

Guest Editor: Bhim S. Pandhi

Thalassemia Minor and Major: Current Management

Ved Prakash Choudhry^{1,2}

Received: 15 February 2017 / Accepted: 17 February 2017 / Published online: 24 April 2017
© Dr. K C Chaudhuri Foundation 2017

Abstract Thalassemia is a common genetic disorder. It has been estimated that in India nearly 5 crore people are thalassemia carriers. They are asymptomatic and are detected on blood tests. These people are at same risk of developing iron deficiency anemia as general population and need iron therapy in the presence of iron deficiency anemia. Nearly 12,000 children with thalassemia major (Homozygous state) are born every year. These children often present with significant anemia along with hepatosplenomegaly during infancy and require early diagnosis and institution of therapy with repeated blood transfusions and chelation therapy. Adequate dose of chelation therapy is essential to maintain serum ferritin around 1000 ng/ml. With present protocol of management, thalassemic children have near normal life. Bone marrow transplantation offers cure for these children; results of bone marrow transplantation are best when performed below 7 y of age.

Keywords Thalassemia minor · Thalassemia major · Chelation therapy · Long term survivals

Thalassemia Minor

India has ethnically diverse population of 1.25 billion. Prevalence of thalassemia carrier/trait/minor varies between

1 and 17% of population with an average of 3.5%. In a large multi-centric study undertaken in six states of India by Indian Council of Medical Research which involved over 56,000 school-children, the prevalence of thalassemia minor was 2.78% [1]. It is a heterozygous state and the individual has a mutation in one chain of β -globin for hemoglobin. Individuals with thalassemia minor are usually asymptomatic. They often have mild anemia varying between 9 and 11 g/dl; some individuals have normal hemoglobin levels. Anemia worsens in presence of nutritional deficiency such as iron, folic acid or vitamin B₁₂. Red cell indices reveal mean corpuscular volume (MCV) below 80 fl/cell and mean corpuscular hemoglobin (MCH) below 27 picograms/cell. Red cell counts may be normal or slightly increased. Peripheral smear show microcytic hypochromic picture with occasional target cells. Diagnosis of thalassemia minor/carrier/trait is confirmed by estimation of HbA₂ which is more than 3.5% on hemoglobin electrophoresis by high performance liquid chromatography (HPLC). It is essential to differentiate it from iron deficiency anemia [2] (Table 1). Rarely, HbA₂ may be low in presence of severe iron deficiency anemia due to suppression of hematopoiesis. In such a situation, hemoglobin electrophoresis by HPLC should be repeated after correcting iron deficiency anemia. Thalassemia carriers have same risk of developing iron deficiency anemia as general population. They should be given iron therapy whenever they have evidence of iron deficiency anemia.

Now, silent thalassemia carrier state has been identified in which persons are asymptomatic and their all RBC indices such as hemoglobin level, MCV and MCH are within normal limits. In some cases, HbA₂ levels even may be normal. Silent carriers are suspected when their children are diagnosed as Thalassemia major. Following mutations have been identified in persons with silent thalassemia carrier state. At times, some individuals with homozygous state with these mutations are asymptomatic.

✉ Ved Prakash Choudhry
vedpchowdhry@yahoo.co.in

¹ Fortis Escorts Hospital, Neelam-Bata Road, Neelam Chowk, Faridabad, Haryana 121001, India

² Batra Hospital & Medical Research Center, 1, Tughlakabad Institutional Area, Mehrauli Badarpur Road, New Delhi, India

Table 1 Differences between iron deficiency anemia (IDA) and thalassemia minor

	Thalassemia minor	IDA
Hemoglobin	Normal/Low	Low
Erythrocyte count	Normal/Slightly increased	Decreased
Peripheral smear	Microcytic & hypochromic	Microcytic & hypochromic
Serum iron	Normal	Reduced
UIBC	Normal	Reduced
TIBC	Normal	Increased
Transfusion saturation	Normal	Decreased
Serum ferritin	Normal	Reduced
Protoporphyrin & haem ratio	Normal	Increased
HbA ₂ level	Increased	Normal

UIBC Unsaturated iron binding capacity; TIBC Total iron binding capacity

1. Cap + 1 (A–C) (4% of carriers in Punjab have this mutation)
2. IVS-II – 844
3. 92 C (C–T)
4. 101 ?(C–T)

It is essential to exclude silent carrier while counseling an individual with thalassemia minor for marriage.

Management

Children with thalassemia minor are usually asymptomatic. Their hemoglobin levels may be normal or mildly sub-normal. Hemoglobin levels usually vary between 10–12 g/dl. Various hematological parameters are normal including serum iron studies and serum ferritin levels. MCV and MCH values are low while RBCs counts are high. These individuals are at the same risk of developing anemia as the general population, and the causes of anemia are similar to that of the community. Anemia in these individuals may develop from other causes such as megaloblastic anemia, anemia secondary to blood loss due to various factors, paroxysmal nocturnal hemoglobinuria (PNH), refractory anemia, celiac disease, aplastic anemia, myelodysplastic anemia *etc.* During pregnancy, iron deficiency develops commonly, but needs to be confirmed by iron studies. Thalassaemic minors should be given iron therapy only if iron deficiency is established by serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin levels. Iron therapy should be given for a period of six months after establishing the diagnosis. All individuals with thalassemia minor should receive folic acid routinely.

Thalassemia Major

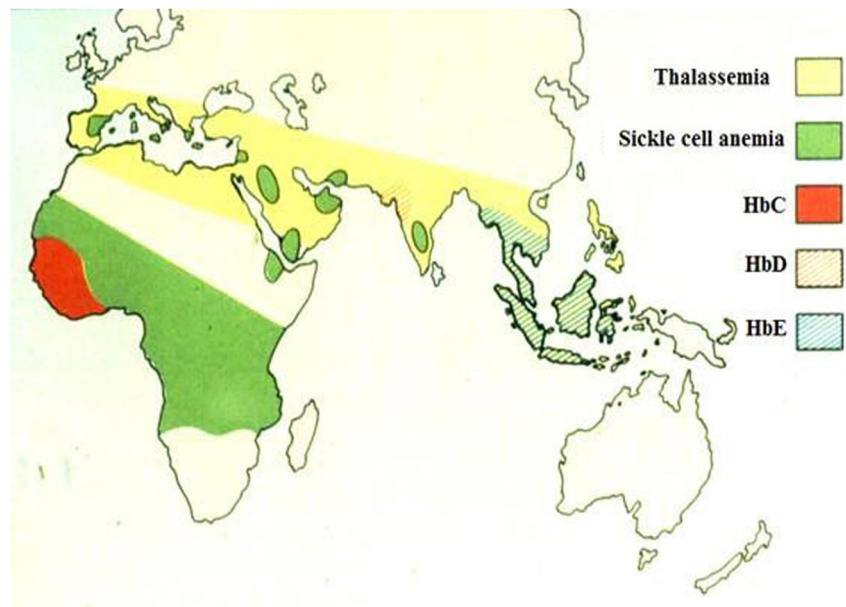
WHO has estimated that 4.5% of the World's populations is affected by thalassemia and allied disorders. Thalassemia belt spans across countries such as Italy, Greece, Cyprus, Sardinia, Turkey, Saudi Arabia [3], Iran, Afghanistan, Pakistan, India

and South East Asian countries like Indonesia, Burma and Thailand (Fig. 1). Nation-wide survey by ICMR under Jai Vigyan Mission project has revealed that nearly 4% of people in India have Thalassemia minor (5 crores), while nearly twelve thousand children with Thalassemia major are born in India every year. There are nearly 1.25 lakh thalassaemic children in India. Thalassemia is very common in certain communities like Punjabies, Sindhis, Gujaratis, Bengalis, Parsis, *etc.* It is more common among Punjabies who have migrated from West Pakistan with prevalence of over 15%. Prevalence of thalassemia in North West and North East part of India is higher while it is less common in South. Hemoglobin E disease either alone or in combination with thalassemia is much more common in North Eastern states.

Clinical Presentation

It is a serious inherited blood disorder in which red cell survival is greatly reduced due to imbalance between α and β chains. The clinical picture is dependent on four major factors *viz.* (i) reduced hemoglobinisation of red cells (ii) increased hemolysis (iii) ineffective erythropoiesis and (iv) extramedullary hematopoiesis [4].

Infants are normal at birth and develop anemia between 3 and 18 mo of age. Anemia is progressive, persistent and does not respond to any hematinic therapy. Infants become irritable and have poor development if left untreated. They develop prominence of frontal and facial bones and hepatosplenomegaly as a result of ineffective erythropoiesis. Facial changes are termed as thalassaemic facies (Fig. 2). These children are at a higher risk of developing recurrent infections due to decreased immunity. Iron absorption increases as a result of (a) hypoxia and (b) ineffective erythropoiesis and gets deposited in skin, liver, heart and endocrine glands. However, the main source of iron overload in these children is from blood transfusions. Poor growth, abnormal facies and hepatosplenomegaly does not occur if these children are managed early with current protocols.

Fig. 1 World map of thalassemia

Diagnosis

The diagnosis is based upon the presence of (a) moderate to severe anemia (b) reduced red cell indices such as MCH, MCV, mean corpuscular hemoglobin concentration (MCHC) (c) microcytic and hypochromic picture with anisocytosis and poikilocytosis on peripheral smear (d) increased fetal hemoglobin level for age (20–90%) and normal or reduced HbA₂ levels. Bilirubin levels may be raised which will be predominantly unconjugated. S. iron levels, transferrin saturation and ferritin levels may be normal or raised depending upon the age of the child. Radiological changes are often present in older children, which are secondary to marrow expansion and include sun-ray appearance of skull, cortical thinning of long bones with osteoporosis of vertebrae and (b) small bones of hands and feet.

Management

With current protocols of management (Table 2) it has been observed that children born after 1995 have normal life (Fig. 3).

**Fig. 2** Beta thalassemia major – bone changes

Blood Transfusion Therapy

Current recommendations state that blood transfusion therapy should be initiated as soon as the diagnosis is established and if the hemoglobin levels are below 7 g/dl at least on two occasions [5].

Investigations such as a) Complete blood grouping (ABD, Rh, + along with Kell, Kidd, M,N, lewis *etc.* systems) b) Family studies for genetic counseling c) HLA typing of sibling and parents for future possibility of bone marrow transplantation should be carried before starting transfusion therapy and d) Hepatitis B vaccination should be given if it has not been given earlier.

Among various transfusion regimens, now it is recommended to treat these children with high transfusion therapy in which pre transfusion hemoglobin should be maintained at 10 g/dl because of its multiple advantages (Table 3).

It is preferable to transfuse fresh blood which is leucodepleted as transfusion of lymphocytes results in (a) suppression of the immune system (b) reduces the risk of non-hemolytic febrile

Table 2 Principles of management of thalassemia

- i) Regular blood transfusion to maintain pre transfusion Hb above 10 g/dl
- ii) To maintain S. ferritin levels below 1000 ng/ml by use of iron chelators either singly or in combination
- iii) Early detection and management of complications of blood transfusion and chelation therapy
- iv) Regular monitoring of growth and development, hematological & biochemical parameters
- v) Splenectomy, if required
- vi) Early detection and management of endocrine problems
- vii) Psychosocial support

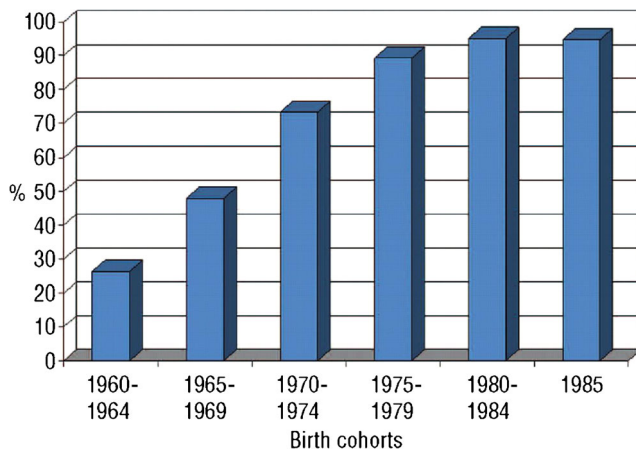


Fig. 3 Survival in 2009 of Italian patients included in the Seven Centers Study, according to birth cohort. (Ref: Caterina Borgna-Pignatti. *Haematologica* March 2010;95:345–8)

reaction, (c) prevents the development of alloimmunisation of human leucocyte antigen (HLA) class I antigens and (d) prevents cytomegalovirus (CMV) infection. Packed cell transfusion should be given at 3–4 weekly interval and each time 10–15 ml/kg of blood can be transfused over 3–4 h.

Approximately 180 ml/kg of packed cells are required per year in non-splenectomised children.

Children with cardiac disease or congestive cardiac failure should receive only 5 ml/kg of blood under close monitoring.

Chelation Therapy

Each unit of packed cell contains 200–250 mg of elemental iron which is released in the body with breaking of the red cells. It is the major source of iron which gets deposited in the liver, heart and various endocrine glands. Increasing iron deposition in various organs results in their dysfunction. Body iron levels can be measured by (a) serum ferritin (b) liver and cardiac biopsies, (c) SQUID & MRI T2 Ferri scan *etc.* Among these, serum ferritin is the most practical and can be monitored every three monthly. Among various other tests MRI T*2 is now practical and provides liver and cardiac iron overload more precisely. Now, it is of great help in chelation therapy. Other tests are carried to assess the function of various organs,

Table 3 Advantages of high transfusion therapy

- i) Ensures normal growth and development
- ii) Decreases ineffective erythropoiesis and prevents osteoporosis and facial deformities.
- iii) Prevents splenomegaly
- iv) Decreases iron absorption from intestine
- v) Normal development of immune system
- vi) Normal physical and psychological well-being
- vii) Better quality of life

such as ECHO, TSH, T3 and T4 levels, growth hormone levels, serum testosterone, FSH, LH, bone mineral density *etc.*

Presently, three iron chelators have been approved and are being widely used either alone or in combination to ensure effective chelation therapy. Chelation therapy should be initiated when S. ferritin is > 1000 ng/ml or the child has received 15–20 units of transfusion.

Desferrioxamine (DFO) is a hexadentate where one molecule of DFO binds with one molecule of iron. It has a very short life and needs to be administered continuously with the help of infusion pump subcutaneously (SC) over 12–14 h daily. It should be started by 2 y of age and ferritin levels should be maintained between 1000 and 1500 ng/ml. It is given in a dose of 30–50 mg/kg/d. Addition of vitamin C (100 mg/d) increases the iron excretion. It is fairly safe and has minimal toxicity. Its parenteral administration may result in bradycardia, hypotension, rigors, headache and photophobia. Subcutaneous administration causes local pain, induration, irritability and redness. Prolonged administration may result in peripheral field defects and sensori-neural hearing loss.

Deferiprone [6] is the first oral drug developed in Hider's laboratory. It has been shown to be effective in a dose of 70–100 mg/kg/d. It is more effective than DFO in mobilizing intracellular iron from the heart. It needs to be given in 2–3 daily doses. Its side-effects include nausea, abdominal pain and diarrhea. Nearly 20% of children with high serum ferritin level develop arthropathy and less than 1% develop severe neutropenia.

ICL-670 is a new class of tridentate in which two molecules of chelator binds with one iron molecule to form ferric molecule complex. It is twice as effective as DFO. It chelates iron from reticulo-endothelial cells and parenchymal cells of various organs. It also prevents myocardial cell iron uptake and removes iron directly from the myocardial cells. This drug has a half life of 11–16 h and needs to be given in a single dose of 30–40 mg/kg daily. Its side-effects include abdominal pain, diarrhea, vomiting, skin rash, *etc.* These symptoms are usually mild. There is no arthralgia, cardiac, ocular or vestibular side-effects. It is now considered as a gold standard chelating agent.

Combination Therapy Children who have high levels of serum ferritin or have cardiac, liver and endocrine dysfunctions should be treated with combination therapy such as a) DFO and deferiprone b) DFO and ICL-670 or c) Deferiprone and ICL-670 [7]. The advantages of combination therapy include a) access to different iron pools, b) prevention of non-transferrin bound iron accumulation, c) better compliance and above all; improvement of the quality of life. DFO may be given twice or thrice a week while other agents are given daily. It is preferable that combination therapy should be administered under supervision of an expert care.

Splenectomy

It has been proved that if hemoglobin levels are maintained above 10 g/dl, hypersplenism does not occur. With standard treatment, splenomegaly and hypersplenism have become a rarity in the developed countries. However, in India, many children develop splenomegaly and hypersplenism because of poverty and poor facilities. If the child has already developed splenomegaly and signs of hypersplenism, then splenectomy is indicated. It should be undertaken only after 6 y of age because of higher chances of sepsis in younger age group. Splenectomy is also indicated if the yearly requirement of packed cells is 200 cc/kg or more. Decrease in WBC and platelet count is a late manifestation of hypersplenism. All children needing splenectomy should receive pneumococcal, *H. influenzae* and meningococcal vaccines at least 3 to 4 wk prior to the surgery. The family should be counseled regarding the risks and benefits of splenectomy. Prophylactic penicillin therapy must be continued life-long after splenectomy. Episode of infection should be treated promptly with broad spectrum antibiotics and children should be hospitalized. All efforts should be made to isolate the microorganism for appropriate antibiotic therapy.

Bone Marrow Transplantation (BMT)

Bone marrow transplantation offers permanent cure and better future for children. The credit for the first bone marrow transplantation in thalassemia major goes to E. Donald Thomas who performed this procedure in an 18-mo-old thalassemia child in 1982 using an HLA matched elder sister as the donor. This child was cured of thalassemia. Since then many centers in the world and twenty five in India have initiated BMT facilities. The principles of bone marrow transplantation include (a) to destroy and prevent regeneration of defective stem cells, (b) sufficient immune suppression for good engraftment, (c) to infuse stem cells with the normal gene, (d) to prevent Graft versus host disease (GVHD) with proper combination of immunosuppression and infection management [8].

Three most important adverse prognostic factors for survival and event-free survival have been observed in large studies which include: a) Presence of hepatomegaly (2 cm below costal margin), b) Portal fibrosis and c) Iron overload (S. ferritin > 1000 ng/ml).

Based upon these factors, children have been divided into three classes: Class I, when all these factors are absent; Class II, when one or two factors are present and children with presence of all factors are termed as Class III. Event-free survival is seen in more than 97% of cases in Class I and 66% in Class III cases. All children should be treated with current protocols to maintain them in Class I and perform BMT at the earliest possible.

Long Term Survival

Over the years, long term survival with current management protocols has increased significantly. Multicentric studies have revealed that children born after 1995 have near normal life (Fig. 3) [9]. In India, survival has improved and majority of children who are on adequate transfusion and chelation therapy from early childhood are seen in second and third decade of life.

Key Messages

1. Thalassemia is very common in India.
2. Diagnosis should be established during infancy.
3. Current protocols of therapy have improved the survival & quality of life. Now, a child with thalassemia can live near normal life.
4. Bone marrow transplant offers, complete cure and should be undertaken as soon as possible.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

References

1. Mohanty D, Colah RB, Gorakshakar AC, et al. Prevalence of β -thalassemia and other haemoglobinopathies in six cities in India: a multicenter study. *J Community Genet.* 2013;4:33–42.
2. Choudhry VP. Anemia. In: Choudhury N, Bharucha ZS, editors. A textbook on laboratory and clinical transfusion medicine. Good clinical transfusion practices, vol. 3. New York: Nova; 2016. p. 1–34.
3. Weatherall DJ. Haemoglobin and the inherited disorders of globin synthesis. In: Hoffbrand, Catovsky, Tuddenham, editors. *Postgraduate hematology.* 5th ed. Hoboken: Blackwell Publishers; 2005. p. 85–103.
4. Choudhry VP, Aroa JS. Thalassemia. In: Gupta P, Menon PSN, Ramji S, Lodha R, editors. *PG textbook of pediatrics,* vol. 2. New Delhi: Jaypee Health Science; 2015. p. 1556–64.
5. Trompeter S, Cohen A. Blood transfusion. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. *Guidelines for the clinical management of transfusion dependent thalassemia.* 3rd ed. Cyprus: Thalassemia International Federation Publication; 2014. p. 28–41.
6. Choudhry VP, Pati HP, Saxena A, et al. Deferiprone, efficacy and safety. *Indian J Pediatr.* 2004;71:213–6.
7. Taher AT, Musallam KM, Cappellini MD, Weatherall DJ. Optimal management of β -thalassemia intermedia. *Br J Hematol.* 2011;152: 512–23.
8. Chandu M. Stem cell transplantation in India. *Bone Marrow Transplant.* 2008;42:S81–4.
9. Borgna-Pignatti C. The life of patients with thalassemia major. *Haematologica.* 2010;95:345–8.