Editorial

PRESENT STATUS OF HEMOGLOBINOPATHIES IN INDIA

The last decade has witnessed an enormous progress in the field of hemoglobinopathies. This explosion in knowledge came in the wake of advances in the field of molecular biology. Where 15 years ago we were yet trying to understand the molecular basis of hemoglobinopathies, today, we are in a position to prevent and cure many of these disabling, lifelong illnesses. India has lagged behind in this progress due to a lack of advanced molecular genetic laboratory facilities. This situation may soon be rectified, and the research in the field of hemoglobinopathies will prove fruitful to epidemologists and hematologists.

The difference between normal and abnormal hemoglobin lies in the protein (globin) part of the molecule. The protein component is a globin tetramer which, in the case of normal adult hemoglobin, is composed of two α-chains and two β-chains. Nearly 90% of the abnormal hemoglobins arise from a single amino acid substitution corresponding to a single base substitution in the globin chain gene. In thalassemias, the biosynthesis of globin is affected although the globin chains that are produced are structurally normal. Less than one-third of the hemoglobinopathies are associated with clinically significant effects, and most of these are due to abnormalities in β -chain. The inheritance of hemoglobinopathies follows classical mendelian pattern with only the homozygotes manifesting significant clinical problems. Due to the high prevalence of different abnormal genes, compound heterozygotes are common and can manifest significant disease *(e.g.,* HbSC, HbE- β -thalassemia).

Epidemiology

India is unique in being populated by a large number of groups which are mutually nonmarrying (or endogamous). This has led to the preservation of certain abnormal hemoglobins in particular population groups. An example of this phenomenon is the sickle hemoglobin (HbS) which is restricted in its prevalence to tribals (Adivasis) and scheduled castes in various parts of India(1). The incidence of sickle trait in certain tribes is as high as 40%(2). HbE is common in Bengal and adjacent areas. j3-thalassemia gene has a wide prevalence. Compound heterozygotes are seen frequently: S β -thalassemia (from various regions), D β -thalassemia (Punjab and other regions), E β-thalassemia (Bengal). The distribution of abnormal hemoglobins is shown in *Table I.*

Beta-thalassemia imposes the largest burden on our health system. The subsequent discussion will focus on this disease.

Beta-Thalassemia

It is estimated that 8,000 homozygotes of β -thalassemia are born in India every year. The prevalence of heterozygotes varies between 1-15% in various groups, being higher in Northern and Western India. There is also a substantial population of compound heterozygotes (S-thalassemia, E-thalassemia).

Beta-thalassemia is extremely hetero-

TABLE I–*Distribution of Abnormal Hemoglobin in India*

	Abnormal hemoglobins	Affected regions
1.	Hbs	Bastar & Ujjain District, Mainpuri District (UP), Nilgiri Hills, Waynad District, Parts of AP, Surat District, Nagpur District, Arungabad, Bombay Assam, Khoratpur, Midnapur.
2.	HbD	Sikhs and Punjabi Hindus, Gujarat, Goa, Migrants from Pakistan, Bengal, MP, UP
3.	HbE	Bengal (Hindus & Muslims), Assam Punjab*, Tamil Nadu*, UP*, Kerala, Maharashtra.
4.	HbJ	Gujarat*, Maharashtra*, Punjab*
5.	HbK	Tamil Nadu*, Bengal*, Goa*
6.	HbL	Gujarat*, Punjab*
7.	HbM	Punjab*, Gujarat*
8.	HbQ	Sindhi (Bombay)*
9.	B-Thal	Bengal, UP, Madras, Punjab, Gujarat, Bihar, Orissa, Kerala
10.	A-Thal	Calcutta*, Bombay*

* Case reports
Adapted from Sukumaran PK(1).

genous at the molecular level, with well over a hundred mutations already identified. The existing data on the mutations responsible for β -thalassemia in India comes from studies conducted on migrant Indians in Western countries. DNA analysis using Southern blotting was performed on 51 thalassemics of Indian origin in Britain(3). The results showed that Indians differ from other populations in two aspects: (a) No single predominant mutation exists. However, 5 common mutations account for 80% of the cases, *(b)* Majority of the patients are homozygotes compared to double heterozygotes found in other populations. The 5 common mutations that were identified were: (i) 619 bp deletion at 3' end of β-globin gene, *(ii)* IVSI-5 (G→C), *(iii)* F/S codon 8/9 (+G), (iv) IVSI-1 (G→T), and (v) F/S codon 41/42 (-TCTT). These findings have important implications for prenatal diagnosis and carrier detection.

Several management problems arise in these children. The thalassemia associations, with the help of the local blood bank societies, are trying to provide regular transfusion facilities to thalassemic children. However, the demand usually outstrips the supply and, therefore, it is generally impossible to follow the current recommendation of maintaining pretransfusion and mean hemoglobin level of 9.5 g/dl and 12 g/dl, respectively(4). The problem with iron chelation therapy, on the other hand, is its high cost. In the absence of state subsidy, over 80% of families (>90% in our clinic) are unable to afford the cost of desferal (DFO) therapy which is currently estimated to be Rs. 80,000-90,000 per year.

The average child with thalassemia in India would be undertransfused and iron overloaded, entering the second decade with multiple problems (short stature, failure of puberty, liver disease, endocrinopathies, psychosocial problems) and with little likelihood of surviving into the third decade. We can conclude that despite advances' in therapy over the last decade, the physical and mental health of thalassemic children in India is far from normal:

It is pertinent, in this context, to discuss new approaches to the management of thalassemia These treatment modalities are palliative (oral iron chelators, pharmacologic manipulation of gamma-chain synthesis), curative (bone-marrow transplantation, gene therapy) or preventive (primary prevention,- prenatal diagnosis).

Oral Iron Chelators

Two drawbacks of DFO therapy - high cost and low compliance - led to a search for an orally effective and inexpensive iron chelating agent. The only candidate drug on the horizon today is deferiprone (LI or 1, 2-dimethyl 3-hydroxyprid-4-one). The drug generated so much enthusiasm that clinical trials were started in 15 countries involving over 400 patients. In India, a multicentric trial is currently going on to establish the safety and efficacy of deferiprone. Initial results were encouraging - high degree of compliance, iron excretion comparable to DFO, achievement of negative iron balance and decline in serum ferritin level and liver iron stores were demonstrated. Side effects were infrequent - transient granulocytopenia (5 cases), transient musculoskeletal joint pains (20%), gastric intolerance (6%) and zinc deficiency (2%). Side effects diminish with a decrease in dosage and till now no clinical trial has been suspended although some patients have had to discontinue the drug.

Recently, however, more worrisome side effects have been described(5) and pertain to drug induced immunological changes. Five fatalities have occurred during deferiprone therapy although they have not been shown to be unequivocally related to the drug. That the issue of longterm safety of deferiprone is becoming increasingly emotional is evident from the ongoing debate amongst different authorities(6).

It would appear, at present, that it may be some time before deferiprone is approved for routine clinical use. The strongest argument that it carries in its favor is the extreme need for an inexpensive oral iron chelator which would be within the reach of the majority of patients, who otherwise are doomed to succumb to organ failure secondaryto an iron overloaded state. The side effects observed thus far occur in less than 20% of the patients and are reversed either by decreasing the dosage or by stopping the drug.

Butyrate

The coinheritance of gene for enhanced production or gamma-chain causes amelioration of the severity of β-thalassemia. Drugs that stimulate gamma-chain synthesis (hydroxyurea, cytarabine, vinblastine, 5-azacytidine) have been tried but were given up because of unacceptable toxicity. Success has been reported recently with the use of intravenous infusion of arginine butyrate(7). The reported rise in HbF synthesis exceeds that seen with previous agents and there are no significant side effects. Efforts are currently underway to develop on oral preparation of butyrate.

Bone Marrow Transplantation

The current figures for overall survival

and.disease free survival after bone marrow transplantation (BMT) for thalassemia are 80% and 75%, respectively(8). In good risk patients undergoing BMT, 94% have long term event free survival and become transfusion independent. BMT for thalassemia has been started recently in Vellore with cost estimated to be a mere fraction of the precious foreign exchange reserves required for the procedure abroad. There is an urgent need for developing more such facilities within the country. The saving in terms of money and blood, and the benefits to patients and family are self evident.

Gene Therapy

Gene therapy of hematologic disease requires the introduction of cloned genes into the bone marrow stem cells and a regulated expression of the newly introduced genes in the appropriate cell lines. Regulated expression of β-globin gene was recently demonstrated in mice reconstituted with virus infected bone marrow cells(9). It is expected that, within the next decade, gene therapy for thalassemia may become a new, and probably safer, cure for thalassemia compared to BMT.

Prevention of Thalassemia

Prenatal diagnosis of thalassemia is possible through DNA analysis of fetal tissue obtained by chorionic villus biopsy, or through measuring globin chain synthesis in fetal red blood cells obtained by cordocentesis. This prevents the birth of a second affected child within the same family but, the effect on the overall incidence of thalassemia is small. The birth of a first affected child can be prevented only through *population screening* for heterozygotes. Carriers are detected by determination of RBC indices, HbA_2 and hemoglobin electrophoresis. Pre and postmarital counselling and prenatal diagnosis are offered to the heterozygotes. Initiation of such screening programs and creating a heightened awareness amongst vulnerable groups is the prime concern of individuals, governmental organizations and societies devoted to the care of such disorders. The task is uphill but, motivation and dedication would go a long way in progressing towards achieving the near zero birth rate of thalassemic children attained by Cyprus(10).

Hemoglobinopathies impose considerable financial, emotional and psychological stress on the patient and family besides draining valuable resources of the country. Although advances in therapeutics and curative modalities promise a lot for the future of thalassemic patients, the way forward in these disorders lies in their prevention. The emphasis in our country, with limited financial, blood and medical resources, must shift to preventive aspects. Screening for heterozygotes must be made mandatory for senior school and college students among communities at high risk for carrying genes of these disorders. Such programs coupled with enhanced prenatal diagnostic facilities would result in tremendous benefits and alleviation of suffering.

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