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Review Article

Genetic problems at present and their challenges in the future: Thalassemia as a model

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Compared to the infectious diseases, genetic disorders are not so frequently encountered in the clinic, so that there has been a trend that they are neglected by people or even by the authorities. Our government is still fighting against infectious diseases and nutritional disorders. The immunization programs of the government have indeed reduced the occurence of many infectious diseases. Actually, the government has to begin to think how to handle the emerging genetic disorders, after having eradicating infectious diseases.

In Western countries, less then hundred years ago, infant mortality rate was about 120-150‰, whereas in poor rural areas and in overpopulated cities it might reach 200-300‰. At present time, since there is an improvement of the living conditions, the infant mortality rate diminished to 15-20‰. Health statistics in several of the wealthier countries show that congenital diseases become the major cause of infant mortality, accounting for 25-35% of the whole infant deaths.[1]

There has been an increasing interest for congenital and genetic disorders in the Western countries during the last decades. This is not only true for medical professionals but also ethicist, lawyers, certain managers of industry, administrators, politicians, and general public. The reasons of this increasing interest are due to several factors:

1. Congenital disorders have not only become the major cause of infant mortality, but these disorders are also responsible for a considerable proportion of infant morbidity.
2. More and more couples want to limit their family size, by having a normal and healthy child.
3. There have been major developments in the methodology of early diagnosis of disease and of carriers of genetic disorders. It makes prenatal monitoring possible and able to do selective termination if it is necessary.
4. The increasing cost of health care has directed the attention of many governments to perform prevention programs in facing the genetic disorders and other disorders which need a long-term treatment.
5. Advances in basic research in molecular genetics, biochemistry, and cell biology, have given better insight into the molecular basics of hereditary disorders. These studies have led to experimental manipulation of genetic material derived from several organisms.

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Children with genetic disorders need 12-24 times longer of hospital stay and 5 times more frequent to be hospitalized than the normal one.[1]

Genetic disorders may be caused by a single gene mutation, chromosomal aberration, multifactorial (genetic and environment), and mitochondrial disorders. Several genetic disorders which have been found in Indonesia are: 1) metabolic disorders (carbohydrate, fat, amino acid, etc), 2) hemophilia, 3) thalassemia and hemoglobinopathies. The management of those disorders is not simple, because high quality laboratory is required for the exact diagnosis of the disease. The expenses of the optimum treatment of those disorders which are very high causes burden upon patients, families, and national health services. Besides, the disorders create big medico-social problems.

Are genetic disorders preventable? Yes, most of those disorders are preventable or at least the symptoms can be minimized if early detection can be performed, either during prenatal or postnatal period.

In this paper, the authors would like to use thalassemia as a model, because it is the most frequent genetic disorder in the world. Thalassemia is a preventable disease; the birth of a baby with thalassemia major can be prevented by avoiding marriage of 2 carriers or by performing an ante-natal diagnosis to the wife of a high risk couple. There must be a big program to perform these 2 options, without the **political will** of the government this prevention programs will not succeed. A high quality and equipped laboratory should be available, to make an exact diagnosis of thalassemia, with about 200 mutations.

People should be informed about the existence of these genetic disorders, especially thalassemia, the most frequent genetic disorders in the world, so that they know what should be done to avoid this disease.

In the declaration of Alma Alta (1978) "Health by the Year of 2000", it has been emphasized that the prevention and control of the local endemic diseases including genetic prevention must be integrated into the primary health care services.[2] The declaration urged the governments to formulate national policies, strategies and plans of action to perform and sustain primary health care as a part of comprehensive health service. Health authorities are therefore already officially committed to the prevention of thalassemia in areas where the disease is endemic.

Thalassemia and hemoglobinopathies create a burden to public health problems in the world. Not less than 300,000 affected children born each year, and about 60,000-70,000 of them are α-thalassemia major.[3] Those figures are actually like a top of an iceberg, because there are still many areas in the world where epidemiological studies have not yet been established properly. According to the WHO (1994),[4] approximately 250 million people (4.5% of the world population) carry a hemoglobinopahty gene. It is estimated that 1.5% of the world's population are carriers of α-thalassemia (80-90 million people).

How about thalassemia in Indonesia? About 28 thalassemia gene mutations have been reported in Indonesia. The large number of α-thalassemia mutations give a big variety of clinical pictures of patients, from a very mild to a severe one. Those severely affected patients cause major public health burden, medical treatment and psychosocial problems. So many researches in all aspects concerning this disease have been done and billions of dollars has been spent for this purpose but the results of those studies are still obscure. The disease is not yet curable until this moment. The available treatment is just to prolong the patients' life, yet causes new problems like how they as a handicapped person can be accepted by the society. They should be helped to integrate into adult society and to gain acceptance for higher education and appropriate jobs. On the other side they still need medical, psychological, and social treatments. Psychologically they feel very depressive and suffer from inferiority complex; some of them refuse to receive treatment any more, they prefer to choose a quick demise, because they feel that they are the burden of their families. It is clear that the disease cause huge medico-psychosocial problems for the patients themselves, the family, the community, and the health authorities.

Although the pathophysiology of the thalassemia is well known, the disease is still far from being able to be cured. Is this disorder a preventable disease? Yes, thalassemia is a preventable disease and is inherited through an autosomal recessive pattern, according to the Law of Mendel. The affected child was born, from of 2 carriers couple **(Figure 1)**.

From **Figure 1**, we can see that from the marriage of 2 carriers couple, the possibility of having an affected child is 25%, 50% carriers, and 25% a healthy child for every conception. The number of carriers in

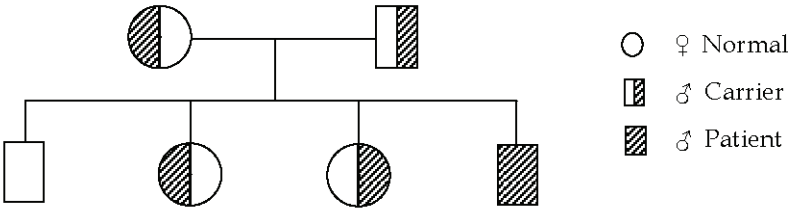

FIGURE 1. INHERITANCE PATTERN OF Â-THALASSEMIA

the population will be increasing. They may deliver an affected child if he or she married another carrier. An effective prevention program will give more benefit to the society and government compared to the treatment of the existing patients. According to WHO,[5] the annual cost of a nationwide prevention program in most countries is approximately equal to the cost of treating one patient for one year. Annual prevention costs are relatively constant while annual treatment cost rise from year to year. If we succeed to suppress the birth of affected children, the amount of budget for treating the patient can be used for the development of several projects in the country such as education and health. Without political will of the government, the prevention program will not become a reality.

In Indonesia the frequency of thalassemia carrier is about 3-5%, in some areas it may reach 10%.[6] It means that 3-5 out of 100 people are carriers of thalassemia. The birth of affected children in one year of an area or country can be roughly calculated by using Hardy-Weinberg equation, if we know the amount of population, percentage of carrier of the disease and the birth rate in the area.

Suppose that the percentage of thalassemia carrier in Indonesia is 5%, the birth rate is 20‰, and the population is 200 million so that there will be 2,500 affected babies born each year in the country. If there are only 1,500 of them registered by the health personal, then by the year of 2020, 15 years later, there will be 22,500 children, who need to be treated medically and psychologically. The cost of the optimum treatment in the Department of Child Health, Medical School, University of Indonesia, Jakarta, has been calculated to be Rp 100-150 million per child per year. In European countries the optimum cost was US$ 5,000-10,000, 20 years ago.[7] At this time it must be more expensive. In some countries the governments take over a part or the whole cost of treatment.

Not less than Rp 20-30 trillion (US$ 2.5 billion) should be spent for treating those 22,500 children by the year of 2020, besides the cost of treatment of the old patients who are already existing. Such a big amount of money could actually be spent for other purposes in the country.

So the best options in facing thalassemia and other genetic diseases are prevention and early diagnosis. The results of the programs will be seen many years later if we can suppress the birth of the predicted affected child. In Cyprus, a small country with 17% carrier of thalasemia, the cost of 8 weeks prevention program is equal to the cost of 1 week treatment of the existing patients.[2] The Ministry of Health of Israel announced that the cost of treatment of thalassemia is 4.22 higher than that of prevention program in the country.[2]

The key strategies in launching prevention program are:[5]

1. Securing government will and commitment.
2. Establishing powerful health educational campaigns and raising the public and health professional awareness.
3. Establishing high quality laboratories for screening and prenatal diagnosis.
4. Promoting genetic and obstetric services and counseling.

Health education plays a very important role in any diseases prevention program. The public has to be aware of the genetic diseases, especially about thalassemia as the most frequent genetic disorders found in the country. Public education on genetics should be started at school until the higher educa-

tion. Especially about thalassemia, they have to know the simple signs and symptoms of the disease, and how it is inherited. Courses in medical genetics should be provided to the medical students and other health professionals. Mass media should be involved in spreading this issue.

Screening (carrier testing) is aimed to identify carriers of thalassemia, or other hemoglobin disorders in certain population or area (prospective screening), or to be done to the families having already affected children (retrospective screening). The guideline for screening programs has been published by WHO (1993).[8] The best way of prospective screening is by performing it to the school children; the parents of carriers should be informed for the future of their children.

Genetic counseling is required for high risk persons before they are getting married. Being a carrier of thalassemia has actually no adverse health effect, they can have normal life. But if they married to a carrier partner, then there is a 25% possibility of having an affected child at every conception.

In Cyprus, the church recommend couples to have a certificate of carrier testing, before they can be married. If the couples are carriers the church still allows them to marry after having necessary information from doctors in the Thalassemia Center.[2] Genetic counseling is the most sensitive topic, because genetic diagnosis is often difficult due to the enormous diversity of the disease. Misdiagnosis and misinformation can have disastrous consequences to the individuals and their families, in making their decisions. Therefore, training for genetic counselors is very important.

Prenatal diagnosis is an important procedure in detecting weather the fetus of the high risk couple will be an affected or unaffected one. It is inhuman if the high risk couples are not allowed to marry. They are advised to make prenatal diagnosis at 10-12 weeks of gestation. If the fetus is an affected one, they are suggested to terminate the pregnancy, after having information concerning the difficulty and consequences of treating the child after birth. This is one of the reasons why a high quality laboratory for an exact diagnosis should be available. There are some homozygous mutations which give very mild clinical symptoms.

In countries of the southern part of Europe such as Italy, Greece, and in Turkey, the national prevention programs which started about 25 years ago have brought successful results. Cyprus has been able to reduce the birth of affected child up to 95% of the predicted number **(Figure 2)**.[5] Those countries have saved quite a lot of money which are used for education and health programs.

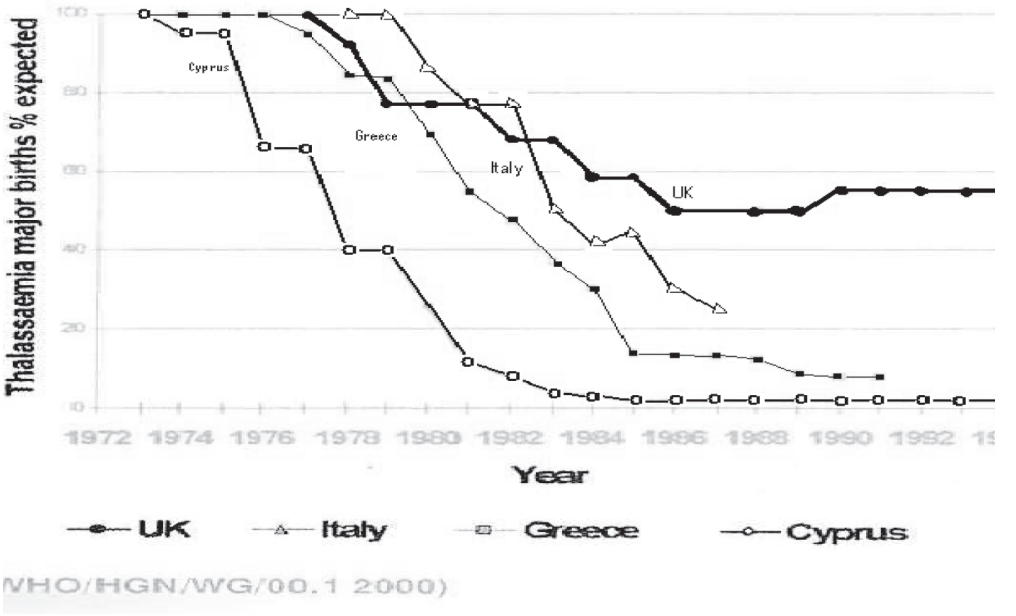

Figure 2. Prevention of thalassaemia in UK, Italy, Greece, and Cyprus (Cited from: About thalassemia, 2003)

In 1980, there were about 250 cases of thalassemia in the Department of Child Health in Jakarta.[9] At this time (2005) there are about 1100 patients who come regularly for blood transfusion, their age are ranging form 4 months to 36 years.[10] Most of the 250 patients have died already at the age of 7-8 years; several cases could reach the age of 17 years only. The treatment at that time was only blood transfusion. Thalassemia Foundation which was established in year 1987 has supported the patients quite a lot in terms of providing iron chelator (Deferoxamine®) and infusion pump. Many of them can reach the adult age and several are getting married and having children **(Figure 3)**. There are about 75 new cases registered in the Thalassemia Center in Jakarta each year.

Regular blood transfusion and iron chelator administration have prolonged their life **(Figure 4)**.[11] It is clear that the national prevention program in Southern Europe countries have been successfully performed due to the commitment of their government, without their support the program would fail. The prevention program introduced by WHO has to be planned carefully, adjusted to the situation and condition of our

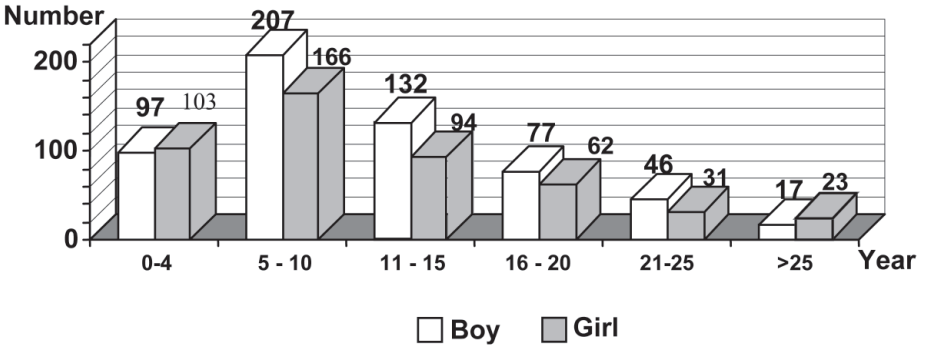

FIGURE 3. THALASSEMIA PROFILES IN JAKARTA, 1056 CASES (2004).

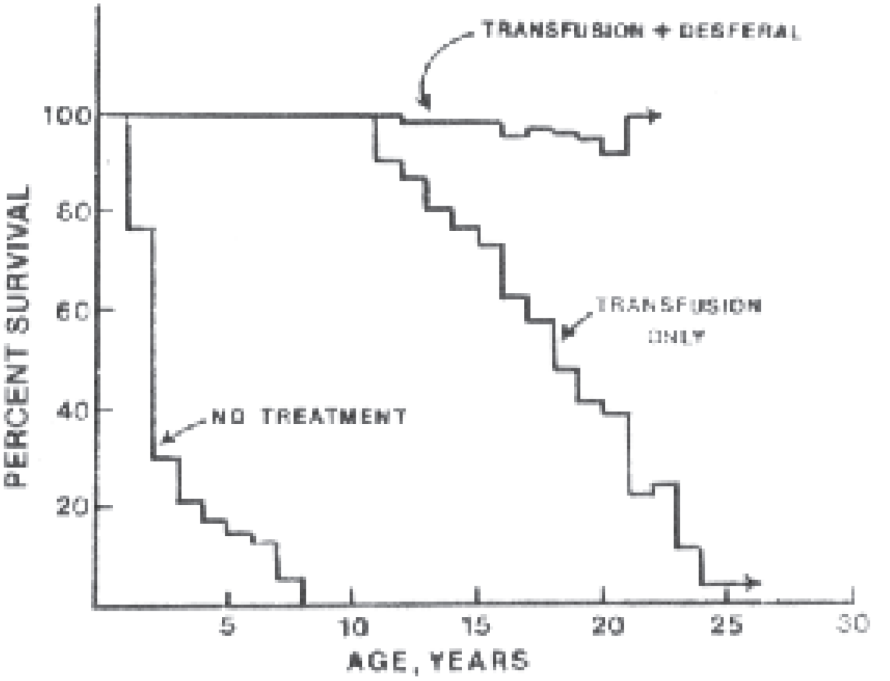

FIGURE 4. SURVIVAL OF PATIENTS WITH MAJOR HAEMOGLOBINOPATHIES THALASSEMIA (CITED FROM THALASSEMIA: RECENT ADVANCES IN DETECTION AND TREATMENT, 1982)

country with so many islands and ethnic groups with their own social cultures.

Last but not least, pilot projects could be established in area with high prevalence of thalassemia trait and several high quality and equipped laboratories should be provided in some big cities which have affiliation with the medical schools such as Eijkman Institute (Jakarta), Gadjah Mada (Yogyakarta), Airlangga University (Surabaya), North Sumatera University (Medan), and Hasanuddin University (Ujungpandang). A good coordination should be established between those centers.

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