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Review Article

Thalassemias in Manipur, India

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ABSTRACT

Thalassemia is a group of inherited blood disorders. It presents a significant health challenge in Manipur, India, due to the high prevalence of hemoglobinopathies such as hemoglobin E (HbE) and β-thalassemia. This region exhibits unique genetic characteristics, with the Meitei population showing a notably higher incidence of HbE hemoglobinopathies. Thalassemia is classified phenotypically into transfusion-dependent thalassemia (TDT) and non-TDT (NTDT). The management of these disorders are complex, involving regular blood transfusions for TDT patients and occasional transfusions or other treatments, such as hydroxyurea and splenectomy, for NTDT patients. This review highlights the challenges in managing thalassemias, emphasizing the importance of early and accurate classification to prevent unnecessary transfusions. Furthermore, complications such as iron overload, alloimmunization, and splenectomy-related risks underscore the need for tailored, careful treatment approaches. This research provides insights into the epidemiology, management strategies for thalassemia in Manipur, contributing to a better understanding of the disorder in this specific population.

Keywords: Non-transfusion-dependent thalassemia, Thalassemia, Transfusion-dependent thalassemia

INTRODUCTION

Manipur is situated in the extreme north-eastern corner of India. It is sorrounded by the Somra tract and the upper Chindwin areas of Myanmar on the east, the Cachar hills of Assam on the west, the Naga hills of Nagaland on the north, and the Chin Hills of Myanmar on the south. The majority of people living in this part of the country have a slightly different demographic and genetic characteristics as compared to the mainland India. Whenever any patient is diagnosed with low hemoglobin (Hb) with thalassemias, they are being managed as beta thalassemia major and start regular blood transfusion. This is due to the lack of awareness among many doctors about the various subtypes of hemoglobinopathies.

The thalassemias can be divided into two main groups. The first group is due to defective synthesis of one or more alpha or beta global genes. According to the chain whose synthesis is impaired, the thalassemias are called α, β, γ, δ, δβ, or εγδβ thalassemias. The second group is due to structural Hb variants such as Hb S, C, and E. A variety of thalassemia syndromes may result due to inheritance of different mutations from each parents or co-inheritance of thalassemia together with structural Hb variants. Based on their clinical severity and transfusion requirement, thalassemia syndromes can be classified phenotypically into two main groups as transfusion-dependent thalassemias (TDTs) and non-TDTs (NTDTs).[1,2]

The TDT is conventionally managed with lifelong regular transfusion requirements for survival and bone marrow transplantation whenever possible. The TDTs comprise beta thalassemia

major, severe HbE/β-thalassemia, and non-deletional Hb H thalassemia. On the other hand, the NTDTs do not require lifelong regular transfusions for survival. They may require occasional transfusions in certain clinical settings such as fever, pregnancy, and surgery. Sometimes, more frequent transfusion may be required in condition like poor growth or development specific comorbidities.[3] The NTDTs encompasses three clinically distinct forms: β-thalassemia intermedia, HbE/β-thalassemia (mild and moderate forms), and α-thalassemia intermedia (HbH disease).[4]

EPIDEMIOLOGY OF THALASSEMIA IN MANIPUR

The β-thalassemia constitutes 1.5% of the global population.[5] About 23,000 children are born with transfusion-dependent β-thalassemia major each year, while a smaller ill-defined number has the NTDT form β-thalassemia intermedia. The HbE is observed throughout India, Bangladesh, Thailand, Laos, and Cambodia where carrier frequencies may reach as high as 80%.[6] HbE//ethalassemia currently affects approximately 1,000,000 people worldwide.[7] Worldwide, HbE//-thalassemia was detected in 19,000 newborn each year with half of them having a severe transfusion-dependent form. The αhthalassemia constitutes 5% of the worldit population being carriers and an approximate of 1,000,000 patients are affected with the various αathalassemia syndromes worldwide.[8]

Singh *et al*. had studied blood samples of 1234 apparently healthy individuals belonging to four endogamous populations, namely the Meitei, Kabui, Koireng, and Simte of Manipur from March 2005 to October 2009. In their study, the Meitei group had highest incidence of HbE. The Meiteis had 18.207% HbE hemoglobinopathy. Of this 15.81% are heterozygous Hb E, 1.917% homozygous Hb E, and 0.48% compound heterozygous of HbE and beta-thalassemia. Incidence of HbE among the Kabui, Koireng, and Simte was 6.67%, 5.75%, and 2.44%, respectively.[9] A cross-sectional study by Karthika *et al*. in the Department of Physiology and Department of Pathology, Regional Institute of Medical Sciences, Imphal, between January 2014 and February 2015 on the prevalence of hemoglobinopathies in Manipur surveyed 400 patients and studied 354 patients with anemia. Their study detected the presence of hemoglobinopathy in 51 cases. Their study showed that 14.4% had presence of abnormal hemoglobin. Of which 7% were found to be beta-thalassemia carrier, 0.5% were homozygous B-thalassemia, 4% heterozygous Hb E, 1% homozygous Hb E, and 0.25% hereditary persistence of Hb F.[10] Another cross-sectional study conducted between June 2016 and May 2017 by Sharma *et al*. They studied a total of 453 cases with microcytic hypochromic anemia. They found hemoglobinopathies in 35%. Of these abnormalities, 16% were found to be beta-thalassemia carrier, 11.69% heterozygous Hb E, 6.62% homozygous HbE, 0.4% beta thalassemia major, and 0.7% had hereditary persistence of Hb F.[11]

Achoubi *et al*. did a community genetic screening of 602 blood samples from unrelated Meitei Brahmins (n = 300) and Meitei Muslims (n = 302). The Meitei Brahmins were Caucasoid type with consequent upon marriage with Meitei women (Mongoloid group) thus showing both Caucasoid and Mongoloid features. While the Muslim got married to Meitei women and had setteled in Manipur. In their study, 21.67% and 21.43% were heterozygous Hb E among the Meitei Brahmins and Meitei Muslims respectively. The study also found that 14.28% of Muslims showed the presence of homozygous Hb E. Interestingly, about 3.33% of the Brahmin samples showed the presence of β-thalassemia, while none of the Meitei Muslim samples showed the presence of β-thalassemia. Sequencing of the whole βholenci gene confirmed a very rare β-thalassemia (−90 C→T) in one Meitei Brahmin with β thalassemia trait.[12] The above studies showed that the majority of patients suffering from thalassemias in Manipur are due to HbE either as heterozygous, homozygous, or compound heterozygous inheritance with βithalassemia.

HAEMOGLOBIN E/β-THALASSAEMIA

HbE is caused by a substitution of glutamic acid by lysine at codon 26 of the βheoneic gene. HbE//ethalassemia is further classified into mild, moderate, and severe. The severe disease behaves as transfusion-dependent, clinical symptoms similar to β-thalassemia major and has a Hb level as low as 4–5 g/dL. The moderate ones behave like transfusion-independent, clinical symptoms similar to β-thalassemia intermedia with Hb levels between 6 and 7 g/dL, whereas the mild diseases are transfusion-independent, usually do not develop clinically significant problems and the Hb levels are between 9 and 12 g/dL. Mahidol score is used for the classification of HbE//ethalassemia. The score is calculated from the following variables including steady Hb level, age of onset, age at the first blood transfusion, requirement of transfusion, spleen size, and growth retardation. The total sum of all scores is then interpreted as follows: Mild HbE//-thalassemia (severity score <4), moderate HbE/β/thalassemia (severity score 4–7), and severe HbE//ethalassemia (severity score >7).[2]

An observational study was done by Peepa and Singh in the department of Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Manipur, from 2018 to 2020 to study the various subtypes of thalassemias attending JNIMS. The study included transfusion-dependent and NTDT receiving occasional transfusion and excluded the carriers. The severity of Hb Eb thalassemia was done by adopting Mahidol scoring. The study enrolled 76 patients who fit the inclusion criteria. There were 48 (63.15%) mild Hb-Eβ thalassemia, 20 (26.3%) moderate Hb-E- thalassemia, 6 (7.8%) severe Hb Eb thalassemia, and 2 (2.6%) β2thalassemia major only. In the study, the majority (43.5%) of

patients were above 30 years of age, followed by 26.3% among 10–20 years. The time of diagnosis was maximum in the age group of 5–10 years (32.9%) [Table 1].[13] From the above studies, we can understand that the patients in Manipur are vastly different from other parts of India. The patients suffering from βuthalassemia major were hardly seen unlike other parts of India.

BLOOD TRANSFUSION PRACTICE IN THALASSEMIAS

Patients with NTDT may not need regular transfusion. A transfusion program is not recommended even if a few transfusions have been administered in acute conditions during which Hb might have been lower. Patients with HbE// ethalassemia have a remarkable facility to adapt for low Hb levels.[8] The patients of well-being, particularly with respect to activity, growth, development, and the early appearance of skeletal changes, are the factors to be taken into consideration for starting a transfusion program.[14] Occasional blood transfusions should be considered in NTDT patients within any setting with anticipated acute stress, Hb drop, or blood loss such as pregnancy, surgery, and infections. More frequent transfusions should be considered in the following settings, with reassessment for tapering or withdrawal when a sustained clinical benefit is achieved. They include as follows:[2]

- Declining Hb level in parallel with profound enlargement of the spleen (at a rate exceeding 3 cm/year in periods of maximal growth and development)
- Growth failure (height is more indicative of growth pattern than weight)
- Poor performance at school
- Diminished exercise tolerance
- Failure of secondary sexual development in parallel with bone age
- Signs of bony changes
- Frequent hemolytic crisis (Hb H disease)
- Poor quality of life.

Table 1: Baseline characteristics of the thalassemia patients.

Characteristics	*n* (%)
Age distribution (years)	
1–10	14 (18.4)
10–20	20 (26.3)
20–30	9 (11.8)
>30	33 (43.5)
Age at diagnosis (years)	
1–5	16 (21)
5–10	25 (32.9)
10–15	10 (13.2)
15–20	11 (14.4)
>20	14 (18.4)
Sex distribution	
Male	48 (63.1)
Female	28 (36.9)
Religion	
Meitei Hindu	73 (96.05)
Meitei Muslims	1 (1.3)
Christian	2 (2.6)
Types of thalassemia	
Mild Hb E B thalassemia	48 (63.1)
Moderate Hb E B thalassemia	20 (26.3)
Severe Hb E B thalassemia	6 (7.8)
B thalassemia major	2 (2.6)

Hb: Hemoglobin

The study by Peepa and Singh tried to find the percentage of patients who were receiving blood transfusion program before attending the Hematology clinic. It was found that 13.15% had received monthly transfusion and 86.8% had received occasionally. After properly analyzing the patients using Mahidol score, the monthly transfusion was continued in 10.5% whereas occasional transfusion was 35.5%. After the patients were properly classified as mild, moderate, and severe, 53.9% of patients did not require any transfusion.[13] This is due to the fact that many of the mild Hb-E- thalassemia which consists of majority of patients were put into transfusion. Similar scenarios may be happening in other parts of India as well. Hence, it is very essential to know that all the patients with low Hb may not be TDTs. Majority of the NTDTs may only require transfusion ocassionally.

SPLENECTOMY IN THE MANAGEMENT

Patients with NTDT may be advised for splenectomy commonly to increase Hb level. However, it is associated with a variety of adverse outcomes.[15] Post-splenectomized patients with NTDT have a higher risk of venous thromboembolism (~5- fold), pulmonary hypertension (~4-fold), leg ulcers (~4-fold), and silent cerebral infarction than non-splenectomized patients.[16] Moreover, post-splenectomized NTDT patients have an increase the risk of morbidity and mortality due to infection. Therefore, splenectomy in NTDT should be reserved for cases of:[2]

- Worsening anemia leading to poor growth and development when transfusion therapy is not possible or iron chelation therapy is unavailable.
- Hypersplenism leading to worsening anemia, leukopenia, or thrombocytopenia and causing clinical problems such as recurrent bacterial infections or bleeding.
- Splenomegaly accompanied by symptoms such as left upper quadrant pain or early satiety and massive

splenomegaly (largest dimension >20 cm) with concern about possible splenic rupture.

In the patients with TDT also, the splenectomy is recommended as a guarded approach. It should be restricted since they are at increased risk of thrombosis, pulmonary hypertension along with overwhelming infection. The indications of splenectomy include hypersplenism, symptomatic splenomegaly, and increased blood requirement that prevent adequate control with iron chelation which is not related to auto or allo-antibody or blood loss. In the study done by Peepa and Singh, 9 patients had undergone splenectomy. Two cases belonged to severe Hb E/B-thalassemia and 7 cases belonged to moderate Hb E/B thalassemia [Table 2].[13]

FETAL Hb INDUCER IN NTDT

The increased production of γ-globin by hydroxyurea binds excess α-chains. This leads to improvements in αnprovemen chain imbalance and more effective erythropoiesis. Hydroxyurea is a potent fetal Hb inducer in above being a cytotoxic drug. In splenectomized patients with NTDT, hydroxyurea therapy theoretically has the potential to ameliorate the hypercoagulable state and subsequent vascular disease in patients with NTDT. The proportion of patients having total Hb increases of >1.0 g/dL ranged between 40% and 70%.[17] The doses of 10 and 20 mg/kg/day were used in NTDT patients. Response to treatment is usually noted in the first 3–6 months, with further improvements noted up to 12 months of therapy. This treatment is recommended in the following conditions: [2]

- βoThalassemia intermedia homozygous for the xmnI polymorphism
- Patients with lepore or δβ-thalassemia
- Patients for which a transfusion course is required but are alloimmunized
- Patients with the following clinical morbidities:
  - Pulmonary hypertension
  - Extramedullary hematopoietic pseudotumors
  - Leg ulcers.

In the study conducted by Peepa and Singh, hydroxyurea was initiated at 10 mg/kg in the NTDT. If no response was achieved by 3 months, the dose was increased to maximum of 20 mg/kg. The response was achieved in 80.4%. This response is slightly higher than the previous reports. This may be due to lesser number of sample size. The side effects were gastrointestinal upsets in 53.3% and mucocutaneous changes in 19.6% like blackening of nails.[13]

IRON OVERLOAD IN THALASSEMIA

Iron overload is common in TDT due to blood transfusion. However, despite less blood transfusion, cases of NTDT also may cause iron overload due to ineffective erythropoiesis, which promotes increased intestinal iron uptake. Hence, iron chelation should be done in both NTDT and TDT. Iron overload was detected in all 6 patients with severe Hb E β Thalassemia, 60% of moderate Hb E β thalassemia, 8.3% of mild Hb E β thalassemia, and 50% β thalassemia major patients [Table 2].[13]

ALLOIMUNISATION IN THALASSEMIA

Alloimmunization is defined as an immune response to donor RBC leading to the formation of alloantibodies that react with donor RBCs and typically cause delayed hemolytic transfusion reactions. The prevalence of alloimmunization in thalassemia has been estimated to be in the range of 10–50%. Starting the transfusion program at a younger age and extended antigen matching or molecular matching may be associated with a lower rate of alloimmunization. Inravenous immnogloblins (IvIg) and steroids have been used as an option for management. A case of moderate Hb E β thalassemia was detected at 4 years of age and had received multiple RBC transfusions for 1 year. She was advised to avoid blood transfusion as far as possible and go for splenectomy if blood counts were reduced from higher center. When she was 22-year old, she was detected to have a Hb level of 3.5 g/dL. She went to emergency department of a tertiary hospital. She received 3 units of RBCs and got discharged.

Table 2: Characteristics of various subtypes of thalassemias in Manipur.

Characteristics	Mild Hb E B thalassemia (*n*=48)	Moderate Hb E B thalassemia (*n*=20)	Severe Hb E B thalassemia (*n*=6)	B thalassemia major (*n*=2)
Hemoglobin g/dL (Mean±SD)	7.8 ± 1.7	7.7 ± 1.4	6.2 ± 0.5	6.0 ± 0
Ferritin (Mean±SD)	427.48 ± 257.4	1361.0 ± 950.9	2364.6 ± 913.7	1395 ± 558.5
Iron overload (%)	4 (8.3)	12 (60)	6 (100)	2 (100)
Growth retardation <5th percentile (%)	8 (16.6)	10 (50)	6 (100)	2 (100)
Bony deformity (%)	0 (0)	2 (10)	5 (83.3)	2 (100)
Splenectomy (%)	0 (0)	7 (35)	2 (33.3)	0 (%)

Hb: Hemoglobin, SD: Standard deviation

The following day when the Hb was checked again, Hb had dropped to 3 g/dL. With this history, she came to our center. She was extremely pale, weak, icteric. Bony changes in the form of prominent maxillary (cheek) were noticed. She had splenomegaly of 15 cm below the left costal margin. Further investigation revealed total leucocyte count (TLC) of 3360 and platelets of 65000/cumm. Serum bilirubin was 2.6 mg/dL, reticulocyte count was 11.6%, and direct coombs test (DCT) was 1+. Serum ferritin was 734 ng/mL. She was diagnosed as compound heterozygous Hb Eβ thalassemia with hypersplenism and alloimmunization. She was started on steroids and further transfusion was stopped for the time being. She underwent splenectomy on October 20, 2022 despite having a very low Hb. She was started on hydroxyurea at 10 mg per kg body weight. After 1 month of splenectomy, she came with complaints of pain abdomen in the epigastric area. On evaluation with US doppler, there was portal vein thrombosis with extension to splenic vein and superior mesenteric veins. She was started on anticoagulation with LMWH 1 mg/kg twice daily for 5 days followed by dabigratan 150 mg twice daily for 6 months. After 2 months of treatment, her Hb started increasing. She has Hb level of 9.3 g/dL without any transfusion support. She was diagnosed as a case of compound heterozygous Hb Eβ thalassemia, alloimmunization, post splenectomy, and portal vein thrombosis.[18] This patient sums up a perfect scenario of an NTDT with complications and management challenges.

CONCLUSION

Thalassemia, particularly the hemoglobin Eβ-thalassemia, a variant, poses a unique and significant health challenge in Manipur. The region's distinct genetic profile contributes to a higher incidence of these disorders, necessitating careful clinical management. The classification of thalassemia into TDT and NTDT is very essential for appropriate treatment strategies. The complexity of managing thalassemia in Manipur is compounded by complications such as iron overload, alloimmunization, and splenectomy-related risks. It is crucial to adopt a tailored approach to patient care, including early and accurate classification of the various subtypes to avoid unnecessary transfusions. Research in the region has highlighted the variability in the severity of hemoglobin E/β-thalassemia. With the majority of patients falling under mild–to-moderate forms, where transfusions are occasionally required. However, the challenge lies in ensuring that only those with TDT are placed under regular transfusion programs. Furthermore, the use of hydroxyurea and the management of iron overload in both TDT and NTDT patients are vital components of comprehensive care. This review emphasizes the importance of awareness and research in improving diagnostic accuracy and treatment protocols, ultimately enhancing the quality of life for affected individuals in Manipur. The need for continued research into genetic screening, treatment advancements, and patient management strategies is paramount to addressing the ongoing challenges posed by thalassemia in this unique population.

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