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Initiative for rare donor registry for A_2/A_2B subgroups with Rh phenotyping: A first of its kind

Sadhana Mangwana, Dolly Gohel, Shashi Kumar

ABSTRACT

Aims: Aim of this study is to create donor registry of A_2/A_2B subgroup blood donors with Rh and Kell phenotype, to provide transfusion to multi-transfused A_2/A_2B subgroup patients and to prevent adverse transfusion reaction due to immunological stimulation by pre-existing anti-A_1 antibodies having enhanced titer and thermal amplitude. Prevalence of A_2/A_2B subgroup in Indian population is rare with highest prevalence of "e" antigen among the five Rh antigens, phenotyped serologically, and "E" antigen being the lowest in prevalence. Anti-A_1 antibodies appear as cold agglutinins in A_2/A_2B individuals and can be clinically significant when reactive at 37 °C, causing hemolysis of A_1 RBCs.

Methods: A retrospective data analysis was done in a tertiary care hospital-based blood center at capital city of India from January 2016 to December 2020. All donors were subjected to ABO Rh grouping, Rh and Kell phenotyping by solid phase method. Tube technique was used to distinguish A_2/A_2B by agglutination reaction with anti-A_1 lectin.

Results: Total 40,051 donors were analyzed during study period, of which, A and AB groups constituted 21.26% and 9.01% respectively; out of these, only 0.47% belonged to A_2 subgroup while A_2B subgroup was more frequent (1.06%). The rarest Rh phenotypes found were R1Rz, r"r, r'r" in A_2/A_2B blood donors.

Conclusion: There is a need to create rare donor registry for A_2/A_2B subgroups and clinically significant blood group antigens and share at various levels. This is a first small step to create a rare donor registry of A_2/A_2B subgroups with Rh and Kell phenotype, to provide transfusion to A_2/A_2B patients to prevent adverse transfusion reaction due to immunological stimulation by pre-existing anti-A_1 antibodies having enhanced titer and thermal amplitude and to ensure improved quality of transfusion therapy.

Keywords: A_2 subgroup, Rare donor, Rh phenotype

Sadhana Mangwana[1], Dolly Gohel[2], Shashi Kumar[3]

Affiliations: [1]MD, MBA, Head, Department of Transfusion Medicine and Immunohematology, Sri Balaji Action Medical Institute, A-4, Paschim Vihar, New Delhi, India; [2]MD, Senior Resident, Department of Transfusion Medicine and Immunohematology, Sri Balaji Action Medical Institute, A-4, Paschim Vihar, New Delhi, India; [3]DNB Resident, Department of Transfusion Medicine and Immunohematology, Sri Balaji Action Medical Institute, A-4, Paschim Vihar, New Delhi, India.

Corresponding Author: Dr. Sadhana Mangwana, Department of Transfusion Medicine and Immunohematology, Sri Balaji Action Medical Institute, A-4, Paschim Vihar, New Delhi 110063, India; G-17, Pocket-2, Naraina Vihar, New Delhi 110028, India; Email: sadhanamangwana@yahoo.co.in

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INTRODUCTION

Prevalence of ABO antigens for "A" blood group in Indian population is 21.77% and 9.09% for "AB" blood group, making chances of prevalence of A_2/A_2B subgroup rare. Among the five Rh antigens, phenotyped serologically, the highest prevalence in Indian population is of "e" antigen followed by "D," "C," "c," and "E" being the lowest prevalent Rh antigen [1]. There are various studies from India and across the world reporting more frequent prevalence of subgroup A_2B than A_2. Anti-A_1 antibodies appear as cold agglutinins, present in 0.4% of A_2 subgroup and 25% of A_2B subgroup individuals, making

it clinically significant when reactive at 37 °C, causing hemolysis of A_1 red blood cells (RBCs) [2]. Individuals with an A_2B phenotype are more likely to produce anti-A_1 antibody than A_2 phenotype because of the relative reduction of A antigens on A_2B cells [3]. Development of clinically significant anti-A_1 antibody occurs either from an exposure by transfusion with non-A_2 red cells or a pregnancy [4]. Once an A_2/A_2B individual develops an anti-A_1 antibody, they can only be transfused with antihuman globulin (AHG) cross match compatible red cell concentrates (RCC) of group A_2B, B, A_2, or O. Cases are reported from all over the globe of A_2/A_2B subgroup patients having clinically significant anti-A_1 antibody with implicated hemolytic transfusion reactions (HTR) and death; and no transfusion could be given to such patients with rare Rh phenotypes due to non-availability of blood and database of A_2/A_2B donors with rare Rh phenotypes who can be asked for directed donation. Therefore, this study was undertaken with an objective of creating donor registry of A_2/A_2B blood donors with Rh and Kell phenotype, to provide transfusion to all A_2/A_2B patients, to prevent adverse transfusion reaction due to immunological stimulation by pre-existing anti-A_1 antibodies having enhanced titer and thermal amplitude.

MATERIALS AND METHODS

A retrospective data analysis was done in a tertiary care hospital-based blood center at capital city of India from January 2016 to December 2020. As a part of routine serological testing, all donors were subjected to ABO Rh grouping, Rh and Kell phenotyping by solid phase red cell adherence (SPRCA) method (Immucor NEO/Galileo). As a routine practice of our department, for all A/AB group samples, conventional tube technique was used to distinguish A_2/A_2B subgroup by agglutination reaction with anti-A_1 lectin antisera (Tulip Diagnostics). Data was analyzed by Excel sheet.

RESULTS

A total 40,051 donors were analyzed during study period, of which, A and AB groups constituted 21.26% (n=8517) and 9.01% (n=3611) of donor population respectively, out of which only 0.47% (n=189) belonged to A_2 subgroup while A_2B subgroup was more frequent; 1.09% (n=440). Out of total 629 donors having A_2/A_2B subgroup, blood samples of 15 donors were found to be reactive on mandatory transfusion transmissible infections (TTI) testing, and hence were excluded from the study (Figure 1). The detailed sex-based distribution of A_2/A_2B subgroup blood donors for registry (n=614) is shown in Table 1. Out of 614 blood donors included in the study, 186 (30.3%) males and 3 (0.48%) females had A_2 subgroup and 420 (68.4%) males and 5 (0.81%) females had A_2B subgroup. The detailed distribution of Rh phenotype among A_2/A_2B subgroup donors is shown in Table 2. R1R1, R1r, R1R2, and R2r, in decreasing order, were found to be the commonest Rh phenotype in A_2/A_2B subgroup blood donors. There was complete absence of R2Rz, RzRz, r'r', and r''r'' in both A2 and A2B group donors (highlighted green in Table 2). In A_2B subgroup donors, the least prevalent phenotypes found, were r'r, R1Rz, r''r and r'r'' (n=5 and 1 case each) (highlighted yellow in Table 2) while they were absent in A_2 subgroup blood donors (Table 2). Out of total 614 A_2/A_2B donors, only 3.42% donors of A_2/A_2B subgroup were found to be Kell positive (K+), while majority (96.58%) donors were Kell negative.

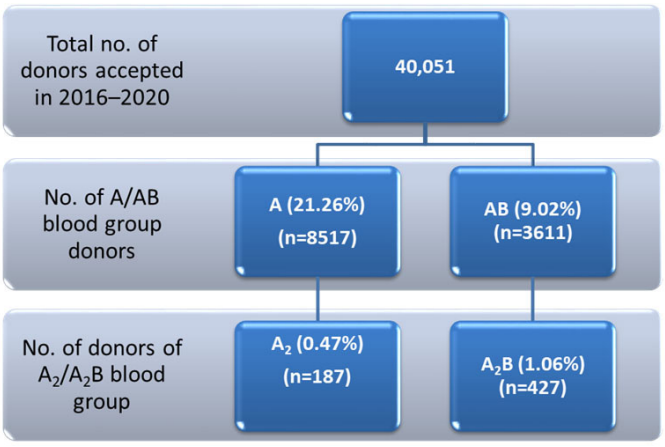

Figure 1: Distribution of A, AB, A_2, and A_2B group blood donors in study population.

Table 1: Sex-based distribution of A_2/A_2B subgroup donors

	Total no. of A_2 subgroup donors		Total no. of A_2B subgroup donors	
	Rh positive	Rh negative	Rh positive	Rh negative
Males	175	11	384	36
Females	2	1	5	0

Table 2: Distribution of Rh phenotype frequencies in A_2/A_2B donors

		Antigen frequencies in A2/A2B donors				% in Total donors population (n=40,051)	
Rh phenotype		A2		A2B		A2	A2B
Classification—Fisher (Weiner)	Race	No. (n=187)	%	No. (n= 427)	%	%	%
CCDee (R1R1)		76	40.6	170	39.8	0.189	0.424
CcDee (R1r)		64	34.2	150	35.13	0.159	0.374
CcDEe (R1R2)		25	13.4	37	8.66	0.062	0.092
ccDEe (R2r)		6	3.2	21	4.92	0.014	0.052
ccDee (Ror)		2	1.07	9	2.1	0.004	0.022
ccDEE (R2R2)		3	1.6	4	0.94	0.007	0.009
CCDEe (R1Rz)		0	0	1	0.23	0	0.0025
CcDEE (R2Rz)		0	0	0	0	0	0
CCDEE (RzRz)		0	0	0	0	0	0
ccddee (rr)		11	5.88	28	6.55	0.027	0.069
Ccddee (r'r)		0	0	5	1.17	0	0.012
CCddee (r'r')		0	0	0	0	0	0
ccddEe (r"r)		0	0	1	0.23	0	0.0025
CcddEe (r'r")		0	0	1	0.23	0	0.0025
ccddEE (r"r")		0	0	0	0	0	0

DISCUSSION

Differences between A_1 and A_2 are quantitative and qualitative. Qualitative differences of A_1 and A_2 subgroup lie in their chemical structures. Individuals with A_1 phenotype express Aa, Ab, Ac, and Ad determinants while A_2 subgroup has only Aa and Ab antigenic determinants. Absence of Ac and Ad determinants is assumed to be the cause of development of anti-A_1 in A_2 and A_2B subgroup individuals [5]. The genetic basis of high prevalence of anti-A_1 antibodies in A_2B is due to the *R101 allele. This allele is present in 41% of A_2B subgroup as compared to A_2 subgroup individuals (1%) [6]. Usually anti-A_1 antibodies exist as naturally occurring IgM with thermal amplitude of less than 25°C. However, cases of anti-A_1 reacting at 37°C have also been reported in the literature [7, 8]. Anti-A_1 antibody is one of the causes of ABO discrepancies, can develop HTR and its clinical manifestations have also been reported in hematopoietic stem cell and organ transplantation. Identification of A_2 subgroup is important for identification of prospective donor for renal transplant in O and B group patients and for managing platelet inventory of A_2/A_2B subgroup platelet, as it can be safely transfused with good recovery and corrected count increment (CCI) in O and B group patients [9].

To the best of our knowledge, this is the largest population study in which 40,051 donors were included to find A_2/A_2B subgroups with extended Rh and Kell phenotyping. Comparison of various studies showing A_2/A_2B subgroup donors is analyzed (Table 3) but could not find literature categorizing A_2/A_2B subgroup donors with Rh phenotyping. Prevalence of A_2 and A_2B donors vary with different ethnic, regional, and geographic differences.

Cases have been reported from India as well as from other parts of world when lot of time and resources were consumed in finding an appropriate cross match compatible unit of A_2 subgroup and the patient was given non-group specific RCC transfusion due to non-availability of blood or database of A_2 donors in their local donor pool.

In a case reported from Southern state of India of a 31-year-old obstetrics patient of central placenta previa with antepartum hemorrhage (APH), serological testing of patient's samples indicated presence of rare subgroup of A_2 (RhD positive). The blood samples were found to be incompatible with all ABO groups on major cross matching. However, due to non-availability of database of blood donors having A_2 subgroup or RCC units of A_2 subgroup in the local major blood banks, nearly 600 units of "A" positive were screened to find four units of compatible A_2 subgroup (RhD positive) [4]. Generally an A_2 subgroup is not identified until they have developed an antibody to A_1 cells. This occurs either from an exposure by transfusion or a pregnancy. Once an A_2 group individual has developed an anti-A_1 antibody, the A_2 subgroup individual can only be transfused with A_2 subgroup or with O group RCC that is compatible [10].

In another case reported from India of a 42-year-old male patient diagnosed as acute on chronic pancreatitis, the blood group of patient was confirmed, on serologically

testing, as "A_2B with anti-A_1 antibodies, RhD positive." Due to non-availability of A_2B group RCC unit, compatibility test with two units each of O RhD positive and B RhD positive was undertaken. O group RCC units had minor match problems due to donor anti-B antibody. Hence, the patient was transfused with eight units of compatible B RhD positive RCC over 36 hours [11].

One more case of acute hemolytic transfusion reaction (AHTR) is reported in a 96-year-old female who died shortly after transfusion due to a warm reactive anti-A_1 antibody. She was non-alloimmunized, having blood group "A_2 with an anti-A_1." The patient was transfused electronically cross matched "A" group RCC, shortly after which the patient expired. Investigations confirmed intravascular hemolysis caused by existent anti-A_1 antibody [12].

Rh phenotyping is associated in this study which will help in building database of donors having rare subtypes as well as rare Rh phenotype (e.g., R1Rz, r"r, r'r"). In our analysis, we could find only one A_2B donor each of Rh phenotype R1Rz, r"r, and r'r" in donor population of five years, making their prevalence of 0.0025% each. There are several cases reported from India where due to non-availability of database of donors having rare Rh phenotype, the patient could not be transfused at all. One such case reported is of a 25-year-old male patient, known case of β-thalassemia intermedia, whose blood group was determined to be "O" RhD positive and on Rh phenotyping, it was found to have R2R2 (DccEE). Since the patient underwent multiple transfusions during his lifetime, he had alloimmunization to multiple antibodies and was advised R2R2 phenotype matched RCC transfusion. Since R2R2 is a rare phenotype, even after screening more than 100 donor units, not a single Rh phenotype matched RCC unit could be found. This rare phenotype R2R2 could not be availed and transfusion was not given to this patient [13]. With all these problematic cases in literature, an algorithm is planned in our institute (Figure 2) and staff is trained accordingly to help patients serve safe blood as per requirements.

Table 3: Comparison of number and percentage of A_2 and A_2B subgroups in various studies

Study (sample size) [References]	Prevalence of A_2/A_2B donors	
	A_2	A_2B
Yoshida A et al. (4540) [14]	6 (0.13%)	11 (0.24%)
Mishra et al. (2874) [9]	37 (1.28%)	34 (1.18%)
Shastry S et al. (40,113) [2]	192 (0.47%)	280 (0.69%)
Giriyan et al. (20,864) [15]	60 (0.28%)	176 (0.84%)
Present study (40,051)	187 (0.47%)	427 (1.06%)

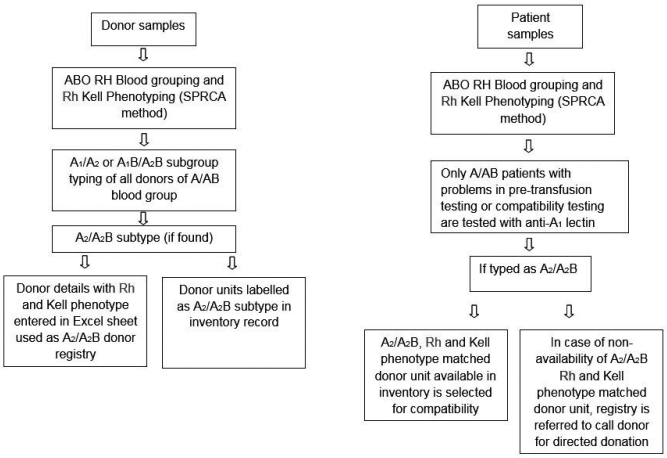

Figure 2: Algorithm for maintaining A_2/A_2B donor registry and its utility for transfusion therapy in A_2/A_2B patients.

The establishment of a state, national, and international register of donors of rare blood groups and their alleles would aid in creating awareness of their existence. Maintenance of rare group registry will help to overcome such difficulties. This study is our small contribution toward preparing rare donor registry of India and we will try to incorporate this registry with other donor registries at various levels, wherever possible.

Life-threatening transfusion reactions occurring due to minor incompatibilities can be avoided by knowing the prevalence of these subgroups and Rh phenotypes. The transfusion safety could be further enhanced by doing molecular characterization of the subtypes; however, it needs further studies with large sample size.

CONCLUSION

There is a need to create rare donor registry for A_2/A_2B subgroups and clinically significant blood group antigens and share at different levels. This is a first small step to create a rare donor registry of A_2/A_2B subgroups with Rh and Kell phenotype, to provide transfusion to all A_2/A_2B patients to prevent adverse transfusion reaction by pre-existing anti-A_1 antibodies having enhanced titer or thermal amplitude to ensure improved quality of transfusion therapy.

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Author Contributions

Sadhana Mangwana – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Dolly Gohel – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shashi Kumar – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.