Original Article

Alloimmunization in Thalassemia Patients: New Insight for Healthcare

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Abstract

Background: Development of alloantibodies against the foreign red blood cell (RBC) (alloimmunization) is a well-known complication in thalassemia patients when performing multiple transfusions. The study was conducted to know the prevalence of alloimmunization in thalassemia patients, in the Caspian Sea coastline. **Methods:** This study is a descriptive, retrospective analysis of transfusion records of 190 patients with β-thalassemia major who received regular transfusions. To detect the type of alloantibodies, two cells panel tests (kits; Iranian Blood Transfusion Organization [IBTO], 3 RBC cells and IBTO, 11 RBC cells) were used. **Results:** Forty-seven patients were positive for alloantibodies (24.7%). Of them, 18.4% (35 cases) had only one alloantibody, and 6.3% (12 cases) had at least two or more of alloantibodies. The vast majority of alloantibodies were anti-Kell followed by anti-E, and anti-D, respectively. **Conclusions:** Blood matching for Rh and K antigens in patients with transfusion-dependent thalassemia could reduce the rate of RBC alloinununization.

Keywords: *Alloantibody, blood transfusion, Iran, thalassemia*

Introduction

Thalassemia is an important health problem in more than sixty countries in the world and especially in the eastern Mediterranean region. Heterozygous populations are about 4.5% of world healthy population. Iran is located in the middle of thalassemia belt with more than 18,000 affected individuals.[1,2] The pattern of the prevalence rate of thalassemia is different in throughout of Iran, ranging from 3 per 100,000 people in central regions 100 per 100,000 people in north and south of Iran. The Caspian Sea coast in northern Iran and the Persian Gulf and Oman Sea coasts in southern of Iran are more prevalent areas (areas with higher prevalence!) for thalassemia.

To correct anemia in the β-thalassemia major patients, regular blood transfusion regimen every 3–4 weeks was recommended that could lead to alloimmunization to erythrocyte antigens.

Today, development of alloantibody against the foreign red blood cell (RBC) (alloimmunization) is a well-known complication in thalassemia patients when performing multiple transfusions, because their immune system recognizes the donor RBC surface antigens as foreign entity.[3-6] Hence, the life span of red blood cells is shortened and the patients are clinically dependent on increased (repeated) RBC transfusions. Thus, alloantibodies and/or autoantibodies of RBC that lead to difficulty in cross-matching and delay in obtaining compatible blood for transfusion are a serious problem in patient blood management of thalassemia.

The previous study reported that alloinununization rate among thalassemia patients is ranging from 2.5%–37% indifferent parts of the world.[7,8] In Iran, pretransfusion testing includes ABO grouping and Rh (D) typing, and the groups other than ABO and Rh "D" (e.g., Kell, Duffy, Kidd, MNS, Lewis, etc.) are not routinely performed.[9] Thus, the extent of the red cell antigen profile among donor populations, particularly the groups other than ABO and Rh "D" (e.g., Kell, Duffy, Kidd, MNS, Lewis, etc.) are not known, as there are no data in the literature on these groups and any statistical disparities among various racial groups. Previous studies have reported that the rate of immunization varies from 70% for Rh "D" antigen to 0.5% for the Duffy antigens when recipients lacking the antigen.[10]

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The main aim of this study was to identify the prevalence of alloimmunization in thalassemia patients, in Northern of Iran (Guilan province), to identify red cell phenotypic differences between blood donor and thalassemia populations.

Methods

This study is a descriptive, retrospective analysis of transfusion records of 190 patients with β-thalassemia major who received regular transfusions. Most of them had begun regular transfusion before they were 1-year-old. Demographic data including age, sex, age at the onset of blood transfusion, blood group, the number of blood transfusions, and ethnicity were collected by a questionnaire.

Study area and populations

Guilan province is located in northern Iran bordering the Caspian Sea with a population of about 2.5 million inhabitants. Today, a total of 1160 living patients with β-thalassemia major have been registered in Guilan province with the median age of 25 years. The age at start of blood transfusions ranged from 3 to 12 years. In northern Iran as the whole country, Guilan Blood Transfusion Organization reached 100% involuntary blood donation since 2007 and excluded family replacement donation system. On the other hand, we began using poststorage leukodepletion using a bed-side filter in hospitals of study area since 2000, as prestorage leukodepletion has been implemented in Guilan Blood Transfusion Center (as the whole country) for blood supply in the thalassemia patients since 2008. Guilan Blood Transfusion Center is an exclusive referral center for antibody identification and RBC phenotyping among 31 governmental and private hospitals in the study area.

Laboratory process

In accordance with an Iranian Blood Transfusion Organization (IBTO) standard operating procedure, both kits for antibody screening tests (IBTO home-made, 3 RBC cells) and antibody identification panels (IBTO home-made, 11 RBC cells) were used (reference laboratory with 28 day expiration date). Both of them contain at least 18 RBC antigens (nine blood group system) recommended by US Food and Drug Administration. In northern Iran, as whole country, two 6 ml blood samples were collected in ethylenediaminetetraacetic acid vacutainer tubes for each patient. One sample was tested for ABO group and Rh (D) type and antibody screen test (IBTO home-made kit) with standard tube method procedure. The second sample is used for repeated confirmation. To identify the alloantibodies, standard tube method was used in 3 phases. Immediate Spin, 37°C and anti-human globulin, when antibodies screening test results were positive for each patient.

Statistical analysis

Descriptive statistics and bivariate analysis were applied. Statistical analysis was performed using software (SPSS Version 10.5, SPSS Inc., Chicago, IL, USA).Chi-square test or Fisher's extract tests were used to test the association between gender and age group.

Results

A total of 190 thalassaemics have been examined at our blood transfusion center. Positive alloantibodies were observed in 47 subjects (24.7%). Of them, 18.4% (35 cases) had only one alloantibodiy and 6.3% (12 cases) had at least two or more of alloantibodies, which would be expected to be clinically significant. There were 23 (49%) males and 24 (51%) females. Patient's age ranged from 10 to 39 years and had the mean age of 26 ± 5.9 years. The largest patient's age group that was positive for alloantibodies was 20–29 years old (32 cases, 68%). Regarding age group, nine cases (19%) were between 30 and 39 years, and there were six cases (13%) between 10 and 19 years. This study also found that more than two-third of all subjects were above the age of 25 [Table 1].

Regarding ABO blood group distribution among alloimmunized thalassaemia patients, this study showed that 23 (49%), 13 (28%), 7 (15%), and 4 (8%) cases of O, A, B, AB blood group were alloimmunized, respectively. In final, 63 alloantibodies were detected in 47 patients. The most prevalent alloantibodies were anti-kell with 21 subjects (33%), followed by anti-E with 16 subjects (25%) and anti-D with 12 subjects (19%), respectively [Table 2]. There was a significant correlation between the rate of

Table 1: Distribution of red blood cell alloantibodies by age group and gender

Alloantibody specificity	<25	≥25	Total
Male			
Kell	4	3	7
E	2	4	6
D	1	4	5
C, D	0	1	1
Kell, C, E	1	0	1
Kell, E	1	1	2
C	0	0	1
Fy^b, S	0	1	1
Total	9	14	23
Female			
Kell	1	7	8
E	0	5	5
D	1	0	1
C, D	0	2	2
Kell, C, D	1	1	2
Kell, C, E	0	1	1
Kp^a	0	2	2
C	1	0	1
C, E	1	0	1
Kp^a, D	0	1	1
Total	5	19	24

Table 2: Profile of alloimmunized thalassaemia patients by blood group and units transfusion

Blood group	Alloantibody specificity	Units transfusion		Total
		<250	≥250	
A^+	Kell	2	1	3
	E	0	3	3
	Kp	0	1	1
A^-	C, D	1	2	3
	D	1	0	1
	Kp^a, D	0	1	1
	Kell, C, D	1	0	1
B^+	Kell	1	3	4
	E	0	1	1
B^-	D	0	1	1
	Kell, C, E	0	1	1
AB^+	Kell	1	0	1
	C	1	0	1
	Kell, C, E	1	0	1
AB^-	D	0	1	1
O^+	Kell	0	7	7
	E	3	3	6
	D	0	2	2
	Kell, E	1	1	2
	Kp^a	0	1	1
	Fy^b, S	1	0	1
O^-	E	0	1	1
	D	0	1	1
	C, E	0	1	1
	Kell, C, D	0	1	1

alloantibody production and the amount of blood units exposure.

Discussion

Regular blood transfusion regimen among thalassemia patients might produce antibodies of IgG class (frequently) against minor blood group systems such as kidd, kell, duffy, and Rh system (E, C, _e,…) which may give increase to hemolytic reaction. The results of this study provide additional information about alloimmunized thalassaemia patients. The prevalence rate of anti-red cell alloantibodies was 24.7% in our patients. This rate is much higher than alloimmunization prevalence in thalassaemia patients for cases in Pakistan (6.8%, 9.2%),[11,12] Malaysia (8.6%),[13] and Asian patients who had received transfusion predominantly from white donors (22%).[7] Indeed, our report of alloimmunization prevalence is not comparable to that of known high-risk population in Taiwan (37%),[14] and Arab (30%).[15] This disparity puts forward that something other than that geographical environment is contributing to the high rate of alloimmunization. For example, one of the diverse results is the difference in age when the transfusion began; in the study population, most of the cases started their blood transfusion at the age of 5 years, and hence RBC exposure in alloimmunized patients was very high. On the other hand, early age at transfusion might lead to some immune tolerance.[7] However, it is not contributed as a risk factor for alloimmunization.

Second, the heterogeneity in red blood cell antigens between recipients and donors in each area is also another factor associated with alloimmunization; as noted above, Guilan province had a homogenous population of RBC antigen between the blood donors and recipients, and a low rate of alloimmunization is expected in such population. Splenectomy is a risk factor for alloimmunization among thalassemia patients. However, there is only five cases involved in the absence of spleen. The study also documented that the most frequent alloantibodies were against kell (33%). This is the unexpectedly high frequency of anti-K.

Finally, malaria disease was prevalent in Guilan province. There is a hypothesis for malaria disease which relies on the high carrier frequency in hemoglobinopathies in areas with malaria endemicity.[16] Today, malaria disease is prevalent in the study area, so it is seem, hemoglobinopathies such as sickle cell anemia could be increasing in population. It is probably, there was a high frequency of persons with sickle-cell anemia in blood donor population in the study area. If there is, this situation is in accordance with western countries.[17-20] Remember, the specificity of alloantibodies in sickle-cell population following transfusion is more likely to show ethnic disparities between the recipients and their blood donors.

Conclusions

Blood matching for Rh and K antigens in patients with transfusion-dependent thalassemia could reduce the rate of RBC alloimmunization. RBC phenotyping should be performed in blood donors to determine the RBC antigenic profile among Guilan blood donors. Therefore, the availability of compatible blood for patients with thalassemia will be easy. Multicenter studies suggest formulating evidence-based transfusion guidelines for thalassemia patients in Iran.

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Conflicts of interest

There are no conflicts of interest.

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