Understanding Beta-Thalassemia with Focus on the Indian Subcontinent and the Middle East

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Abstract: Beta-thalassemia is one of the most prevalent autosomal disorders in the world. Mutations in the HBB gene underlie deficiencies in hemoglobin production, which can interfere with oxygen delivery resulting in wide range of disease severity. Although >535 mutations have been characterized in the HBB gene, beta-thalassemia is broadly classified into three groups, based on clinical severity: beta-thalassemia major, beta-thalassemia intermedia and beta-thalassemia minor. In this article we review: 1) the molecular and biochemical basis of beta-thalassemia; 2) clinical features; 3) the range of common molecular variants of beta-thalassemia in a subset of geographic regions within the Indian Subcontinent and the Middle East; 4) potential molecular diagnostics; and 5) current and future treatments. We suggest that efforts to more completely characterize the HBB mutation distribution in high-risk areas, such as the Indian Subcontinent and the Middle East, may lead to improved diagnosis with earlier and more effective intervention strategies.

INTRODUCTION

Beta-thalassemia is an important disorder that has attracted the attention of medical research towards the various paradigms of this multifaceted disease [6-12]. Beta-thalassemia is an autosomal hematological disorder that is the result of genetically deficient synthesis of the beta-globin chains of hemoglobin [13]. Most frequently, this disorder is found in the malarial, tropical and sub-tropical regions of Mediterranean countries, the Middle East, Transcaucasia, Central Asia, the Indian Subcontinent (South Asia) and Southeast Asia [15] (Fig. 1).

Hemoglobin (Hb) is responsible for oxygen delivery from the lungs to peripheral tissues [16]. Hb is a tetrameric iron-containing protein, composed of two alpha-globin and two beta-globin chains. The alpha-globin and beta-globin chains join to form Hb in developing erythrocytes, or red blood cells (RBCs), and remain together for the life of the RBC [17]. In the event of altered beta-globin chain structure or function, in which one or both copies fail to quantitatively or qualitatively produce normal beta-globin,
The imbalance of the globin chains results in beta-thalassemia [16], with the precipitation of excess alpha-chains contributing to excessive destruction of RBCs, which begins a cascade that ends with significant morbidity and mortality [16].

THE BETA-GLOBIN LOCUS

The beta-globin chain is encoded by the \( HBB \) gene, which spans 1.6 kb on the short-arm of chromosome 11 (11p15.4; MIM: 141900) [18, 19]. The genomic sequence of \( HBB \) contains three exons, two intervening sequences (IVS1 and IVS2) and the 5' and 3' untranslated regions (UTRs) (Fig. 2a). The \( HBB \) gene is regulated by a 5' promoter region that contains the classical TATA, CAAT and duplicated CACCC boxes (Fig. 2a). Upstream of the beta-globin cluster is another regulatory element for \( HBB \), namely the locus control region (\( \beta \)LCR). The expression of individual globin genes is governed by direct physical interaction between the \( \beta \)LCR and globin promoters, mediated by the binding of tissue-restricted and ubiquitous transcription factors [20]. The most important transcription factor for \( HBB \) is the erythroid Kruppel-like factor (EKLF), which binds the proximal CACCC box [18].

The beta-globin locus harbors, in addition to the \( HBB \) gene, the \( \epsilon \)-globin (\( HBE \)) gene, the two \( \gamma \)-globin (\( HBG \)) genes (\( HBG-G \) and \( HBG-A \)), and the \( \delta \)-globin (\( HBD \)) gene (Fig. 2b) [21]. Most genes at this locus are expressed at specific time points in development. During embryonic development, the \( HBE \) gene is expressed along with the alpha-globin gene to form embryonic-hemoglobin or Hb-E [21]. Twelve weeks post-conception, the fetus primarily uses fetal hemoglobin (Hb-F) which is composed of two \( \gamma \)-globin and two alpha-globin chains [21]. Around the time of birth, \( \gamma \)-globin production decreases while beta-globin synthesis increases such that most individuals have only trace amounts of Hb-F detectable 7 or 8 months after birth [21, 22]. The combination of two alpha-globin genes and two beta-globin genes comprises a normal adult Hb, which becomes the predominant form within 18 to 24 weeks after birth [21, 22]. Less than 3% of adult hemoglobin is Hb type A2, which is composed of two \( \delta \)-globin chains and two alpha-globin chains [22].

VARIANTS OF BETA-THALASSEMIA

There are >535 \( HBB \) gene mutations [21, 23] with a subset of ~40 mutations responsible for the majority of beta-thalassemia cases globally, as defined by population studies [15]. Moreover, frequencies of beta-thalassemia are very high in malarial, tropical and sub-tropical regions such as the Indian Subcontinent and the Middle East, a fact hypothesized to be the result of a thalassemia heterozygote advantage against severe forms of malaria [24].

Different classes of \( HBB \) mutations underlie beta-thalassemia, in descending order of frequency: missense/nonsense [25, 26], splicing [27], regulatory [28], small or gross gene deletions [27, 29], including the common deletion of the terminal portion of \( HBB \) [30], gene insertions [31], small insertion-deletions [32], and complex rearrangements [33]. In rare instances, the causative defect is due to a deletion of the \( \beta \)LCR [18], mutations in another gene within \[34\] or outside [16] the beta-globin locus. Beta-thalassemia rarely arises due to the complete loss of the \( HBB \) gene [34].

In the past, a descriptive, non-molecular ontology for beta-thalassemia deduced the existence of two disease-related alleles, \( B^0 \) and \( B^+ \). The \( B^0 \) allele was considered to produce non-functional beta-globin protein [16, 21]. Subse-
quent molecular characterization showed that the absent beta-globin chain from the putative “B0 allele” was actually due to a variety of nonsense, frameshift, or sometimes splicing mutations [34]. In contrast, the B+ allele was considered to be mutation that resulted in reduced quantity of beta-globin protein [16, 21]. Subsequent molecular characterization showed that reduced beta-globin production related to the “B+ allele” resulted from mutations in the promoter region, polyadenylation signal, 5’ or 3’ untranslated region, or splicing sites [34].

Moreover, three classes of beta-thalassemia have long been recognized clinically: beta-thalassemia major, intermedia and minor. The three thalassemia types are differentiated clinically by the degree of anemia, with thalassemia major and minor having the most and least severe anemia, respectively. Subsequent molecular characterization has shown some genotype-phenotype correlation, with clinical severity roughly related to the mutation type (Fig. 3) [34].

**Thalassemia Major**

Thalassemia major, also known as Cooley’s anemia and Mediterranean anemia, is the most severe form of beta-thalassemia, since both mutations of both HBB alleles results in severely impaired beta-globin chain production [21, 35]. Three of the general allele combinations are responsible for this thalassemia phenotype — B0/B0, B0/B+, and sometimes B+/B+ (Fig. 3a) [34].

In thalassemia major, the excess unpaired alpha-globin chains aggregate to form inclusion bodies [18]. These chain inclusion bodies damage RBC membranes, leading to intravascular hemolysis [18]. In addition, there is damage and premature destruction of RBC precursors, causing ineffective erythropoiesis [18]. Anemia is severe and oxygen transport is compromised [35]. In some patients, death would result without chronic blood transfusions. Other clinical manifestations include listless, fatigue, dyspnea, poor appetite, hepatosplenomegaly, heart failure and bone deformation and delayed puberty [16, 21, 35]. Laboratory abnormalities include microcytic anemia with abnormally shaped RBCs and abnormal Hb electrophoresis. Thalassemia major presents within the first two years of life and, with treatment affected individuals can live five decades or more [35].

**Thalassemia Intermedia**

Patients with beta-thalassemia intermedia have mild to moderate anemia and in most cases do not require blood transfusions [36]. This condition is milder than thalassemia major due to inheritance of a HBB mutation associated with reduced beta-globin chain production (Fig. 3b) [18]. The deduced genotype is most commonly B+/B+ [34]. The clinical phenotype of thalassemia intermedia is roughly intermediate between thalassemia major and minor [37]. Common clinical features include splenic enlargement due to entrapment of damaged RBCs, with risk of iron overload due in part to increased intestinal absorption [16, 21, 36]. Although thalassemia intermedia can be associated with poor growth and bone abnormalities, it presents later in life and rarely affects longevity [16, 36]. Patients require regular monitoring because the clinical severity varies widely between patients and within a patient over time, with possible deterioration to the thalassemia major phenotype.

Several rare HBB variants phenotypically manifest thalassemia intermedia. For instance, individuals with dominantly inherited beta-thalassemia or inclusion body beta-thalassemia clinically exhibit thalassemia intermedia [38, 39]. These patients have moderate anemia and splenomegaly. More than 30 dominantly inherited beta-thalassemia cases have been described, resulting from a spectrum of molecular lesions ranging from missense mutations to nonsense muta-

![Fig. (3), Schematic representation of inherited beta-globin variants and related beta-chain and red blood cell (RBC) phenotype. The HBB variants are represented in grey exons while the wild type alleles are represented in blue exons. Production of beta-globin from a single/double wild type alleles are represented by one/two colored schematic of the beta-globin protein respectively. Grey colored beta-globin diagrams refer to below-normal synthesis levels of the protein, created by mutant HBB variants. Bright red-colored RBCs represent normal cell phenotype, while pink colored ones represent microcytic, hypochromic cells characteristic of beta-thalassemia phenotype. Relative number of RBC reflects relative levels of anemia amongst the three classes of beta-thalassemia and in comparison to the wild type RBC pool.](image-url)
tions [40]. A rare variant form called “silent beta-thalassemia” results from a mild imbalance of globin chain synthesis due to reduced beta-globin synthesis, leading to thalassemia intermedia. Silent beta-thalassemia 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 [41], which underlies most thalassemia intermedia cases in the Mediterranean region [42]. Thalassemia intermedia has also been observed in patients with a retro-transposition insertion of a L1 family transposable element in the HBB gene. This ~7 kb DNA insertion in IVS2 expresses ~15% of the full length beta-globin chain [43]. In addition, trans-acting genetic determinants, independent of the beta-globin locus, can cause the thalassemia intermedia phenotype [44]. For instance, mutations in the XPD/ERCC2 gene, which is causative for trichothiodystrophy (MIM 601675) [19], have also been associated with the beta-thalassemia phenotype [45], as demonstrated by reduced levels of beta-globin synthesis and mRNA levels. The XPD protein coded by this gene is a subunit of the TFIIH transcription factor, involved in basal transcription and DNA repair [45].

**Thalassemia Minor**

Thalassemia minor is most common form of beta-thalassemia, and is also known as the ‘thalassemia trait’, in which affected individuals are asymptomatic (Fig. 3e) [18, 21]. These subjects are typically heterozygous for beta-thalassemia since they carry one normal HBB allele and one thalassemia allele - either B0 or B+ [34]. Asymptomatic patients are usually detected through routine hematologic testing, but in retrospect some newly diagnosed patients are observed to have mild anemia and small RBCs [16]. The primary caution for individuals with thalassemia minor is a potential risk of having children affected with more serious thalassemia if their partner is also a carrier of thalassemia minor [34].

**GENETIC SUSCEPTIBILITY UNDERLYING BETA-TALASSEMIA COMPLICATIONS**

Complications in older patients with beta-thalassemia appear to develop in part as a result of certain genetic susceptibilities [13]. For instance, hyperbilirubinemia and cholelithiasis are common complications among beta-thalassemia patients, since bilirubin is the breakdown product of RBCs and can be a component of certain gallstone types. There appears to be an increased incidence of these complications in patients who carry an insertion polymorphism in the promoter region of the uridine diphosphate-glucoronyltransferase type IA (UGTIA) gene [13]. Also, common polymorphisms of the vitamin D receptor (VDR) and collagen type alpha1 (COLIA1) genes [13] can modulate the severity of progressive osteoporosis and osteopenia in beta-thalassemia. In addition, decreased frequency of the APOE (apolipoprotein E) E4 allele has been shown to be a risk factor for development of ventricular failure in beta-thalassemia [13].

**PREVALENCE OF BETA-TALASSEMIA IN THE INDIAN SUBCONTINENT (SOUTH ASIA)**

Within the Indian Subcontinent (or South Asia), which includes the countries of Pakistan, Sri Lanka and India, there are ~45 million carriers (carrier rate of ~1:20) of beta-thalassemia [46]. There are four common beta-thalassemia mutational ‘hotspots’ in the HBB gene found in this population: g.63201_63819del619 (619bp deletion), c.27_28insG, c.92+1G>A and c.92+5G>C [18] (Fig. 1).

In beta-thalassemia patients from Pakistan, there was a high consanguinity rate (81%) [47, 48]. The polymorphism at c.92+5G>C, in the HBB gene, was the most common mutation (37.0%), followed by c.27_28insG and 619bp deletion with allele frequencies of 21.0% and 12.0%, respectively [48] (Table 1).

In Sri Lanka, the two most prevalent HBB mutations were c.92+5G>C and c.92+1G>A with allele frequencies of 56.0% and 27.0%, respectively [48] (Table 1).

In Indian patients, five mutations accounted for 92% of the beta-thalassemia alleles (Table 1). The most common mutation was c.92+5G>C, as in Pakistan and Sri Lanka. The other four mutations were c.92+1G>T, 619bp deletion, c.27_28insG, and at c.124_127delTTCT. Regional differences in prevalence across north, east and south India, has also been demonstrated [48]. Within the Northern states, including Punjab, the mutations and allele frequencies are quite similar to those of Pakistan where the two most com-

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Pakistan</th>
<th>Sri Lanka</th>
<th>North India</th>
<th>East India</th>
<th>South India</th>
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<td>[48]</td>
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*N/A—data not available; ‡619bp deletion: g.63201_63819del619.

*mutational hot spots shared with the Middle East.
mon mutations were c.92+5G>C (43.5%) and c.27_28insG (38.5%) [47]. The similarity in mutation frequencies in these regions reflects their geographical proximity. In addition, 6.6% of confirmed cases in northern India harbored the HBB c.124_127delTTCT mutation [47]. Within the Eastern region of India, including the state of West Bengal, the frequency of HBB c.92+5G>C was 48.8% [49]. Interestingly, 31.9% of mutations involved the HBE gene, a pattern that was particular for the eastern region of India. In South India, including the province of Andhra Pradesh, the HBB c.92+5G>T mutation frequency was 74% [50]. Other important South Indian HBB mutations were not found among other common South Asian HBB mutations, indicating regional differences in the genetic architecture of beta-thalassemia. Such differences in HBB mutation may reflect a high prevalence of consanguinity and non-random mating that occurs within some rural South Indian communities [50].

Overall these studies in the Indian Subcontinent demonstrate the importance of collecting and replicating HBB mutation frequencies, since this is the first step in establishing a successful prenatal diagnosis program [48].

PREVALENCE OF BETA-THALASSEMIA THROUGHOUT THE MIDDLE EAST

There is a high prevalence of beta-thalassemia in countries of the Middle East including Iraq, Lebanon, Egypt and Morocco, with an average carrier rate of ~1:30. More than 90% of affected individuals in the Middle East have HBB mutations within one of several mutational ‘hotspots’, including: c.25_26delAA, c.27_28insG, c.92+5G>C, c.118C>T, c.135delC, and c.315+1G>A (Fig. 1).

In Iraq, beta-thalassemia is an evident health problem, specifically in the Dohuk region located in the northern part of the country [51]. The Dohuk region lies midway between Iran, Turkey and Syria, countries also characterized by a relatively high frequency of beta-thalassemia. The disease prevalence in Dohuk is reinforced by the high rate of consanguineous marriages in the region, which were estimated at 25.3% [51]. Molecular testing of 104 (50 male, 54 female) registered beta-thalassemia patients from Dohuk detected 12 mutations. The eight most common mutations observed accounted for 81.7% of the thalassemia alleles [51]. The mutations in descending order of frequency were: c.315+1G>A, c.135delC, c.17_18delCT, c.92+1G>A, c.92+6T>C, c.118C>T, c.27_28insG, and c.92+5G>C (Table 2). The remaining four infrequent mutations were: c.25_26delAA, c.68_74delAAGTTGG, c.93G>C and c.93-21G>A. Further studies are required to provide a more thorough and accurate representation of common beta-thalassemia mutations in other Iraqi subpopulations. The frequencies of observed beta-thalassemia mutations in neighboring countries suggested mutational flow from Iraq; for instance, the HBB c.135delC mutation was much more frequent (12.5%) in Dohuk than in the neighboring regions of Syria, Turkey and Iran (0-2.6%), suggesting it originated in Dohuk.

In Lebanon, beta-thalassemia is the most common genetic disorder [52]. In a recent study of 255 patients from Lebanon, 6 HBB mutations were found in >85% of beta-thalassemia patients [52]. These mutations in descending order of prevalence, were: c.93-21G>A, c.92+1G>A, c.92+6T>C, c.90C>T, c.315+1G>A, and c.17_18delCT [52] (Table 2). The Lebanese population also has a religious gra-

<table>
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<tr>
<th>Mutation</th>
<th>Iraq</th>
<th>Lebanon</th>
<th>Egypt</th>
<th>Morocco</th>
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*N/A—data not available.
*mutational hot spots shared with the Indian Subcontinent.
dent of \( HBB \) mutational diversity. Sunni Muslims had the highest beta-thalassemia carrier rate and also the greatest mutational heterogeneity, with 16 \( HBB \) different mutations. Shiite Muslims had 13 \( HBB \) mutations, while Maronites had 7 different \( HBB \) mutations, while other religious factions including Orthodox, Druze, Greek Catholic and Latin, had progressively less mutational diversity. \( HBB \) locus haplotype analysis showed that the observed genetic diversity originated from both new mutational events and gene flow from population migration [52].

Among Egyptians, beta-thalassemia is the most common cause of chronic hemolytic anemia and represents a major health concern. A recent study of 95 Egyptian beta-thalassemic cases illustrated that the three most common \( HBB \) mutations observed were at c.92+6T>C, c.93-21 (25.8%), and c.92+1 (19.0%) [53], similar to the findings in other studies carried out on Egyptians [54-56] (Table 2). Moreover, the seven most frequent alleles in this study accounted for 84.2% of the observed thalassemic alleles in Egypt.

Finally, in a study of beta-thalassemia in Morocco, six \( HBB \) mutations were seen in >75% of patients [57, 58]. These were in descending order of frequency: c.118C>T, c.25-26delAA, c.92+6T>C, c.92+1G>A, c.20delA, and c.-79A>G (Table 2). Regional predominance was observed in the Gharb and West regions for the c.92+6T>C mutation. The distribution of mutations was suggested to correlate with historical migration patterns of Berbers, Phoenicians, Carthaginians, Romans, Arabs, and Vandals, Byzantines and Sub-Saharan Africans [57].

Studies in the Middle East and Indian Subcontinent reveal an overlap in mutational hotspots for beta-thalassemia (Tables 1 and 2). Such overlap may be due to genetic relatedness and intermarriages between these two regions. More importantly, it may be indicative of starting points for development of effective molecular therapy methods for both geographical regions.

**MOLECULAR DIAGNOSTIC TESTING**

While beta-thalassemia is observed in most global populations, each population or subpopulation has its own unique spectrum of beta-thalassemia mutations [48]. In both the Indian Subcontinent and the Middle East, beta-thalassemia is a major public health problem [46, 48]. It has been estimated that 10% of the world’s beta-thalassemia major infants are born either in the Indian Subcontinent or the Middle East [5, 46]. In fact, there are ~12,300 total beta-thalassemia births per year in Indian Subcontinent and the Middle East. The cost for blood transfusions for beta-thalassemia major has been projected at ~3200 USD per child per year [46] while the lifetime healthcare costs of caring for a person born with thalassemia major has been projected at 284,154 USD [59]. Since this exceeds the economic reach of most families in the Indian Subcontinent and Middle East, genetic counseling and prenatal diagnosis are an important component of multi-pronged strategy to reduce the burden of beta-thalassemia in these jurisdictions [46, 60]. Thus, it is important to collect, replicate and corroborate the frequencies of specific \( HBB \) mutations in these jurisdictions, especially when the presence of a few common mutations explains a large proportion of cases, enabling relatively cost-effective molecular diagnosis of carriers and prenatal diagnosis [48].

Unknown \( HBB \) mutations must be discovered using screening methods such as direct sequencing of genomic DNA, single strand conformation polymorphism analysis or denaturing gradient gel electrophoresis [61]. However, since these techniques require specialized skill and reagents, they are expensive [61]. They are presently not ideal for economically-unstable countries within Indian Subcontinent and the Middle East. Therefore, the strategy of developing dedicated allele-specific methods to find the most prevalent graphically-relevant mutations causing beta-thalassemia based on screening for a small number of known mutations that underlie a majority of cases is a more realistic goal [47].

Current technologies for clinical detection of specific mutant alleles include: 1) Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) and 2) Reverse Dot-Blot (RDB) analysis, among many others. ARMS-PCR amplifies both wild-type and mutant alleles, together with a control fragment, in a single tube reaction [62]. Two allele-specific (inner) primers and two non–allele-specific (outer) primers amplify both the wild-type and the mutant amplicons, resulting in products of different lengths that can be easily identified using agarose-gel electrophoresis [62]. In contrast, RDB involves amplification and biotin-labeling of the DNA sequence of interest, followed by hybridization of the amplified products to oligonucleotide probes immobilized on a membrane [63]. Indeed in many studies, fetal DNA from chorionic villus sampling was screened tests including ARMS-PCR method and by RDB analysis [47-50]. Once fetuses were diagnosed, the option of pregnancy termination can be offered, within the boundaries of consideration given to appropriate cultural and ethical sensitivities.

**CURRENT TREATMENTS FOR BETA-TALASSEMIA**

The outlook for patients with beta-thalassemia has improved steadily during the last two decades due to developments in treatment [11, 64]. In addition, newer treatments currently under investigation will have a great impact in the next few years and ease the clinical burden of this disorder [22]. However, as a result, some treatments have been associated with an increase in the development of iatrogenic complications.

**Blood Transfusion Therapy and its Complications**

The commonest form of life-long treatment for individuals with beta-thalassemia major is regular blood transfusions in order to maintain a Hb blood concentration >90 g/L and to compensate for ineffective erythropoiesis [16, 65]. Moreover for beta-thalassemia major, patients are unable to grow and develop at infancy and may die if untreated by regular transfusions [66]. However, regular and recurring blood transfusions can be complicated by high rates of blood-borne infections; for instance ~70% of transfused children in some developing countries may acquire hepatitis C and even hepatitis B [13, 24]. Aggressive treatment approaches for hepatitis are being used to avoid eventual liver cirrhosis and hepatocellular carcinoma [35].
Iron overload is an important complication due to the iron present in the transfused blood as well as excessive iron absorption [67]. Iron overload - acquired hemochromatosis - produces reactive oxygen species that damage the heart (cardiomyopathy), liver (fibrosis and cirrhosis), nervous system, can lead to diabetes mellitus, hypothyroidism, hyperparathyroidism as well as adrenal and pituitary insufficiencies [21]. Susceptibility to specific endocrinopathies should be monitored and treated as they develop. Iron overload also plays a pivotal role in cochlear siderosis and is the cause of various neurological disorders [18]. Pituitary iron overload, which results in hypogonadotropic hypogonadism, may lead to low fertility [22].

In order to minimize iron overload and its complications, iron chelation is provided as an adjunct to regular blood transfusion. Chelators in-ertly and tightly bind iron ions and remove excess iron. Deferoxamine (Desferal®), an iron chelator, is administered parenterally [67]. Chelator treatment is expensive because of the dosage, equipment and skill required [64]. To decrease expense and dosage requirement while increasing effectiveness, a combination of chelators should be employed, such as deferoxamine together with such orally-active chelators as deferiprone or deferasirox (ICL670) [22]. However, secondary complications have arisen from deferoxamine therapy. For instance deferoxamine predisposes patients to Yersinia septicemia, which is problematic in regions with endemic Yersinia such as the Middle East or Indian Subcontinent [24]. In addition, side effects of deferoxamine include ocular and auditory toxicity, growth retardation, and occasionally, renal impairment and interstitial pneumonitis [18]. Thus, patients with beta-thalassemia who receive regular blood transfusions together with deferoxamine should be monitored. Magnetic resonance imaging (using the T₂ relaxometry method) can be utilized for non-invasive, safe and accurate assessment of affected tissues, such as cardiac tissue, since iron overload causes deposition in vulnerable areas such as ventricular walls and epicardial layer, potentially leading to serious arrhythmias or congestive heart failure [22, 68].

Depressed Immunity

Beta-thalassemia patients, having survived severe anemia due to early management and diagnosis often have depressed immunity [22]. As a result, bacterial and fungal infections contribute to high mortality in beta-thalassemia patients [24]. Major microbial infections, including Klebsiella (mainly in Asia), Escherichia coli and Streptococcus pneumonia, have been observed [24]. Recently, in Asia, a fungus-like infection called pythiosis from Pythium insidiosum has been observed in patients with beta-thalassemia [24]. Treatment has been difficult because anti-fungal drugs and anti-fungal vaccines are often ineffective. Moreover, many of these infections are endemic in the Indian Subcontinent and the Middle East and pose a risk to immune-suppressed beta-thalassemia patients.

Other Common Therapies

Adults with beta-thalassemia are susceptible to thrombosis, the most serious clinical outcome of which is pulmonary embolism and pulmonary hypertension [7, 69]. A daily low-dose of aspirin prescribed prophylactically can reduce this risk [6, 16]. Other forms of treatment for thalassemia major and severe cases of thalassemia intermedia include folate supplements [18] and splenectomy to decrease transfusion requirements [35]. Severe infections, such as pneumococcal meningitis and pneumonia, may possibly complicate splenectomy [24, 70]. As a result patients would benefit from prophylactic antibiotics and vaccinations.

The only treatment that can cure thalassemia major is allogeneic bone marrow (stem cell) transplantation. Since it was developed by the Pesaro group in 1981 there have been more than a 1000 patients with transplantsations with a thalassemia-free survival rate of 68% [71]. Thus far, allogeneic bone marrow transplantation seems to provide a definitive cure of this disease. Due to the high risks involved, careful decision-making is necessary when considering such transplants. When transplantation is the treatment of choice, it is pursued only for patients with human leukocyte antigen-matched donors [72].

FUTURE THERAPIES

A novel approach that provides an alternative to high-risk donor transplantation for severe beta-thalassemic patients is the transfer of normal human beta-globin gene in autologous hematopoietic stem cells [73]. Another approach to improve the clinical status of beta-thalassemia patients aims to increase the synthesis of Hb-F, an alternative source of Hb. This treatment option is especially used in cases of beta-thalassemia intermedia and can help alleviate anemia [74]. Production of Hb-F was noted to be reactivated during the recovery from marrow suppression after treatment of hematologic malignancies with cytotoxic drugs. Thus, it was postulated that the hypomethylating agent 5-azacytidine, which switches off expression of adult to fetal Hb form in adult baboons, and butyrate may alter the pattern of erythropoiesis in humans with beta-thalassemia and increase the expression of γ-chain genes [64]. Although the mechanism is unknown, hydroxyurea treatment has been observed to increase Hb levels, reduce brain masses and leg ulcers [65]. Also, studies in mouse models are being pursued for gene correction in hematopoietic stem cells using lentiviral vectors [64].

But while advances in therapy continue to be made, management of primary and secondary complications has had a major impact on the quantity and quality of life in patients with beta-thalassemia. Further investigations as well as individual-based therapies may allow for more efficient treatment methodologies in the future.

CONCLUSION

In conclusion, beta-thalassemia is highly prevalent and is a major public health problem in the malaria endemic areas of the Indian Subcontinent and Middle East. Cross-sectional surveys indicate that in many regions of the Indian Subcontinent and Middle East, only a few prevalent HBB mutations underlie the majority of patients with beta-thalassemia. This suggests that relatively cost-effective dedicated carrier screening methods could be implemented in these areas. However, imminent application of molecular screening in the Indian Subcontinent and Middle East is complicated by regional differences and the fact that sizable minorities of patients with beta-thalassemia in some areas do not result from previously known HBB mutations. Although early diagnosis and treatment measures are available, they can be
expensive and some, such as blood transfusion and treatment with iron-chelators, can have potentially serious complications. Thus, prenatal diagnosis or other preventative approaches may be the most important strategy to control the clinical problems arising from beta-thalassemia. Along with this, millions of abortions are performed annually due to molecular diagnostic testing that raise many ethical and economical challenges, for which time and financial assistance should be invested to effectively handle this issue.

AUTHORS’ CONTRIBUTIONS

All authors participated in literature review and manuscript preparation. All authors approved the final version of the manuscript.

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Understanding Beta-Thalassemia with Focus


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