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Red Blood Cell Alloimmunization in Patients with Sickle Cell Disease from Abha, Asir Region, Saudi Arabia.

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Abstract

Background. Red blood cell (RBC) transfusion is a mainstay of treatment for sickle cell disease (SCD), but is associated with alloimmunization, leading to delayed hemolytic transfusion responses and limiting availability of suitable blood. There is little regional data from the south of Saudi Arabia.

Method. This cross-sectional study was performed in Abha, Asir Region, from 2018 to 2020. Two hundred patients aged 14–69 years with SCD were examined for RBC alloantibodies. Blood samples were screened for antibodies and phenotyped (ABO; Rh D, C, c, E, e; K; Fya, Fyb; Jka, Jkb; Lea, Leb; M, N, S, s) using the gel method on an automated platform (Ortho Clinical Diagnostics).

Results. Alloantibodies were detected in 29 of 200 patients (14.5%; 95% CI 10.3 to 20.0%): 16 of 116 males (13.8%) and 13 of 84 females (15.5%). Fifteen of the twenty-nine had multiple antibodies. The most prevalent specificity was anti-E (17 patients, 58.6% of positives) followed by anti-K (11, 37.9%), anti-c (7, 24.1%) and anti-C (4, 13.8%). In 27 of 29 (93.1%) Rh- or K-positive individuals, antibodies to these antigens were detected. Positive individuals had received a median of 12 transfusions (range 5-26).

Conclusions. In Abha, approximately one in seven SCD patients who had transfusion were alloimmunized largely against Rh (E, c, C) and Kell (K) antigens. Further large prospective trials are suggested, along with prophylactic Rh and K matching, preferably prolonged matching, and leukoreduced units.

Keywords: alloimmunization, sickle cell illness, red blood cell antibodies, transfusion, Saudi Arabia, Abha.

Introduction

Sickle cell disease (SCD) is a hereditary condition caused by a single mutation in the sixth codon of the β-globin gene that substitutes glutamic acid with valine, therefore producing sickle hemoglobin (HbS). Deoxygenated HbS polymerizes and distorts red cells resulting in hemolytic anemia, vaso-occlusion, ischemic organ damage and severe crises (Setty et al., 2019; Wihak et al., 2020). The illness is a serious public health concern in Saudi Arabia and is mostly reported in the Southwestern and Eastern Provinces (Al-Asmari et al., 2024).

A fundamental component of SCD management is blood transfusion. It increases the oxygen carrying capacity and dilutes HbS (Fasano et al., 2019). The major immunologic cost is RBC alloimmunization, the development of antibodies to donor antigens not present in the patient (Tanhehco et al., 2022). The most significant result is delayed hemolytic transfusion response in which hemoglobin might drop below pretransfusion levels when both transfused and autologous cells are destroyed (hyperhemolysis). Multiple alloantibodies additionally complicate the search for suitable units.

Reported alloimmunization rates in SCD vary from 2.6% to 76% (Meda et al., 2014). In certain cohorts from the US and Brazil rates are above 50% (Rossi et al., 2023; Zanette et al., 2010) and lower in Uganda (6.1%; Natukunda et al., 2010). Studies from Saudi Arabia show 13.7% and 34.2% in various series (Bashawri, 2007) and 12.8% in Jeddah (Alboog et al., 2015). The antibodies most often involved are those against the Rh, Kell, Kidd, Duffy, Lewis and MNS systems (Gammon et al., 2023). The fluctuation is due to differences in donor and recipient antigen frequencies among ethnic groups and geographies.

We are not aware of any previous studies reporting alloimmunization in SCD patients from the southern part of Saudi Arabia. The objectives of this study were to: (1) estimate the prevalence of RBC alloimmunization among SCD patients in Abha, Asir Region; (2) identify RBC alloantibodies by employing gel method with polyspecific anti-human globulin; and (3) identify the specificity of the antibodies.

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2. Materials and methods

2.1 Design and participants

This cross-sectional study was performed in Abha, Asir Region, Saudi Arabia between 2018 and 2020 in patients with confirmed SCD. Eligible patients were chosen by a consultant in the hematology department. We recruited patients aged 14–69 years with a confirmed diagnosis of SCD who required blood transfusion and included 200 individuals. To eliminate any bias, patients with severe anemia (Hb < 5 g/dL), persistent infections or other serious health issues were removed.

2.2 Data collection

Clinical and demographic data were extracted from the clinical notes and a structured questionnaire on to a standard case record form. Age, sex, ethnicity, ABO/Rh group, transfusion history (number of transfusions), splenectomy, hospitalizations, acute pain episodes, sequelae and antibody status.

2.3 Sampling and laboratory analysis

Venous blood was obtained in two EDTA tubes (one for automated complete blood count and one for antibody test) with a total volume of 5 mL. An additional 3 mL was drawn for chemical markers. Tests included forward and reverse ABO grouping, Rh typing, antibody screen, direct antiglobulin (Coombs) test (DCT), and extended phenotyping (Rh D, C, c, E, e; K; Fya, Fyb; Jka, Jkb; Lea, Leb; M, N, S, s). Alloantibodies were discovered by a polyspecific anti-human globulin and found in patients with a positive screen. All tests were performed using gel method on a fully automated platform (Ortho Clinical Diagnostics).

2.4 Statistical analysis

Data were input twice into a database and evaluated with SPSS. Results are described by counts and percentages, and continuous variables by mean ± SD or median and range. This is a cross-sectional study, hence the proportion of patients having alloantibodies is presented as a frequency (period prevalence) and a 95% Wilson confidence interval, rather than as an incidence rate. $p < 0.05$ deemed significant.

2.5 Ethics

The protocol of the study was authorized by the Research Ethics Committee of the College of Applied Medical Sciences, King Saud University (ethics number CAMS-125a-3839; approved on 9 April 2018). Participants, or parents or guardians with participant assent for minors, provided written informed consent. Participation was optional and findings were given to the treating physicians.

3. Results

3.1 Frequency of alloimmunization

In 200 individuals (116 males, 84 females; age 14-69 years) 29 (14.5%; 95% CI 10.3-20.0%) had one or more RBC alloantibodies and 171 had none. The positive patients were 16 men (13.8% of males) and 13 females (15.5% of females) aged 19-57 years (median 31). They had undergone 5–26 transfusions (median 12, mean 13.8). Fourteen had one antibody and 15 had two or more; the median number of transfusions was 8.5 in the single-antibody group and 16 in the multiple-antibody group. Transfusion counts were not provided for the 171 antibody-negative individuals, and hence a comparison of transfusion load across groups could not be made. DCT was positive in four of the 29 patients (13.8%), without clinical signs of autoimmune hemolysis.

3.2 Distribution by ABO/Rh group

Of the 200 patients, 105 were O+, 57 were A+, 19 were B+, 11 were AB+, 3 were A−, 3 were B− and 2 were O−. Table 1 Antibody positive patients by blood group O+ patients were 65.5% of the positive cases but also 52.5% of the cohort, therefore the within-group rate is the fairer comparison: 17.8% in group O (19/107), 8.3% in group A (5/60), 22.7% in group B (5/22) and 0% in group AB (0/11). These are unadjusted descriptive rates from tiny subgroups and were not assessed for significance.

Table 1. Blood group distribution of antibody positive patients

Blood group	Positive / total	Within-group rate (%)	Share of the 29 positives (%)	Male / female positives
O+	19 / 105	18.1	65.5	10 / 9
A+	4 / 57	7.0	13.8	3 / 1
B+	4 / 19	21.1	13.8	2 / 2
AB+	0 / 11	0	0	0 / 0
A−	1 / 3	33.3	3.4	0 / 1
B−	1 / 3	33.3	3.4	1 / 0
O−	0 / 2	0	0	0 / 0
Total	29 / 200	14.5	100	16 / 13

By sex, O+ accounted for 62.5% of positive males and 69.2% of positive females.

3.3 Antibody specificities

The most common specificity was anti-E in 17 of 29 positive individuals (58.6%), alone or in combination with other antibodies, followed by anti-K (37.9%) and anti-c (24.1%). Six individuals (20.7%) were anti-E only. Antibodies to Rh antigens (D, C, c, E, e) were detected in 23 individuals (79.3%), and to Rh or K in 27 patients (93.1%).

Antibodies outside of Rh and Kell (Duffy, Kidd, Lewis, MNS, Lutheran) were found predominantly in patients with numerous antibodies.

Table 2. Alloantibody specificities in the 29 seropositive individuals

Antibody	Patients (n)	% of positives
Anti-E	17	58.6
Anti-K	11	37.9
Anti-c	7	24.1
Anti-C	4	13.8
Anti-Fya	3	10.3
Anti-M, Anti-s, Anti-Jka, Anti-Lea (each)	2	6.9
Anti-D, Anti-e, Anti-Jkb, Anti-S, Anti-N, Anti-Lua (each)	1	3.4

Percentages are based on 29 as denominator. A patient with multiple antibodies is tallied once for each. The widest profile (case 18, O+ man, 23 transfusions) exhibited six antibodies (anti-C, -e, -Lea, -N, -s, -Lua). The solitary anti-D case was an A− female with anti-D, anti-E, anti-K and anti-C after 26 transfusions.

4. Discussion

In this initial research from the southern part of Saudi Arabia 14.5% of patients with SCD exhibited RBC alloantibodies and almost half of them had more than one specificity. This percentage is comparable to that reported from Jeddah in the west of the kingdom (12.8%) (Alboog et al., 2015) and the lower of the two rates recorded in the Eastern Province (Israelyan et al., 2024). This is lower than the 31.5% rate from Oman (Alkindi et al., 2017) and the 18–37% rate usually recorded for transfused SCD patients in other parts of the world (Boateng et al., 2019; Leal et al., 2023; Aggarwal et al., 2020; Campbell-Lee and Kittles, 2014). This is greater than the rates from Sudan (4%) Abbas et al., 2013 and Uganda (6.1%) Natukunda et al., 2010. Other potential reasons that were not investigated in this study include differences in donor-recipient antigen mismatch, transfusion volume, matching policy, and the genetic and ethnic composition of donors and patients.

The most frequent were anti-E and anti-K and 93% of positive individuals had a Rh or K antibodies. Anti-E is the most prevalent alloantibody in SCD (Wahl et al., 2012) and was the most common specificity in Israelyan et al. (2024). Anti-c was more prevalent than anti-C here but the contrary is observed in certain US series (Tanhehco et al., 2022; Leal et al., 2023) which may represent differing antigen distributions. Antibodies to Kidd, Duffy, Lewis, MNS and Lutheran antigens were also observed as in Omani patients (Alkindi et al., 2017). The prevalence of Rh and K is consistent with at least partial matching for these antigens, which has been demonstrated to reduce alloimmunization (Tanhehco as al, 2022; Leal et al, 2023). Also recommended is expanded matching that includes Fy, Jk and S since antibodies to additional systems were detected (O'Suoji et al., 2013; Venkateswaran et al., 2011).

Most positive patients were in group O, however this is probably a reflection of the fact that group O was the biggest group in the cohort. Based on tiny numbers within groups, group B and group O had the greatest and group A the lowest rates. We did not evaluate whether ABO group is connected with alloimmunization.

Patients with multiple antibodies had undergone more transfusions (median 16) than those with one (median 8.5). This is consistent with a risk associated to exposure, but we did not have transfusion counts for antibody-negative individuals and did not control for confounders so this should not be interpreted as a dose-response finding. Responder status is also affected by patient-related variables such as HLA type, inflammation, genetics and ethnicity (Yazdanbakhsh et al., 2012; Wong et al., 2022).

Four individuals had a positive DCT but no evidence of autoimmune hemolysis. Autoantibody development following alloimmunization is reported in transfused patients (Versino et al., 2024) and leukoreduction has been suggested to decrease immunostimulatory material from stored white cells (Kaur, 2018). This study cannot demonstrate the etiology of positive DCT in these individuals.

Strengths and limitations

This is the first report of RBC alloimmunization in SCD from the southern part of Saudi Arabia with comprehensive phenotyping and standardized automated gel testing. Limitations include a small sample size, single-region sample, and cross-sectional design. It can't tell when the antibodies developed, or how many transfusions it took to make them. The stated rate represents a proportion of patients, not an incidence rate. There is no transfusion data for antibody negative individuals and antibody identification is only performed at reference blood banks in the region, which may bias the case finding.

5. Conclusions and recommendations

Red blood cell alloantibodies were identified in about 14.5% of the SCD patients in Abha, with anti-E and anti-K being the most common and many patients had multiple antibodies. We thus urge that at least Rh antigens (D, C, c, E and e) and the K antigen should be matched prophylactically and, where possible, expanded matching for other clinically important antigens such as Fy, Jk and S. We also advocate the use of leukocyte-reduced RBC units for

patients with SCD to promote safer transfusion practice and to prevent transfusion-related morbidity.

We also propose regular monitoring of antibodies and the creation of precise, unambiguous national guidelines for transfusion therapy in patients with SCD. Consider the establishment of an immunohematology database of donor phenotypes at reference blood banks in Saudi Arabia; this would support antigen-matched transfusion and enhance transfusion planning. Finally, bigger prospective investigations of the Saudi population, ideally with transfusion histories for all patients, are necessary to more precisely characterize clinically important antigen distributions and risk variables.

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