA THALASSEMIA MAJOR

Regular Blood transfusion is the main stay of beta thalassemia major treatment. The goals of transfusion therapy are correction of anaemia, suppression of erythropoiesis and inhibition of gastrointestinal iron absorption, which occurs in non-transfused patients as a consequence of increased, although ineffective, erythropoiesis. The most widely accepted transfusion regime aims at apre-transfusion Hb level of 9 to 10 g/dl and a post-transfusion level of 13 to 14 g/dl. This prevents growth impairment, organ damage and bone deformities, allowing normal activity and quality of life. The frequency of transfusion is usually every two to four weeks [13]. Dedicated computerized programs are available to monitor transfused thalassemia patients accurately. Iron overload is the most relevant complication [15].

Other adverse associated with red cell transfusions are-

- Infections- Viral (HIV, HCV, HBV), Bacterial, Parasitic
- Haemolytic reactions of Acute, Delayed, Autoimmune types

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

- Non-haemolytic reactions- Allergic and Anaphylactic reactions, Febrile non-haemolytic reactions, Transfusion-related acute lung injury (TRALI), Transfusion-associated graft-versus-host disease, Circulatory overload, post-transfusion purpura [15].

XI. ASSESSMENT AND TREATMENT OF IRON OVERLOAD

Patients maintained on a regular transfusion regimen progressively develop clinical manifestations of iron overload: hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hypoparathyroidism (4%), diabetes (6-10%), liver Fibrosis, and heart dysfunction (33%). These conditions are to be managed by a multidisciplinary team of specialists [15].

Iron status needs to be accurately assessed in order to initiate chelation therapy and it can be assessed by several methods. Serial measurements of serum ferritin are a reliable and the easiest method to evaluate iron overload and efficacy of chelation therapy. In recent years, nuclear magnetic resonance imaging (MRI) techniques and magnetic biosusceptometry (SQUID) have been used for assessing iron load in the liver and heart. Iron Binders or chelators remove excess iron through urine and or stool. Iron chelation treatment is initiated once the patient has had 10-20 transfusions or when ferritin levels rise above 1000 ng/ml [15].

Iron chelators available for treatment are-

1) Deferoxamine (DFO), It cannot be orally absorbed and needs parenteral administration, usually as a subcutaneous 8 to 12-hour nightly infusion, 5-7 nights a week. Average dosage is 20-40 mg/kg body weight for children and 30-50 mg/kg body weight for adults. In high-risk cases, DFO is administered continuously via an implanted delivery system (Port-a-cath) or subcutaneously, at doses between 50 and 60 mg/kg per day [15].

Implanted delivery systems are associated with risk of thrombosis and infection. The most frequent adverse effects of DFO are local reactions at the site of infusion, such as pain and swelling. Serious complications associated with high doses of DFO are: sensorineural hypoacusis, ocular toxicity, retarded growth and skeletal changes, infections by Y. Enterocolitica, K. Pneumoniae and other pathogens. Hence, patients receiving DFO regularly should be monitored with audiometric and ophthalmologic tests and with regular evaluation of growth and bone changes. Because of the inconvenient parenteral administration compliance is an issue with DFO, limiting its usefulness [15].

2) Deferiprone DFP

It is an orally active iron chelator, an orphan drug, is as effective as DFO at doses of 75-100 mg/kg/day. Agranulocytosis is the most serious side effect associated with the use of DFP, occurring in about 1% of the patients. DFO and DFP can be used in combination to achieve levels of iron excretion that cannot be achieved by either drugalone without increasing toxicity [15].

3) Deferasirox (DFX)

It is a once-daily, orally administered iron chelator shown to be effective in adults and children. European Union declared it as an orphan drug in 2002 and was authorized for marketing in most countries in 2006. The recommended dose of DFX for most patients is between 10 to 30 mg/kg/day depending on the number of transfusions a patient is receiving. Mild, nonprogressive increases in serum creatinine has been observed in approximately a third of patients [15].

In 2019, the U.S. Food and Drug Administration (FDA) approved Ribosyl (luspatercept-aamt) for the treatment of anaemia in adult patients with beta thalassemia who require regular red blood cell transfusions. The medication reducesthe need for regular blood transfusions but does not cure the condition [11]

Splenectomy

Sometimes patients might need splenectomy, especially when annual red cell requirement exceeds 180-200 ml/Kg of RBC andalso in cases of hypersplenism and increasing iron overload despitegood chelation [15].

Bone marrow and cord blood transplantation

Bone marrow transplantation (BMT) is the only definitive cure presently available for patients with thalassemia. The outcome of BMT is related to the pre-transplantation clinical conditions, specifically the presence of hepatomegaly, extent of liver Fibrosis, history of regular chelation and hence severity of iron accumulation. In patients withoutthe above risk factors, stem cell transplantation from an HLA identical sibling

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:11/November-2023 Impact Factor- 7.868 www.irjmets.com

has a disease-free survival rate over 90%. The major limitation of allogenic BMT is the lack of an HLA-identical sibling donor for the majority of affected patients. In fact, approximately 25-30% of thalassaemic patients could have a matched sibling donor. Chronic graft-versus-host disease (GVHD) of variable severity may occur in 5-8% of individuals. Cord blood transplantation from a related donor offers a good probability of a successful cure and is associated with a low risk of GVHD [15].

Management of thalassemia intermedia

Treatment of individuals with thalassemia intermedia is symptomatic.As hypersplenism may cause worsening anaemia, retarded growth andmechanical disturbance from the large spleen. Splenectomy is indicated in cases of hypersplenism. Prevention of post-splenectomy sepsis includes immunization against encapsulated bacteria (Streptococcus Pneumoniae, Haemophilus Influenzae and Neisseria Meningitidis) and antibiotic prophylaxis as well as early antibiotic treatment for fever and malaise. Because of the elevated prevalence of cholelithiasis, cholecystitis should be considered during splenectomy and removed in case with or to prevent gallstones. Treatment of extramedullary erythropoietic masses, detected by magnetic resonance imaging, is based on radiotherapy, transfusions, or hydroxycarbamide. Regular blood transfusions, zinc supplementation and pentoxifylline, and the use of an oxygen chamber have been proposed for leg ulcer treatment. Recently promising results have been obtained with platelet derived growth factor. Because individuals with thalassemia intermedia may develop iron overload from increased gastrointestinal absorption of iron or from occasional transfusions, Chelation therapy is to be used incases when the serum ferritin concentration exceeds 300 ng/ml or when iron overload is demonstrated by direct or indirect methods. Supplementary folic acid can be prescribed to patients with thalassemia intermedia to prevent deficiency from hyperactive bonemarrow [15].

XII. NOVEL THERAPIES UNDER INVESTIGATION

1) HbF inducers- Induction of foetal haemoglobin synthesis can reduce the severity of beta-thalassemia by improving the imbalance between alpha and non- alpha globin chains. Various drugs like 5-azacytidine, decitabine, butyrate derivatives, have shown encouraging results in clinical trials. There use in management of Beta thalassemia is still under investigation. Hence further controlled and randomised studies are needed to establish its use in management of thalassemia major [15,2]. Hydroxy carbamide has shown beneficial effect in Beta thalassemia intermedia (reduction of extramedullary masses, increase in Hb level etc), but its efficacy is compromised by its suppressive effects on bonemarrow function and it may have mutagenic effects also [15,2]

2) Gene-Therapy- The possibility of correction of the molecular defect in hematopoieticstem cells by transfer of a normal gene via a suitable vector or by homologous recombination is being actively investigated [15]. The most promising results in the mouse model have been obtained with lentiviral vectors. In 2009, orphan designation was granted by the European Commission for autologous haematopoietic stem cells transduced with lentiviral vector encoding the human beta globin gene for the treatment of beta-thalassemia major and intermedia [7].

3) CRISPR/Cas 9 is a unique technology that enables geneticists and researchers to edit parts of the genome by removing, adding or altering sections of the DNA sequence. It consists of 2 key moleculesthat introduce a change/mutation into the DNA. These are, an enzyme called Cas9 that acts as a pairof molecular scissors that can cut the 2 strands of DNA at a specific location in the genome and a piece of RNA called guide RNA (gRNA) which consists of predesigned RNA sequence (about 20 bases long) that guides Cas9 to the right part of the genome. This technology has been used to modify the genome in cases of beta thalassemia patients (increased the expression of gamma-globin and production of HbF, reduction of alpha-globin chain, correction of mutation causing beta thalassemia) and has shown promising results and can prove to be a novel therapeutic strategy for Beta-thalassemia [1,8].

XIII. CONCLUSION

Allogenic stem cell transplant remains the only option for a cure for beta thalassemia major patients. Thus, prevention of the birth of an affected child is a feasible and realist option. prevention starts with creating awareness about thalassemia in the society. Social organisations like the rotary clubs, thalassaemia support foundation and various NGOs andThalassemia Parents-Patients societies have been conducting education and awareness programmes. The National Health Portal of the Ministry of Health and Family Welfare, Govt. of India

now provides information on thalassemia for the public and professionals [10,16]. Implementation of screening programmes to identify carriers is the next important step. Ideally the screening should be universal like the newborn screening program of UK [3]. But this is difficult to implement in developing countries, thus, targeted screening in high risk groups (ethnic groups with consanguineous marriages), young individuals like high school children, premarital screening of females and newborn screening for SCD and Thalassemia. CBC and HPLC analysis of haemoglobin is usually used for screening. Individuals suspected to have beta thalassemia on screening should be subjected to a definitive molecular genetic testing to identify the mutation. These individuals should then undergo genetic counselling and in cases where the person is already pregnant, they should be offered a prenatal diagnosis (CVS, amniocentesis). The crux of genetic counselling is to make the family aware of the genetic disorder, its clinical presentation and severity along with the risk of recurrence and mortality associated with the disease [16].

To create awareness at a global level World Thalassemia Day is celebrated on 8th of May every year [12].

ACKNOWLEDGEMENTS

I am immensely grateful to professor Caryll Wagget from Allegheny College Pennsylvania for her invaluable guidance and mentorship throughout my research paper, which greatly enriched my academic journey. Her expertise and support were instrumental in my success.

XIV. REFERENCES

[1] CRISPR/Cas9. . . https://crisprtx.com/gene-editing/crispr-cas9.

[2] Decitabine as hemoglobin F inducer in hemoglobin E/β thalassemia. https://ashpublications.org/blood/article/130/Supplement%201/2224/71397/Decitabine-As-Hemoglobin-F-Inducer-in-Hemoglobin-E.

[3] Understanding haemoglobinopathies. . . https://www.gov.uk/government/publications/handbook-for-sickle-cell-and-thalassaemia-screening/understanding-haemoglobinopathies#normal-haemoglobin.

[4] Hassan T, Badr M, Safy UE, et al. B-thalassemia: Genotypes and phenotypes. IntechOpen; 2016. https://www.intechopen.com/chapters/52171. Accessed Aug 4, 2023. 10.5772/64644.

[5] ß thalassaemia. https://www.learnhaem.com/courses/anaemia/lessons/haemoglobinopathies/topic/b-thalassaemia/. Accessed Aug 4, 2023.

[6] Thiyagarajan A, Bhattacharya S, Sharma N, Srivastava A, Dhar DK. Need for a universal thalassemia screening programme in india? A public health perspective. J Family Med Prim Care. 2019;8(5):1528-1532. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6559078/. Accessed Aug 4, 2023. doi: 10.4103/jfmpc.jfmpc_90_19.

[7] Puthenveetil G, Scholes J, Carbonell D, et al. Successful correction of the human beta-thalassemia major phenotype using a lentiviral vector. Blood. 2004;104(12):3445-3453. Accessed Aug 4, 2023. doi: 10.1182/blood-2004-04-1427.

[8] CRISPR/Cas9, a promising approach for the treatment of β-thalassemia: A systematic review | Springer Link. https://link.springer.com/article/10.1007/s00438-022-01978-z. Accessed Aug 4, 2023.

[9] Untitled. https://mts.intechopen.com/storage/books/8450/authors_book/authors_book.pdf. Accessed Aug 4, 2023.

[10] Thalassemia support foundation - national organization for rare disorders. https://rarediseases.org/non-member-patient/thalassemia-support-foundation/. Updated 2022. Accessed Aug 4, 2023.

[11] Beta thalassemia - symptoms, causes, treatment | NORD. https://rarediseases.org/rare-diseases/thalassemia-major/. Accessed Aug 4, 2023.

[12] World thalassaemia day 2023: Date, history, significance, theme. Hindustan Times Web site. https://www.hindustantimes.com/lifestyle/health/world-thalassaemia-day-2023-date-history-significance-theme-101683447790401.html. Updated 2023. Accessed Aug 4, 2023.

[13] Guideline for the clinical management of thalassemia. . . Thalassemia International Federation. Guidelines for the clinical management of thalassemia. 2. 2008. http://www.thalassemia.org.cy [Google Scholar].

[14] Flint J, Harding RM, Boyce AJ, Clegg JB. The population genetics of the haemoglobinopathies. Baillieres Clin Haematol. 1998;11(1):1-51. Accessed Aug 4, 2023. doi: 10.1016/s0950-3536(98)80069-3.

[15] Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893117/. AccessedAug 4, 2023. doi: 10.1186/1750-1172-5-11.

[16] Burden of thalassemia in india: The road map for control - ScienceDirect. https://www.sciencedirect.com/science/article/pii/S2468124517300748. Accessed Aug 4, 2023.