Hematological Genetic Disorders: A Review

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ABSTRACT: Thalassaemia major requires regular blood transfusions to maintain an adequate supply of haemoglobin and sustain life. As a result of multiple transfusions, organs become severely overloaded with iron and a specific treatment is needed to manage this condition. Thalassaemias can be cured by a successful bone-marrow transplant, however this procedure is expensive and not readily available in most settings. Recently, gene therapy has been successfully applied to a patient with thalassaemia. The most cost-effective strategy for reducing the burden of haemoglobin disorders is to complement disease management with prevention programmes. In expensive and reliable blood tests can identify couples at risk for having affected children. This screening is especially opportune before marriage or pregnancy, allowing couples to discuss the health of their family. Subsequent genetic counseling informs trait carriers of risks that the condition may be passed along to their children, the treatment needed, if affected by a haemoglobin disorder, and the possible options for the couple. Prenatal screening of genetic diseases raises specific ethical, legal and social issues that require appropriate consideration.

Key word: Thalassaemias, sickle cell disease

1. INTRODUCTION

Thalassaemia and Sickle Cell Anaemia (SCA) is a hereditary blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. It is a genetic defect in the synthesis of hemoglobin and is the best-known hemoglobinopathy in man (Kato GJ, 2007). It

occurs as a result of the substitution of glutamic by valine at position 6 of the amino-acid sequence, which leads to the formation of defective hemoglobin molecules and causes sickling of the red blood cells (Ballas SK, 2002). Even though thalassaemia is present from birth, but symptoms are rare before the age of three to six months because of the high level of fetal hemoglobin (HbF) which is present at birth. It is of interest to note that cells are less prone to sickling in individuals who retain a high level of HbF. The HbF inhibits the polymerization of the HbS owing to its high oxygen affinity. The HbF ($\alpha 2\ \gamma 2$) dissociates to a dimer, which when combined with HbS, gives a tetramer that does not form a polymer, symptoms of thalassaemia are almost completely eliminated with HbF levels above 25%; however, any increment in HbF level was observed to improve the overall survival (Atweh GF, 2001), (Bank A,2006). The production of HbF is normally switched off soon after birth in favor of production of adult-type HbA.

2. REVIEW OF LITERATURE

2.1 Facts about haemoglobin disorders

It is estimated that each year over 300000 babies with severe forms of these diseases are born worldwide, the majority in low and middle income countries. Approximately 5% of the world's populations are healthy carriers of a gene for sickle-cell disease or thalassaemia. The percentage of people who are carriers of the gene is as high as 25% in some regions. These conditions are most prevalent in tropical regions; however population migration has spread these diseases to most countries. Thalassaemias are the most common in Asia, the Mediterranean basin, and the Middle East. Sickle-cell disease predominates in Africa

2.2 What causes haemoglobin disorders

Haemoglobin disorders are inherited from parents in much the same way as blood type, hair colour and texture, eye colour and other physical traits. Sickle-cell disease and severe forms of thalassaemia (thalassaemia major) can occur only when both parents are carriers of trait genes for the particular condition. A child who inherits two of the same trait genes one from each parent will be born with the disease. However, a child of two carriers has only a 25% chance of receiving two trait genes and developing the disease, and a 50% chance of being a carrier. Most carriers lead completely normal, healthy lives.

2.3 What are haemoglobin disorders

Haemoglobin disorders are inherited blood diseases that affect how oxygen is carried in the body. Hemoglobinopathy is a kind of genetic defect that results in abnormal structure of one of the globin chains of the hemoglobin molecule. Haemoglobinopathies are inherited single gene disorders caused by genetic mutations that result in abnormal, disfunctional hemoglobin molecules or lower levels of normal haemoglobin molecules in red blood cells. (Old, 2003; Sylvie Langlois *et al.,* 2008; Rekha Vij *et al.* 2010).

The patients with different haemoglobinopathies suffer from various complications such as growth retardation (De Sanctis, 2002; Zemel *et al.* 2007) impaired immune status, severe anemia, endocrine complications (Rund, 2005; Abdelrazik *et al.* 2007) spinal deformities, nerve compression, fractures, severe osteoporosis and painful vasoclusive episode (Hasanato, 2006). The cumulative effects of various factors like trace elements, vitamins and growth hormones are involved in various haemoglobinopathies. Trace elements like copper and zinc play a vital role in preventing the oxidative stresses in human (Hennig *et al.* 1999). Haemoglobin disorders fall into two main categories: sickle-cell disease and thalassaemias.

2.4 Sickle cell anaemia (sca)

SCA is characterized by a modification in the shape of the red blood cell from a smooth, donut-shape into a crescent or half moon shape. The misshapen cells lack plasticity and can block small blood vessels, impairing blood flow. This condition leads to shortened red blood cell survival, and subsequent anaemia, often called SCA. Poor blood oxygen levels and blood vessel blockages in people with sickle-cell disease can lead to chronic acute pain syndromes, severe bacterial infections, and necrosis (tissue death).

Drepanocytosis also known as sickle cell anemia is hereditary disease resulting from the inheritance of two abnormal allelomorphic genes that control the formation of the β chains of haemoglobins (Hb). The symptoms of this disease result from an ultimate aggregation of haemoglobins in the HbSS erythrocytes due to lowered oxygen tension, resulting in the characteristics distorted sickled shapes (dipicted in figure 1) (Gentilini, 1986; Lehninger, 1994; Voet and Voet, 1998; McGaw *et al.*, 2000; Kambizi and Afolayan, 2001 Mehanna *et al.,* 2003). Sickle cell anaemia has been affecting people of African origin for centuries (Benardin, 1999; Neuwinger, 2000; Mehanna, 2001).

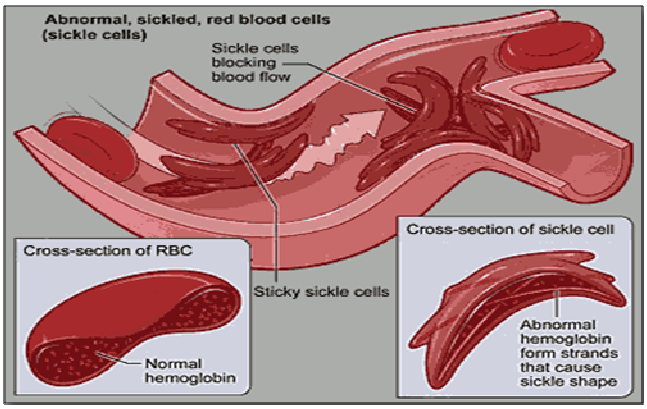

Figure 1: Normal Red blood cells & Sickle cells

2.5 Thalassaemia

Thalassaemias are also inherited blood disorders. People with thalassaemia are not able to make enough haemoglobin, which is found in red blood cells. When there is not enough haemoglobin in the red blood cells, oxygen cannot get to all parts of the body. Organs then become starved for oxygen and are unable to function properly. The term thalassaemia is derived from the Greek, thalassa (sea) and haima (blood) (Thein, 2005). Thalassaemia syndromes are a family of genetic blood disorders characterized by an imbalance in the synthesis of globin chains, which may result in the absence or reduction in production of adult hemoglobin (Clegg, 1996; Weatherall, 1997). About 4.5% all human beings carry a gene for thalassaemias (Angastiniotis *et al.*, 1998; Weatherall *et al.*, 2001). It is prevalent across the world. Affected population estimated rates are: Europe 0.9%; Asia 4.1%; Africa 13.3%; Oceania (including Australia, New Zealand, Papua New Guinea and Fiji) 1.3%; and the Americas 2% (WHO 1994). Cooley and Lee in 1925 first described a form of severe anemia occurring in childhood associated with splenomegaly and characteristic bone changes. The condition was called Cooley anemia but later named Thalassaemia (Whipple *et al*. 1993). It may be defined as genetic blood disease that affect the body's ability to produce a protein in the red blood cells called hemoglobin. Hemoglobin carries oxygen and nutrients throughout the body (Figure 1) (eMedicine, 2007; Eliza-beth *et al*., 2010).

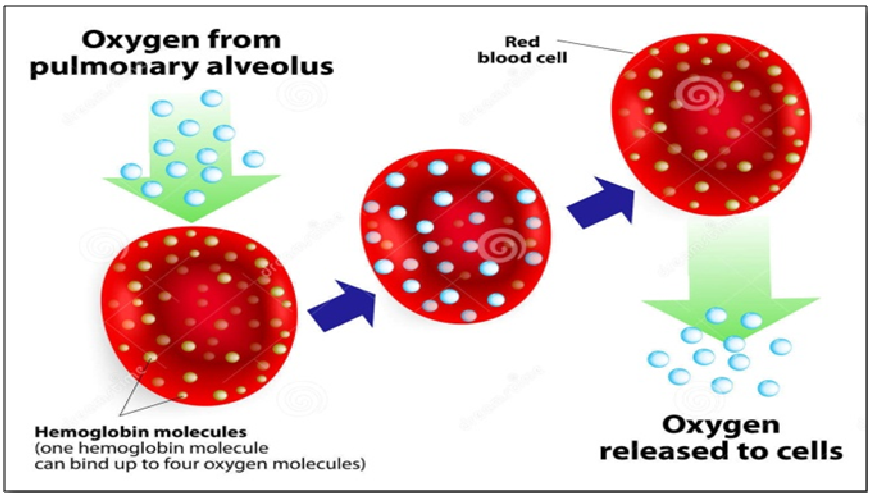

Figure 2: Function of Haemoglobin Molecule

People with mild variety of thalassaemia usually do not present any symptom. In more severe cases of thalassaemia, symptoms may include:

- Weakness,
- Pale skin or jaundice,
- Dark urine,
- Fatigue,
- Lightheadedness,
- Rapid heartbeat,
- Abnormal facial bones and poor growth,
- Protruding abdomen with enlarged spleen or liver.

Thalassaemic patient require blood transfusions, Due to repeated blood transfusions, many patients with β-thalassaemia may be infected with either hepatitis C virus (HCV) or hepatitis B virus (HBV) (Aach *et al*. 1991). Cure may be possible with stem cell transplantation. However, This form of treatment is possible only for a minority group of patients who have a suitable HLA-matched donor (Fucharoen *et al*., 2007).

Thalassaemia is named with reference to the affected globin chain: α-thalassaemia involves the-chain and β-thalassaemia the β-chain (Ford *et al.* 2008). In α- thalassaemia, there are four severities are involved: Hydrops fetalis (four gene deletion), Haemoglobin H (Hb H) disease (three gene deletion), α-thalassaemia minor (two gene deletion); Slient carrier (one gene deletion). While β-thalassaemia have been classified into three clinical categories: β-

thalassaemia major (two gene mutations); β-thalassaemia intermediate (two gene mutations) and β-thalassaemia minor (one or two gene mutations) (Bunn *et al.* 1986; Dheeraj *et al.* 1999).

Types of Thalassemia

There are two major types of thalassaemia, alpha and beta, which are named for the two protein chains that make up normal haemoglobin. Alpha and beta thalassaemia have both mild and severe forms.

2.5.1 Alpha-Thalassaemia

Alpha-thalassaemia is a common hereditary condition caused by deletions or point mutations in one or both alpha-globin genes, located on chromosome 16 (Weatherall, 1997; Sen *et al.*, 2004; Higgs *et al.* 2009). With this disorder, the failed genes are almost invariably lost from the cell. The genes that are most commonly associated with alpha thalassaemia are HBA1 and HBA2 (Galanello *et al.,* 2008). α-Thalassaemia refers to a deletion of both α globin genes on the same chromosome, while α+-thalassaemia refers to a deletion of a single α globin gene, leaving the other α globin gene on that chromosome intact (Leung *et al.* 2005). Alpha thalassaemia is one of the most common single gene disorders, affecting 5% of the world's population (Chui *et al.* 1998).

Hemoglobin H (HbH) disease, the clinically significant intermediate form of alpha-thalassaemia, is characterized by mild to moderate (sometime severe) microcytic, hypo chromic hemolytic anemia, jaundice, hepatosplenomegaly, and occasionally mild thalassaemia like bone modifications. Most commonly HbH disease results from deletion or dysfunction of 3 of 4 alpha-globin genes, and rarely from deletions in the upstream regulatory region (Viprakasit *et al.* 2003; Fucharoen *et al.* 2009).

The severity of alpha thalassaemia depends on the number of defective genes:

2.5.1.1 Silent carrier

With one defective gene, the body still makes hemoglobin. Therefore, the person will not have any symptom and can lead a normal and healthy life.

2.5.1.2 Alpha Thalassaemia minor

The loss of two normal genes causes the red blood cells to be smaller than usual. Except for possible mild anemia, patients remain in good health.

2.5.1.3 Haemoglobin h disease

Hemoglobin made from only one gene does not carry oxygen properly. Patients with hemoglobin H disease can suffer from severe anemia.

2.5.1.4 Alpha thalassaemia major

With all four genes failing to produce the alpha chain, the body has a significant loss of hemoglobin which results in a severe form of anemia (DeMaeyer,*et al*., 1985; Bunn *et al.* 1986; Kliegman, *et al.,* 2009).

2.5.2 Beta-thalassaemia

Beta-thalassaemia syndromes are a group of hereditary blood disorders caused by mutations in the ß- globin genes on chromosome 11 and characterized by reduced or absent beta globin chain synthesis, resulting in reduced Hb in red blood cells (RBC), decreased RBC production and anemia (Leung *et al.* 2005; Galanello *et al.*2010). The geographic distribution of this disease has made it a worldwide health problem with a high frequency in Africa, India, Southeast Asia and the Mediterranean area (Pearson *et al.* 1996).>400,000 new borns affected per year worldwide (Angastiniotis *et al*., 1998).

It is a hereditary anemia caused by more than 200 point mutations and rarely by deletions (Higgs *et al.* 2001) and characterized by absent to decreased synthesis of β- globin chains resulting in imbalance between α- and β- chains and ensuing ineffective erythropoeisis and hemolysis (Schrier, 1997; Olivieri, 1999). The only curative treatment for this disaese currently available is allogeneic bone marrow transplantation (BMT), which involves significant risks such as graft vs. host disease and engraftment failure (Rivella *et al.*2003*).* Three classes of beta-thalassaemia have been recognized clinically:

- Beta-thalassaemia major,
- Beta-thalassaemia intermediate,
- Beta-thalassaemia minor (Thein, 2004; Galanello and Origa, 2010).

2.5.2.1 Thalassaemia major

Thalassaemia major, also known as Cooley's anemia and Mediterranean anemia, is the most severe form of beta-thalassaemia, with mutations of both *HBB* alleles' results in severely impaired beta-globin chain production (Rund *et al.,* 2005). Three of the general allele combinations are responsible for this thalassaemia phenotype- B□/B□, B /B^{+}, and sometimes

B^+/B^+ (Thein, 2004). In thalassaemia major, the excess unpaired alpha-globin chains aggregate to form inclusion bodies. These chain inclusion bodies damage RBC membrane, leading to intravascular hemolysis (Cao., 2005). This form of beta thalassaemia presents within the first two years of life and, with proper treatment affected individuals can live five decades or more (Wonke., 2001).

2.5.2.2 Thalassaemia intermediate

This condition is milder than thalassaemia major due to inheritance of a *HBB* mutation associated with reduced beta-globin chain production (Cao, 2005). Patients with beta-thalassaemia intermediate have mild to moderate anemia and in most cases do not require blood transfusion (Taher *et al.* 2006). Common clinical features include splenic enlargement due to entrapment of damaged RBCs, with risk of iron overload due in part to increased intestinal absorption. Although thalassaemia intermediate can be associated with poor growth and bone abnormalities, it presents later in life and rarely affects longevity (Bunn *et al.* 1984). A rare variant form called "Silent beta thalassaemia" results from a mild imbalance of globin chain synthesis due to reduced beta-globin synthesis, leading to thalassaemia intermediate. Silent beta- thalassaemia mutations are found mainly in the regulatory regions, *HBB* promoter and 5' and 3' UTRs. The most common silent mutation is the nt-101C>T (c.-151C>T) transition in *HBB* (Gonzalez- Redondo *et al.* 1989).

2.5.2.3 Thalassaemia minor

Thalassaemia minor is most common form of beta thalassaemia, and is also known as the 'thalassaemia trait', in which affected individuals are asymptomatic (Rund *et al.* 2005). These patients are typically heterozygous for beta thalassaemia since they carry one normal *HBB* allele and one thalassaemia allele-either B^o or B^+ (Thein, 2004). Asymptomatic patients are usually detected through routine hematologic testing (Bunn, 1984). The primary caution for individuals with thalassaemia minor is a potential risk of having children affected with more serious thalassaemia if their partner is also a carrier of thalassaemia minor (Thein, 2004).

2.6 How can haemoglobin disorders be reduced

Haemoglobin disorders can be effectively reduced through a strategic balance of disease management and prevention programmes.

Sickle-cell disease can be managed by simple procedures including:

- high fluid intake
- healthy diet
- folic acid supplementation
- pain medication
- vaccination and antibiotics for the prevention and treatment of infections
- a number of other therapeutic measures

Thalassaemia major requires regular blood transfusions to maintain an adequate supply of haemoglobin and sustain life. As a result of multiple transfusions, organs become severely overloaded with iron and a specific treatment is needed to manage this condition. Thalassaemias can be cured by a successful bone-marrow transplant, however this procedure is expensive and not readily available in most settings. Recently, gene therapy has been successfully applied to a patient with thalassaemia.

The most cost-effective strategy for reducing the burden of haemoglobin disorders is to complement disease management with prevention programmes. Inexpensive and reliable blood tests can identify couples at risk for having affected children. This screening is especially opportune before marriage or pregnancy, allowing couples to discuss the health of their family. Subsequent genetic counselling informs trait carriers of risks that the condition may be passed along to their children, the treatment needed, if affected by a haemoglobin disorder, and the possible options for the couple. Prenatal screening of genetic diseases raises specific ethical, legal and social issues that require appropriate consideration.

2.7 Epidemiology

2.7.1 Worldwide status

Thalassaemia is one of the most common genetic blood disorders in the world, affecting approximately 240 million people worldwide who are heterozygous for β-thalessemia and approximately 200,000 affected homozygotes are born annually (Cao *et al.,* 2005). About 5% of the world population is affected by it. Its prevalence is more around the Mediterranean Sea i.e. countries like Greece, Italy, Turkey and North African countries. It is also seen in Saudi Arabia, Iran, Afghanistan, Pakistan (Ahmed *et.al*., 2010) India (Agarwal, Mehta., 1982) and south East Asian countries like Thailand (Riewpaiboon *et al.,* 2010) and Indonesia (illustrate in table1). The prevalence is highest in Italy, Greece and Cyprus (Hazza and Jamal,

2006). In worldwide 4.83 percent of the world's population carry globin variants, including 1.67 percent of the population who are heterozygous for alpha-thalassaemia and beta–thalassaemia (Angastiniotis, 1998).

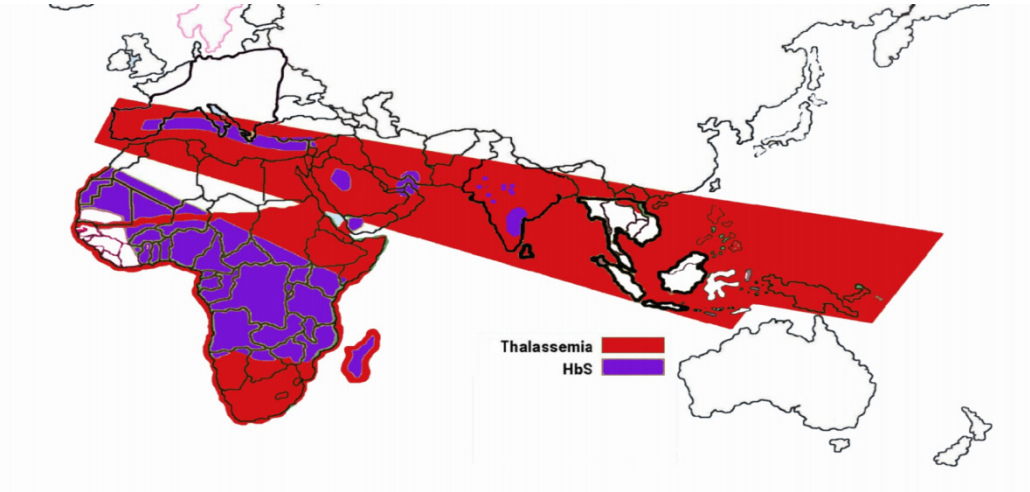

Figure4. The Worldwide Geographical distribution of Haemoglobinopathies. http://upload.wikimedia.org/wikipedia/commons/2/26/Red_Blood_Cell_abnormalities.png

Table:- 1 distribution of thalassaemia in world

SN	*COUNTRY*	*THALASSAEMIA TYPE*	*DISTRIBUTION (%)*	*YEAR*	*REFERENCES*
1.	Turkey	β-thalassaemia	2.10%	1971	Cavdar *et al*
2.	Cyprus	β-thalassaemia	14%	1998	Flint *et al.*
3.	Sardinia	β-thalassaemia	10.3%	1998	Flint *et al.*
4.	Southern China	α- thalassaemia	5%	2003	Westwood *et al.*
5.	India	β-thalassaemia trait	3.5%	2004	Shah
6.	Northern Europe	β-thalassaemia	1.5%	2005	Vichinsky
7.	Asia	α- thalassaemia	3-14%	2005,1998	Chui et al
8.	Northern thailand	α- thalassaemia	4.6%	2005,1998	Chui et al
9.	Hong kong	α- thalassaemia	4.1%	2005,1998	Chui et al
10.	China	α- thalassaemia	4.1%	2005,1998	Chui et al

2.7.2 Asia

The thalassemia belt stretches across African continent, Mediterranean regions, Middle East, Indian subcontinent, South east Asia, Thailand (Riewpaiboon *et al.,* 2010), Cambodia,

Laos, Vietnam, Malaysia, Singapore, Southern China. The prevalence of Thalassemia and Falciparum Malaria are similar, suggesting the hypothesis that nature developed genetic mutation to overcome mortality and morbidity of malaria (Dallaman, 1987; Seshadri 1990; Gomber *et al*., 1998; NFHS, 2000). Thalassaemia is more prominent among the Malays and Chinese, whereas the Indians are less affected (Tan *et al*., 2006). The frequency of the genes is 20% for α- thalassaemia (3-5%, α°, α", 16%), 3- 50% for Hb E, 3-4% for β-thalassaemia, and 1-

4% for Hb Constant Spring (George, Khuziah, 1984). In Pakistan, the estimated carrier rate is 5-7%, with 9.8 million carriers in the total population (Ahmed *et al.*, 2010).

2.7.3 India

In India prevalence of the β-thalassaemia trait is about 3.5%, Sindhis and Punjabis are known to carry the β-thalassaemia gene more commonly than other Indian populations (Shah, 2004). β-thalassaemia is detected in almost every Indian population, however, it is seen with highest frequency in north-west and Far East. Sindhis, Gujaratis, Bengabhlis, Punjabis and Muslims account for most of β-thalassaemia. Carrier state for β-thalassaemia in India varies from 1-17% with an average of 3.2% (Agarwal, Mehta., 1982). The frequency of β-thalassaemia, varies from 1· 0% to 6· 0% and 0% to 9· 5% in different districts of Maharasthra and Gujarat. The rate of homozygosity per 1000 births annually was 0·28 in Maharashtra and 0·39 in Gujarat (Colah *et al*., 2010). Table2 illustrate the distribution of thalassaemia in various community of India.

Table-2. Distribution of Thalassaemia in various community of India

S.N.	*COMMUNITY*	*THALASSAEMIA TYPE*	*DISTRIBUTION*	*YEAR*	*REFERENCES*
1.	Sindhi	β-thalassaemia trait	3.5%	2004	Shah
2.	Khandyat	β-thalassaemia	30.3%	2005	Balgir
3.	Brahmin	β-thalassaemia	21.1%	2005	Balgir
4.	Karan	β-thalassaemia	9.2%	2005	Balgir
5.	Teli	β-thalassaemia	8.5%	2005	Balgir
6.	Gauda	β-thalassaemia	5.6%	2005	Balgir
7.	Muslim	β-thalassaemia	2.1%	2005	Balgir

8.	Chasa	β-thalassaemia	0.2%	2005	Balgir
9.	Kshatriya	β-thalassaemia	0.3%	2005	Balgir
10.	Agharia	β-thalassaemia	0.2%	2005	Balgir
11.	Pana	β-thalassaemia	0.2%	2005	Balgir
12.	Haddi	β-thalassaemia	0.2%	2005	Balgir
13.	Gonda	β-thalassaemia	0.2%	2005	Balgir
14.	Dhoba	β-thalassaemia	0.2%	2005	Balgir
15.	Bhulia/Tanti	β-thalassaemia	0.2%	2005	Balgir
16.	Domb	β-thalassaemia	0.3%	2005	Balgir
17.	Kurmi	β-thalassaemia	2.1%	2005	Balgir
18.	Barber	β-thalassaemia	3.5	2005	Balgir
19.	Punjabi	β-thalassaemia trait	3.5%	2004	Shah

2.7.4 Madhya Pradesh

Abnormal haemoglobin among Sindhi community of Jabalpur city is shown in table 3. The prevalence of β- Thalassaemia trait was 20.7%. Comparatively it was higher than all other populations of this area (Pande *et al.,* 1999). In Bhopal region the overall prevalence of β-thal trait in the study population was 9.59% [95% confidence interval (95% CI) 8.78-10.4%]. The prevalence of β-thal trait varied across the states of origin and within the state of Madhya Pradesh (Chatterjee *et al.*, 2010).

Table-3. Prevalence of Beta Thalassaemia in Madhya Pradesh.

S.N.	*STATE*	*DISEASE*	*PERCENTAGE*	*YEA*	*REFERENCES*
1.	Jabalpur	□-Thalassaemia trait	20.7	1999	Pande *et.al.*
2.	Jabalpur	□-Thal major	0.2	1999	Pande *et.al.*
3.	Bhopal	□-Thalassaemia trait	9.59	2010	Chatterjee *et al.*

2.8 Worldwide study

The red cell shows increased osmotic resistance due to mild form of jaundice (Rietti., 1925). The first definitive evidence that Cooley's anemia is genetically determined (Angelini., 1937). The work on genetic transmission of thalassaemia was seminal, named mild form of anemia 'Thalassaemia Minor' & severe type 'Thalassaemia Major' (Valentine *et al*., 1948). So, picture may clear that Cooley's anemia is homozygous state for recessive or partially dominant mendelian gene & heterozygous by extremely mild anemia with osmotic resistance red cells. Thalassaemia might result from a defect in Hb A synthesis with persistent production of Hb F (Rich., 1952).

Globin consists of two identical half molecule each made of two different peptide chains, α & β (Ingram., 1956). There are two major classes of disease α & β-thalassaemia, in the same way as there are two major types of structural hemoglobin variants i.e. abnormal α & β chains. (Ingram., 1959). The presence of large, ragged inclusion bodies in the red cell precursor of patient with β-thalassaemia that precipitate α chains was first clue for destruction of red cell and their precursors.(Fessas.,1963). The free α chains that are produced in β-thalassaemia are unstable and rapidly precipitate to become associated with red cell membrane (Bargellesi*et al*., 1968).

The first successful identification of a single nucleotide base substitution, G--A, at nucleotide 110 of the first intervening sequence (IVS 1) of β-globin gene, causing β^{+}-thalassaemia by gene sequencing (Spritz *et al*., 1981; Westway*et al*., 1981). A major breakthrough in isolating mapping and transcription in vitro of β^{-} globin gene (Jackson *et al*., 1981). The expression of βE-globin genes introduced into HeLa cells & revealed two abnormalities of RNA processing, excision of intervening sequence-1 (IVS-1) & alternative splicing into exon-1 at cryptic donor sequence within which the codon 26 nucleotide substitutions resides. These results demonstrated that a disturbance in the expression of βE-globin gene attributed solely to the exon mutation - a notable mechanism for gene mutation (Orkin*et al*., 1982).

3. CONCLUSION

In the present study which is conducted on subject suffering with genetic disorder like haemoglobinopathies major imposes highly clinical, psychological burden on the patients and economical burden their family and hence this article briefly describes the epidemiology, types, clinical features, diagnosis and management of the β-thalassemia. From the information known so for said it can be well that the Thalassemia is a dangerous disorder which is spreading

worldwide important point to be considered that about 10% people in india are affected by it and the cases may increase as it is a hereditary disorder. Every year about 15,000 infants are born with haemoglobinopathies in India. Nearly 28 mutations are reported in beta Thalassemia Indian population of which eight accounts for 95% of the cases.

So, it is important to take into consideration about this disorder as it may prove deadly one. The marked increase in survival, to the fifth decade of life, of patients with well-managed β-thalassemia in developed countries represents one of the most dramatic alterations in morbidity and mortality associated with a genetic disease but in our county 75 years after the fascinating initial description of "peculiar bone changes" and other signs and symptoms of the disorder, the *β*-thalassemias have emerged as a huge public health problem worldwide. They remain a therapeutic challenge for the next millennium.

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