J. Afr. Ass. Physiol. Sci.9 (2): 113-117, December 2021

Journal of African Association of Physiological Sciences

Official Publication of the African Association of Physiological Sciences
http://www.jaaps.aapsnet.org

Research Article

Erythrocyte antigens as markers and risk factors for myeloid leukaemias in Nigerian subjects

M.O. Ibikunle and O.I. Ajayi

Departments of Medical Laboratory Science and Physiology, University of Benin, Benin City, Nigeria.

Keywords:
erythrocyte antigens, myeloid leukaemias, acute myeloid leukaemia, chronic myeloid leukaemia, case control.

ABSTRACT

Background: Erythrocyte antigens have long been associated with the aetiology and pathogenesis of several disease conditions including various cancers and some human behaviour. This study investigates the association of these antigens with myeloid leukaemias. **Methods:** This is a case-control study on subjects with age range of 6 to 67 years, undergoing management for the disease in our study facility at Lagos State University Teaching Hospital. 24 cases of myeloid leukaemias comprising of 13 chronic myeloid leukaemias (CML) and 11 acute myeloid leukaemias (AML) were investigated with 25 apparently healthy, age and sex - matched subjects as control. Erythrocyte antigens such as A, B, O, RhD, RhC, Rhc, RhE, Rhe, Fya, Fyb, Jka and Jkb were determined on all subjects and controls. The absence of A and B antigens is represented as O. All the antigens were detected with standard serological methods. Statistical analyses were done using Graphpad Prism 8.0.1. **Results:** We recorded positive association of antigens D, e, Jka, O, E and C with the associated risk of development of CML in the order of D>>e>>Jka>>O>>E>>C ($P<0.05$, respectively) while antigens D, e, Jka, Fyb, E, O and A were positively associated with the risk of development of AML in the order D>>e>>Jka>>Fyb>>E>>O>>A ($P<0.05$, respectively). **Conclusion:** The antigens D, e, Jka, O, E, C implicated in this study can serve as risk factors for the development of CML while antigens D, e, Jk, Fyb, E, O, A could be risk factors for the development of AML or can contribute majorly to tumour aggression and therefore can be considered as markers for early diagnosis of the malignancies.

INTRODUCTION

Red blood cell antigens are carbohydrate or protein structures located on the outer surface of the red blood cell membrane and serve important functions as membrane transporters, adhesion molecules, chemokine receptors, enzymatic activities and as receptors for microorganisms' attachment and entering into cells. They consist of antigens which are carbohydrates attached to proteins or lipids, some with a specific portion of protein and carbohydrates while a few are carried on proteins that are adsorbed from the plasma (Lichtman *et al*., 2006). They are inherited characters or traits and therefore are present in an individual throughout life (Nambiar *et al*., 2017).

*Address for correspondence:
Email: ibikunlefemi31@gmail.com

Erythrocyte antigens in form of blood groups have been reported to be closely related to medical conditions or diseases. The ABO blood groups, in particular, have been shown to have a significant effect on haemostasis with major quantitative effect on von Willebrand factor and factor VIII levels in plasma (Zhang *et al*., 2012). Increased association of myocardial infarction, ischemic stroke and venous thromboembolism are reported in blood groups A and AB (Wiggins *et al.*, 2009). Also, a higher risk of cerebral venous thrombosis has been published in non-O groups (Tufano *et al*., 2013). Group AB is associated with increased risk of preeclampsia (Hiltunen *et al*., 2009). Micro-organisms carry structures with a blood group activity. The severity of infection with *Vibrio cholerae* is found in group O (Anstee, 2010). An association exists between non-secretors of ABH antigen and susceptibility to *Candida albicans*, *Neisseria meningitides*, *Streptococcus pneumoniae* and *Haemophilus influenzae* (Lichtman *et al*., 2006). Studies have also suggested the association of ABO

system with malignancies. Blood group A has been positively correlated with chronic hepatitis and pancreatic cancer (Wang *et al.*, 2012), while blood group B is found to be positively associated with ovarian cancer (Gates *et al*., 2011). Blood group A is found to be prevalent among persons with cancer of the salivary glands, stomach, colon or ovary and with thrombosis. Blood group O is found to be more common in patients with duodenal and gastric ulcers, rheumatoid arthritis and von Willebrand disease (Lichtman *et al*., 2006). Associations between disease incidence and ABO blood group in leukaemia have also been documented (Tavasolian *et al*., 2014). Reports of weakened ABH expression on red blood cells (RBCs) have been noted in acute myeloid leukaemia which may result from reduced transferase activities; however, regular antigen expression returns with disease remission (Lichtman *et al*., 2006).

Myeloid leukaemias are group of myeloid malignancies which are clonal diseases of haematopoietic stem cells and progenitor cells. They arise as an effect of genetic mutation or alteration that disturbs normal processes of proliferation, differentiation, and self-renewal (Murati *et al*., 2012). Myeloid leukaemias are subgrouped into acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) based on the degree of cell differentiation. This study was designed to investigate the disease association of some red blood cell antigens with the risk of myeloid leukaemia beyond the ABO blood group system.

METHODS

The study was carried out in the Haematology and Paediatric clinics of Lagos State University Teaching Hospital Ikeja, Nigeria with written approval obtained from the ethics committee of the institution. It was a hospital-based case-control study to assess erythrocyte antigenicity in adult and childhood myeloid malignancies. The study subjects consisted of patients diagnosed with chronic myeloid leukaemia (CML) and acute myeloid leukaemia (AML) with ages between 6 and 67 years, attending clinics in our study facility. A total of 24 cases of myeloid leukaemia were studied comprising 13 chronic myeloid leukaemias (CML), 11 acute myeloid leukaemias (AML) and 25 apparently healthy individuals that served as control. Informed consent was obtained from all the participants before inclusion and the study was carried out within a period of 12 months . Three milliliters of blood were collected from the antecubital vein into plain vacutainer plastic tube with the aid of vacutainer needle and allowed to clot at room temperature. The samples were centrifuged at 500 rpm for 3 minutes after clotting and the serum separated from the cells. Blood group antigens such as A, B, O, RhD, RhC, Rhc, RhE, Rhe, Fya, Fyb, Jka and Jkb were detected using standard antibodies from Lorne Laboratory, UK and Albaclone Bioscience, UK by standard serological method on the washed cells. Statistical analyses were done using Graphpad Prism 8.0.1. The level of statistical significance was determined at 95% confident limit ($P<0.05$).

RESULTS

The percentage distribution of A, B and O antigens obtained in CML were 11%, 22.2% and 66.67% respectively. The distribution of RhD, C, c, E and e antigens were 100%, 55.55%, 100%, 35.33% and 100% respectively. Also the percentages of Fya, Fyb, K, Kpa, Kpb, Jka and Jkb were 0%, 0%, 0%, 0%, 0%, 11.11% and 66.67% respectively. Antigens D (100%) (OR=2.568), e (100%) (OR=1.462), Jka (11.11%) (RR= 3.500), O (66.67%) (RR=2.462), E (33.33%) (RR=2.400) and C (55.55%) (RR=1.016) were positively associated with the development of CML ($P<0.05$, respectively) in the order D>>e>>Jka>>O>>E>>C. All other antigens show no-risk association with CML.

The percentage occurrence of A, B and O antigens obtained for AML were 25%, 25%, and 50% respectively. The percentages for RhD, C, c, E and e antigens were 100%, 37.5%, 100%, 50% and 100% respectively. Also, the percentages obtained for Fya, Fyb, K, Kpa, Kpb, Jka and Jkb were 0%, 12.5%, 0%, 0%, 0%, 25% and 50% respectively. Antigens D (100%) (OR=2.297), e (100%) (OR=1.308), Jka (25%) (RR=4.333), Fyb (12.5%) (RR=3.857), E (50%) (RR=3.667), O (50%) (RR=1.545) and A (25%) (RR=1.000) were positively associated with the development of AML ($P<0.05$, respectively) in the order D>>e>>Jka>>Fyb>>E>>O>>A. All other antigens show no-risk association with AML.

DISCUSSION

In this study, subjects with CML recorded a higher number with blood group O (66.67%), followed by blood group B (22.22%) and group A (11.11%). This study is in agreement with the work of Ino-Ekanem *et al.*, (2018) who reported that O blood group were more common among CML patients in a study carried out in Uyo, Nigeria. However, it is in contrast with the study of Yadav *et al*., (2018) which assessed the distribution of ABO and Rh blood group in myeloproliferative diseases in Varanasi, India. They reported that blood group B (40.14%) was more common in CML followed

Table 1: Association of blood group antigen phenotype with relative risk of CML

CML (n=13) and control (n=25)					
BG	**T (%)**	**C (%)**	**P-value**	**OR**	**RR**
A	1(11.11)	5(25.0)	0.6328	0.375	0.4792
B	2(22.22)	7(35.0)	0.6749	0.5306	0.6349
AB	0(0)	1(5.0)	1.000	0.6842	0.000
O	6(66.67)	7(35.0)	0.2256	3.714	2.462
D	13(100)	18(90)	1.000	2.568	Infinity
C	6(55.55)	11(55.0)	1.000	1.023	1.016
c	13(100)	20(100.0)	AIP	AIP	AIP
E	3(33.33)	2(10.0)	0.2872	4.500	2.400
e	13(100)	19(95)	1.000	1.462	Infinity
Fy^a	0(0)	0(0)	-	-	-
Fy^b	0(0)	0(0)	-	-	-
K	0(0)	0(0)	-	-	-
Kp^a	0(0)	0(0)	-	-	-
Kp^b	0(0)	0(0)	-	-	-
Jk^a	1(11.11)	0(0)	0.3103	7.235	3.500
Jk^b	6(66.67)	15(75.0)	0.6749	0.6667	0.7619

Key: BG = Blood Groups, T = Test, C = Control, *P < 0.05 indicates statistically significant difference, OR = Odds Ratio, OR < 1.00 indicates protection, OR >1.00 indicates risk exposure, OR=1.00 indicates that the antigen is not a risk factor, RR = Relative Risk, D = Rhesus D antigen, C = Rhesus C antigen, c = Rhesus c antigen, E = Rhesus E antigen, e = Rhesus e antigen, Fya = Duffy A antigen, Fyb = Duffy B antigen, K = Kell antigen, Kpa = Penny antigen, Kpb = Rautenberg antigen, Jka = Kidd A antigen, Jkb = Kidd B antigen.

Legend: The closer OR is to 1, the more significant the value and this predetermines the RR which shows the risk value of the occurrence of any antigen to a particular disease, the non-significant RR values indicate a relative no- risk association. The RR value for CML is in the order: D>>e>>Jka>>O>>E>>C.

Table 2: Association of blood group antigen phenotype with relative risk of AML

AML (n=11) and control (n=25)					
BG	**T (%)**	**C (%)**	**P-value**	**OR**	**RR**
A	2(25)	5(25)	1.000	1.000	1.000
B	2(25)	7(35)	1.000	0.619	0.7037
AB	0(0)	1(5)	1.000	0.7647	0.000
O	4(50)	7(35)	0.6715	1.857	1.545
D	11(100)	18(90)	1.000	2.297	Infinity
C	3(37.5)	11(55)	0.6776	0.4909	0.6000
c	11(100)	25(100)	-	-	-
E	4(50)	2(10)	0.0384	9.000	3.667
e	11(100)	19(95)	1.000	1.308	Infinity
Fya	0(0)	0(0)	-	-	-
Fyb	1(12.5)	0(0)	0.2857	8.200	3.857
K	0(0)	0(0)	-	-	-
Kpa	0(0)	0(0)	-	-	-
Kpb	0(0)	0(0)	-	-	-
Jka	2(25)	0(0)	0.0741	15.769	4.333
Jkb	4(50)	15(75)	0.3715	0.3333	0.4737

The RR value for AML is in the order: D>>e>>Jka>>Fyb>>E>>O>>A.

by group A (29.57%) and group O (16.99%) while group AB was the least common (13.38%) in their study group (Yadav *et al*., 2018). However, there was no subject with blood group AB recorded in our study. All the cases of CML in this study were RhD positive, (100%) while 55.3%, 100%, 33.33% and 100% were positive for antigens C, c, E, and e respectively. Majority of the CML patients in the study of Yadav *et al*., (2018) were also Rh-positive though the authors did not specify the Rh antigens detected. The RhD and e, antigens seem to be highly associated with the risk of developing CML as the RR value was highly significant (3.500, P<0.05). This is a novel report as no literature has been linked with such observation either in Nigeria or in the Western countries. The order of relative risk association of antigens with CML is D>>e>>Jka>>O>>E>>C. This indicates that the presence of these antigens in an individual could predispose such to developing CML. The differences in the red blood cell antigen distributions recorded in this work compare with authors from Western countries could be due to variation in factors such as ethnicity and race since red blood cells antigenicity is influenced by these factors (Torun *et al*., 2017; Kar *et al*., 2018).

Blood group O has the highest prevalence (50%) in the study on AML followed by A and B blood group antigens which have equal percentage of occurrence (25% respectively). This is in contrast to the study of Alavi *et al*., (2006) whose report showed that there were more patients with A blood group in a study of the distribution of ABO blood groups in childhood acute leukaemia in Tehran and Shiraz, Iran (Alavi *et al*.,

2006). In addition, in the study by Kar *et al*., (2018) in Turkey, it was found that AML is the most common type of leukaemia and blood group A positive was found to be the most common in AML and in all other types of leukaemia (ALL, CML, and CLL) followed by O and B blood groups (Kar *et al*., 2018). The RhD, c and e antigens have higher occurrences among the Rh antigens investigated in our study. The relative risk (RR) values for developing AML indicated that the D, e and E antigens are highly implicated ($P<0.05$, respectively). Also, in the rare blood group antigen systems, the Jka (Kidd A antigen) and Fyb (Duffy B antigen) were implicated ($P<0.05$, respectively) in the development of AML. The relative risk values for antigens associated with AML followed the order D>>e>>Jka>>Fyb>>E>>O>>A. This is the first time a report of these antigenic associations with AML will be made especially in Nigerians. This also infers those individuals having the presence of these antigens might be susceptible to AML.

CONCLUSION

This study has revealed that there are close associations between various erythrocyte antigens beyond the ABO antigens linked to the risk of developing CML and AML and that these antigens can serve as possible markers for the identification, early detection, and prediction of any of these diseases in a population. Antigens D, e, Jka, O, E and C can be used as possible markers for CML while antigens D, e, Jka, Fyb, E, O and A can be possible diagnostic indices for AML. However, further study of a larger population especially at their molecular levels will help in further elucidation of these associations.

CONFLICT OF INTEREST

Authors declare no conflict of interest related to this work.

AUTHOR CONTRIBUTION

This study was designed, analyzed and interpreted by O.I.A and M.O.I. The laboratory analysis was carried out by M.O.I

REFERENCES

Alavi S, Ashraf H, Rashidi A, Hosseini N, Abouzari M, Naderifar M.(2006). Distribution of ABO blood groups in childhood acute leukaemia. *Pediatr Hematol Oncol* . **23(8**): 611-617

Anstee DJ. (2010). Relationship between blood groups and disease. *Blood*. **115**: 4635-4643.

Gates MA, Wolpin BM, Cramer DW, Hankinson SE, Tworoger SS. (2011). ABO blood group and incidence of epithelial ovarian cancer. *Int J Cancer*. **128**: 482-486.

Hiltunen LM, Laivuori H, Rautanen A, Kaaja R, Kere J, Krusius T, et al. (2009)..Blood group AB and factor V Leiden as risk factors for pre-eclampsia: a population-based nested case-control study. Thromb Res. **124(2):** 167-73

Ino-Ekanem MB, Ekwere TA, Ekanem AM.(2018). The frequency and distribution of ABO Blood groups in patients with haematological cancers in Uyo, Nigeria. A hospital based retrospective study. *International Blood research & Reviews* **8(3):**1-8.

Kar F, Andic N, Kusku-Kiraz Z, Albayrak SO, Aydin B, Capar E, et al. (2018). (Distribution of Blood groups in different types of Leukaemia Patients in Eskisehir, Turkey. *Turk J of Life Sci* **3(1):** 214–217.

Lichtman MA, Kipp TJ, Kaushansky K, Beutler E, Seligsohn U, Prchal J. (2006).William's Haematology. 7th edition. McGraw-Hill 2119 – 2136.

Murati A, Brecqueville M, Devillier R, Mozziconacci M-J, Gelsi-Boyer V, Birnbaum, D. (2012). Myeloid malignancies: mutations, model and management. *BMC Cancer* . **12**: 304.

Nambiar RK, Narayanan G, Prakash NP, Vijayalakshmi K. (2017). Blood group change in acute myeloid leukaemia. *Proc Bayl Univ Med cent.* **30(1):** 74-75.

Tavasolian E, Abdollahi E, Vakili M, Amini A. (2014). Relationship between ABO blood group and acute lymphoblastic leukaemia. *Iran J Ped Hematol oncology* **14(1):** 1-4.

Torun YA, Kaynar L, Karakukcu C, Yay M, Ergul AB, Turanoglu C, et al. (2017). Phenotype frequencies of blood group systems and alloantibodies to red blood cells in blood transfusion recipients in Kayseri (Turkey). *Turgut Ozal Med Cen.t* **24(4):** 434-436

Tufano A, Coppola A, Nardo A, Bonfanti C, Crestani S, Cerbone AM, et al. (2013). Non- O blood group as a risk factor for cerebral vein thrombosis. *Thromb Haemost.* .**110(1**): 197-199.

Wang DS, Chen DL, Ren C, Wang ZQ, Qiu MZ, Luo HY. (2012). ABO blood group, hepatitis B viral infection and risk of pancreatic cancer. *Int J Cancer*; **131**:461-468.

Wiggins KL, Smigth NL, Glazer NL, Rosendaal FR, Heckbert SR, Psaty BM. (2009). ABO genotype and risk of thrombotic events and hemorrhagic stroke. *J Thromb Haemost* . **7**:263-269.

Yadav S, Chandhary J, Kumar N, Kannauje PK, Kumar K, Bhattnagar R, et al. (2018). Distribution of ABO and Rh blood group in myeloproliferative diseases. *Acta Med In.* **5**:39-43.

. Zhang H, Mooney CJ, Reilly MP. (2012). ABO blood groups and Cardiovascular Disease. *Int J Vasc Med* . ID 641917. *http://dx.doi.org/10.1155/2012/641917*

REFERENCES

Alavi S, Ashraf H, Rashidi A, Hosseini N, Abouzari M, Naderifar M.(2006). Distribution of ABO blood groups in childhood acute leukaemia. *Pediatr Hematol Oncol* . **23(8**): 611-617

Anstee DJ. (2010). Relationship between blood groups and disease. *Blood*. **115**: 4635-4643.

Gates MA, Wolpin BM, Cramer DW, Hankinson SE, Tworoger SS. (2011). ABO blood group and incidence of epithelial ovarian cancer. *Int J Cancer*. **128**: 482-486.

Hiltunen LM, Laivuori H, Rautanen A, Kaaja R, Kere J, Krusius T, et al. (2009)..Blood group AB and factor V Leiden as risk factors for pre-eclampsia: a population-based nested case-control study. Thromb Res. **124(2):** 167-73

Ino-Ekanem MB, Ekwere TA, Ekanem AM.(2018). The frequency and distribution of ABO Blood groups in patients with haematological cancers in Uyo, Nigeria. A hospital based retrospective study. *International Blood research & Reviews* **8(3):**1-8.

Kar F, Andic N, Kusku-Kiraz Z, Albayrak SO, Aydin B, Capar E, et al. (2018). (Distribution of Blood groups in different types of Leukaemia Patients in Eskisehir, Turkey. *Turk J of Life Sci* **3(1):** 214–217.

Lichtman MA, Kipp TJ, Kaushansky K, Beutler E, Seligsohn U, Prchal J. (2006).William's Haematology. 7th edition. McGraw-Hill 2119 – 2136.

Murati A, Brecqueville M, Devillier R, Mozziconacci M-J, Gelsi-Boyer V, Birnbaum, D. (2012). Myeloid malignancies: mutations, model and management. *BMC Cancer* . **12**: 304.

Nambiar RK, Narayanan G, Prakash NP, Vijayalakshmi K. (2017). Blood group change in acute myeloid leukaemia. *Proc Bayl Univ Med cent.* **30(1):** 74-75.

Tavasolian E, Abdollahi E, Vakili M, Amini A. (2014). Relationship between ABO blood group and acute lymphoblastic leukaemia. *Iran J Ped Hematol oncology* **14(1):** 1-4.

Torun YA, Kaynar L, Karakukcu C, Yay M, Ergul AB, Turanoglu C, et al. (2017). Phenotype frequencies of blood group systems and alloantibodies to red blood cells in blood transfusion recipients in Kayseri (Turkey). *Turgut Ozal Med Cen.t* **24(4):** 434-436

Tufano A, Coppola A, Nardo A, Bonfanti C, Crestani S, Cerbone AM, et al. (2013). Non- O blood group as a risk factor for cerebral vein thrombosis. *Thromb Haemost.* .**110(1**): 197-199.

Wang DS, Chen DL, Ren C, Wang ZQ, Qiu MZ, Luo HY. (2012). ABO blood group, hepatitis B viral infection and risk of pancreatic cancer. *Int J Cancer*; **131**:461-468.

Wiggins KL, Smigth NL, Glazer NL, Rosendaal FR, Heckbert SR, Psaty BM. (2009). ABO genotype and risk of thrombotic events and hemorrhagic stroke. *J Thromb Haemost* . **7**:263-269.

Yadav S, Chandhary J, Kumar N, Kannauje PK, Kumar K, Bhattnagar R, et al. (2018). Distribution of ABO and Rh blood group in myeloproliferative diseases. *Acta Med In.* **5**:39-43.

. Zhang H, Mooney CJ, Reilly MP. (2012). ABO blood groups and cardiovascular disease. *Int J Vasc Med* . ID 641917. *http://dx.doi.org/10.1155/2012/641917*