Delay in Diagnosis of Hemoglobulinopathies (Thalassemia, Sickle Cell Anemia): A Need for Management of Thalassemia Programs

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Abstract

Background: Hemoglobulinopathies (Thalassemia, Sickle cell anemia) are an important public health challenge worldwide with an estimated number of 330,000 affected newborns annually. Delay in diagnosis not only increases the morbidity and mortality rates, but also can lead to uncertainties about success of thalassemia prevention program (TPP). This study is the first to determine the delay in thalassemia diagnosis in Iranian population.

Methods: This registry-based cross-sectional study was conducted on 1003 enrolled thalassemic patients in 2015 in Shiraz, Iran. Univariate and multivariate ordinal logistic regression models were used to assess the factors associated with delay in diagnosis.

Results: Of 981 patients, 48.5% were female, 71.2% were thalassemia major, and 23.8% were death cases. The delay in diagnosis was observed among 64.9% of the patients with a mean of 13.4 months (95% CI: 10.9, 15.9). Multivariate ordinal logistic regression showed that girls (adjusted OR = 1.32), and dead patients (adjusted OR = 1.95) were more likely to have delayed diagnosis. There was an increasing trend of risk in delayed diagnosis associated with one-year per birth cohort. The ORs were 1.0, 1.52, 1.55, and 2.22, for birth cohort 1980 and earlier, 1981 - 1990, 1991 - 2000, and 2001 to the present, respectively (P for trend = 0.014). In addition, the odds of delayed diagnosis in thalassemia major patients were significantly 0.58 times lower than those with thalassemia intermedia.

Conclusions: A high proportion of delayed diagnosis was found. These results could explain the poor outcomes for thalassemia patients. Educational programs for community and revising the TPP are required for early detection of the disease.

Keywords: Delayed Diagnosis, Thalassemia, Sickle Cell Anemia, Iran

1. Background

Thalassemia disease is an important public health challenge in both developed and developing countries with an estimated number of 330,000 affected newborns annually (1, 2). It is markedly more prevalent in Middle Eastern countries such as Iran, which is geographically located in the "thalassemia belt".

Nation-wide and local epidemiologic studies on the disease conducted in Iran have provided powerful data about the disease and health care system. The findings of a review study show the success of thalassemia prevention program (TPP) in the reduction of new thalassemia births (3). Another study supported the functionality of the prevention program (4). In addition, some studies have reported a significant improvement in treatment (5) and the quality of life in patients (6), decreasing mortality (7), and improving the survival rate (8). Notwithstanding the mentioned issues, it is estimated that over 300 new cases are born every year (9).

Previous studies on other diseases have shown that delay in diagnosis, or treatment, would result in worsening of the prognosis and the survival rate (10-12). On the other hand, delay in diagnosis is associated with more advanced disease requiring more advanced treatment. This leads to increased morbidity and decreased survival. Thalassemia is an inherited hemoglobin disorder which can be recognized by prenatal testing (13). There is no published study from Iran or other countries on the delay in diagnosis or treatment of thalassemia patients. Therefore, this study is the first to gain insight into delay in thalassemia diagnosis to improve prognosis of the disease in this population.

2. Methods

2.1. Study Setting and Patients

This registry-based cross-sectional study was conducted on 1003 beta-thalassemia (major, intermedia), or sickle cell patients in 2015 in Shiraz, the capital city in southern province of Iran. The study was approved by the ethics review committee and supported by a grant (No. 94-7610) from Shiraz University of Medical Sciences.

2.2. Thalassemia Prevention Program in Iran

The pilot TPP was initiated in 1991 and established throughout the country in 1997 (14). This program consists of three stages: The first stage screens couples prior to marriage, second stage screens families of thalassemic patients, and the last one screens carrier couples who had married prior to 1997. Moreover, prenatal diagnosis (PND) was a main element of this program (14). Although this program helps the disease be detected before birth, many new cases of thalassemia are still born annually (13).

2.3. Instruments

The patients with thalassemia receiving regular blood transfusions were prospectively tracked by a referral hospital in Shiraz. Data collection was carried out using a checklist including date of birth, date of death (if applicable), sex, type of thalassemia (major, intermedia) or sickle cell, education level and occupation of the parents. Date of birth was defined as birth cohort and was divided into four birth cohorts (1980 and earlier, 1981 - 1990, 1991 - 2000, and 2001 to the present). The birth cohort of 1980 and before was considered to be the reference group. The Patients with missing data or those who had no medical record were excluded from the study. Delayed diagnosis was defined as the time between birth date and the date of final hematological (electrophoresis) diagnosis. It was divided in three categories of no delay, delay less than 12 months, and delay more than 12 months.

2.4. Statistical Analysis

Descriptive analyses were used to calculate means, frequencies and percentages. T-test and one-way ANOVA were used to compare the delay mean between the groups. To assess the factors associated with delay, univariate and multivariate ordinal logistic regression models were used, and unadjusted and adjusted odds ratios (OR) were determined within 95% confidence intervals (95% CI). All statistical analyses were performed at 0.05 significance level using Stata 11 (StataCorp, College Station, TX, USA).

3. Results

Overall, 1003 thalassemia patients were registered in the referral hospital. Of these, 22 subjects (17 from alive and 5 from deceased patients) were excluded due to missing data (Response rate = 97.8%). Of the 981 patients, 48.5% were female, 71.2% had thalassemia major, and 23.8% were death cases. The delay in diagnosis was observed in 64.9% of the patients with a mean of 13.4 months (95% CI: 10.9, 15.9).

The additional descriptive statistics of the thalassemia patients based on categories of delay in diagnosis are shown in Table 1.

Table 2 shows unadjusted and adjusted associations between the delay in diagnosis and some independent factors. In bivariate analysis, delayed diagnosis was associated with gender, maternal education, type of thalassemia, birth cohort, and patient's status.

In multivariate ordinal logistic regression, our findings showed that girls were more likely to have delayed diagnosis compared to boys (adjusted OR = 1.32, 95% CI: 1.02, 1.71). The odds of delayed diagnosis in thalassemia major patients were significantly 0.58 times lower than in those with thalassemia intermedia. There was an increasing trend of risk in delayed diagnosis associated with one-year per birth cohort, the ORs were 1.0, 1.52, 1.55, and 2.22, respectively for birth cohort 1980 and before, 1981 - 1990, 1991 - 2000, and 2001 to the present (P for trend = 0.014). Deceased patients were 1.95 times more likely to have the delayed diagnosis compared to alive patients.

No statistically significant associations were observed between delayed diagnosis and maternal education and occupation, and father's education.

4. Discussion

Our results show that thalassemia patients are facing an important challenge in terms of diagnosis delay. The main goals of TPP are early diagnosis of thalassemia and prevention of new cases. Despite significant improvements in the TPP in Iran, the rate of delay in diagnosis must be considered by policymakers to modify the program. Assessing factors associated with diagnosis delay might be an important way to identify how to improve the quality of thalassemia program. Accordingly, the results of our study can help policymakers in this purpose.

After the establishment of TPP in Iran, the program has been evaluated from different perspectives. The first study conducted by Samavat et al. (14) in 2004, and another one in 2007 (15) showed a significant success in decreasing the rate of thalassemia newborns, which was further validated by other studies (16-18). Khorasani et al. (16) in a study to evaluate the success of the program concluded that the TPP has significantly reduced the financial burden upon thalassemic patients and their families. On the other hand, some other studies have reported program weaknesses. Findings of a study to evaluate the Iranian TPP during 2007-2009 revealed that the program should be revised in at-risk provinces especially in Sistan-Baluchestan and Kohkiluyeh Boyer-Ahmad (19). In addition, the delay in registration of thalassemic patients in the disease registration system as a limitation of the program has been pointed in previous

Table 1. Descriptive Statistics of the Thalassemia Patients Based on Categories of Delay in Diagnosis

	Category	Delay in Diagnosis			Mean (95% CI)	P Value
		No Delay	≤ 12 Months	> 12 Months		
Gender	Male	184 (36.4)	221 (43.8)	100 (19.8)	10.9 (8.1, 13.7)	0.042
	Female	160 (33.6)	185 (38.9)	131 (27.5)	16.0 (11.9, 20.2)	
Type of hemoglobulinopathy	Thalassemia intermedia	99 (37.2)	36 (13.5)	131 (49.3)	23.3 (17.1, 28.8)	< 0.001
	Thalassemia major	238 (34.2)	362 (52.0)	96 (13.8)	8.3 (7.0, 9.6)	
	Sickle cell	6 (37.5)	6 (37.5)	4 (25.0)	-	
Mother's education	Illiterate	58 (29.1)	84 (42.2)	57 (28.7)	12.0 (9.8, 14.3)	0.001
	Primary school	161 (33.3)	188 (38.9)	134 (27.8)	15.2 (11.8, 18.6)	
	Secondary school	56 (39.2)	64 (44.8)	23 (16.0)	9.0 (6.7, 11.4)	
	Academic	14 (30.4)	21 (45.7)	11 (23.9)	36.5 (0.1, 73.0)	
Mother's job	Housekeeper	273 (34.7)	331 (42.1)	182 (23.2)	12.8 (10.6, 15.0)	< 0.001
	Employed	15 (31.2)	15 (31.2)	18 (37.6)	38.0 (2.4, 73.6)	
Father's education	Illiterate	43 (31.9)	51 (37.8)	41 (30.3)	13.4 (10.4, 16.4)	0.199
	Primary school	145 (32.0)	185 (40.8)	123 (27.2)	13.9 (11.6, 16.1)	
	Secondary school	64 (35.0)	81 (44.3)	38 (20.7)	12.7 (5.6, 19.8)	
	Academic	37 (36.6)	41 (40.6)	23 (22.8)	22.9 (6.0, 39.9)	
Birth cohort	1980 and earlier	55 (45.5)	41 (33.9)	25 (20.7)	23.6 (6.3, 40.9)	0.016
	1981 - 1990	157 (34.0)	191 (41.3)	114 (24.7)	13.3 (11.0, 15.7)	
	1991 - 2000	105 (36.0)	123 (42.1)	64 (21.9)	10.3 (8.6, 12.0)	
	2001 to present	26 (26.0)	47 (47.0)	27 (27.0)	10.7 (8.5, 12.9)	
Patient's status	Alive	271 (36.3)	312 (41.8)	164 (21.9)	11.8 (9.7, 13.9)	0.021
	Dead	73 (31.2)	94 (40.2)	67 (28.6)	18.6 (10.9, 15.9)	
Total	-	344 (35.1)	406 (41.4)	231 (23.5)	13.4 (10.9, 15.9)	-

studies (9, 17). Nevertheless, no similar study was found on the delayed diagnosis in thalassemia in Iran or other countries. As far as we know, this is the first study in this regard worldwide. On the other hand, we suppose that policymakers probably think that the diagnosis testing such as PND can detect all of the disease cases. However, there are numerous patient- and health system-related factors associated with the delay in diagnosis.

We found that 64.9% of patients had delayed diagnosis. The high proportion (41.4%) of them had delay less than 12 months. On the other hand, this time, i.e. 12 months after birth, is the time for immunization of children. It, therefore, is concurrent with the immunization program which was launched in Iran in 1984 (20). This issue could explain the shorter mean delay in the birth cohort of 1981 - 1990, 1991 - 2000, and 2001 to the present compared to the birth cohort of 1980 and before. Despite a significant decrease in the mean delay, ordinal logistic regression showed a positive linear trend in birth cohorts which was associated with

delay in diagnosis. This finding suggests that there is still a major problem in the TPP.

Based on both unadjusted and adjusted ordinal logistic models, sex was an important predictor of delayed diagnosis in the patients. Gender disparity in healthcare utilization and health related factors have been widely reported (21-23). In some societies, for example India, gender discrimination is an important determinant of healthcare utilization such as childhood vaccination (21). Our study revealed that the odds of delayed diagnosis were greater in girls than boys. They also had a higher mean delay compared to boys (16.0 vs. 10.9 months, P value = 0.042, respectively). Also in a few studies, significant gender-based differences of delay have been reported in presentation of childhood disorders (24, 25).

The risk of delayed diagnosis in thalassemic patients was lower among high educated parents. Some ways could be noticed that infant health is associated with the level of parental education. For example, Wehby et al. reported

Table 2. Unadjusted and Adjusted Odds Ratios and 95% Confidence Interval From Ordinal Logistic Regression Based on the Delay in Diagnosis in Thalassemia Patients

	Category	Unadjusted OR (95% CI)	P Value	Adjusted[a] OR (95% CI)	P Value
Gender	Male	Reference	-	Reference	-
	Female	1.28 (1.01, 1.61)	0.037	1.32 (1.02, 1.71)	0.034
Type of hemoglobulinopathy	Thalasemmia intermedia	Reference	-	Reference	-
	Thalasemmia major	0.43 (0.32, 0.57)	0.001	0.42 (0.30, 0.57)	< 0.001
	Sickle cell	0.50 (0.19, 1.31)	0.159	0.89 (0.31, 2.76)	0.884
Mother's education	Illiterate	Reference	-	Reference	-
	Primary school	0.88 (0.65, 1.20)	0.421	0.89 (0.61, 1.28)	0.530
	Secondary school	0.60 (0.40, 0.90)	0.009	0.63 (0.38, 1.05)	0.079
	Academic	0.87 (0.50, 1.56)	0.637	0.93 (0.43, 2.03)	0.867
	Trend	0.85 (0.73, 0.99)	0.045	0.88 (0.71, 1.10)	0.246
Mother's job	Housekeeper	Reference		Reference	-
	Employed	1.56 (0.89, 2.73)	0.119	1.21 (0.65, 2.24)	0.540
Father's education	Illiterate	Reference	-	Reference	-
	Primary school	0.92 (0.64, 1.32)	0.658	1.03 (0.67, 1.58)	0.905
	Secondary school	0.74 (0.49, 1.12)	0.156	0.98 (0.58, 1.66)	0.951
	Academic	0.74 (0.46, 1.20)	0.222	1.03 (0.54, 1.96)	0.923
	Trend	0.88 (0.77, 1.02)	0.089	0.99 (0.82, 1.21)	0.969
Birth cohort	1980 and earlier	Reference	-	Reference	-
	1981 - 1990	1.50 (1.03, 2.19)	0.036	1.52 (0.97, 2.36)	0.066
	1991 - 2000	1.34 (0.90, 2.00)	0.150	1.55 (0.97, 2.47)	0.066
	2001 to present	1.93 (1.18, 3.17)	0.009	2.22 (1.28, 3.85)	0.005
	Trend	1.14 (0.99, 1.31)	0.070	1.22 (1.04, 1.42)	0.014
Patient's status	Alive	Reference	-	Reference	-
	Dead	1.33 (1.01, 1.75)	0.041	1.95 (1.33, 2.85)	0.001

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Adjusted for all other variables listed in the table.

that the higher parental education increased the number of prenatal care visits and decreased the risk of preterm birth (26). Numerous previous studies have also reported a significant relationship between maternal education and infant health (27, 28). Accordingly, since high maternal education is an important predictor of child health, expanding the health educational programs are required to improve health literacy and health knowledge of mothers. In our study, the mean delay was significantly higher among those patients who had employed mother, and ordinal logistic regression also showed a higher odds of delayed diagnosis among employed mothers than unemployed ones, but without significance. Maternal occupation may affect infant health that was also considered in several studies

(29, 30). Time, for example maternal time for receiving healthcare, is an important factor to determine well-baby care receipt (31).

4.1. Study Limitations and Strengths

This study encountered some limitations. First, we performed a retrospective cross-sectional study and used data recorded by the registry center. Hence, we were unable to assess the quality of the recorded data. This might raise information bias. On the other hand, there are probably other factors associated with patients and healthcare system delay that could not be assessed in this study. The main strength is its novelty in reporting of delay in diagnosis

with an appropriate sample size from a developing country. It may help policymakers who plan preventive programs reduce thalassemia rate.

4.2. Conclusions

A high proportion of delayed diagnosis was found. These results could explain the poor outcomes for thalassemia patients. We suggest that the PND errors and the causes of delayed diagnosis be recorded and analyzed. Educational programs for the community and revising the thalassemia prevention program are required for early detection of the disease.

Acknowledgments

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