

## Community genetics and health approaches for bringing awareness in tribals for the prevention of beta-thalassemia in India

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### Abstract

Beta ( $\beta$ ) thalassemia syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of  $\beta$ -globin chains. In the homozygous state,  $\beta$ -thalassemia (i.e., thalassemia major) causes severe transfusion-dependent anemia. Inherited  $\beta$ -thalassemia syndromes cause high degree of hemolytic anemia, recurrent fever, clinical jaundice, frequent infections, bossing of cheek bones, growth retardation, splenomegaly, etc. and are responsible for high infant morbidity, mortality and fetal wastage in India. The victims include the infants, growing children, adolescent girls, pregnant women and a large chunk of ignorant people. In view of heavy genetic load, frequent requirement of blood transfusions, high cost of treatment and management, physical trauma, and mental and psychological harassment to the patients and their families, it has been realized that preventive community health and genetics approach is the most suitable for India. After carrier detection, prenatal diagnosis, and genetic counselling are the important options for couples at high risk for  $\beta$ -thalassemia. A prerequisite for successful prevention and intervention approach in India is the health education, bringing public awareness, sensitization, and community screening for the identification of heterozygotes or carriers in the concerned community. Some suggestions for the prevention of  $\beta$ -thalassemia in the vulnerable communities of India have been over emphasized for amelioration.

### Introduction

In this era of rapidly unfolding the mysteries of nature especially in human genetics, the public health professionals have a significant role in translating this new knowledge into improved health outcomes. Knowing which communities have a genetic variation that puts them at increased risk for diseases such

as beta-thalassemia, sickle cell disease, will help us to develop and implement public health interventions that will improve outcomes and reduce health care costs.<sup>1,2</sup> We must provide guidance to policy makers as they address the new issues that will require legislation to preserve confidentiality, provide protection against discrimination based on genetic information, and regulate commercialized genetic products and services.<sup>3</sup> In order to achieve these goals, whether management policy, behavior and education, epidemiology, biostatistics, or environmental health, we must all contribute our expertise to create an informed public health workforce.

The advances in human genetics that have occurred during the past twenty years have revolutionized our knowledge and the role of inheritance in health and disease.<sup>4</sup> We now know that our DNA determines not only the cause of catastrophic single-gene disorders, which affect millions of people worldwide, but also predispose to cancer, diabetes, heart disease, psychiatric (mental) disorders and even to some infectious diseases. In some hospitals, these services provide a high quality integrated service covering all aspects including diagnosis, clinical care, counselling, screening, predictive testing, education and professional training. The aim of providing these services is to reduce the impact of genetic conditions on those who may be affected and their care takers/families, and assist in their ability to make informed choices.

There are a number of ways to control the spread of beta-thalassemia in India. It all depends upon the type of programs being implemented. The economics and logistics of these approaches need urgent study and careful evaluation.<sup>5</sup> Population screening is one approach,<sup>6</sup> followed by community genetics<sup>7</sup> prenatal diagnosis approach, and bone marrow or stem cell transplantation. Routine check up and symptomatic treatment strategy can be adopted, if one encounters occasional cases of hemoglobinopathy in a community or population. At present, the developing countries including India, which have a major health burden of hemoglobinopathies,<sup>5</sup> are confused about how best to plan for future. These are all difficult decisions but none of them can be made without adequate knowledge of the likely burden of the disease based on good community or population screening and finding their incidence/ prevalence.<sup>6,7</sup> What is urgently needed, are some adequate pilot studies to find out which technology would best suit to individual communities although it would take a long time for screening and counselling, followed by advice from health demographers and planners about the efficient and most cost-effective way to proceed. Moreover, it is better to watch what is already done in other countries and to apply the well-established methods

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that are more suitable to local conditions. Following the specific and effective control and preventive strategies, the high prevalence of  $\beta$ -thalassemia have already been reduced or even eliminated in some countries, namely Cyprus, Greece, Italy, Turkey, etc.

### Beta-thalassemia in India

Thalassemia syndromes are a heterogeneous group of single gene disorders, inherited as an autosomal recessive manner, and prevalent only in certain parts of the world. The disease is found most commonly in the Mediterranean region, Africa, and Southeast Asia with an incidence as high as 10%.<sup>8</sup> There are about 15 million people worldwide who have clinically apparent thalassaemic disorders with about 240 million carriers of  $\beta$ -thalassemia. In India alone, the number is approximately 30 million with a prevalence range between 3-17% with the mean prevalence being 4.2%.<sup>5</sup> Every year approximately 100,000 children with Thalassemia Major are born world over,<sup>8</sup> of which 15,000 are born in India.<sup>5,9</sup> The carrier rate for  $\beta$ -thalassemia gene varies from 1-3% in Southern India to 3-15% in Northern India. Certain communities in India, such as Sindhi and Khatri/Arora from Northern India, Bhanushali, Kutchi, Lohana from Gujarat, Mahar, Neobuddhist, Koli and Agri from Maharashtra, Gowda and Lingayat from Karnataka, Brahmin, Khandayat, Karan, Chasa, Teli, and Gauda from the state of

Orissa, etc. having comparatively a higher carrier rate.<sup>10</sup>

Once a child is diagnosed to have homozygous thalassemia disorder, he/she has to take lifelong treatment. Management includes 3 weekly filtered packed red cell transfusions regularly, chelation therapy for iron overload, management of complications of iron overload and transfusions, including osteoporosis, cardiac dysfunction, endocrine problems, Hepatitis B and C, HIV infection, etc. However, this optimal treatment comes at a prohibitive cost. Therefore, not more than 5-10% of thalassemic children born in India receive optimal treatment.<sup>11</sup> Stem cell transplantation as a curative treatment, which costs between 6 to 16 lacs rupees per person is out of the reach for majority of children.<sup>10</sup>

### Severity of $\beta$ -thalassemia major

The severity of symptoms depends on the severity of the disorder. Silent carriers of  $\alpha$ -thalassemia generally have no signs or symptoms of the disorder because the  $\alpha$ -globin protein is so small that hemoglobin works normally. People who have  $\alpha$  or  $\beta$  thalassemia trait can have mild anemia but a majority remain asymptomatic. Mild anemia can make one feel tired. It's often mistaken for iron-deficiency anemia.

People with beta thalassemia intermedia have mild to moderate anemia. They also may have other health problems such as:

- Slowed growth and delayed puberty. Anemia can slow down a child's growth and development.
- Bone problems. Thalassemia may make bone marrow (the spongy material inside bones that makes blood cells) expand. This causes the widening of bones than the normal. Bones also may be brittle and break easily.
- An enlarged spleen. The spleen is an organ that helps one's body to fight infection and removing unwanted material. When a person has a thalassemia, the spleen has to work very hard. As a result, the spleen becomes larger than normal. This makes anemia worse. If the spleen becomes too large, it must be removed.

People with beta-thalassemia major (also called Cooley's anemia) have severe form of thalassemia. Signs and symptoms occur within the first 2 years of life. They may include severe anemia and other serious health problems such as:

- Pale and listless appearance
- Poor appetite
- Dark urine
- Slowed growth and delayed puberty
- Jaundice (a yellowish color of the skin or eyes)
- Enlarged spleen, liver, and heart
- Bone problems (especially bones in the

face)

The physical findings are related to severe anemia, ineffective erythropoiesis, extramedullary hematopoiesis, and iron overload resulting from transfusion and increased iron absorption:<sup>1</sup>

- Skin may show pallor from anemia and jaundice from hyperbilirubinemia.
- The skull and other bones may be deformed secondary to erythroid hyperplasia with intramedullary expansion and cortical bone thinning.
- Heart examination may reveal findings of cardiac failure and arrhythmia, related to either severe anemia or iron overload.
- Abdominal examination may reveal changes in the liver, gall bladder, and spleen. Hepatomegaly related to significant extramedullary hematopoiesis typically is observed. Patients who have received blood transfusions may have hepatomegaly or chronic hepatitis due to iron overload; transfusion-associated viral hepatitis resulting in cirrhosis or portal hypertension also may be seen. The gall bladder may contain bilirubin stones formed as a result of the patient's life-long hemolytic state. Splenomegaly typically is observed as part of the extramedullary hematopoiesis or as a hypertrophic response related to the extravascular hemolysis.
- Extremities may demonstrate skin ulceration.
- Iron overload also may cause endocrine dysfunction, especially affecting the pancreas, testes, and thyroid.

In a cross sectional study for growth, puberty and endocrine dysfunctions in relation to iron overload in multi-transfused 35 Indian thalassemia major patients aged 13 to 24 years, were assessed clinically based on the laboratory values of various hormone levels in stratified age and sexual maturity.<sup>12</sup> Results showed that 57.14% patients were short, 60% had not attained puberty, and 87.5% of the girls had primary amenorrhea; 14.29% had low FSH and 2.86% low LH levels; 89.47% of the boys had low free testosterone and 43.75% of the girls had low estradiol levels. While 20% had high TSH levels, 40% had high PTH levels, of which 92.8% had low levels of Vitamin D. Low levels of IGF-1 were noted in 51.43%. It was concluded that short stature and hypogonadism were frequent in thalassemia major patients. The need for vigilant clinical evaluation of growth and puberty, as well as appropriate hormonal evaluation in poly transfused thalassemic children in order to detect and treat endocrine dysfunction early was emphasized and recommended aggressive and adequate chelation from early life so that permanent damage to the endocrine glands can be prevented. Similar results were obtained by Shamshirsaz *et al.*<sup>13</sup> and Argyropoulou *et al.*<sup>14</sup>

In an evaluation of cardiac iron load by cardiac magnetic resonance in 60 transfusion dependant thalassemia major patients with 10 controls during the period 2008-2009,<sup>15</sup> it was found that 50% of patients had no cardiac siderosis; 33.3% had mild to moderate and while 16.7% had severe cardiac siderosis. In contrast, only 8.3% had normal liver iron values, 55.7% had mild to moderate and 36% had severe iron stores. Mean serum ferritin of all 60 cases was  $3528.6 \pm 1958.6$  ng/mL showed statistically significant differences in the mean cardiac T2 values of patients. Thalassemia patients had significantly higher cardiac iron stores as compared to controls. Serum ferritin and liver iron values did not correlate with cardiac iron values. Three of non-patients <10 years showed evidence of myocardial siderosis.

Long term responses to deferiprone therapy in beta-thalassemia major patients were evaluated by Daar and Pathare<sup>16</sup> and Panigrahi *et al.*<sup>17</sup>

### Community genetics

The community genetics approaches can handle the problem of beta-thalassemia in the following way:

- i) Identification of vulnerable (at risk) communities
  - Primary Health Center/Community Health Center/Block Level Registry of Community-wise Incidences of Cases;
  - District Hospital Level Community-wise Incidences of Cases;
  - Holding Health Camp at Primary Health Center/Community Health Center/Block/District Level;
  - Organizing District Level Health Camps (Swasthya Mela);
  - Medical College & Hospital Level Referral Services;
  - Non-Governmental Organisations (NGOs) working in a particular area pointing out the Local Health Problems;
  - Community Welfare Organisations or Community Self identified Health Problems;
  - Conducting Random Community or Population Surveys.
- ii) Self-Reporting (Identification of individuals/Families)
- iii) Research Conducted by Medical Research Institutes in the Area

The usefulness of cation exchange high performance liquid chromatography (CE-HPLC) was found to be a simple, rapid and reliable method for the detection of hemoglobin variants at community level.<sup>18</sup> Hemoglobin electrophoresis and family studies play a valuable role in difficult cases. The overall prevalence of  $\beta$ -thalassemia trait in voluntary blood donors who were accessible and cooperative for screening purpose was recorded to be 9.59% at Bhopal in Madhya Pradesh state of central

India.<sup>19</sup> The prevalence of  $\beta$ -thalassemia trait varied across the states of origin and within the state of Madhya Pradesh. It was concluded that blood donors offer an attractive adjunct to  $\beta$ -thalassemia trait detection in national program and the study offered insights into the  $\beta$ -thalassemia trait gene flow and migration in India.

In profiling  $\beta$ -thalassemia mutations in India at state and regional levels and their implications for genetic education, screening and counseling program, it was emphasized that appropriately designed community-based studies are required as a health priority to correct earlier sampling inequities which resulted in the under-representation of many communities, in particular rural and socio-economically under-privileged groups.<sup>20</sup>

### Curative options

- i) Cost of treatment of one thalassaemic child per year for both transfusion and chelation therapy is very high in India, which is unaffordable by many families because of poverty.
- ii) Bone marrow transplantation (BMT) is specific treatment, but non-availability of HLA-identical or matched donors, high cost of tests and treatment, lack of expertise, etc. are major prohibitory factors.
- iii) Cord blood (Stem Cell) transfusion (CBT) is still in infancy stage in India.
- iv) Prenatal diagnosis is confined only to Metro cities in India.
- v) Preventive genetics approach is cost effective solution to  $\beta$ -thalassemia problem, but only if, it is possible to make antenatal diagnosis available to all couples at risk of  $\beta$ -thalassemia major in India.<sup>10</sup> Lack of antenatal diagnosis after screening is a cause of heavy psychological and ethical problems, which are very difficult to accept in the enlightened world today.

### Awareness

For bringing awareness in the community or population, the program for beta-thalassemia can be launched at various levels like:

- i) Door-to-door awareness campaign by holding meeting/discussion along with Anganwadi Teacher/Health Workers;
- ii) Through Mahila Mandals;
- iii) Group/Village level holding interactive meetings, delivering lecture (in local language), holding discussions;
- iv) District Collector/Child Development and Project Officer/District Welfare Officer/Chief District Medical Officer level holding meeting and discussion;
- v) District Public Relation Officer through Drama, Skit, Street play, showing Documentary picture (in case of tribals in Weekly/Monthly Markets);
- vi) Through Electronic media, National

Television Channel/Doordarshan/Media (Newspapers advertisement), Pamphlets (Information, Education and Communication), and Public announcements;

- vii) Through Radio in local language, advertisement in Public Transport System (Railways, Buses, Rickshaws, etc.), advertisement in Cinema Halls, Distributing Pamphlets;
- viii) Live-demonstrations: case studies;
- ix) Through induction of other family members (Maternal/Paternal Uncles/Aunties and Cousins);

### Prevention

The public health problem of hemoglobinopathies especially the beta-thalassemia can be prevented in India<sup>21</sup> by adopting the following procedures:

- i) Voluntary screening (Testing):
  - Individual
  - Family
  - Community
- ii) Carrier detection
  - Neonatal screening of hemoglobinopathies is useful only to detect sickle cell affected patients and accordingly to plan follow up and treatment for them.
  - Screening of Anganwadi/Creches/Nursery schools has poor impact on prevention because of ethical reasons and non-compliance/caring by some ignorant/broken poor families in India, etc.
  - Screening at Schools (including Ashram Schools), High school, and College level (Adolescents). Young adults are more sensitive to receive information regarding their near future life.
- iii) Before marriage
- iv) After marriage before pregnancy
- v) During pregnancy (in 1<sup>st</sup> trimester) both partners
- vi) Already affected child in the family – Through induction of other family members or relatives
- vii) Prenatal diagnosis (between 11<sup>th</sup> to 12<sup>th</sup> week of pregnancy) – Selective abortion by following any one of the procedures depending upon the period of pregnancy:
  - Amniocentesis;
  - Celocentesis (7-9<sup>th</sup> week of pregnancy is now available for DNA diagnosis of hemoglobinopathies in some countries). At 5-12 weeks of gestation the amniotic sac is surrounded by celomic fluid, which contains cells of fetal origin. This fluid can be sampled by celocentesis, which involves the ultrasound-guided insertion of a needle through the vagina. The aim of this study was to examine the feasibility of prenatal diagnosis of hemoglobinopathies from the celomic fluid using a specific protocol. Celocentesis was performed at 7-9 weeks gestation in 26 singleton pregnancies at

risk for hemoglobinopathies. In 25 cases more than 30 fetal cells were recovered from the celomic fluid and in all these cases molecular analysis for hemoglobinopathies was possible and the results were confirmed by subsequent chorionic villus sampling or amniocentesis. Results of this study suggest that reliable diagnosis of thalassemia syndromes can be performed from 7 weeks gestation by celocentesis. Further work is necessary to demonstrate the safety of celocentesis before widespread use;<sup>22</sup>

- Chorionic Villus;
- Fetal Blood;
- Non-invasive (Study of Fetal cell in maternal blood).
- viii) Genetic counselling:
  - Retrospective
  - Prospective
- ix) Adoption of a healthy child

### Current treatment strategies

- x) Stem cell/Bone marrow transplantation
- xi) Cord Blood Banking
- xii) Pre-implantation Diagnosis and use of donor in Assisted Reproductive Transplant Therapy (ART)

More elaborated and sophisticated, and medical technological procedures are followed after cross matching the human leucocyte antigen (HLA) in beta-thalassemia bone marrow transplantation. Major-histocompatibility-complex alleles determine the tissue compatibility that is necessary for the acceptance of transplanted tissues. Graft survival after bone marrow transplantation is influenced by the extent of the HLA compatibility between the donor and the recipient. Early studies showed that HLA mismatching between the donor and the recipient increases the risk of graft failure after bone marrow transplantation. This risk increases when the donor is heterozygous and the recipient is homozygous at the same HLA locus. More recent studies showed that disparity between donor and the recipient at the HLA-A, B, and C loci is a risk factor for graft failure after marrow transplantation from unrelated donors in the beta-thalassemia patients.

After matching the HLA, cord blood may be used as substitute for bone marrow transplantation. In the Pre-implantation and Assisted Reproductive Therapy (ART), the fertilized embryos are tested for the disorder (Beta-thalassemia) before implantation in the woman's uterus.

### Suggestions for the prevention of beta-thalassemia in India

In a poverty stricken country like India, it is

still a dream to go for stem cell or bone marrow transplantation without ample facilities for cord blood banking, bone marrow transplantation with huge amount of money involvement for a beta-thalassemia patient.<sup>1,2,10</sup> The most practical approach for the prevention of beta-thalassemia is the preventive genetics strategies as streamlined below:

- Mass Community Screening for Beta-thalassemia;
- Sensitization, bringing awareness, and motivation for carrier detection;
- Propagation for induction screening (Other members of affected child);
- Establishment of Special Clinics/Regional Centres for high-risk communities preferably near their vicinity;
- Providing basic diagnostic facilities with referral provision;
- Establishment of prenatal diagnostic facilities near the high-risk communities;
- Providing genetic/marriage counseling to affected families;
- Social and economic support for combating the disease;
- Maintenance of registry for future planning strategies.

To conclude, it is emphasized that several integrated preventive genetics and health approaches simultaneously can be adopted for bringing awareness at community level with community participatory strategies for the prevention of beta-thalassemia in India. Success of the strategy depends on the logistic involvement at each and every stage of the program with full cooperation from the concerned community.<sup>23</sup> A prerequisite for successful prevention and intervention in India is the health education, public awareness, sensitization, and community screening for identification of heterozygotes or carriers. There is a need of will or mindset of the people.

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