A REVIEW ON EFFECT OF SICKLE CELL DISEASE AND THALASSEMIA IN HUMAN HEALTH

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ABSTRACT

Sickle cell disease (SCD) and Thalassemia (Thal) is unit of monogenetic disorders due to single base-pair genetic mutation within the β-globin gene leading to the substitution of the amino acid essential amino acid for glutaminic acid within the Beta-globin chain. Constitution variation within the clinical presentation and illness outcome may be a characteristic feature of the disorder. Understanding the pathologic process and pathophysiology of the disorder is central to the selection of therapeutic development and intervention. During this special edition for newborn screening for haemoprotein disorders, it's pertinent to explain the genetic, pathologic and clinical presentation of red blood cell illness as a prelude to the justification for screening. Through a scientific review of the literature mistreatment search terms about SCD and Thal up until 2019, we have a tendency to known relevant descriptive publications for inclusion. The scope of this review is especially an summary of the clinical options of pain, the cardinal symptom in SCD and Thal, that gift following the visit craniate haemoprotein as young as 5 to 6 months when birth. The relative impact of hemolysis and small-vessel occlusive pathology remains polemical, a mix of options in all probability contribute to the different pathologies. We have a tendency to additionally offer a summary of rising therapies in SCD.

Keyword: *- Sickle cell disease (SCD), Thalassemia (Thal), Beta- globin gene, Red blood cells (RBCs), pathophysiology.*

1. INTRODUCTION

Hemoglobinopathies is known as the genetic disorders that include Thalassemia and abnormality in hemoglobin like Hemoglobin S, D, and E etc. [2] Estimation throughout the world population approximately 7% of people carry abnormality in hemoglobin i.e. hemoglobin disorders. The annual rate of hemoglobin disorders ranging from 3, 00,000-5, 00,000 (appx.). This type of disorders show two major types of syndromes / groups

a. Thalassemia (Thal.)
b. Sickle cell Disease (SCD) / Sickle cell syndromes

The new born babies or the adolescence children are affected by SCD than Thal. 70% of births are affected by the SCD than the Thal. Others are affected due to thalassemia. [1]

Clinically Thalassemia divided into below catagories:

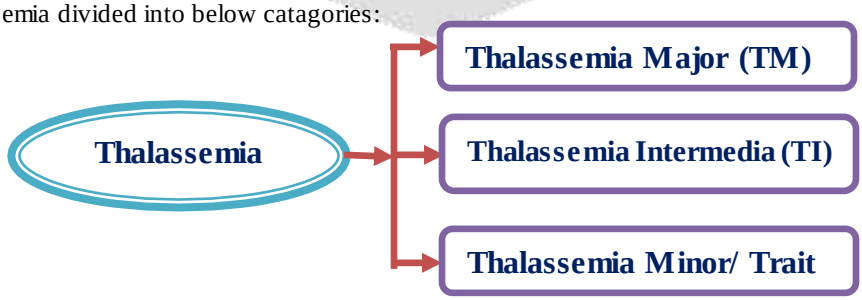


Figure.1: Characterization of Thalassemia disease

The Thalassemia major and the severity of Thalassemia intermediate are not curable. They require blood transfusion and iron chelating for their entire life. But in the minor or the trait stage the person seem like carrier but he /she looks clinically normal and commonly referred as β (beta)- thalassemia trait (BTT). Abnormal β-thalassemia gene inheritance from carrier or the Sevier (major) to their offspring or their next generation may cause the transmission of abnormal variant hemoglobin genes (HbE, HbS) from parents to others.

Sickle cell disease is a hemoglobin disorder that may cause by inheritance of two abnormal HbS genes i.e. one from each parent or from one parents like that HbE / β-thalassemia gene from the other parents. Sickle cell syndromes includes sickle cell disease (SCD) that also called as sickle cell anemia (SCA), that is caused due to sickle cell genes such as Hb C, E or β-thalassemia.

Carrier of any genes that caused hemoglobinopathy is called as "carriers" because they don't suffer only carry the abnormal genes to next generation. Carriers cannot identified clinically but only by some special blood tests. In case of both the parents is carrier, than there may be a chance of their children to be transmitted by the abnormal genes and showing the carrier or severe thalassemia / sickle cell syndrome or may be normal without any abnormal gene shown in below **figure.2**.

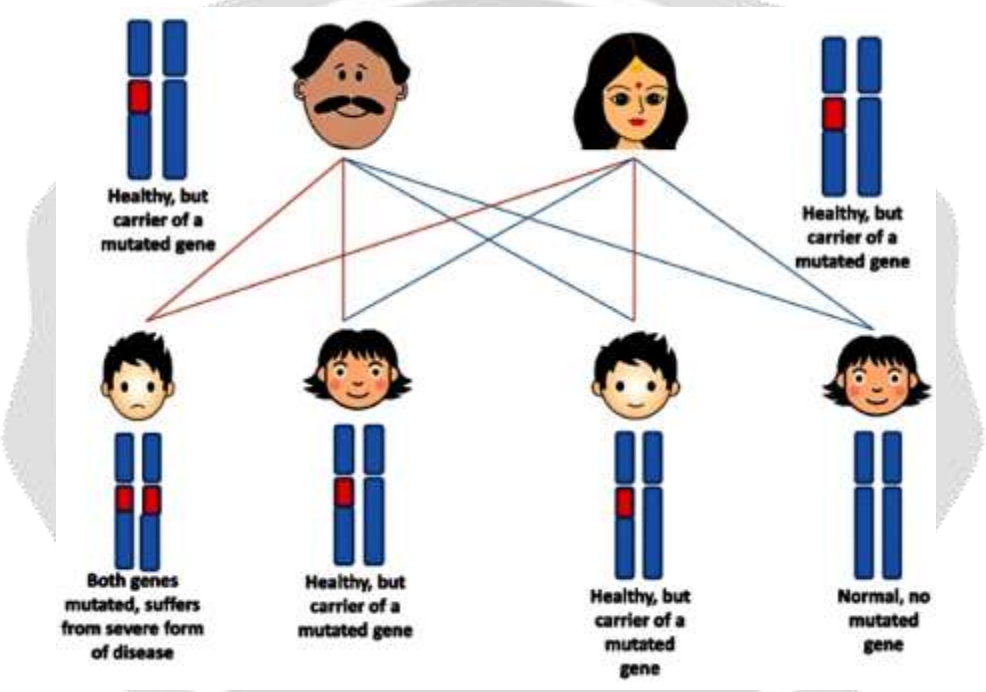


Figure.2: The figure showing the case scenario in which both the parents have one mutant allele

Autosomal inheritance pattern seen in transmission of the disease β-thalassemia major. In the above figure depicts the case scenario in which both the parents have one mutated beta globin gene, so they are called asymptomatic carriers (β-thalassemia trait). The genetic disorders that caused by both the genes to be abnormal for the disease to manifest called as "autosomal recessive". [3]

Here the child inheriting chances are like-

- 25% chance of inheriting two normal genes.
- 50% chance for one altered gene and one normal gene.
- 25% chance of inheriting two altered genes (Thalassemia major)

3-4 % chances of β-thalassemia prevention cases are shown in India. [4,5,6] Certain communities like, Sindhis, Punjabis, Gujuratis, Bangalis, Mahars, Kolis, Saraswats, Lohanas and Gaurs [6, 7] show high frequencies of this disease. HbS is highly prevalent in the tribal and rural areas populations of southern, central and western states high as 48% in some communities [8]. HbE common for North Eastern states and has carrier frequency as much as 50% in some area. Like that 2% of people in some Eastern states like Bihar, West Bengal and Uttar Pradesh are on minor category.

In estimation about 10, 000- 15, 000 new born babies with Thalassemia major and Sickle cell disease (SCD) are born every year [10]. So according to the treatment and the precaution taken for the TM cases in babies, Bone Marrow Transplantation (BMT) also called as Hematopoietic stem cell transplant (HSCT) is the appropriate cure for them. Due to high cost, paucity of BMT centres, or non- availability of HLA matched donor, few patients can afford for the treatment. Therefore regular blood transfusion by iron chelation therapy is given to the patients of Hemoglobinopathies.

2. SICKLE CELL DISEASE (SCD)

Sickle cell anemia (SCA) is the kind of abnormal blood disease which is also called as Sickle cell Disease (SCD). In human body blood flows through small circular shape inside the veins and arteries, which carries oxygen to organs, but in sickle cell cases the blood cells are sickle shaped cells / disc shape as shown in below **figure.3**.

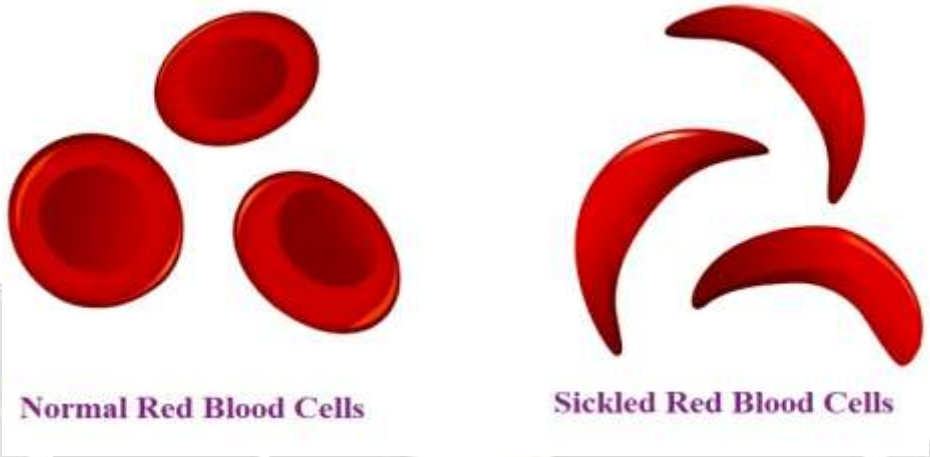
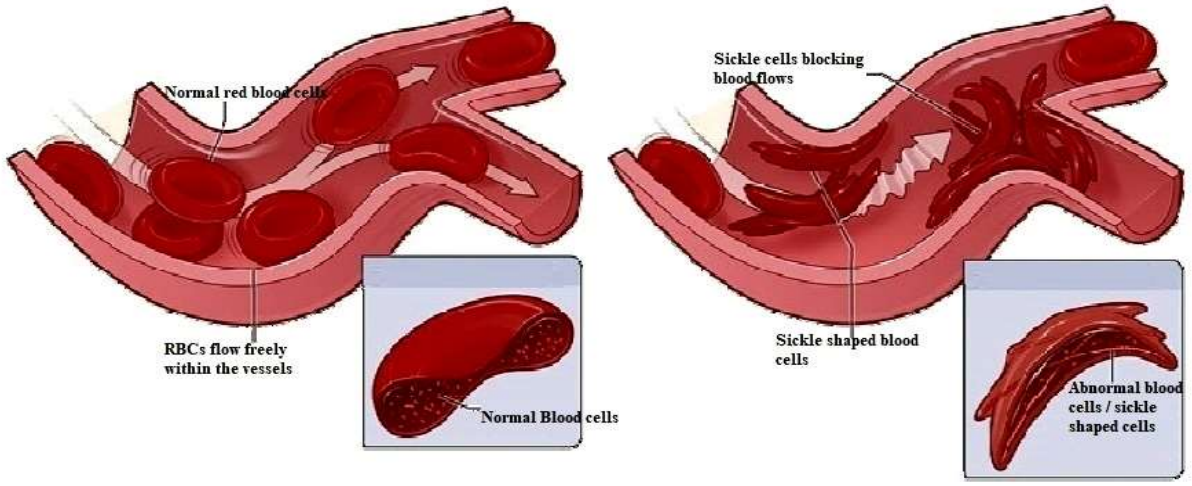


Figure.3: Structure of Normal RBCs and Sickle RBCs

Life span of a normal blood cell is approximately 120 days, so after that new blood cell is generated [10]. Sickle blood cell life span is 10-20 days [11], which inherited disorder that affects normal blood cells i.e. Red Blood Cells (RBC) [10, 12]. The presence of sickle blood cells in the hemoglobin that leads the formation of sickle shaped



cells, which are very rigid and sticky as shown in below **figure.4**.

Figure.4: Diagram of the flow of RBCs in the Vessels in normally and Sickle cell cases

In the above **figure.4**, we can see that the normal blood cells flow in the vessels freely but the sickle shape cells are sticky, due to that they stop the blood flow. In normal blood flow the oxygen circulation is properly done from organ to organ but in SCD the blood flow is blocked, so that oxygen circulation will stop at any moment. Due to the blockage of blood cells different body stress will start like severe body pains, heart strokes, and swelling of body parts etc. Treatments like taking antibiotics like prophylactic, immunizations, folic acid tablets and hydroxyurea and blood transfusion are taken for curing of this disease. The severe affected patients are advised to go with BMT, which is treated as high impacted treatment for SCD [13, 14].

SCD is a very rare blood disorder which is observed in every stages of life of human but especially newborn baby. Due to its sticky and stiff blood cell, the blood flow stops. If one organ affected slowly it will be spreading the entire human organs then it leads to death of that human. For its prevention blood transfusion during every 1-2 month for proper oxygen flow and nutrition will take place. In a study [15] by Narcisse Elenga et al. has focused on the complications at the time of pregnancy like numerous obstetrical, non obstetrical and fetal complications and their precaution including primary physician, Obstetrician and an integration of Centre for Sickle Cell Disease.

Gardner [16] in the late 1910, Sickle cell Disease was discovered and abbreviated as SCD. It was first discovered in US but the discussion was held in Africa. On the basis of the reports of Dr. James B. Heerick (Cardiologist) on a dental student studying in Chicago named Walter Clement Noel, who was suffering from body pains and symptoms of anemia and testing by Dr. Emest Iron the red blood cells are " shape of sickle" be known and later in a publication termed as "sickle shaped cells".

In India [17] first case was identified in the Nilgiri hills of northern Tamil Nadu in 1952. Later it was widespread among Tamil Nadu and north Kerala. In worldwide and it is observed particularly in Spanish speaking regions (i.e. The Caribbean, Central America and South America), Saudi Arabia, India, Mediterranean countries includes (Greece, Italy and Turkey) and Sub- Saharan Africa. New born babies were observed during 1999-2002 in African and America, where the observation show 42% of young children below 4 years get affected by SCD, but with the help of vaccination in 2000 protection against pneumococcal disease was taken. Like that in different countries different records were found against SCD, which now a day a big problem to control over it [15].

2.1. TYPES OF SICKLE CELL DISEASE (SCD)

Most common types of SCD are as follows, which was characterized by its severity.

a. **Sickle Cell Anemia (SS):** Here the child is inherited by β- globin genes (Sickle cell gene) from each parent by one substitution. High frequencies of the population affected by this disease are from African and Indian descents.
b. **Sickle Hemoglobin- C Disease (SC):** This disease causes similar symptoms but less anemia effect due to higher blood count level. Here slightly different level of substitution in their β- globin gene producing hemoglobin- S and C are formed. West African, Mediterranean and Middle Eastern region show high frequencies of infection.
c. **Sickle Beta- Plus Thalassemia (SB):** Both β- globin genes are substituted in this case. Severity of this disease cause according to the amount of normal β- globin genes produced. In the severe case of this disease chronic blood transfusion need. Populations of Mediterranean and Caribbean descents are mostly affected by this category of disease.
d. **Sickle Hemoglobin- D Disease (SD):** Individuals with SD disease have moderately severe anemia and occasional pain in their body parts. Populations of Asian and Latin American descents are mostly affected by SD.
e. **Sickle Hemoglobin- O Disease (SO):** It shows the similar symptoms of Sickle cell anemia but frequency of severity is high than SD. This type of diseases is found in North Africa, Arabian and Eastern Mediterranean region [18].

2.2. CAUSES OF SICKLE CELL DISEASE

Shortage of hemoglobin in blood is the main cause of SCD disease. It is caused by the blocking of blood flow in the veins and arteries due to Sickle shaped Red Blood Cells (RBC). So that defect in the genes responsible for production of hemoglobin occurs.

2.3. SIGNS AND SYMPTOMS OF SICKLE CELL DISEASE

Different symptoms are shown in the body affected by the Sickle cell disease according to the severity of the disease. Blockage of blood flow causes the pains in different part of body. The general symptoms of SCD are like [19]:

- Pain in different body parts like, joints, chest and abdomen.
- Swelling of hands and feet.
- Organ damage and infection in body.
- Body growth is delayed due to lack of oxygen.
- Blur vision problem for insufficient blood circulation to the eye sights [19].

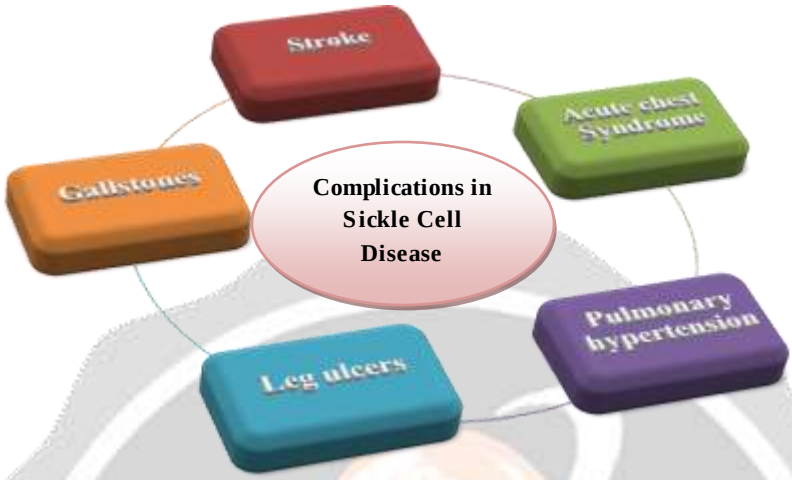


Figure.5: Side effects and complications in Sickle Cell Disease

2.4. TESTS FOR SICKLE CELL DISEASE

No specific test for SCD is done. Normal blood tests and CBC are done for testing the level of hemoglobin (Hb). According to the Hb level the severity of the SCD is calculated. But for identification and characterization of the SCD disease different tests are performed [20, 23].

- **Blood Tests:** Abnormal Hb level ranging from 6-8 grams per deciliter and the irregularity of RBCs structure is shown.
- **Hb electrophoresis:** Different types of hemoglobin in the blood are measured in this test. It is the confirmed test for Sickle cell disease [21].
- **Blood Smear test:** It is a simple test of blood on the glass slide for seeing the structure of the RBCs structure.
- **Complete Blood Count (CBC):** Different level of blood test in all the aspects of blood content is performed in this test. All the tests including SCD test are done in this test [22, 24].

Figure.6: Advance technology used in District Headquarter Hospital for identification and Characterization of Sickle Cell Disease

2.5. MEDICATIONS FOR SICKLE CELL DISEASE

The SCD disease is a hereditary disease that inherited from parents. As it is caused in the blood by the deficiency of haemoglobin, so that it cannot be cured but its effect can reduced for which its severity will reduce by using some medications like, **Hydroxyurea (Hydrea), L- glutamine oral powder (Endari), Voxelotor (Oxbryta) and Crizanlizumab- tmca** etc. These medicines are used for increasing the oxygen level, reduce the number Sickle cells, producing the healthy haemoglobin, and preventing good blood cells for sticking to blood vessels in the blood respectively. So that the blood flow and the oxygen level will be normal inside the body [25].

3. THALASSEMIA (THAL.)

Thalassemia (Thal) also known as Mediterranean anemia, is a group of Inherited / genetic disorder. It makes the body to produce less number of red blood cells (RBCs) and less Haemoglobin (Hb) than normal blood cells. In thalassemia cases insufficient haemoglobin in blood causes less oxygen availability in blood and less iron rich protein in RBCs. So that oxygen does not reach properly in all parts of the body, which causes starvation of O_2 in different organs. Due to that the body parts where the O_2 and the iron rich proteins cannot reach cause inability to function properly and severe body pain. In Thal cases minimum one of the parent is a carrier / trait, or it can cause due to genetic mutation or replication of main gene fragments. The patient having thalassemia will carry three stages of cases i. e. Minor, Moderate and Major [26-28]

Patients with the major cases (Most serious form) i.e Thalassemia Major, two processes are taken for precaution [31]. One is Blood transfusion, which balance the haemoglobin and RBCs level and other is Iron Chelating therapy that controls the body iron level that also control joint pain, body parts damage, infections and pain [32, 33]. But many patients' especially rural areas or low resources areas face many complications due to not getting appropriate treatment [33]. In 2006 WHO designated Thalassemia, a major public health concern [34]. Accurate information about the complications and burdens are identified from many countries of Asia. For the deficiency of information about the patient numbers, genotypes, treatment methods, complications and precaution accordingly with the disease, there is need of advice to the government and the policy makers about the burden of this disease [30].

The Thalassemia patients show mild or sever criteria of anemia characteristics, which produce lower number of red blood cells or not sufficient haemoglobins in the RBCs. It shows the symptoms mainly feeling tired, pale skin, bone problem, enlarged spleen, yellowish skin, dark urine and slow growth in adolescence [26-28]. In thalassemia cases the deficiency of the genes that control the production of the proteins named α- globin and β- globin, which are helpful for production of haemoglobin (Hb). The figure.7 shows the difference between normal blood cells and the thalassemia blood cells.

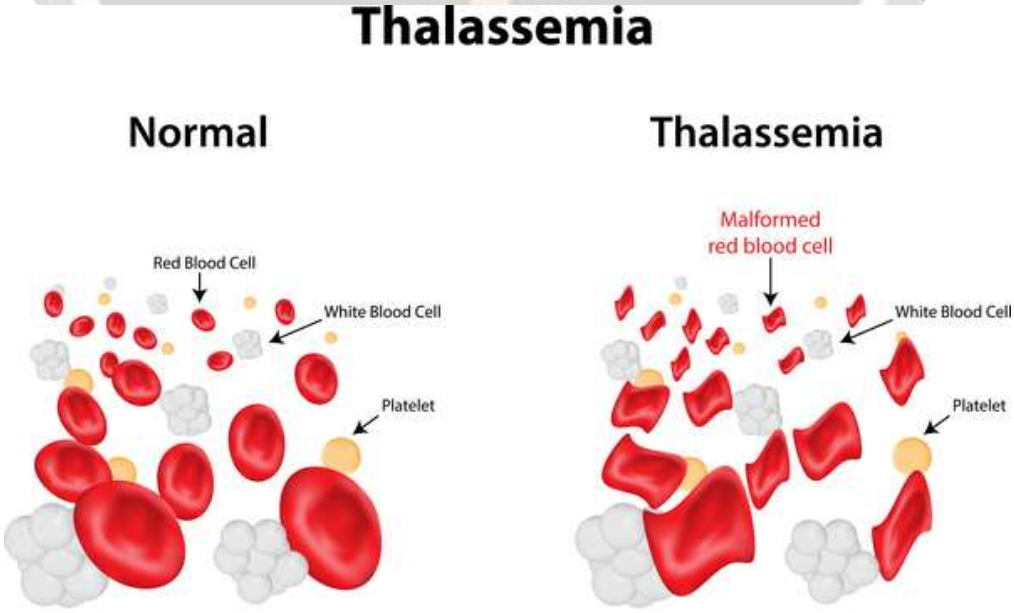


Figure.7: Diagram of Normal Red blood Cell and Thalassemia blood cells

3.1. TYPES OF THALASSEMIA

The main forms of thalassemia are:

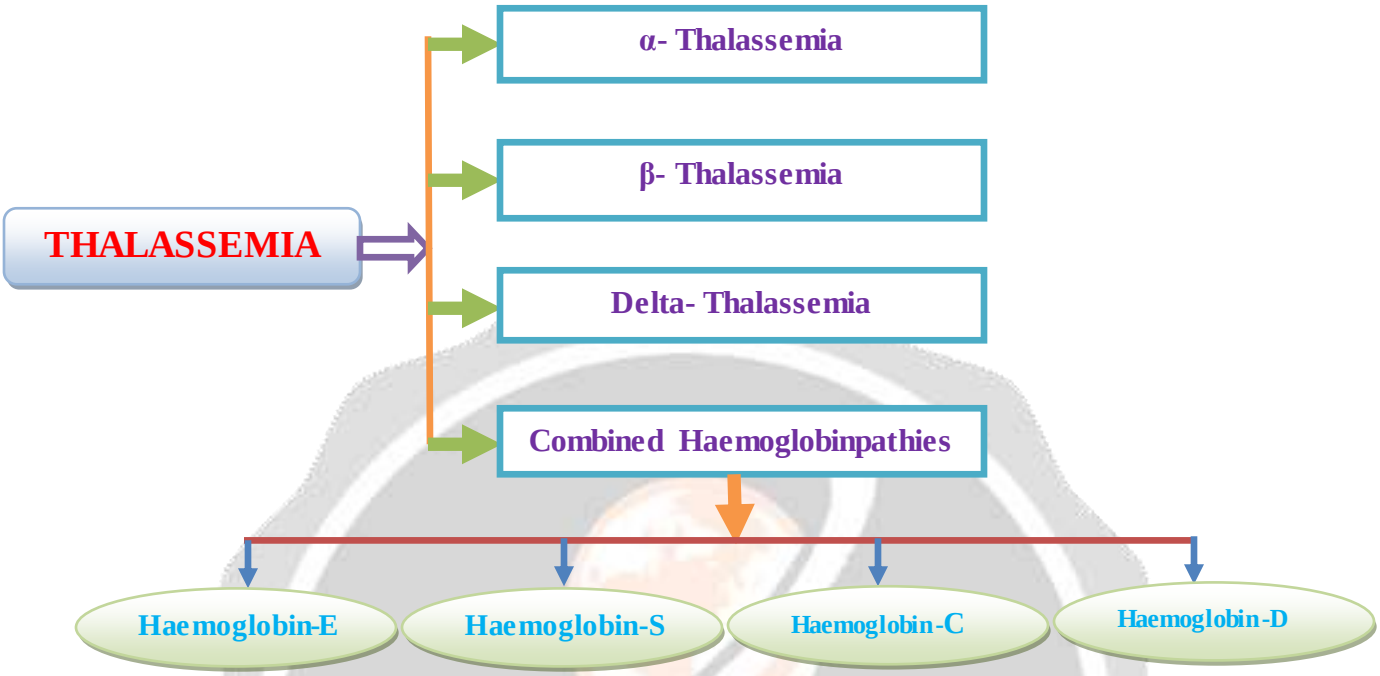


Figure.8: Different types of Thalassemia according to the severity

In **Alpha- thalassemia** the alpha-globins are not formed, so that the anemia affects the baby / the child even before the baby birth. It is a major type of anemia where the pregnant woman carrying the baby is at risk for the infection.
Beta- thalassemia is a major case of life threatening anemia also named as "Cooley's anemia". Paleness, poor appetite, frequent infections, enlargement of organs and jaundice are the major symptoms in this case. This needs regular blood transfusions.
Delta- thalassemia is the type of Thal cases like beta- thalassemia**,** which affect the production of delta chains and also minimize the blood haemoglobin level.
Combined Haemoglobinopathies Thalassemia exists by combining with other Haemoglobinopathies disorders like:

- **Haemoglobin-E** is a major β- thalassemia or intermediate thalassemia, which is common in Thailand, India and Cambodia.
- **Haemoglobin-S** is a criteria of thalassemia which enlarges the spleen and also clinically similar to sickle cell disease. It is common in African and Mediterranean countries.
- **Haemoglobin-C** is a middle stage of anemia causes spleen enlargement. This is common in African and Mediterranean countries.
- **Haemoglobin-D** is common in India and Pakistan causing normal anemia symptoms [26, 29].

3.2. SIGNS AND SYMPTOMS

Major criteria of thalassemia shows severe genetic defect and also produce less haemoglobin. Like that more its severity the results of symptoms is more. But in minor cases no symptoms are shown and usually silent in nature. The symptoms of Thalassemia major is shown in below,

- Fatigue
- Enlarged spleen and liver
- Yellowish skin
- Dark urine
- Jaundice
- Changes in Bone i.e. pain in joints, pale skin etc.

3.3. TREATMENT OF THALASSEMIA

Figure.9: Treatment and Therapy for Thalassemia patient

Depending on the patient's clinical treatment according to its mode of action different therapies including blood transfusion, folic acid, iron chelating agents and hematopoietic cell transplant will be need.

Blood transfusion will help the patients to control the haemoglobin level and the iron level in the blood. This process continues for making the blood deficiencies to control over it [35]. Earlier transfusion process with iron chelating therapy is recommended to reduce the future complications due to Cooley's anemia [36].

Hematopoietic stem cell transplant (HSCT) replaces the unpaired endogenous hematopoietic cells with effective allogeneric alternatives to permanently produced red blood cells. These transplanted patients don't need blood transfusion as it has already produced the normal RBCs [37]. While allogeneic HSCT is often limited by lack of suitable donors, it will transplant with unrelated donor. Recent studies indicate that at the stage of β - thalassemia major cases it is comparable between unrelated donor and identity donor [38-41].

Gene therapy repairs own bone marrow cells by converting the normal b and g - globin gene into hematopoietic stem cells (HSCs) for permanent erythropoietic effect [42]. For clinical investigation it was reported that self mobilization of CD34+ cells in adult with β- thalassemia and the effectiveness of globin gene transfer [43-45].

3.4. MAJOR MEDICATIONS

Iron chelating agents, Deferoxaminemesylate chelates, Deferasirox (Exjade), Deferiprone (Ferriprox), Antipyretics, Vitamines, Hydroxyurea, Antihistamines and vaccines are the medications and therapies used to control over the Thalassemia disorder by different stages with different concentrations. These medications will help the patients to minimize the mode of action and infection of the Thal disease to the body and its parts [46, 47].

4. DIFFERENCE BETWEEN SICKLE CELL DISEASE AND THALASSEMIA [48]

Table.1: Difference between Sickle Cell Disease and Thalassemia Disease

Sickle Cell Disease	Thalassemia
Definition	
An inherited red blood cell disorder, which is caused by the deficiency of healthy red blood cells to circulate oxygen throughout the body.	An inherited disorder, which is caused by the drop in the hemoglobin level, which enables red blood cells to circulate oxygen throughout the body.
Mutation	
Mutation on chromosome 11	Mutations in the DNA of cells
Symptoms	
Fever Delay in growth.	The signs and symptoms depend on the type and severity. General symptoms include:

Episodes of pain. Vision problems. Swelling of hands and feet. More prone to infections. Show all the symptoms of anemia.	Fatigue Retard growth. Abdominal swelling. Dark colored urine. Pale or yellowish skin. Facial bone deformities.
Diagnosis	
HPLC Sickling test. DNA sequencing. Mass spectrometry. Isoelectric focusing. Haemoglobin electrophoresis.	DNA analysis. Amniocentesis and other Prenatal testing. Blood tests to check the size, shape and colour of the red blood cells.
Treatments	
There is no cure for sickle cell anemia. Medications and other treatments are given to relieve pain and help prevent complications associated with the disease.	Stem cell transplant. Intake of Irons supplements. Lifelong blood transfusions. Hyper-transfuse to suppress erythropoiesis.
Complications	
Stroke Blindness Pulmonary hypertension. Pregnancy complications. Damage to nerves and other organs.	Can cause anemia and in some rareconditions, resulting in bone deformities andheart problems.

5. STEPS FOR AWARENESS AND CONTROL OF SCD AND THAL IN SOCIETY [49-54]

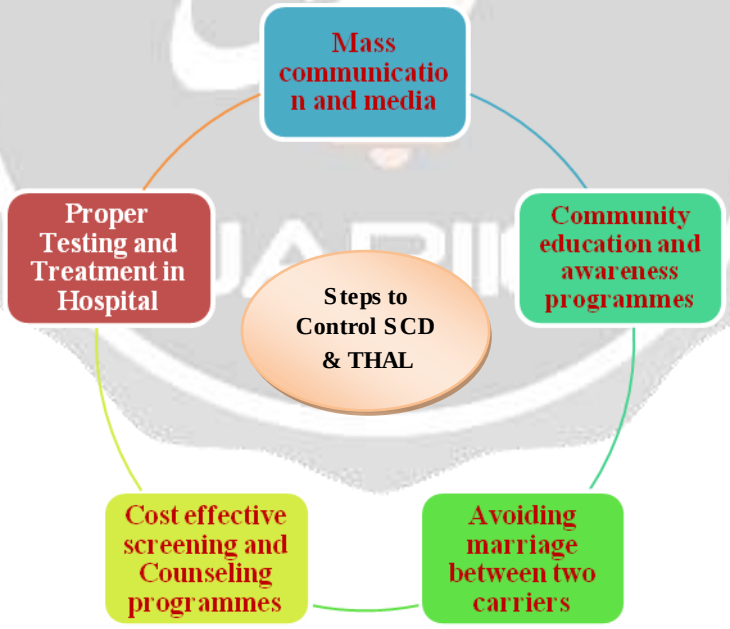


Figure.10: Steps for controlling the Sickle cell disease and Thalassemia in community level.

6. CONCLUSION

Improving case management and developing a culture to focus on rare and chronic disorders, which are recently appearing in the spectrum of clinical experience of local specialists, is a challenge. The organization of healthcare services for *unfamiliar* conditions to the authorities, raising awareness to a health burden which is now increasing,

requires resilience in health service management, when concerns over adequacy of budgetary support are paramount. The fact that poor monitoring and treatment now will increase complications and costs over time is not known to many services. Change in some settings takes time, especially where a culture of networking and collaborative care is a necessity. Such networking is possible because centers of expertise do exist in most European countries. The management of hemoglobin disorders shares the same difficulties with other rare conditions in Europe. Additional issues arise because the conditions are recently *imported*, and the social considerations of immigrant populations. Nonetheless, there is ample international expertise and knowledge to be offered for the appropriate clinical management and care of patients with hemoglobin disorders that would guarantee an improved quality of life.

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