Red blood cell alloimmunization and minor red blood cell antigen phenotypes in transfused Ghanaian patients with sickle cell disease

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BACKGROUND: The routine pretransfusion investigations in Southern Ghana involve only ABO-D blood group typing and ABO compatibility testing without screening for irregular red blood cell (RBC) antibodies. The prevalence and specificities of RBC antibodies and frequencies of most minor blood group antigens in transfused patients with sickle cell disease (SCD) in Ghana are not known and are the objectives of this study.

STUDY DESIGN AND METHODS: This was a cross-sectional study that investigated transfused patients with SCD for the presence of irregular RBC antibodies and Rhesus, Kell, Duffy, Kidd, and Ss antigens.

RESULTS: From a total of 154 patients (median age, 9 years), 10 patients (6.5%) possessed 13 antibodies, predominantly against D, C, and E antigens. In three patients, the antibodies (anti-D, anti-D + C, and anti-C + e) were against antigens they possessed by serology. Genotyping showed that two of these patients had variant *RHCE* genes that encode for weak and partial e antigens and one patient had a partial *RHC* gene. Frequencies of most RBC antigens were comparable with frequencies established among the African American population; however, K–k– and Jk(a–b–) phenotypes were more frequent and were present in 21% and 17% of patients, respectively.

CONCLUSION: The prevalence of RBC alloimmunization in transfused Ghanaian patients with SCD was 6.5% and the majority of antibodies were against antigens of the Rh system. Our findings stress the need to include pretransfusion testing for RBC antibodies in patients with SCD, to improve transfusion safety.

Sickle cell disease (SCD) is the most common monogenic disorder, with the greatest occurrence in sub-Saharan Africa (SSA). More than 75% of SCD births are currently in SSA and has been predicted to increase to almost 90% by the year 2050.[1] Death rate has been estimated at 50% to 90% for children with SCD in SSA before the age of 5 years.[2] In Ghana, 2% of newborns have SCD and up to 30% carry the sickle cell gene.[3] Most individuals with SCD in SSA are diagnosed when they present with symptoms (i.e., dactylitis, splenic sequestration) during childhood, at a mean age of 2 years. Although highly cost-effective, screening newborns for early detection and timely treatment of SCD is, in contrast to the United States and many European countries, not routine in Ghana.[4]

Abbreviations: KATH = Komfo Anokye Teaching Hospital; SCD = sickle cell disease; SSA = sub-Saharan Africa.

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This study was funded by Science Technology Engineering and Mathematics (STEM) of the African Studies Centre, University of Michigan.

Received for publication October 10, 2018; revision received January 22, 2019, and accepted January 24, 2019.

doi:10.1111/trf.15197

TRANSFUSION 2019;59;2016–2022

Red blood cell (RBC) transfusions in SCD are used to improve oxygen-carrying capacity by correcting anemia, to suppress the production of sickle reticulocytes and to prevent or reverse complications related to vasoocclusion and hemolysis. RBC transfusion has shown tremendous improvement in patients' well-being.[5,6] However, RBC alloimmunization is a major complication in transfused patients with SCD and the frequency ranges from 2% to 63%.[7–14] The pathophysiology of RBC immunization is considered multifactorial. Besides the disparity in RBC antigens between donors and recipients, other contributory factors include sex, age, patients' age at first transfusion, exposure to episodic transfusions, patients' immune regulatory state, and genetic status.[15–19]

Red blood cell alloimmunization may delay or even prevent blood transfusion or complicate pregnancies (i.e., hemolytic disease of the fetus and newborn) and increases the risk of delayed hemolytic transfusion reactions.[20,21] In addition, alloimmunized patients have an increased risk of developing additional alloantibodies and autoantibodies.[22–24]

In Ghana, the main indications for RBC transfusions in patients with SCD are low hemoglobin (resulting mainly from RBC hemolysis and malaria) and acute crisis. There are little or no chronic transfusion programs. The routine pretransfusion investigations involve only ABO-D blood group typing and ABO compatibility testing (immediate-spin crossmatch) without screening for irregular RBC antibodies. Consequently, the frequency of most blood group antigens other than ABO-D and RBC alloimmunization in transfused patients with SCD in Ghana are not known. We studied the prevalence and specificities of RBC antibodies and the frequencies of some common minor blood group antigens in transfused patients with SCD at Komfo Anokye Teaching Hospital (KATH), Kumasi, Southern Ghana.

MATERIALS AND METHODS

Patient recruitment

In a cross-sectional study, patients with SCD were recruited, between January and November 2016, at the sickle cell clinic of the KATH, with approval from the Committee on Human Research, Publication and Ethics, Kwame Nkrumah University of Science and Technology. KATH is a 1200-bed hospital with approximately 17,000 transfusions annually, of which 80% is transfused as whole blood. Blood is sourced from both voluntary (80%) and (family) replacement donors (20%). Blood is neither irradiated nor leukoreduced before transfusion. The sickle cell clinic treats and transfuses approximately 5000 and 150 SCD patients annually, respectively. It has approximately 1000 transfused patients with SCD of whom 600 have received up to four RBC transfusions.

The study inclusion criteria were patients with SCD of any age and SCD genotype, with at least one RBC transfusion event and the last transfusion at least 2 weeks before enrollment into the study. Patients with the last transfusion at least 2 weeks before the time of enrollment were selected to allow a time window within which (new or boostered) antibodies might develop after transfusion. Informed consent was obtained from participants of 18 years and older and from guardians of those less than 18 years of age.

Data collection

Participants' basic demographic characteristics, number of previous transfusions, age at first transfusion, and indication for transfusion were retrieved from patients' hospital files and recorded on clinical record forms. Patients or their caretakers provided us with this information and transfusions in hospitals other than KATH, if missing from the hospital file. However, because patients' (or guardians') memory may not be exactly accurate, the numbers of transfusions were categorized as 1, 2 to 4, and 5 or more RBC units.

Sample processing and laboratory investigation

Patients' blood samples were separated into RBC with buffy coat and plasma. RBC antigen typing was performed at the hematology unit of KATH. Frozen RBC and plasma samples were transported to the University of Michigan Reference Laboratory for antibody screening and identification tests and molecular genotyping. Genotyping was performed when antibodies were present against antigens the patient possessed with serology.

RBC antigen and antibody investigations

Serologic blood group antigen (D, C, c, E, e, K, k, Fy^a, Fy^b, Jk^a, Jk^b, S, and s) typing was performed with commercially available antisera (Immucor, Inc., and Ortho Clinical Diagnostics, Inc.), using the conventional tube method, according to the manufacturer's instructions. RBC antibody screens were performed with the indirect antiglobulin technique, using a low-ionic-strength saline (LISS) gel test and a two-cell screen panel (Ortho Clinical Diagnostics, Inc.). Antibody identification was performed on samples with a positive screen using a 12-cell panel by the same technique. Antibody specificities that could not be identified with the LISS technique were subjected to further gel column agglutination testing with enzyme (ficin)-treated panel cells.

Frozen RBC samples from patients with antibodies to antigens they typed positive for by serology were sent to Grifols Immunohematology Center for genotyping using computer software (BLOODchip ID CORE XT v.4.0, BID XT, Grifols), allele-specific polymerase chain reaction, and Sanger DNA sequencing.[25]

Statistical analysis

Median and range described nonnormally distributed continuous variables. Univariate logistic regression was used to determine the association of patient characteristics, that is,

sex, age at enrollment (continuous), age at first transfusion (categorized as ≤1, 2–5, 6–9, and ≥10), SCD genotype (SS and other), ethnicity (Akan and other), and number of transfused units (categorized as 1, 2–4, and ≥5), with the presence of antibodies. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A p value of less than 0.05 was considered significant. Statistical analyses were performed with computer software (Statistical Package for the Social Sciences, SPSS Inc.).

RESULTS

A total of 154 patients with SCD (male-to-female ratio, 1.3; median age, 9 years; range, 1–50 years) were recruited. Patients were mainly from the Akan tribe (81%) and 87% had the SCD SS genotype. The transfusion history revealed that 32% of patients had received 1 RBC unit, 55% received 2 to 4 units, and 12% received more than 4 RBC units. While 23% of patients received the first RBC transfusion during the first year of life, only 7% did so at or after age 10 (Table 1).

In 10 patients (6.5%; 95% CI, 3.3%–11.9%), antibody screening was positive, and identification revealed 13 RBC antibodies. Nine antibodies were against antigens in the Rh system, three against the M antigen, and one against a low-frequency antigen of unknown specificity. Three patients had multiple antibodies against Rh system antigens (Table 2). In three patients, the antibodies (anti-D, anti-D + C, and anti-C + e) were against antigens they possessed by serology. Genotyping showed that the two serologically D+ male patients had *RHD*deletion* and variant *RHCE* genes that encode for weak and partial RHe antigens. The patient with anti-C + e had partial *RHC* and normal *RHe* genes (Table 2).

Univariate logistic regression revealed that age at enrollment, age at first transfusion, SCD genotype, and ethnicity were not associated with the presence of antibodies. Alloimmunization showed a trend to be lower in females compared to males (OR, 0.30; 95% CI, 0.06–1.48; p = 0.14) and was significantly associated with the number of transfused units (OR, 2.87; 95% CI, 1.02–8.08; p = 0.046; Table 3). The frequency of patients with antibodies increased from 2% in the 50 patients who had received only 1 unit, to 7% in 85 patients with 2 to 4 units, and 16% in 19 patients with more than 4 RBC units. In multivariate analysis, including sex and number of transfusions, only the number of transfusions was associated with the presence of antibodies (adjusted OR, 2.87; 95% CI, 1.02–8.08; p = 0.046).

TABLE 1. Demographic and transfusion characteristics of the 154 transfused patients with SCD in Southern Ghana*

Characteristic	Alloimmunized	Nonalloimmunized
Number of patients (%)	10 (6.5)	144 (93.5)
Males/females	80/20†	55/45
Age (years) at enrollment, median (range)	8 (2–22)	9 (1–50)
SCD genotype: SS/other	90/10	87/13
Ethnicity: Akan tribe/others	80/20	81/19
Age (years) at first transfusion: ≤1/2–5/6–9/≥10‡	30/30/30/10	23/46/24/7
Number of transfused units: 1/2–4/≥5	10/60/30	34/55/11

* Data are expressed as percentages, unless stated otherwise.
† The two females with antibodies were 6 and 13 years of age.
‡ Data available for 127 of 144 (88%) nonalloimmunized patients.

Due to limited reagent availability, serologic RBC antigen typing was performed in 78 to 133 patients. The D, c, e, and s antigens were present in more than 90% of patients; k and Jk^a in approximately 75%; A, B, C, E, Jk^b, and S in 24% to 47%; and Fy^a, Fy^b, and K antigens in less than 5% of patients (Table 4). The Fy(a–b–) phenotype was present in 92% of the 116 Fy^a- and Fy^b-typed patients and the S–s– phenotype in 0.9% of 107 S- and s-typed patients. The K–k– phenotype was present in 21% of 71 K- and k-typed patients and the Jk(a–b–) phenotype in 17% of 126 Jk^a- and Jk^b-typed patients (Table S1 [available as supporting information in the online version of this paper], including an overview of studies on RBC antigen phenotypes in other Ghanaian ethnicities and published in African Americans). None of the patients with the K–k– and the Jk(a–b–) phenotypes were known family members.

DISCUSSION

This cross-sectional study, conducted in Southern Ghana, which recruited 154 transfused patients with SCD, predominantly children from the Akan tribe, revealed an alloimmunization prevalence of 6.5%. The number of transfused units was associated with the presence of antibodies. The majority of antibodies were against antigens from the Rh blood group system. To the best of our knowledge, this is the first study reporting on the prevalence and nature of RBC antibodies in transfused patients with SCD in Ghana. In our previous study, 9.4% of 106 patients, predominantly transfused adults with other diseases from the same area in Ghana, were alloimmunized.[26] A meta-analysis comprising 11 studies from SSA, and mainly in transfused patients of various ages with SCD, showed that 6.7% (95% CI, 5.7%–7.8%) had clinically significant RBC alloantibodies. Antibodies against Rh antigens were the most prevalent, comparable with our results.[27] The alloimmunization prevalence observed in our study is consistent with the 2.9%–6.1% established in other studies that were performed in (predominantly) children with SCD from other SSA countries.[7–11]

The frequency of patients with antibodies in our study increased from 2% after 1 RBC unit to 16% in patients who had received more than 4 units. Previous studies showed a higher risk for alloantibodies with increasing number of transfused RBC units in patients with and without SCD.[12,28–30] Since patients with SCD are lifelong transfusion dependent, preventive extended RBC antigen matching,

TABLE 2. RBC alloantibody specificities and Rhesus antigens serology and genotyping results in the 10 alloimmunized patients with SCD in Southern Ghana

Antibody specificity	Number	D, C, c, E, and e pheno- and genotypes		
		Serology	Genotyping	Predicted phenotype
M	3	NA	NA	NA
D	1	D–, C–, c+, E–, e+	NA	NA
D	1	D+, C–, c+, E–, e+	Homozygous *RHD*deletion,* Homozygous *RHCE*ceAG*	D–, C–, E–, c+, partial-e
E	1	D+, C– c+, E–, e+	NA	NA
D + C	1	D+, C+, c+, E–, e+	Homozygous *RHD*deletion RHCE*ce(48C)* and *RHCE*ceAG*	D–, C–, E–, c+, weak e/partial e
C + e-like	1	D+, C+, c+, E–, e+	*RHD*deletion* and *RHD*r's RHCE*ce* and *RHCE*ce[733G,1006T]*	D–, partial C, E–, c+, e+
E+C^{w}	1	D+, C–, c+, E–, e+	NA	NA
LFA*	1	NA	NA	NA

* Antibody against an unknown low-frequency antigen.
NA = not applicable.

especially for C and E antigens, should be considered. A study exploring Rh blood group antigen frequencies among 1533 blood donors from the Akan tribe found C and E antigens less frequent compared to our patients with SCD (19% vs. 37% and 17% vs. 28%, respectively).[31] The ccee phenotype was present in 65% and 82% of the D+ and D– donors, respectively, suggesting that matching for C and E antigens is feasible. However, considering that 1) homozygous serologic expression of C or E antigens was only present in none and two of our patients, respectively, 2) there is frequent presence of *RH* variant alleles in black persons, and 3) most of our patients received transfusion for unplanned emergencies, a more pragmatic approach would be to transfuse all patients with SCD with C– and E– RBCs.[32,33] This will require a pool of C and E antigen–typed donors, which will be challenging in Ghana.

Three patients had anti-M, which is often naturally occurring, usually of IgM type, relatively common in children (with and without SCD), may appear in response to an infection, and is often clinically insignificant.[34,35] However, transfusion reactions due to anti-M reactive at 37°C have been reported and patients with warm-reacting anti-M should receive M– RBCs.[36,37]

One patient had anti-D and one anti-C + D but tested both D+ by serology. Genotyping revealed *RHD*deletions*, absence of C alleles, and variant e alleles (ce(48C) and ceAG)) in both, the latter frequently present in African Americans.[38] A number of variant Rhce proteins such as ceCF, ceRT, and ceSL carry D-specific amino acids or express D-like epitopes that can react with some monoclonal anti-D.[39] For ceAG, this has not been described, so incorrect serologic D typing

TABLE 3. Univariate analysis of variables associated with the presence of RBC antibodies in 154 transfused patients with SCD in Southern Ghana*

Characteristic	OR	95% CI	p value
Sex (male† vs. female)	0.30	0.06–1.48	0.14
SCD genotype (SS† vs. other)	0.73	0.09–6.10	0.77
Ethnicity (Akan† vs. other)	1.08	0.22–5.39	0.92
Age at first transfusion‡ (≤1, 1–5, 6–9, and 10)	1.07	0.51–2.42	0.86
Age at enrollment (continuous)	1.01	0.91–1.12	0.82
Number of transfused units (1, 2–4, and ≥5)	2.87	1.02–8.08	0.046

* In multivariate analysis, including sex and number of transfused units, only the number of transfused units was associated with the presence of antibodies (adjusted OR, 2.87; 95% CI, 1.02–8.08; p = 0.046).
† Reference.
‡ Data were available for 127 of 144 (88%) nonalloimmunized patients.

TABLE 4. Frequencies of minor RBC antigens in patients with SCD from Southern Ghana

RBC antigen	Number of patients tested	Antigen frequency (%)	RBC antigen	Number of patients Tested	Antigen frequency (%)
A*	129	33	K	105	0
B*	129	24	k	78	78
D	132	96	Fy^{a}	116	4.3
C	133	37	Fy^{b}	133	3.8
E	132	28	Jk^{a}	132	75
c	133	100	Jk^{b}	127	47
e	133	99	S	118	39
			s	116	94

* ABO blood group frequencies were as follows: O 50%, A 26%, B 17%, and AB 7%.

cannot be ruled out. The C+e+ patient with anti-C and auto- or e-like antibody had an *RHC*-variant allele, serologically detectable by some anti-C reagents.

Frequencies of most RBC antigens in our patients were comparable to those published in a textbook for the black, mainly African American, population.[40] Frequencies of k (78 and 100%), Fy^b (4 and 23%), and Jk^a antigens (75 and 92%) were markedly lower, reflecting differences in the frequencies of some RBC antigens between predominantly Akan patients with SCD and the black population. Our finding that 17% of our patients had the Jk(a–b–) phenotype is in accordance with the study by Acquaye who reported a Jk(a–b–) phenotype in 13% of 121 Southern Ghanaian donors from Ewe ethnicity.[41] In addition, this phenotype was found in 38% of 158 Ghanaian donors from Ga ethnicity and in 87% of 162 pregnant women from various ethnicities in Western Nigeria, further stressing that blood group prevalence can vary substantially among African ethnicities.[42,43] So far, more than 40 variant Kidd alleles have been described in many different ethnic groups. These variants can silence protein expression or produce weak or partial antigens, hampering serologic typing.[44] The high frequency of the K–k– phenotype in our patients is a novel finding. Similar to Kidd, more than 40 variant *KEL* alleles lead to the K_0 phenotype or reduced expression of Kell glycoprotein, termed Kmod phenotype.[45] Only a few studies determined the frequency of Kell system blood groups in SSA populations and almost all were limited to the K antigen. The frequency of k antigen is largely unknown but presumed to reach almost 100%. Blood group antigen frequencies quoted for black persons are often based on African Americans and obviously do not reflect distributions in African regions. For instance, the Kp^b antigen from the Kell blood group system is, like k antigen, presumed a high-frequency antigen almost universally present on RBCs. However, a study from Cote d'Ivoire showed that 17% of 651 blood donors had the Kp(a–b–) phenotype.[46] These novel findings deserve further explorations, including genotyping to determine the molecular basis of these phenotypes, but financial restraints prohibited this in our study.

Pretransfusion investigations in Ghana are limited to ABO-D blood group typing and ABO compatibility testing. Little is known on the risk of transfusion reactions in patients with SCD receiving not completely crossmatched transfusions in SSA and transfusion reactions were not recorded in our study. However, in a 1-year study in our hospital in 372 patients without SCD, the prevalence of acute (within 24 hr after transfusion) hemolytic transfusion reactions was 9.3 per 1000 transfusions.[47] None of the reactions were attributable to ABO incompatibility, but the presence of irregular RBC antibodies was not investigated and cannot be ruled out as having been implicated.

Our study had several limitations. First, despite our thoroughness of investigation, demographic and transfusion information were not completely available for all patients, due to suboptimal hospital documentation. In addition, transfusion history may be impaired because patients' (or guardians') memory may not be exactly accurate. Second, the optimal period after transfusion for antibody detection is largely unknown; therefore, our antibody screening might have been too soon after the last transfusion to detect new antibodies or too late resulting in evanescence of antibodies.[48] Both result in an underestimation of antibody frequency. Also, because the actual number of RBC units before antibodies were formed were not known—cross-sectional study design and patients might have been transfused in other hospitals—the precise immunization rate per transfused unit could not be determined. Finally, the study consisted of patients predominantly from the Akan tribe and results may not be generalizable for patients with SCD from other ethnic groups in Ghana.

In conclusion, the prevalence of RBC alloimmunization in transfused patients with SCD in Southern Ghana was 6.5% and alloantibodies were in the majority of cases against D, C, and E antigens. Our findings stress the need to test for the presence of RBC antibodies in SCD patients before transfusion, preferably using a standardized RBC panel of "African origin" (i.e., expressing V, VS, and Js^a antigens), but at least by performing an indirect antiglobulin compatibility test with donor RBC and patient serum to improve transfusion safety. The latter is probably cheaper and easier to implement in Ghana. However, to effectively improve safety, knowledge of blood group antigen frequencies in ethnic groups in SSA, RH genotyping, and (limited) antigen matching may be essential in the future.

ACKNOWLEDGMENTS

The authors express their gratitude to the University of Michigan transfusion reference laboratory for donating RBC antisera for antigen typing and Imelda Bates for critically reviewing the manuscript. We also acknowledge Adam Mahe Mohammed, Francis Abban, Harrison Eyison, and Edward Afriyie for supporting recruitment of study participants.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest

AUTHOR CONTRIBUTIONS

LB, AC, RD and AO conceived and designed the study; LB, SH and AA performed the laboratory test and interpreted the results; LB and HS analyzed, interpreted the data and drafted the manuscript; All authors critically revised the manuscript for important intellectual content and gave final approval of the version to be published.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

TABLE S1a Rhesus phenotypes of Ghanaian patients with SCD, Akan blood donors, Ewes blood donors, Ga blood donors and (African American) Blacks

TABLE b**.** Kell, Duffy, Kidd and Ss phenotypes of Ghanaian patients with SCD, Akan blood donors, Ewes blood donors, Ga blood donors and (African American) Blacks.