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Association of ABO groups in malaria infection of variable severity

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ABSTRACT

Background & objectives: Literature reports several studies on ABO groups and malaria but a study with an adequate sample size and controls is not available. ABO groups are genetically controlled, hence, large sample size and comparison with population frequency is essential. To determine whether malaria infection with variable severity has correlation with ABO groups.

Study design & Methods: Blood samples of non-transfused malaria cases were obtained from pathology laboratories and transfused malaria patients' from Blood Bank. The malaria parasites were identified by examination of thick and thin smears. Control (normal population) included 11,303 students.

Results: The ABO group frequency of normal population was 'O' 32.3%, 'A' 22.2%, 'B' 36.7% and 'AB' 8.8%. The overall ABO group distribution in 8028 malaria cases was 'O' 30%, 'A' 24.6%, 'B' 35.5% and 'AB' 8.9%. 'A' group incidence was significantly higher than normal ('A' *vs* non-'A' $\chi^2 = 15$, df=1, $p < 0.001$). ABO group frequencies were comparable within *Plasmodium falciparum* and *P. vivax* malaria. There was no significant difference in ABO group distribution in malaria patients having severe anemia or among transfused and non-transfused malaria cases. About 32% of *P. falciparum* cerebral malaria cases and 36% DIC cases were of 'A' group. Compared to 22.2% 'A' group in the population, malaria cases showed preponderance of 'A' group. Because of the small numbers statistical evaluation was not done.

Conclusion: 'A' blood group is more susceptible to have malaria infection and risk of cerebral malaria and DIC in malaria is also more in 'A' group individuals.

Key words ABO groups; cerebral malaria; DIC in malaria; malaria; *P. falciparum; P. vivax*; severe anemia

INTRODUCTION

ABO blood group system is genetically controlled and proportions of various ABO groups differ significantly in different populations and ethnic groups[1]. Thus, any national or international study reporting association of ABO groups with a disease must use population frequency of ABO groups as the base for comparison. Cserti and Dzik[2] reviewed 22 publications in the year 2007 that investigated relationship between *P. falciparum* malaria and ABO groups. They did not find a study with adequate sample size and also commented that most of the studies are flawed by the absent or inappropriate control groups. In a recent study by Carvaltho *et al*[3] in Brazilian Amazon region, only 142 control and 98 cases of malaria have been investigated.

A, B, H antigen synthesis involves addition of sugars to paragloboside, N-acetyl galactose amine is specific for 'A', D galactose for 'B' and L fucose for 'H'[1]. 'O' group erythrocytes are less prone to form rosettes with *P. falciparum* parasite-infected RBC because of the reduced cyto-adhesion and rosette formation with parasites[4]. Hence, 'O' group individuals have reduced risk of severe malaria[5–7]. However, 'O' group shows significant association with placental *P. falciparum* malaria infection[8]. Akanbi *et al*[9] have observed that 'A' group has more parasite density than 'B' and 'O'. 'O' group red cells have minimum density. Fry *et al*[10] have tested three African populations for ABO alleles by molecular methods. They observed that haplotypes in 'O' and non-'O' individuals are different and might lead to malaria susceptibility of the population.

Plasmodium falciparum and *P. vivax* malaria infections are endemic in India. Thakur and Verma[11] analyzed 258 malaria cases and reported that ABO groups do not show susceptibility to malaria. We planned a larger study and incorporated ABO group frequency in the population as control to determine the relationship between malaria and ABO groups. We also correlated severe malaria infection, judged by associated severe anemia, transfusion requirement, pregnancy, cerebral malaria and disseminated intravascular coagulation (DIC) with ABO group distribution.

MATERIAL & METHODS

The study was undertaken during the period from January 2006 to April 2011 after getting approval from the Institutional Ethics Committee. The EDTA blood samples were obtained from two sources after getting informed oral consent, (i) Blood samples of non-transfused malaria cases

were collected from the private pathology laboratories; and (ii) Pre-transfusion malaria patients' blood samples received in our blood centre for grouping and cross-matching. All these samples were investigated for confirmation of presence of malaria parasite by blood smear examination using Giemsa stain for thick and Wright's stain for thin smears. The hemoglobin (Hb) concentration was measured on Nihon Kohden fully automatic hematology analyzer and ABO forward and reverse grouping was done by tube technique using commercially available reagents.

To determine ABO group frequency of Surat population, we collected blood of college students attending hemoglobinopathy screening camps, after getting their informed written consent. Students were investigated for Hb and ABO groups. The statistical evaluation of the data was done by mean, standard deviation (SD), χ^2 and paired Student's *t*-test.

RESULTS

Study included 11,303 college students having mean age 17.9±2.7 yr, 4765 of them were females and 6538 males. They represented Surat population, a normal control for ABO group and the distribution is shown in Table 1. We investigated 2653 non-transfused malaria cases having mean age of 30.8±11.8 yr and 1885 of them were males and 768 females. Transfused malaria cases were 5375 having mean age of 22.1±21.3 yr and 1975 cases were males and 2400 females. The ABO group distribution data of 8028 malaria cases revealed that 'A' group patients had significantly increased risk of acquiring malaria compared to normal population (χ^2 = 15, 1 df, p <0.001). The incidence of 'O' group patients was slightly lower than normal but χ^2 test did not reveal significant difference (χ^2 = 1.04, 1df, p = Non significant).

Table 1 Number and percentage distribution of ABO groups in normal population and malaria patients

Series	O	A	B	AB	Total
No. of normal subjects (%)	3647 (32.3)	2515 (22.2)	4150 (36.7)	991 (8.8)	11303 (100)
No. of malaria cases (%)	2490 (30)	1978* (24.6)	2848 (35.5)	712 (8.9)	8028 (100)

Significantly higher incidence by χ^2-test in malaria cases p <0.001. Figures in parentheses indicate percentages.

Table 2 shows that there was no significant difference in the ABO group distribution in *P. falciparum* compared to *P. vivax* malaria by χ^2-test (p >0.1). The 35 cases having *P. falciparum* and *P. vivax* malaria infection showed less incidence in 'O' group and higher incidence in 'A' group patients. But the numbers were too small for statistical evaluation. The category of other cases in which malaria was clinically diagnosed but laboratory test was not done for identification of the parasite species showed increase in 'A' group cases.

The mean Hb concentration was 8.1±3.3 g/dl in *P. falciparum* and 11.1±2.9 g/dl in *P. vivax* cases. Paired *t*-test revealed significantly low Hb concentration in *P. falciparum* compared to *P. vivax* malaria (t=390, two sided significance p <0.001). The mean Hb concentration in different ABO groups ranged from 8 to 8.2 g/dl in *P. falciparum* malaria and 11 to 11.2 g/dl in *P. vivax* malaria patients. The paired *t*-test did not reveal any significant difference in mean Hb values in different ABO groups.

Severe anemia was defined as Hb value of ≤7 g/dl. Table 3 gives incidence of severe anemia in different ABO group individuals infected with *P. falciparum* and *P. vivax* malaria. Though 'B' group showed slightly higher incidence of severe malaria, the χ^2-test did not reveal significant difference compared to other blood groups (χ^2 = 1.5 for 1 df, NS). Table 3 also shows that there was no significant difference in ABO group distribution in transfused and non-transfused *P. falciparum* malaria cases. In *P. vivax* malaria, though slightly increased incidence in 'O' group was found in transfused cases and increase of 'A' group in non-transfused malaria cases statistical evaluation did not show significant difference (χ^2 = 1.5 for 1 df, NS).

Malaria cases received RBC transfusion for severe anemia and platelets for thrombocytopenia. Table 4 shows

Table 2. ABO group distribution with respect to parasite species

Plasmodium species	O	A	B	AB	Total
P. falciparum	1323 (30.6)	1051 (24.3)	1564 (36.1)	391 (9)	4329
P. vivax	694 (31.7)	523 (23.9)	770 (35.2)	202 (9.2)	2189
P. falciparum + *P. vivax*	10 (28.6)	11 (31.4)	11 (31.4)	3 (8.6)	35
Not known*	463 (31.4)	393 (26.6)	503 (34.1)	116 (7.9)	1475

* In not known category malaria was clinically diagnosed, parasite species was not identified; Figures in parentheses indicate percentages.

Table 3. Incidence of severe anemia in different ABO groups in transfused and non-transfused malaria cases

Plasmodium species	ABO Groups							
	O		A		B		AB	
	Total cases	Severe anemia (n %)	Total cases	Severe anemia (n %)	Total cases	Severe anemia n (%)	Total cases	Severe anemia n (%)
P. falciparum								
Transfused	732 (31)	499 (68.2)	569 (24.1)	384 (67.5)	853 (36.1)	604 (70.8)	206 (8.7)	141 (68.4)
Non-transfused	284 (29.1)	3 (1.1)	241 (24.7)	5 (2.1)	359 (36.8)	14 (3.9)	91 (9.3)	4 (4.4)
P vivax								
Transfused	135 (34.1)	85 (63)	83 (21)	49 (59)	144 (36.4)	99 (68.8)	34 (8.6)	20 (58.8)
Non-transfused	519 (31)	11 (2.1)	414 (24.6)	2 (0.5)	592 (35.2)	3 (0.51)	155 (9.2)	0 (0)

Figures in the parentheses indicate percent values; Normal population ABO group frequency: 'O'=32.3%, 'A'= 22.2%, 'B' 36.7%, and 'AB'= 8.8%.

Table 4. ABO group distribution and type of blood component transfused*

Component transfused	O	A	B	AB	Total
RBCs	1338 (30.8)	1082 (25)	1544 (35.6)	370 (8.5)	4334
Platelets	210 (32.7)	155 (24.1)	221 (34.4)	56 (8.7)	642
RBCs & platelets	98 (33.9)	62 (21.5)	103 (35.6)	26 (9)	289
Total	1646 (31.3)	1299+ (24.7)	1868 (35.5)	452 (8.6)	5265
Normal population	3647 (32.3)	2515 (22.2)	4150 (36.7)	991 (8.8)	11303

*110 patients transfused only plasma, were excluded; +Comparison of A and non-A transfused and normal population by χ^2-test revealed significant increase in Group A among transfused patients (χ^2 =11.9 for 1df p <0.001).

the ABO group distribution in these cases and normal population. Comparison of 'A' and non-'A' blood groups in transfused and normal population by χ^2-test revealed significant increase in 'A' group among transfused patients (χ^2 =11.9, 1 df, p <0.001).

Plasmodium falciparum malaria was diagnosed in 51 pregnant women, of which 15 (29.4%) were of 'O' group, 15 (29.4%) 'A', 17 (33.3%) 'B' and 4 (7.8%) 'AB'. Considering the population frequency of 'O' group as 32.3% and 'A' group as 22.2%, 'O' group women had less risk and 'A' group had higher risk of malaria. Because of the small numbers statistical significance was not evaluated.

Cerebral malaria was diagnosed in 49 *P. falciparum* malaria cases. Fourteen (28.6%) patients were of 'O' group, 15 (30.6%) 'A', 16 (32.7%) 'B', and 4 (8.1%) 'AB'. Considering the population frequency of 'A' group as 22.3%, A group cases were more susceptible to have cerebral malaria. There were 25 cases of DIC among *P. falciparum* malaria cases of which two patients had cerebral malaria. Nine (36%) patients were of 'O' group, 9 (36%) 'A', 5 (20%) 'B', and 2 (8%) 'AB'. Considering the population frequency, 'A' group cases were highly susceptible to have DIC (22.2% in normal *vs* 36% in DIC cases). The risk of DIC was also more associated with 'O' group (32.3% in normal *vs* 36% in DIC cases) and less with B group. Because of the small numbers statistical significance was not evaluated in cerebral malaria and DIC cases.

DISCUSSION

Blood groups are hereditary characters, hence, while determining association of susceptibility of disease with a particular blood group, population frequency of that particular antigen must be considered. Several studies undertaken to prove relationship between malaria and ABO groups have investigated small number of samples and appropriate controls are not incorporated in most of these studies[3, 5,7, 11,12]. Cserti and Dzik[2] reviewed literature that investigated relationship between *P. falciparum* malaria and ABO groups but did not find a study with adequate sample size. In our study, 8028 malaria cases and 11,303 normal controls were investigated and overall incidence of 'A' group was significantly higher. Though the incidence of 'B' group appeared to be the highest (35.5%), since 36.7% Surat population is born with 'B' group, this group does not have susceptibility to acquire malaria.

Studies have reported different types of associations

with ABO blood groups in malaria infection. Singh *et al*[12] have reported that 'A', 'B' and 'O' groups are equally susceptible to malaria while 'AB' is less susceptible. However, they found significantly lower frequency of 'A' and 'O' groups in *P. falciparum* malaria. Thakur and Verma[11] did not find correlation with ABO groups and susceptibility to malaria. 'A' group frequency was more in *P. falciparum, P. vivax* and *P. falciparum* + *P. vivax* malaria infections in our study. Akanbi *et al*[9] have observed that 'A' group has more parasite density than 'B' and 'O' groups and 'O' group red cells have minimum density. Similarly, Barragan *et al*[13] have observed that 'A' antigen is the co-receptor for *P. falciparum* rosetting. In our study, 'A' group individuals had higher risk of acquiring malaria. 'O' group erythrocytes have reduced rosetting in *P. falciparum* malaria[7]. In the present study, though incidence of 'O' group was decreased in malaria cases we did not find statistical correlation.

Pathirana *et al*[5] reported that cases of severe anemia are significantly less likely to be in group 'O' and more likely in 'AB'. Fischer and Boone[14] reported that group 'A' malaria patients had lower Hb level and more risk of coma. WHO has defined severe anemia in malaria infection as Hb <7 g/dl if there are symptoms and <5 g/dl when there are no symptoms[15]. We considered Hb <7 g/dl as severe anemia and observed significantly higher incidence of anemia in *P. falciparum* cases compared to *P. vivax*. However, we did not find any correlation of ABO groups in severely anemic malaria cases. Present study also reported high risk of cerebral malaria and DIC in 'A' group malaria patients.

Considering the requirement of transfusion as a parameter of severity, we compared ABO group distribution in transfused and non-transfused malaria cases but there was no statistical association with ABO groups. However, compared to ABO frequencies in normal population RBC and/or platelet transfusion requirement for anemia and thrombocytopenia was more often for 'A' group patients.

Thus, our study provides evidence that 'A' blood group is more susceptible to have malaria infection, and risk of cerebral malaria and DIC is more in 'A' group.

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