Asian Biomedicine Vol. 1 No.1 June 2007

Review

Prevention and control of thalassemia in Asia

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***Background*:** Thalassemia and abnormal hemoglobin are the most common inherited diseases. The only treatment readily available in most countries is regular blood transfusion and iron chelation that is recommended in severely anemic patients with iron overload. In the last 20 years there has been much progress in terms of diagnosing, preventing and managing thalassemia. This has lead to the success of prevention and control of thalassemia in many Mediterranean countries such as Cyprus, Italy and Greece.
Objective: To introduce approaches that may be applied for the control of thalassemia in developing countries including Asia where thalassemias are very prevalent.

***Keywords*:** Asia, prevention, thalassemia.

Thalassemia refers to a group of inherited blood disorders. They occur most commonly among Asian people especially Southeast Asian, Southern Asian and people of Mediterranean ancestry [1]. The fundamental abnormality in thalassemia is impaired production of the globin chain. Thalassemia can be classified into alpha and beta thalassemias by their clinical manifestations and their genetic background. Children with beta thalassemia major appear healthy at birth, but during the first decade of life they become pale, listless and fussy with poor appetite. They grow slowly and have persistent jaundice. Without proper treatment, the spleen, liver, and heart become greatly enlarged. Bones turn thin and brittle, and face bones become distorted. Heart failure and infection are the leading causes of death among untreated patients.

Complications of thalassemia can be prevented when children with thalassemia major are treated with regular blood transfusions to keep their hemoglobin level around 10 g/dl (generally once a month). This "hypertransfusion" method enhances the child's growth and well-being, and usually prevents heart failure and bone deformities. The quality of life for children with thalassemia major is greatly improved. Unfortunately, repeated blood transfusions may lead to certain complications, mostly related to blood safety issues, especially blood-transmitted diseases such as hepatitis, AIDS, malaria and syphilis. Moreover, frequent blood transfusions also lead to an accumulation of iron in the body, which can damage the heart, liver and other organs.

Administering an iron chelator can help the body to eliminate excess iron and prevent or delay problems related to iron overload. Desferrioxamine is an iron chelator that has been widely used during the last 40 years. It is usually administered daily via a mechanical pump that administers the drug subcutaneously while the individual is sleeping for 10-12 hours at a dose of 40 mg to 60 mg/kg/day, at least 5 days/week, in patients on regular blood transfusion. Patients with thalassemia major who are treated with regular blood transfusions and iron chelation live longer and are spared much of the suffering endured by untreated patients. During these last few years, extensive researches has been conducted on oral iron chelators. Deferiprone, L1, was the first oral iron chelator and is widely used as a first and second line iron chelator in many countries. Deferasirox, ICL670, is a new oral iron chelator that is being recently approved by the US FDA.

Thalassemia may be cured by stem cell transplantation. However, this form of treatment is possible only for a minority group of patients who have a suitable HLA-matched donor and can afford the costly treatment. The transplant procedure is risky

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and may have many complications. Some patients benefit from splenectomy, especially those with very large spleen and some evidence of hypersplenism. The other treatments for thalassemia are symptomatic and supportive care for infection, osteoporosis and other endocrine complications.

Due to the large number of thalassemic patients in Asia and limited medical service resources it is not possible to give optimal blood transfusions and iron chelating agents to the majority of patients. They receive no or minimal blood transfusions and no iron chelators which are too expensive. These masses of untreated thalassemic patients develop a multitude of complications as previously described. Although we are prepared to use all available cures, they are either not yet available or are available for only a very few individuals. Moreover, we need to develop the necessary human resource and infrastructure to cope with the sheer number of the patients. We are thus left to care for a large number of patients with complications now not seen in the West. The best approaches to cope with thalassemia in developing countries, including many countries in Asia, is to prevent the birth of a new cases with major thalassemic disease.

Thalassemia in Asia

Thalassemia places an enormous burden on healthcare resources throughout the developing world. Thalassemia is very prevalent in Asia causing public health and socioeconomic problems in many countries. The types and frequencies of thalassemias are heterogeneous in this vast region even within a country. Alpha-thalassemia, beta-thalassemia, and hemoglobin (Hb E), are commonly noted as the hallmark of Southeast Asia, Sri Lanka, Bangladesh, Maldives and the eastern region of India. Hemoglobin Constant Spring (Hb CS) is also prevalent in the Southeast Asia Region. Furthermore, the most serious form of thalassemia, Hemoglobin Bart's hydrops fetalis, is almost exclusively found in Southeast Asians and South China [2-5].

Large population screening examinations in Japan and Korea revealed very few thalassemia. Both alpha and beta-thalassemia are prevalent among Southern Chinese, with most cases traced to the Guangxi and Guangdong provinces. The frequency of the various abnormal hemoglobin genes in Asian countries is summarized in **Table 1.**

Table 1. Prevalence of thalassemia and abnormal hemoglobins in Asia. (+ means the present of abnormal gene but the exact frequency is not known.) [4, 5].

Country	% Carriers			
	α	β	Hb E	Hb CS
Bangladesh	ND	3	4	-
Cambodia	(+)	(+)	(+)	-
China : Guang xi	15	5	(+)	-
China : Hong Kong	2.2	3-6	-	-
China : Taiwan	4	1-3	(+)	-
India	5-97	3-4	(+)	(+)
Indonesia	6-16	3-10	1-25	-
Laos	(+)	(+)	(+)	
Malaysia	(+)	4.5	(+)	(+)
Maldives	28	18	0.69	0.4
Myanmar	10	0.5-1.5	2-28	-
Singapore	2.92	0.93	0.64	-
Sri Lanka	(+)	2.2	0.5	-
Thailand	10-30	3-9	10-53	-
Vietnam	2.5	1.5	(+)	-

These abnormal genes in different combinations lead to over 60 thalassemia syndromes. Different thalassemia genotypes have greatly variable severity and even patients with apparently identical genotypes can have remarkably different levels of severity. The two major alpha thalassemic diseases are Hb Bart's hydrops fetalis or homozygous alpha thalassemia 1 (homozygous alpha+ thalassemia), and Hb H disease that occurs from interaction between alpha thalassemia 1 (alpha+ thalassemia) and alpha thalassemia 2 (alpha+ thalassemia) or between alpha thalassemia 1 and Hb CS. Interaction between beta thalassemia genes or beta thalassemia and Hb E genes leads to homozygous beta thalassemia and beta thalassemia/Hb E that are major beta thalassemic syndromes in this region. In beta thalassemia/Hb E disease, although the patients have identical genotype, the degree of anemia varies greatly with hemoglobin levels ranging from 3-13 g/dl [5].

Estimated direct cost for the management of ONE thalassemia major patient who lives until 10-30 years old is about 1.3 to 6.6 millions Baht (US$ 32,500-185,166) (**Table 2**). Thus, thalassemia is recognized as one of the very important public health problems in most Asian countries.

Prevention and control program for thalassemia in Asia

Effective prevention programs for thalassemia have been demonstrated in many European countries where the numbers of carriers of abnormal genes are high, such as Cyprus, Greece and Italy, and now also in the Middel East. Premarital screening for thalassemia is standard practice and national audit data are available. Most at-risk couples are identified early for prenatal diagnosis in the first pregnancy and the majority use this service and produce healthy offspring. Screening program need to be supported by public education and regulatory structures empowering individuals to make informed decisions and to ensure that people are protected against discrimination as a result of their test results [6].

Thalassemia carriers are detected mainly through the expanded family study of cases with thalassemic diseases. Accurate frequencies are still not available in many Asian countries due to inherent difficulties in the diagnosis of thalassemia traits. However, laboratory progress during the last few years has enabled us to undertake mass screening for beta thalassemia and Hb E carriers, with accurate diagnosis using automatic high performance liquid chromatography (HPLC). As aresult, nationwide programs have commenced to prevent and control homozygous beta thalassemia, compound heterozygote beta thalassemia/Hb E, and Hb Bart's hydrops fetalis, with encouraging results in many countries.

However, in some Asian countries, reliable estimates for the prevalence of thalassemia genes are not available at present, and diagnoses of the diseases and management of the patients in the majority of these countries are still far from satisfactiory. Thus, the patients and families suffer miserably due to ignorance of the diseases, misunderstanding, malpractices, etc. To improve this situation will require proper education of health personnel, not only the physicians but downstream to the auxiliaries working in the communities. Genetic counseling, at least for families already afflicted by the diseases or in those who request it, should be provided. This requires accurate diagnoses and a good understanding of the different disorders. While conventional therapy involving blood transfusions and iron chelation are intolerably expensive, prenatal diagnosis and selective abortion are more economical and cost-effective. However, these should not be carried out indiscriminately. Some thalassemic

Table 2. Estimated direct cost for the management of ONE beta thalassemia major for 30 years (number in Thai Baht, US$1 = 36 Baht) [4,5].

Cost (Thai Baht)	1–10 years	11–20 years	21–30 years
1. Blood transfusion plus filter/month	2,500 (1 unit)	5,000 (2 units)	7,500 (3 units)
2. Desferrioxamine Vial/month	5,000 (20 vials)	10,000 (40 vials)	15,000 (60 vials)
3. Hospital care 1 day/month	2,000	2,000	2,000
4. Other: Lab tests/month	1,000	1,000	1,000
5. Total cost/month	10,500	18,500	26,500
6. Total cost/year	126,000	222,000	318,000
7. Total cost/10 years	1,260,000	2,220,000	3,180,000

diseases of identical genotypes may greatly vary in their severity because of environmental factors or modifying genes. This points to the need for accurate diagnoses and good understanding of the diseases.

It is time for international health organizations such as the World Health Organization (WHO) to recognize and include the thalassemias as major international public health problems that require and merit good health planning, if Health for All is to be achieved.

Preparation for control program

Strategy: The strategy of the control program consists of treatment and prevention, i.e. the treatment of existing patients in the most cost-benefit way and a reduction in the birth of new cases.

Target: The specific target is to set up the core of an effective treatment, prevention and training service in each country. This should define the methods of treatment and prevention appropriate to each individual country.

Each country should establish a National Thalassemia Center. The Center should be well equipped and with appropriately trained staff including a hematologist or pediatrician, counseling nurse and technician. This Center will serve as a reference and training facility for local people. It should also perform research, both basic and applied, towards the prevention and control of thalassemia.

The following strategy is recommended for prevention and control programs for thalassemia and abnormal hemoglobins in Asia.

Policy announcement

The prevention and control of thalassemia is announced as the National Policy, and all people have the right to have service under the National Health Care Policy. Details of the service include:

1) All pregnant women to receive genetic counseling for thalassemia.

2) All pregnant women can obtain access to thalassemia screening at no cost. The husband of all women with "positive" thalassemia screening tests will be called up for the same screening procedure.

3) Confirmatory tests will be carried out in all high-risk couples indicated by the screening tests.

4) Prenatal diagnosis for thalassemia will be carried on all pregnancies at risk of having thalassemic babies.

5) The standard health care system towards the prevention and control of thalassemia has been developed at different levels. A network of service and referring systems will also be developed to support this program.

Public education

A nationwide campaign of public education about thalassemia and the risk of having thalassemia children, especially targeted towards school children, couples who intend to marry, and pregnant women, will be continuously carried out. The campaign should include the total health care of family members and provide knowledge of the proper services available. Public eduation should be carried out through all means of mass media such as newspapers, television, radio, workshops, with demonstrations at the village levels.

Manpower development

An extensive program of manpower development should be implemented at the beginning of the program. The aim is to improve the level of knowledge and expertise of paramedical personnels at all levels to familiarize them with thalassemia management, especially with respect to the prevention and control of disease, with high standards and good quality of care essential. Examples of these activities are:

1) Details of the whole program should be introduced to the administrators at all levels, including the Ministry of Public Health, regional health officers and all government hospitals.

2) Seminars, workshops and training to be organized for paramedical personnels at all levels in order to improve their knowledge of thalassemia, so that they can effectively communicate with the target groups.

3) Education provided to secondary school teachers to improve their basic knowledge about modes of genetic inheritance, costs of treatment, risk and alternative therapeutic approaches.

4) The establishment of a Thalassemia Forum in the office of the Ministry of Public Health, with the remit of advising and supervising policy, strategic planning, monitoring and evaluation of the whole program.

Networking

Networks of thalassemia prevention and control should be set up at both local and international levels, so that the members from different regions and countries can support each other, both in knowledge and services.

Monitoring, follow up and evaluation

As noted above, the program should be evaluated and monitored by the Thalassemia Forum Committee. The Committee should have a regular meetings, at least once every three months, for problem-solving and monitoring the direction of the program, establishing the standard services at each level of health care and providing appropriate means of support.

Recent progresses

The increasing problems of thalassemia and sickle cell anemia were recognized by the WHO and reported in *Genomics and World Health* (2002). It was suggested that for the more effective control and management of the thalassemias the principle of North/South partnerships should be pursued and that the possibility of South/South networks should also be examined. With the support of Professor Prawase Wasi, Thailand, Sir David Weatherall, UK and Professor Alan Bittles, Australia, the Asian Network for the Control of Thalassemia was established during the conference on *Genetics and Population Health* held in Fremantle, Australia, 2004.

Representatives from a number of Asian countries together with workers in the thalassemia field from the UK, Canada and Australia will work together towards the prevention and control of thalassemia in Asia. It was agreed that the Network should focus on fact-finding regarding the extent of the problem in individual countries together with an account of the facilities that exist for the diagnosis and management of the different forms of thalassemia in each country. The health burden of the thalassemias in Asia should be translated into Disability Adjusted Life Years (DALYs). Using this approach, it is possible to compare the health burden of the thalassemias with other health problems in Asia. Although the preliminary data indicate that thalassemia will pose a health burden comparable to a number of major communicable diseases, more extensive data are required, particularly on disease gene frequency and accurate costing of both prevention and treatment regimes.

The first full meeting of the Network was held in Bangkok in July, 2005. A draft outline of the Network program and guidelines for the prevention and control of thalassemia in Asia are as follows:

Objectives and priorities of the network

(a) To ensure that each country in the Network has a National Thalassemia Center for providing expertise in the diagnosis, control and management of the thalassemias.

(b) To provide training in the diagnosis and management of the thalassemias required to develop these Thalassemia Centers.

(c) To determine the most cost-effective and accurate approaches to population screening for thalassemia.

(d) To establish a population screening program within each country, to determine more accurately the frequency of the thalassemias and hence the future likely health burden of each country in the future.

Outline of approach to achieve these objectives

(a) Establish a Thalassemia Center in countries in which they currently do not exist.

(b) Establish at least one and possibly two major education and training workshops in the diagnosis and management of thalassemia in the first year of the program.

(c) To sustain the Network, involve local partnerships between countries in which the thalassemia programs are well established and those in which facilities are not yet available. A firm and on-going partnership of this type would probably be the most ideal way to sustain the future of the Network.

(d) Organize at least one annual meeting of the representatives of each country to assess progress and to evolve joint research programs. The evolution of a population screening program should be top of the research priority and hence the way in which this is done should be comparable for each Center.

(e) A start should be made in incorporating help from health economists towards defining the true cost of the control and management of thalassemia in each country.

(f) Through the efforts of the Network, and with the help of the WHO, Thalassaemia International Federation (TIF) and other agencies, governments of countries with a high frequency of thalassemia should be persuaded to identify the importance of developing national programs for achieving these aims.

In May 2006, the WHO and March of Dimes Birth Defects Foundation held a joint meeting in Geneva and the Executive Board adopted a resolution

on sickle cell anemia [7] with recommendations to the World Health Assembly (WHA) to support national and international activities on the control of sickle cell anemia worldwide. Subsequent discussions on thalassemia and other hemoglobinopathies at the WHA regulated the adoption of equivalent resolutions [8].

Conclusion

Thalassemia is one of the major public health problems in Asia. To achieve the success in the prevention and control of thalassemia, an ongoing holistic approach is required. It is expected that with optimal collaboration and support, effective prevention and control of thalassemia can be achieved. This will lead to a healthier new generation which enjoys a better overall quality of life.

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