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The prevalence of minor thalassemia among siblings of major thalassemia patients: A study from Iran

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ABSTRACT

Beta thalassemia is more prevalent in Mediterranean countries such as Iran and Far East. According to the report of center for disease control and management of Iran, there are about 18,000 patients with Beta thalassemia major. According to the excessive expenses for each patient (100,000 USD) and the birth of about 1500 cases annually in Iran, it is important to find carriers by screening those people who are at high risk. This is a descriptive study, which was done on the siblings of 86 major thalassemia patients in central province. They filled out the questionnaires and did the laboratory tests. Among 128 siblings of major thalassemia patients, 53.9% were male. In the final evaluation, 59.4% of cases had minor thalassemia, 34.4% were healthy, and 1.6% had other types of hemoglobinopathies. Also 4.7% had no diagnosis because of incomplete laboratory data. According to Mendelian pattern of inheritance in every pregnancy we expect 25% healthy, 50% minor and 25% major thalassemia. The Chi-2 test shows that there is a significant difference between our results and expected condition. (P -value<0.0001) This difference can be due to the refuse of some of the siblings of patients in our study. The limited number of observations might be another factor. As the prevalence of minor thalassemia is high in these families, we recommend that by recognizing the first case of thalassemia in a family, the evaluation of other children should be done. This method would be more cost-effective.

Key words: Beta thalassemia, screening, siblings

INTRODUCTION

Beta thalassemia syndromes are a group of hereditary hemolytic disorders characterized by a genetic deficiency in the synthesis of beta globin chains. This disease was recognized in 1925 for the first time. [1]. In homozygous beta thalassemia there is a total absence of beta chain synthesis, while there is a reduction in the synthesis of beta globin chains in minor thalassemia. [2] The distribution of thalassemia genes is more prominent in the Mediterranean area, Africa, Middle East, India and Southeast of Asia. This disease is more prevalent in the areas where Malaria is

endemic. [1, 3, 4] The most known type of clinical thalassemia is beta thalassemia which is more prevalent in Greece, Italy, Cyprus and Iran where 3-5% of the residents are carriers for mutant genes of this disease.[5]The highest prevalence of the carrier state has been found in Sardinia (34%), Delta region of the Po River near Ferrara (20%) and Sicily (10%). [6] In Guandong, the southeast province of China, the prevalence is 2.54% for beta thalassemia and the incidence of the homozygous state is approximately 1 in 6000. [7]Every year more than 10000 children with major thalassemia are born in India.[8]In Iran the prevalence of thalassemia is 2.5- 15 %.[9, 10] Homozygous beta thalassemia is usually characterized by severe anemia requiring regular blood transfusion for survival from early childhood. However about 10% of the patients may have a milder clinical presentation with a transfusion independent survival. These cases are categorized as thalassemia intermedia. [11] Beta thalassemia major (Cooley's Anemia) is a severe form of hemoglobinopathy which presents about 3-8 months after birth. The patients require special therapeutic services and they usually have a poor prognosis. Heterozygous state for thalassemia leads to red blood cell hypochromia and microcytosis with or without anemia that can mimic iron-deficiency states. Because beta thalassemia is inherited in a recessive autosomal pattern, we can prevent new cases by inexpensive screening methods before marriage and consulting those couples affected by minor thalassemia. (12)Because of the high prevalence of beta thalassemia in Iran (2.5-15% in different areas) this program is cost-effective. [3, 4, 9, 10] Due to the importance of thalassemia disease and necessity of serious challenges with this disorder, several executive activities and researches have been done in Iran recently. In 1998, Genetics and Cancer Office in Disease Management Center at the ministry of health, followed this issue more seriously than recent decades by using necessary indexes, collecting information and making programs based on two principle factors:

1. Executing effective strategies in screening program to recognize cases of minor thalassemia.
2. Utilization of qualitative control in the program.

In recent years two other strategies have been used besides screening and prenatal diagnosis programs

1. Screening of the families with beta thalassemia major patients
2. Screening of the students in the last year of high school

Unfortunately, in spite of pilot study execution in screening of major thalassemia patients' siblings in some provinces and frequent follow ups, no written reports containing investigations have been obtained. Prevalence assigning and recognition of cases are the first two steps in the diagnosis and treatment of this disease. On the other hand, considering the 50% prevalence of minor thalassemia in patients' families in comparison with the prevalence of the disease in the community (6%), necessity of screening for gene carrier can be felt, so accurate detection of all people at risk is very important. The researcher and staffs recollected the data of major thalassemic patients in central province, investigated their siblings and recognized the carriers of thalassemia genes.

MATERIALS AND METHODS

At first, a list of major thalassemia patients was provided in central province including 142 cases in 105 families. After preliminary investigation with the cooperation of "Society of Thalassemia", only 86 patients in 79 families who were the residents of central province cooperated with the research group. The other patients immigrated to other provinces, died (10 patients), didn't have any siblings or didn't want to participate in the study. From 158 siblings of 86 major thalassemia patients who were included in our study, only 128 people participated in our study. 14 siblings immigrated to other provinces and 16 of them didn't want to be in our study.

Unfortunately, none of the siblings of major thalassemia patients had been evaluated previously and no lab tests had been done for them. A letter of invitation sent to them to come to the laboratory for the following lab tests: CBC, peripheral blood smear, reticulocyte count, serum iron and TIBC. In the first stage CBC by HELENA coulter count system and peripheral blood smear were done by the lab staffs. For those siblings with MCV<80, MCH<25 or abnormal forms of RBC in peripheral blood smear in favor of thalassemia (polychromasia, basophilic stippling, target cell), the blood samples were examined for serum iron, TIBC and hemoglobin electrophoresis by the HELENA system (HB.A2 via columned chromatography and HB.F via alkaline denaturation method).

The siblings with a microcytic anemia with abnormal electrophoresis in favor of thalassemia were considered as minor thalassemia and were excluded from the study. The cases with a normal CBC were considered as normal and those with the features of iron deficiency and a normal hemoglobin electrophoresis were diagnosed as iron deficiency anemia treated by iron 3-6 mg/kg/day with the lab tests repeated after a month.

At the end, the results of the study were submitted to the “Society of Thalassemia” and the families were consulted by the “Society of Thalassemia”.

RESULTS

The data which were collected from the siblings of major thalassemia patients showed that the average age of study individuals was 14.7 years old. The youngest of them was 2 years old and the oldest one was 49 years old. 59 persons (46.1%) were girls.

The result of study showed that there were some abnormal features such as hypochromia, microcytosis, anisocytosis, poikilocytosis and target cells in PBS in 98 cases of 128 siblings (76.5%).

Hemoglobin electrophoresis results using HELENA system detected HB.A1 in 27 cases (48.4%), HB.A2 in 62 cases (78.9%) and HB.F in 2 cases (1.56%).

MCV was less than 80 in 82 cases (64%) and MCH was low (less than 25) in 79 cases (61%).

Finally, from 128 siblings of major thalassemia patients, 76 cases (59.4%) were diagnosed as minor thalassemia.

The frequency of final diagnosis in the siblings of major thalassemia patients and in the children of these families has been summarized in table 1 and 2 respectively.

DISCUSSION

Beta thalassemia major disease can be prevented by carrier screening, genetics consultation and prenatal diagnosis, in high-risk societies.

Since our country with the surface area of 1,648,000 km² and a population of more than 70,000,000 and a birth rate of 1.6 percent is one of the countries located on the thalassemia belt, it is important to use some programs to prevent the birth of the children with major thalassemia. According to the prevalence of thalassemia trait, the number of carriers in Iran is estimated to be about 3-4 million. [3, 9, 10]

According to Iranian Blood Transfusion Organization reports, there are more than 18,000 major thalassemic patients in Iran and 1500 new cases are added to this number each year. In other words, one case of major thalassemia is born in Iran every 6 hours. 50-60% of blood donations is used for thalassemic patients in the country and each year more than 220 million US dollars are spent by the government for the treatment of these patients. [9, 10]

Many studies have regarded the prevalence of minor thalassemia in high risk societies in Iran and other countries, but unfortunately we have only access to a few of them which are related to our subject.

One study in Italy showed that homozygous beta thalassemia was preventable in some high risk societies by a screening of the carriers, genetics consultation and prenatal diagnosis which decreased the birth of major thalassemia cases from 1 in 250 to 1 in 4000.[13]

In another study in Italy between 1987- 1992, the prevalence of beta thalassemia carriers among the children of a school was 3.1% by analysis of HB.A2 and MCV, which was indicative of a high risk zone for thalassemia and required popular screening, evaluation of medical information of the population, genetic consultation and prenatal diagnosis. [14]

The results of our study in the siblings of major thalassemia patients in 78 families showed that 76 persons (59.4%) of them were carriers of thalassemia. This is similar to the result of another study which was done on 50 families in Pakistan where 58% of siblings had minor thalassemia. [15]

The results of this study have been shown in table 2. Normal children, minor thalassemia and major thalassemia were 20%, 35%, 40% respectively. In a Mendelian pattern of inheritance, we expect 25%, 50% and 25% in each pregnancy. Chi square test showed that there was a significant difference between normal, minor and major ratios with expectative ratios (p- value <0.0001). It can be due to non-participation of some of the siblings in the study and

also limited numbers of observations. Meanwhile, this study focused on major thalassemic children and all of them were included in our study but some siblings refused to participate in our study.

Considering the social and psychological consequences of major thalassemia, also its financial burden the prevention of even one major thalassemia case is of value especially in countries, such as Iran, which are located on thalassemia belt.

The results of this study showed high prevalence of beta thalassemia trait among siblings of beta thalassemia patients.

We suggest:

- Since there is a 50% risk of transmission of the thalassemia gene in each pregnancy, the siblings of a patient with major thalassemia comprise a high-risk group. Screening the siblings of each patient with thalassemia is an effective way to prevent the occurrence of new cases in the next generation.
- Screening the siblings of each patient with major thalassemia will avoid the economic and emotional consequences that result from a missed diagnosis.
- Careful education of families for using safe contraceptive methods or prenatal diagnosis facilities if they want to have another child is necessary.
- Supervision and exact control of major thalassemia patients during blood transfusion and while using deferral pump.

Since the prevalence of Iron deficiency anemia is about 15% in this group, those patients who have hypochromic microcytic anemia and normal electrophoresis must be treated with iron for a course and then their electrophoresis should be re-checked, as is mentioned in the references. As the prevalence of minor thalassemia is high in these families, we recommend that by recognizing the first case of thalassemia in a family, the evaluation of other children should be done. This method would be more cost-effective.

Table-1 Frequency of final diagnosis in the siblings of major thalassemia patients in Markazi province, Iran

Final diagnosis	frequency	%
Normal	44	34.4
Minor thalassemia	76	59.4
Other hemoglobinopathies	2	1.5
Missing	6	4.7
Total	128	100

Table-2 Frequency of final diagnosis in the children of patients' family in Markazi province, Iran

Final diagnosis	frequency	%
Healthy	44	20.6
Minor thalassemia	76	35.5
Major thalassemia	86	40.2
Other hemoglobinopathies	2	0.9
Missing	6	2.8
Total	214	100

CONCLUSION

As the prevalence of minor thalassemia is high (59.4% of siblings) in these families, we recommend that by recognizing the first case of thalassemia in a family, the evaluation of other children should be done. This method would be more cost-effective.

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