Thalassemia in Iran
Epidemiology, Prevention, and Management

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Purpose: To determine the prevalence and geographic distribution of thalassemia and to evaluate the success of the thalassemia prevention and treatment programs in Iran.

Methods: Data were obtained from the National Thalassemia Registry of Iran, Iranian Blood Transfusion Organization, genetic laboratories involved in prenatal diagnosis, related pharmaceutical companies, and centers performing bone marrow transplantation for thalassemic patients.

Results: A total of 13,879 living patients have been registered, mostly from the northern and southern parts of Iran with the median age of 15 years. Twenty-three percent of patients were older than 20 years. The number of newly diagnosed cases has been decreased considerably after the start of the prevention program. Since the introduction of prenatal diagnosis, 2819 couples (2549 fetuses) have been tested, with only 6 false results. Elective abortion was not performed in 10 affected fetuses. Most common mutations detected were IVS II-1 and IVS I-5. In 2003, approximately 25% of the national blood products and 6 million vials of desferal were used for thalassemic patients. Overall, 340 patients have received allogeneic bone marrow transplantation, of those 46 patients deceased. Bloodborne infections have also been decreased significantly owing to the national screening of blood products for bloodborne viral infections.

Discussion: Owing to the national prevention program and provided special care, the age distribution of thalassemic patients in Iran is getting adapted to a full prevention and treatment program and life expectancy of these patients has been increased considerably. This shift in the age distribution of thalassemia, a traditionally considered pediatric disease, will face us with new challenges and the health care system should be prepared for this new face of thalassemia.

Key Words: thalassemia, epidemiology, prevention, treatment, prenatal diagnosis

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Thalassemia is one of the most common genetic disorders. It is estimated that 300,000 infants are born with major hemoglobinopathies worldwide each year of whom 60,000 to 70,000 are beta thalassemia major cases especially in the Mediterranean area, Middle East, Far East, and East Asia.[1,2] Severe beta thalassemia accounts for 50,000 to 100,000 deaths per year or 0.5% to 0.9% of all deaths of children under 5 in low or middle income countries.[3] Although thalassemia mostly affects developing countries, there is limited knowledge of its accurate frequency and distribution in these regions. Knowing the prevalence of thalassemia and characterizing clinical features and demographic of patients will enable us to properly measure the burden of disease. These also facilitate the designing of the most proper strategies for disease prevention and treatment and are powerful tools for assessment of effectiveness of these programs.[4] This is especially more important in multiethnic, high-population countries like Iran.

Iran in the middle of the so-called Thalassemia Belt has a high thalassemia carrier rate. Although the impacts of thalassemia on the health care system of Iran were discussed by *Pouya* some 50 years ago,[5] only after challenging major problems like nutritional problems, mortalities owing to infectious diseases and improvement in hygiene, the necessity of a structured and countrywide prevention and treatment program for thalassemia has become appreciated in the past 2 decades[6] which has led to the establishment of one of the biggest national thalassemia screening and prevention programs.

This study was performed to measure the prevalence of thalassemia and frequency of responsible mutations throughout different regions of Iran, to evaluate the effectiveness of thalassemia prevention and treatment programs, and to assess the success of the blood products

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screening program in reducing the transmission of viral infections in thalassemic patients.

MATERIALS AND METHODS

Epidemiologic Data

Although there were some registries of thalassemic patients in the country, these were not accurate. A new and updated registry, the National Thalassemia Registry of Iran, was established by the Charity Foundation for Special Diseases in 2001. In our mind, this registry is unique in the world owing to the high number of registered patients, comprehensiveness of the information, and the fact that it covers almost all of the patients with beta thalassemia major and alpha thalassemia, and most of the patients with thalassemia intermedia in the country. The data of this registry were gathered from all 25 special and 201 hospital centers providing care for thalassemic patients in Iran and include identification data, date of birth and date of diagnosis, ethnicity background, applied treatment, and transfusion-related problems or any other major clinical problems of thalassemic patients. Provided epidemiologic data in this article were obtained from this registry.

Data of Prenatal Diagnosis and Elective Abortions

A questionnaire was designed and sent to genetic laboratories and centers involved in prenatal diagnosis (PND) program and included questions regarding the total number of couples or fetuses tested, number of affected or carrier fetuses, frequency of detected mutations, percentage of false-positive or false-negative results, and causes of failure to perform an abortion in affected fetuses.

Data of Treatment and Bone Marrow Transplantation

To have an estimate of the total number of blood units and amount of drugs being used by thalassemic patients, we directly contacted the Iranian Blood Transfusion Organization and pharmaceutical companies involved in production or distribution of drugs for thalassemic patients in Iran. Data of patients who underwent bone marrow transplantation (BMT) were obtained from the only 2 centers performing BMT in Iran: the Hematology, Oncology, and Bone Marrow Transplantation Research Center at Shariati Hospital in Tehran and Namazi Bone Marrow Transplantation Center in Shiraz.

RESULTS

Epidemiology

The total number of registered living patients until the preparation of this article was 13,879 (approximately 23 patients per 100,000). However, this figure does not cover those patients with thalassemia intermedia who are usually referred to private clinics and their level of disease is not severe enough to seek special care by our designated centers for thalassemic patients.

The age distribution and geographic prevalence of patients are shown in Figure 1. Thalassemia is more prevalent in the northern (Caspian Sea coast) and southern (Persian Gulf and Oman Sea coasts) areas of the country. The overall prevalence ranges approximately from 3 to 100 patients per 100,000 people in different provinces.

In a sample of 3245 patients with thalassemia, 519 patients (16%) were tested positive for anti-HCV Ab. The population of patients was divided into those who received regular blood transfusion before or after the

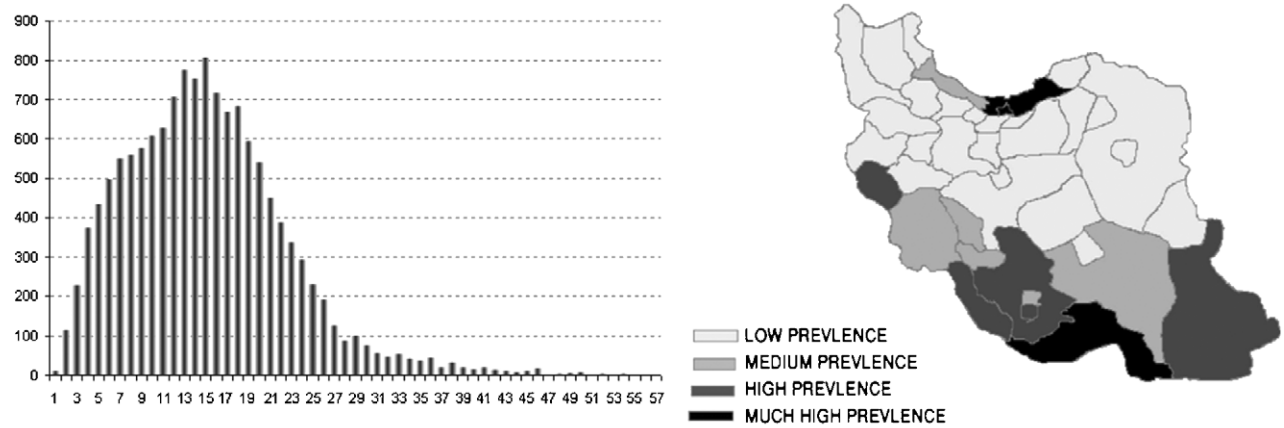

FIGURE 1. Left, Age distribution of thalassemic patients at the end of 2004. Total number of registered patients was 13,879. Median of age of patients was 15 years and 23% of patients were older than 20. An obvious decrease in the number of newly diagnosed thalassemic patients since the start of screening program in 1992 and introduction of PND into the program in 1998 is demonstrated. Please note that in very early years of life, the number of patients does not reflect the total number of born cases. Right, Prevalence of thalassemia in different geographical regions of Iran. Malaria transmission risk has almost a similar geographic distribution in Iran.[7]

application of national blood unit screening for anti-HCV Ab in 1996. This indicated a 22% (493 out of 2240) versus 2.6% (26 out of 1005) positive results, respectively. Fifty-two (1.6%) patients tested positive for HBsAg. The difference between positive results for HBsAg and anti-HCV Ab is due to earlier screening of blood units for HBsAg (1974) and effective national vaccination for HBV in thalassemic patients.

PND

Currently, 9 PND laboratories scattered in 5 provinces offer PND services to thalassemic patients. Data of PND are provided in Table 1. In couples referred for PND, more than 99% of affected fetuses were properly diagnosed and pregnancy was successfully terminated in more than 98% of the affected cases. The most common cause of failure to perform an elective abortion in affected fetuses (8 cases) was late referral to PND centers (in Iran, by law, legal abortion can only be performed before sixteenth-week gestation in cases with a confirmed diagnosis). Multiple gestation with different results in each fetus (one affected and the other not) and cultural issues were reasons of not performing an abortion in 2 cases.

Common beta-globin mutations found are presented in Table 2. Distribution of different mutations has an extreme divergence in different geographical regions. Although our data have not been gathered through random sampling of general population, since they cover all patients referred for PND, we assume that they represent the diversity and nature of existing mutations in Iran. In fact our data have similar results to the previous reports.[8] In brief, although IVS II-1 is the major mutation detected in most regions, in the southern and south-eastern parts of Iran IVS I-5 is the most common mutation. Overall, these 2 mutations were detected in 60% of cases.

Treatment

At present, all thalassemic patients have access to at least a general physician in 226 care centers under the supervision of more than 70 pediatric hematologists. Packed cells produced completely by the Iranian Blood Transfusion Organization are available for all thalassemic patients. Transfusions are given to maintain a pretransfusion hemoglobin concentration of not more than 9.5 g/dL.[9] Strategy of blood collection in Iran is solely on the basis of a voluntary nonremunerated program. Since 1996 all blood products are being screened for HIV, HBV, and HCV (HBsAg as of 1974, anti-HIV Ab as of 1989). Although the exact total number of packed cell units currently being used for thalassemic patients is unavailable, on the basis of the data of average blood transfusions per patient (approximately 2 packed cell bag/mo), it is estimated that nearly 25% of the annual blood production of the country (1,317,578 packed cell bags in 2003) is used for thalassemic patients.

In Iran the main treatment modality for Iron overload is deferoxamine (desferal). During a 1-year period from April 2003 to April 2004, approximately 6 million vials of desferal were used with the average dosage of 30 to 50 mg/kg/d for 5 to 7 d/wk. Deferiprone, an oral iron chelator, has also been accepted in the list of approved drugs for thalassemic patients and is used for patients in special situations such as inability to use desferal (owing to incompliance or severe side effects) or unsatisfactory response.[10] It is prescribed at an average dose of 75 mg/kg/d. Combination iron chelation with deferoxamine and deferiprone is used in patients with severe iron-related organ failure such as cardiomyopathy. Iron-induced cardiomyopathy is still the main cause of death in these patients.

As of 1993, allogeneic BMT for thalassemic patients is being carried out in Iran. Until the preparation of this article, 340 thalassemic patients have received allogeneic BMT, of those 46 patients deceased. Availability of HLA-matched donor and the presence of risk factors such as hepatomegaly, portal fibrosis, and ineffective chelation were major factors affecting the outcome of transplant in thalassemic patients.

TABLE 1. Data of Prenatal Diagnosis

Data	Number
Couples tested	2819
Fetuses tested	2549
Affected fetuses	601 (23.57%*)
Not certainly affected (suspected)	46 (1.80%*)
False results (false positive + false negative)	6 (0.23%*)
Affected pregnancies not terminated	10 (1.66%)

*Percentage of total tested fetuses.

TABLE 2. Percentage of Mutation Found in Couples Referred for Prenatal Diagnosis

Type of Mutation	Percentage (%)
IVS II-1	41
IVS I-5	19
C 8/9	7
C 36/37	6
IVS I-110	5
C 30	3
IVS I-1	3
C 39	3
C 44	2
C 22	2
IVS II-745	2
IVS I-6	1
C 8	1
IVS I-25	1
C 5	1
Other-unrecognized	3
Total	100

DISCUSSION

It is estimated that in Iran nearly 25% of the annual blood production is used for thalassemic patients.

Moreover, progresses in the patient care and increase in the life expectancy of thalassemic patients will further increase the blood demands of the thalassemic population. Hence, utilization of a national thalassemia screening and prevention program has become a health care priority in Iran. The initial phases of the thalassemia prevention program were started in 1992 under the supervision of the Genetic Department of Center for Disease Control. Following successful results of several pilot studies in different regions with high thalassemia prevalence, as of 1997 the National Thalassemia Prevention Program was established for diagnosis of thalassemia carriers at the premarital stage, with the coordination of all 39 medical universities in the country.[11] Figure 2 shows the screening process of carrier detection program. One major concern in the screening process is the interpretation of microcytosis owing to the presence of mild alpha^{+} thalassemia or silent beta thalassemia with normal HbA_2 and HbF that is refractory to iron treatment and may cause problems in genetic counseling and eventually in PND.[11,12]

Application of PND

Premarriage counseling for carrier couples without PND was, to some degree, successful in reducing the marriage of 2 carriers.[11] The mean marriage dissuasion rate was roughly 50% in 1997. Although this figure is remarkably higher than previous reports from Greece (probably because of high rate of arranged marriages in Iran),[3] the results of the beginning years of prevention program in Iran were not acceptable comparing with other countries with well-known thalassemia prevention programs that had benefited from PND in their system.[13–16] This situation made a prevention program only on the basis of the premarriage counseling ineffective and extremely expensive. Application of PND and abortion of affected fetuses could have major impact on prevention of thalassemia birth. Considering these issues, after obtaining the religious decree from major religious leaders of the country, as of 1998, abortion of the affected patients became legal and as a part of the National Thalassemia Prevention Program. Later in 2003, the major insurance companies accepted to cover the cost of

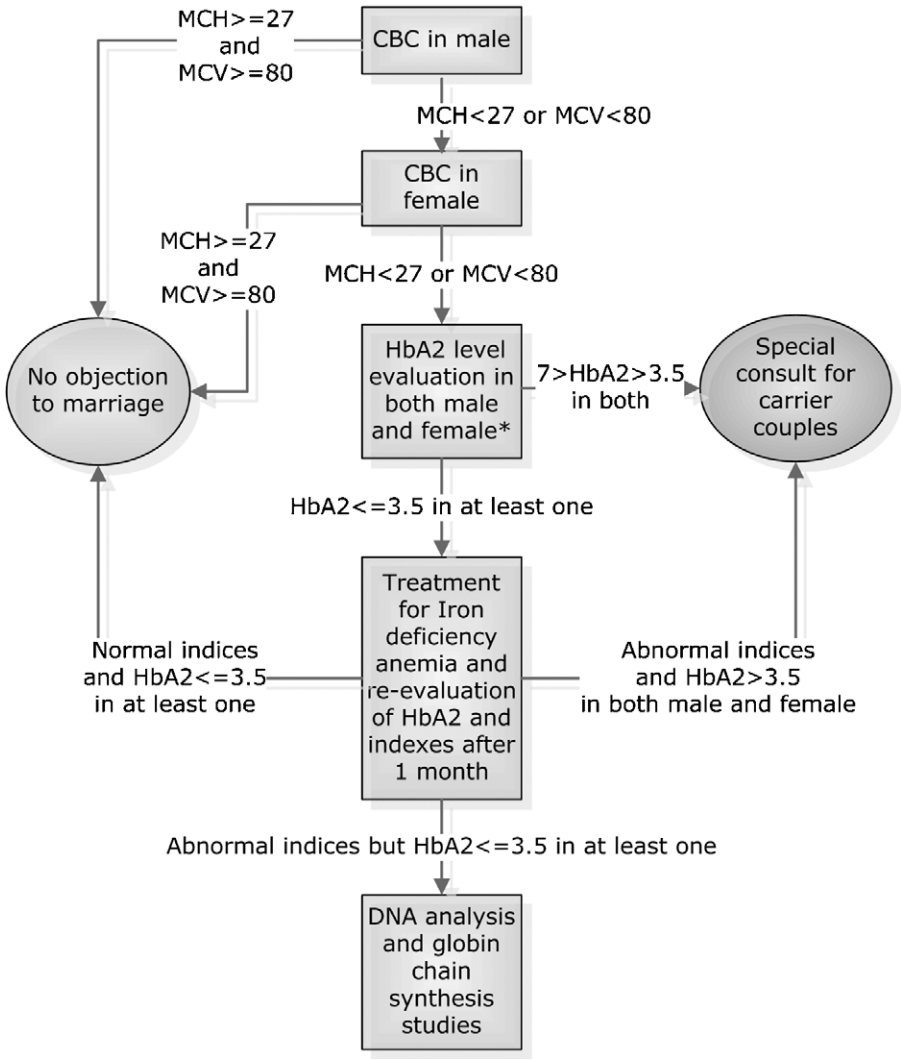

FIGURE 2. Structure of screening for thalassemia in Iran. The primary complete blood count tests are done in men to avoid stigmatization of women. *Although in most parts of the country (especially in areas where other hemoglobinopathies are common) measurement of the HbA2 is done by Hb electrophoresis, it is performed by column chromatography in poor areas.

PNDs. Currently, in the thalassemia prevention program, after thorough and extensive counseling and if the carrier couples decide to marry, they will be referred to family planning units or PND laboratories.

Our results show effectiveness of PND (Table 1). Also a high acceptability of PND and elective abortion in Iranian families has been reported.[17] Premarriage counseling for couples who had decided to marry with special emphasize on describing the serious adverse outcome of ignoring PND plays a major role for convincing families to follow a PND program.

Owing to the prevention program, the age distribution of thalassemic patients in our country is getting adapted to a full prevention program. Yet, there are some obstacles to achieve a complete elimination of thalassemia birth. Unofficial marriage (so called religious marriage) in some regions of Iran, bypasses the designed protocol for detection of carriers. Unfortunately, these regions are areas with high rate of illiteracy and a school screening program may not be effective. Even more important is the pregnancies of carrier couples married before implementation of the thalassemia prevention program and so were not screened. Although a retrospective PND plan for families with thalassemic patients currently exists, we suggest special attention for all pregnant women married before the start of the thalassemia prevention program, in high prevalence regions. Limited access to PND centers and the fact that still a portion of the costs of PND processes, like transportation, is paid for by the couples are 2 other problems in front of families. Better education of patients and establishment of new centers along with complete coverage of the costs of PND processes by the insurance companies will have great results.

Treatment

Currently, desferal vials and special pumps are available for all patients. However, the problems related to the administration of this drug are major factors of incompliance. The use of deferiprone is also limited to special situations which further emphasizes the need for newer oral iron chelator generations. In the recent years, several studies have been carried out or are being performed in the country for the evaluation of stimulator drugs.[18–20]

Availability of BMT in the past decade opened a new horizon in the treatment of patients. Progresses are ongoing and as time passes the better results are being achieved.[21,22] Application of gene therapy for the treatment of thalassemia in Iran is under investigation. Certainly, availability of this option will change the current approach to the management of thalassemia.

As the result of provided care in Iran, a considerable number of patients have become adults and in the next few years, owing to a major decline in the birth and death rate, most of the thalassemic patients will be older than 20 years. This dramatic shift in the age distribution of thalassemia, a traditionally considered pediatric disease, will face us with new challenges and the health care system should be prepared for this new face of thalassemia. Currently, there are very limited special adult care centers in the country that must be expanded and become widely available throughout the country. Serious consideration must now be given to the quality of life of these patients and important issues like fertility and long-term coping with a chronic illness must be addressed.[23]

CONCLUSIONS

On the basis of the level of involvement and available resources, we believe our program for controlling a major public health problem in a national level was very successful. Especially, our efforts and results in application of PND may be encouraging for other countries in the region. Also, a successful thalassemia prevention program shows the feasibility of similar nationwide prevention and treatment programs for other noncommunicable diseases.

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REFERENCES

1. Galanello R, Eleftheriou A, Traeger-Synodinos J, et al. *Prevention of Thalassemias and Other Haemoglobin Disorders*. Cyprus: Thalassemia International Federation Publications; 2003.
2. Angastiniotis M, Modell B, Englezos P, et al. Prevention and control of haemoglobinopathies. *Bull World Health Organ*. 1995;73:375–386.
3. Weatherall D, Akinyanju O, Fucharoen S, et al. Inherited disorders of hemoglobin. In: Jamison DT, Breman JG, Measham AR, et al. eds. *Disease Control Priorities in Developing Countries*. New York: Oxford University Press; 2006:663–680.
4. Modell B, Khan M, Darlison M, et al. A national register for surveillance of inherited disorders: beta thalassaemia in the United Kingdom. *Bull World Health Organ*. 2001;79:1006–1013.
5. Pouya Y. Thalassemia in Iran. In: Jonxis JHP, Dela Fresnaye JF, eds. *Abnormal Haemoglobins*. Oxford: Blackwell Scientific Publications; 1959:263.
6. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ*. 2001;79:704–712.
7. Roll Back Malaria, World Health Organization, UNICEF. Annex 3: Maps. In: World Malaria Report 2005. Geneva, Switzerland: World Health Organization and UNICEF Press; 2005: 281–286.
8. Najmabadi H, Karimi-Nejad R, Sahebjam S, et al. The beta-thalassemia mutation spectrum in the Iranian population. *Hemoglobin*. 2001;25:285–296.
9. Cazzola M, De Stefano P, Ponchio L, et al. Relationship between transfusion regimen and suppression of erythropoiesis in beta-thalassaemia major. *Br J Haematol*. 1995;89:473–478.
10. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood*. 2003;102: 17–24.

11. Samavat A, Modell B. Iranian national thalassaemia screening programme. *BMJ*. 2004;329:1134–1137.
12. Eram SM, Azimifar B, Abolghasemi H, et al. The IVS-II-1 (G– > a) beta0-thalassemia mutation in cis with HbA2-Troodos [delta116 (G18)Arg– > Cys (CGC– > TGC)] causes a complex prenatal diagnosis in an Iranian family. *Hemoglobin*. 2005;29:289–292.
13. Cao A, Galanello R, Rosatelli MC, et al. Clinical experience of management of thalassemia: the Sardinian experience. *Semin Hematol*. 1996;33:66–75.
14. Cao A, Rosatelli MC, Monni G, et al. Screening for thalassemia: a model of success. *Obstet Gynecol Clin North Am*. 2002;29:305–328.
15. Longinotti M, Pistidda P, Oggiano L, et al. A 12-year preventive program for beta-thalassemia in Northern Sardinia. *Clin Genet*. 1994;46:238–243.
16. Loukopoulos D. Current status of thalassemia and the sickle cell syndromes in Greece. *Semin Hematol*. 1996;33:76–86.
17. Karimi M, Peyvandi F, Siboni S, et al. Comparison of attitudes towards prenatal diagnosis and termination of pregnancy for haemophilia in Iran and Italy. *Haemophilia*. 2004;10:367–369.
18. Alebouyeh M, Moussavi F, Haddad-Deylami H, et al. Hydroxyurea in the treatment of major beta-thalassemia and importance of genetic screening. *Ann Hematol*. 2004;83:430–433.
19. Yavarian M, Karimi M, Bakker E, et al. Response to hydroxyurea treatment in Iranian transfusion-dependent beta-thalassemia patients. *Haematologica*. 2004;89:1172–1178.
20. Karimi M, Darzi H, Yavarian M. Hematologic and clinical responses of thalassemia intermedia patients to hydroxyurea during 6 years of therapy in Iran. *J Pediatr Hematol Oncol*. 2005;27:380–385.
21. Ghavamzadeh A, Nasseri P, Eshraghian MR, et al. Prognostic factors in bone marrow transplantation for beta thalassemia major: experiences from Iran. *Bone Marrow Transplant*. 1998;22: 1167–1169.
22. Khojasteh HN, Zakerinia M, Ramzi M, et al. Bone marrow transplantation in thalassaemia patients in Shiraz, Islamic Republic of Iran. *East Mediterr Health J*. 2001;7:835–837.
23. Vichinsky EP, MacKlin EA, Waye JS, et al. Changes in the epidemiology of thalassemia in North America: a new minority disease. *Pediatrics*. 2005;116:e818–e825.