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Causes of Birth of More Than One Thalassemia Major Patient in Families in South-east of Iran: Lessons for Prevention Programs

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Abstract

Background: Beta-thalassemia major (TM) is one of the most common genetic diseases in Iran. Despite some efforts to reduce the incidence of TM, its incidence is still relatively high in some areas of the country.

Methods: This cross-sectional study was performed on 635 families who had children with TM. The families that had more than one child with TM were enrolled. A demographic data questionnaire and a checklist containing queries about the reasons for the birth of the second or subsequent TM children were completed by each family. Finally, the data were analyzed using SPSS version 16.

Results: Among the families that had more than one child with TM, 90, 23, and three families had two, three, and four children with the disease, respectively. Of the 261 patients studied, 125 (47.9%) and 136 (52.1%) had been born prior and after the implementation of the pre-marital screening program for beta-thalassemia in Iran, respectively. Also, in 29.4% of these families, parents were unaware of having thalassemia minor. In other cases, factors such as lack of knowledge about screening tests (14.0%), lack of financial compliance (13.2%), late referral for genetic tests (11.8%), and not undergoing screening tests despite recommendations (9.6%) were among the reasons declared by the families. In addition to these, religious and cultural reasons should also be mentioned as effective factors.

Conclusions: This study showed that in only about 30% of the studied families, the parents were unaware of having thalassemia minor, and in other families, miscellaneous reasons were involved in the birth of the second or subsequent child with TM. In some cases, despite sufficient parental knowledge about the possibility of giving birth to a child with TM, no action was taken to prevent this event.

Keywords: Beta Thalassemia Major, Prenatal Diagnosis, Prevention

1. Background

Beta-thalassemia is a disease with an autosomal recessive inheritance pattern, in which bone marrow progenitor cells are affected due to impaired synthesis of beta-globin chains and subsequently intracellular deposition of alpha-globin chains, leading to a microcytic and hypochromic anemia with varying degrees of severity (1, 2).

The carriers of the defected thalassemic gene are protected against falciparum malaria and more frequently reside in areas such as the Mediterranean region, west Asia, Indian subcontinent, and south-east and south China (3). A large proportion of thalassemia patients are annually born in these areas (4, 5). Iran, as a country located in the thalassemia belt, has many thalassemia carriers. In a study by Abolghasemi et al. (4) in Iran in 2007, the number of registered thalassemia major (TM) patients was reported as 13879, representing an incidence rate of 23 per 100,000 population.

Beta-thalassemia major is the most severe form of thalassemia, in which patients cannot produce adult hemoglobin and develop progressive anemia during infancy. These patients should receive regular blood transfusions and iron chelators and also need to be closely monitored during their entire lives (6-8). Increased life-expectancy in patients with the advent of new treatments and iron overload resulted from blood transfusions lead to complications such as growth retardation, delayed puberty, osteoporosis, diabetes mellitus, cardiomyopathy, liver disease, etc., in TM patients (9, 10). Considering the

importance of TM as a notable non-communicable disease and one of the most prominent health problems in Iran, the National Thalassemia Screening Program has been implemented in Iran since 1997. At the end of 2001, out of 2.7 million couples screened, 10,298 at-risk couples were identified, according to the program's initial five-year results. Over the next few years, with the establishment of this program, the rate of the identification of at-risk couples increased, and they were subjected to genetic counseling (11).

According to studies, in Sistan and Baluchestan province in south-east of Iran, the frequency of beta-thalassemia carriers is about 10%, while in other parts of Iran, it is about 4 - 8% (12-14). A study in Sistan and Baluchestan province showed that the most important causes of the birth of new cases of TM were the lack of premarital screening for thalassemia and being unaware of the importance of prenatal diagnosis (14).

A total of 2091 thalassemia patients from 2001 to 2006 were born in Iran. The main causes were the couples' not using prenatal screening, marriage before the commencement of prevention plans, unregistered marriages, and laboratory errors (15).

Despite the start of the thalassemia screening program in Iran since 1997 and its increasing acceptance and effectiveness during the early years of implementation, the birth of new cases of TM continued even in families who already had children with TM. Therefore, the present study was performed to evaluate the causes of the birth of more than one child with TM (two children or more) among beta-thalassemia carrier couples in Zahedan.

2. Methods

This cross-sectional study was performed on all the families who had TM patients referring to Ali-Asghar Pediatric hospital in Zahedan, south-east of Iran, in 2018. The study was initially reviewed and approved by the Ethics Committee of Zahedan University of Medical Sciences (ethic code: IR.ZAUMS.REC.1395.49). Families with at least two children with TM were included in the study. A total of 116 families with 261 children with TM were enrolled in the study after obtaining informed consent.

Demographic data and patient-related variables, including age, gender, the number of children with TM, frequency of thalassemia in relatives, education of parents, and history of referring for premarital thalassemia screening tests, were recorded. Next, a checklist was used to determine the causes of the birth of more than one child with TM. A checklist was completed by each family, including: failure to perform the first and second phases of prenatal thalassemia genetic tests, lack of financial compliance, religious beliefs, disagreement of the spouse or relatives, lack of knowledge about the screening tests, lack of knowledge about the importance of this subject, laboratory errors, no abortion despite TM diagnosis during the fetal period, and late or non-referral for genetic tests.

The data were entered into statistical package for the social sciences (SPSS) software version 16 and analyzed using descriptive statistics.

3. Results

Of a total of 635 families with TM children (780 patients in total), who had records in the Ali-Asghar Children hospital and were under follow-up and treatment, 116 families (18%) had more than one child with TM (a total of 261 patients).

Regarding nationality, 112 families (96.6%) were Iranians, and four families (3.4%) were Afghans. Overall, 65 families (56%) had close relatives who had thalassemia, and 51 families (44%) had no such close relatives. Also, consanguineous marriage was seen in 80 families (69%). Two families had twin children, and both of them had TM. Two TM patients were a couple and had one child with TM as well.

Our results showed that among 261 patients, 51.3% (n = 134) were male, and 48.7% (n = 127) were female. The mean age of TM patients was 19.1 ± 8.5 years. The minimum age was one year, and the maximum age was 37 years.

Table 1 shows the frequency of the families studied based on the number of TM children, and Table 2 shows the frequencies and the average age of the first, second, third, and fourth children.

Table 1. The Frequency of the Studied Families Based on the Number of Thalassemia Major Children

TM Children in Each Family	Families, No. (%)	Total Number of TM Children
Two children	90 (77.6)	180
Three children	23 (19.8)	69
Four children	3 (2.6)	12
Total	116 (100)	261

Table 2. The Frequency and Mean Age of Children with Beta-thalassemia Major

	No. (%)	Mean Age (y)
First children	116 (44.45)	21.6 ± 7.9
Second children	116 (44.45)	17.2 ± 8.4
Third children	26 (10.0)	16.6 ± 8.9
Fourth children	3 (1.1)	19.3 ± 8.0
Total	261 (100)	19.1 ± 8.5

As shown in Table 3, of the first, second, third, and fourth TM children, 58.6%, 37.9%, 46.1%, and 33.3% were born before the launch of the thalassemia screening program in Iran, respectively. Also, 28 couples (24%) married after the onset of the screening program.

Table 3. The Frequency of Thalassemia Major Children Based on Birth Before or After the Start of the National Thalassemia Screening Program in Iran [a]

	Before	After	Total
First children	68 (58.6)	48 (41.4)	116 (100)
Second children	44 (37.9)	72 (62.1)	116 (100)
Third children	12 (46.1)	14 (53.9)	26 (100)
Fourth children	1 (33.3)	2 (66.7)	3 (100)
Total	125 (47.9)	136 (52.1)	261 (100)

[a] Values are expressed as No. (%).

Table 4 shows the level of education of parents with more than one child with TM.

Table 4. The Educational Level of Parents with More than One Child with Thalassemia Major [a]

Educational Level	Father	Mother
Illiterate	29 (25.0)	61 (52.6)
Lower than high school diploma	62 (53.4)	48 (41.4)
High school diploma or higher	25 (21.6)	7 (6.0)
Total	116 (100)	116 (100)

[a] Values are expressed as No. (%).

The causes of birth of more than one child with TM in the families whose children were born after the onset of the national thalassemia screening program (136 children) have been presented in Table 5. In 29.4% of the cases, parents were unaware that they were carriers of thalassemia. Lack of knowledge about the availability of screening tests (14.0%), lack of financial compliance (13.2%), and late- (11.8%) or non-referral (9.6%) for genetic testing were other frequent causes that led to the birth of the second and subsequent children with TM in the studied families.

Table 5. Causes of the Birth of the Second and Subsequent Child with Thalassemia Major in the Studied Families

Causes	No. (%)
Parental unawareness of them having thalassemia minor	40 (29.4)
Lack of knowledge about the availability of screening tests	19 (14.0)
Lack of financial compliance	18 (13.2)
Late referral to the laboratory	16 (11.8)
Non-referral to the laboratory	13 (9.6)
Spouse's or relatives' disagreement	11 (8.1)
Lack of parental knowledge about the importance of screening tests	10 (7.4)
Lack of information about being pregnant up to the 4th month	5 (3.7)
Religious beliefs	2 (1.5)
Laboratory errors	2 (1.5)
Total	136 (100)

4. Discussion

Due to the prevalence of beta-thalassemia in the Middle East, premarital screening and genetic counseling have been conducted in this geographic region over eight countries. In a review in 2015, a 65 percent reduction in the marriage of at-risk couples and/or the births of thalassemia-affected children was assigned as the threshold of success, but none of the 21 studies reviewed reported this rate of success. However, some studies in Iran, Turkey, and Iraqi Kurdistan have reported a success rate of > 65% in reducing the birth of thalassemia-affected children after the implementation of the screening program (16).

According to a previous study in Iran, the mean frequency of the identification of carrier couples increased from 3 to 4.5 per 1000 people during the first five years of the launch of the National Thalassemia Screening Program. Fifty-three percent of the couples married after premarital counseling, and 29 percent gave up. Also, 18 percent were uncertain about their decision at the time of the study (11).

In Sistan and Baluchestan province, south-east of Iran, with a population of 2.8 million, there are about 3100 registered patients with transfusion-dependent TM, of whom 780 patients are under follow-up and treatment in Zahedan. Among the families of these patients, 18% (116 families) had more than one child with TM and were included in the present study (a total of 261 TM children). The minimum age of the patients was one year old.

Despite the implementation of the National Thalassemia Screening Program in Iran since 1997, our results indicated that more than half of these patients (52.1%) were born after the program's onset. Also, 28 out of 116 couples married after the implementation of the program, and only two of them (7.1%) underwent the first stage of the premarital screening test, and just one family (3.5%) performed both the first and second stages of prenatal diagnosis. Our results also showed that approximately one-quarter of fathers and half of mothers were illiterate, indicating a relatively high frequency for illiteracy.

The results of the study of Miri-Moghaddam et al. (14) in Zahedan in parallel with our findings indicated that

many thalassemia carrier couples did not refer for prenatal diagnostic tests. Also, the low educational levels of parents in both studies highlight this parameter as an underlying factor contributing to non-referral and consequently the birth of infants with TM.

According to the results of the present study, 29.6% of the parents had no information about the fact that they had thalassemia minor. Lack of knowledge about screening tests, lack of financial compliance, late referrals or non-referral for genetic tests, despite recommendations from counseling centers, and religious and cultural factors were other causes leading to the birth of the second or subsequent child with TM in the studied families.

According to a study by Zeinalian et al. in Isfahan from 1997 to 2007 (i.e., after the onset of the National Thalassemia Screening program), the parents of 49% of TM patients did not undergo screening tests, 91.5% of whom were married before the start of the screening program in Iran. Based on the results from non-screened parents who had a child with thalassemia, the most common causes were cultural issues (27.8%) followed by financial problems (5.6%), laboratory errors (5.6%), problems in the surveillance system (5.6%), and delay in the tests' results (5.6%) (17). The differences observed in the frequency of these causes in the studies conducted in Zahedan and Isfahan may be due to other underlying factors such as possible differences in parents' educational levels and cultural conditions.

Prenatal diagnosis and therapeutic abortion are effective ways to avoid the birth of TM patients. Also, in some countries with a high prevalence of thalassemia carriers, prenatal screening and genetic counseling programs are performed (16). While a number of countries such as Italy, Greece, and Cyprus have had good success in preventing the birth of TM patients, in Middle East countries, religious, cultural, and legal issues have reduced the success rate (18-20). One of the limitations of this study was the impossibility of conducting the study in all thalassemia care centers in Sistan and Baluchestan province.

4.1. Conclusions

The present study showed that the lack of awareness of parents about the fact that they were minor thalassemia carriers accounted for only about 30% of giving birth to more than one TM child. Other causes seem to be easily preventable by launching cultural and educational programs, as well as by strengthening health-related projects to raise the awareness of at-risk parents. Also, the low level of education can be considered as a contributing factor for the low level of parental knowledge about TM.

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Footnotes

Authors' Contribution: Ghasem Miri-Aliabad: Study concept, study design, manuscript writing, and literature search. Seyed Mohammad Nasiraldin Tabatabaei: Manuscript editing. Zahra Vaezi: Statistical analysis. Afshin Amini: Manuscript writing. Leila Asgarzadeh: Literature search, manuscript editing.

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