

Genetic Counseling to Prevent Thalassemia and Hemoglobinopathy in the Indian Population

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Abstract

The prevalence of thalassemia carrier in the Indian population is 3% to 4%. Prevention of thalassemia and hemoglobinopathy is feasible through carrier testing by complete blood count examination and high-performance liquid chromatography. Abnormal hemoglobin (Hb) variants can interact with thalassemia traits to give rise to thalassemia major/intermedia or can be clinically silent. It is important to know when to perform invasive testing to prevent thalassemia and refer the patients for genetic counseling.

We selected 100 patients with thalassemia trait or structural Hb variants referred for antenatal genetic counseling. Both patients and their partners were screened for all the traits.

We discuss a step-wise approach to prevent thalassemia major, and highlight the common situations prevalent in India, which need genetic counseling and prenatal diagnosis.

During pregnancy, thalassemia screening should be made mandatory in all antenatal screening centers. Couples where both the partners are carriers of thalassemia or structural Hb variants should be offered genetic counseling to identify whether invasive tests are required.

Key Words: Antenatal screening, structural Hb variants, complete blood count, high-performance liquid chromatography, invasive tests

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Introduction

Hemoglobinopathies are the most frequently occurring hereditary diseases in the world. They have become much more prevalent in India recently because of immigration and mixing of cultures. Hemoglobinopathies can be divided into 2 general types: (1) thalassemias (disorders of decreased globin chain synthesis) and (2) hemoglobin (Hb) structural variants (eg, Hb S and Hb E). Sometimes, a combination of these 2 conditions also exists.

Various interdiction such as social, ethnic, moral, as well as incomprehension about the disease and family influences make the management of thalassemia difficult, in India.

Global Burden of Thalassemia

It is estimated that there are 270 million carriers, globally, with abnormal Hbs and thalassemias, of which 80 million are carriers of β -thalassemia. Recent surveys suggest that between 3,00,000 and 4,00,000 neonates are born with a life-threatening Hb disorders, each year (23,000 with β -thalassemia major); up to 90% of these births are in low- or middle-income households.¹⁻⁷

The prevalence of thalassemia is high in the Mediterranean Basin, some parts of Africa, the Middle East, India, Southeast Asia, Malaysia, and the Pacific Islands.^{4,5}

Incidence of thalassemias and other hemoglobinopathies in India

In the Indian population, the prevalence of β -thalassemia carriers is 3% to 4%. The ethnic groups that are at a high risk comprise Sindhis, Kutchi people, Lohanas, Punjabis, and a few Muslim groups and tribal populations (5%–17%).^{8,9}

The overall prevalence of α -thalassemia carriers (in whom an α gene has been deleted) is around 13% but varies from 3% to 18% in different regions and castes. The highest prevalence of α -thalassemia is among the Punjabi population originating from the northern region of India. Hb H disease is uncommon.¹⁰

In the Indian population, $\delta\beta$ -thalassemia and hereditary persistence of fetal hemoglobin (HPFH) are less commonly seen. Hb S carriers are commonly seen in the tribal populations as well as in a few nontribal groups (5%–40%). Hb E trait is commonly observed in the northeastern population, and the prevalence varies between 3% and 64%. The prevalence of Hb D is 3% to 4% in Punjabis and is mainly seen in the northwestern region. The compound heterozygous conditions (eg, Hb S– β -thalassemia, Hb E– β -thalassemia, and Hb D– β -thalassemia) are seen in different regions because of migration and cultural mix-ups.¹¹

Antenatal Screening

The aim of prenatal hemoglobinopathy screening is to detect and counsel asymptomatic individuals whose offspring are at a risk of thalassemia major/intermedia. A couple can make reproductive preferences based on this information.

Various antenatal clinics in India (both private and government sectors) screen for β -thalassemia. In this article, we enumerate various steps needed to prevent transfusion-dependent thalassemia syndromes. A screening algorithm for the prevention of thalassemia is presented in the Figure.

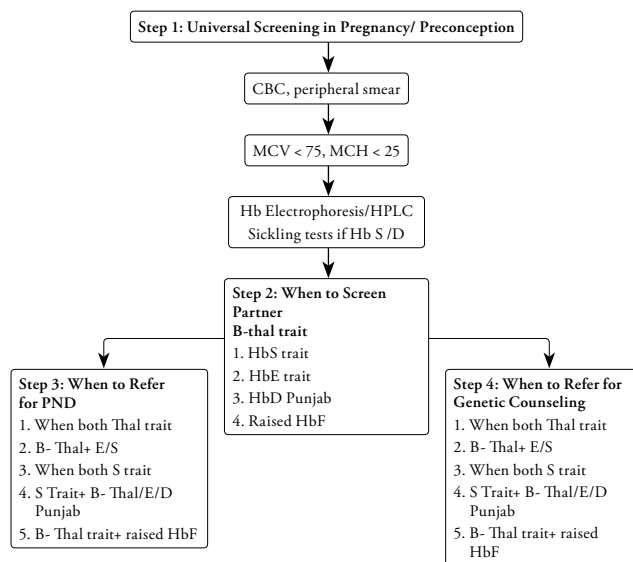


Figure. A Screening Algorithm for the Prevention of Thalassemia

CBC, complete blood count; HPLC, high-performance liquid chromatography; MCH, mean cell Hb; MCV, mean corpuscular volume; PND, prenatal diagnosis.

Step 1: Universal screening during early pregnancy

In all antenatal clinics, all women should be screened at their first antenatal visit and in the second trimester also for the carrier status for controlling the related disorders in the subsequent pregnancies, if required.

A baseline screening should involve complete blood count (CBC) and peripheral smear examinations. Decreased red cell indices (mean corpuscular volume [MCV] < 80 fL and mean cell Hb [MCH] < 27 pg) with raised RBC count suggest a thalassemia trait. In patients with microcytosis, a high-performance liquid chromatography (HPLC) helps detect the carrier state of β -thalassemia and structural Hb variants. Decreased red cell indices in association with HbA₂ \geq 3.5% help detect most of the β -thalassemia carriers; this would also help detect other Hb variants such as Hb S, Hb C, and Hb E. These conditions exhibit clinically significant interactions with β -thalassemia.

Step 2: Screening of partner

The partners of women who are carriers with the Hb variants such as β -thalassemia, Hb D Punjab, Hb S, Hb D Iran, Hb Lepore, Hb C, Hb E, Hb D- β -thalassemia, Hb Q India- β -thalassemia, and $\delta\beta$ -thalassemia should be screened as well.

Step 3: Genetic counseling

If both the partners are carriers of thalassemia/structural variant, molecular confirmation of abnormal Hb variants is advised. The information available in the literature concerning the methodology for counseling by thalassemia centers is limited. The spectrum of cases referred for genetic counseling and prenatal cases at our genetic clinic are mentioned in the Table.

We included 100 patients for the analysis. About one-third patients were referred for prenatal diagnosis—31 patients with β -thalassemia, 2 with sickle cell anemia, and 1 with E- β thalassemia. Of the 100, 66 patients were referred for genetic counseling, which indicates that there is a high need of genetic counseling for hemoglobinopathy. In the 20 patients referred for

Table. Indications of Abnormal Hb Variants Seen at Our Genetic Clinic ($n = 100$)

Hb Variant	No. of Cases
Prenatal Diagnosis	34
β -Thalassemia	20
Hb E	15
Hb D Punjab	12
Hb D Iran	8
Hb Q India	2
Hb J	2
α -Thalassemia	2
Raised Hb F	1
Hereditary Persistence of Hb F	1
Thalassemia Major /Intermedia	3

Hb, hemoglobin.

counseling for thalassemia trait, only 1 partner was identified with β -thalassemia trait; in 15% of patients, referral was because of Hb E trait in the wife; 12 patients referred had Hb D Punjab trait in one partner and β -thalassemia in another; and 8% had Hb D Iran trait in one partner. We did not seek ethics committee approval as these patients themselves sought genetic counseling.

The major objective of genetic counseling is to evaluate which cases are clinically silent and which cases would require invasive tests.

Some combinations of abnormal Hb variants—both couple Hb E trait; both couple hereditary persistent Hb F; both couple Hb D Punjab trait; both couple Hb C; one among the couple with Hb D Punjab trait + another with β -thalassemia trait; Hb Q India + β -thalassemia; Hb J Meerut + β -thalassemia; and α -thalassemia trait trans ($-- a/-- a$) / ($-- a /-- a$)—are clinically silent.¹² These combinations of various structural variants and β -thalassemia trait/ α -thalassemia trait will not lead to transfusion-dependent thalassemia major, and hence invasive testing such as chorionic villus sampling/amniocentesis is not recommended. Confirmed molecular genetic testing and genetic counseling are required in all such combinations.

In India, 2 common situations, both couple Hb E trait and one of the couple with Hb D Punjab and the other

with β -thalassemia trait, would result in clinically silent conditions/mild anemia, and genetic counselling is recommended in such cases.

Step 4: Prenatal diagnosis by chorionic villus sampling/ amniocentesis

Thalassemia variants and several abnormal Hbs interact to produce a broad range of disorders causing transfusion-dependent thalassemia major or thalassemia intermedia. Four main categories of severe disease states, thalassemia major, sickle cell syndromes, Hb E thalassemia (coinheritance of β -thalassaemia variants with Hb E), and Hb Bart hydrops fetalis syndrome (homozygous α -thalassaemia, genotype, and [rarely] Hb H), require genetic counseling and, possibly, prenatal diagnosis.¹³

Various combinations of these abnormal Hb variants/thalassemia traits that would result in transfusion-dependent thalassemia syndromes are both couple β -thalassemia trait, both couple $\delta\beta$ -thalassemia trait, both couple Hb Lepore, Hb E trait + β -thalassemia trait, Hb Lepore + β -thalassemia trait, Hb C trait + β -thalassemia trait, both couple Hb S trait, Hb S trait + β -thalassemia trait, Hb S trait + Hb E trait, Hb S trait + $\delta\beta$ -thalassemia, Hb S trait + Hb D Punjab trait, and α -thalassemia trait cis ($--/a$ a)/($--/a$ a). The risk of thalassemia is 25% in these Hb variants homozygous/compound heterozygote.

As a general principle, Hb S/E trait with any other Hb variant should be referred for invasive testing.

Conclusions

Thalassemia and hemoglobinopathy can be prevented by detecting the carrier status of the couples in the early stages of pregnancy with the help of carrier testing (ie, CBC and HPLC). Abnormal Hb variants can interact with thalassemia trait to give rise to thalassemia major/intermedia or can be clinically silent. Deciding on the phase of the pregnancy for invasive tests is very important for preventing thalassemia.

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