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Relationship between ABO blood groups and malaria with clinical outcome in rural area of South India

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ABSTRACT

Background **A number of studies have shown that susceptibility to several infectious diseases is related to the patient's blood group. Although the relationship between blood group and susceptibility to malaria has been studied by several researchers, the results have been contradictory. Since malaria has re-emerged as a major problem in India during the past few years, it would be useful to know whether there is any relationship between blood group and infection.**

Objectives **The study will be undertaken to correlate the blood groups and clinical presentations in malaria patients and to understand the differential host susceptibility in malaria.**

Method **Over a period of 4 years malaria positive samples identified by peripheral smear (thin and thick smears) will be evaluated in this study. Haemoglobin, total leucocyte count, differential leucocyte count and platelet count of each patient done on an automated cell counter will be retrieved from the data. Blood group was determined by forward and reverse method. The demographic details of the patients and clinical details were obtained from case records of the patients. Malarial species and the severity of clinical course were correlated with blood groups**

Results **A total of 205 patients were included in the study, of which 123 cases were positive for plasmodium falciparum and 78 cases were positive for P. vivax infection and 4 patients had mixed infection. The results of blood groups showed 33 -'A' group, 84 -'B' group, 70 -'O' group and 18 were 'AB' group. When the clinical courses between different groups were compared using the following parameters for severe infection- a parasitic load of > 10/1000 RBCs, severe anemia with haemoglobin <6gm%, platelet count of <10,000/mm^3, hepato or splenomegaly or clinical signs of severe malaria such as fever >101° F and the other organ involvement, it was observed that there was no significant relationship between ABO blood group and malaria in our population, this could be due to various demographic reasons.**

Conclusions **The present study indicate that individuals of blood group A and B are more susceptible to malaria infection as compared with individuals of blood group O, however the severity of infection differs due to differential host susceptibility.**

Keywords: *blood groups, host susceptibility, malaria, parasitemia*

INTRODUCTION

The ABO blood groups consist of A, B and H carbohydrate antigens which can regulate protein activities during infection and antibodies against these antigens[1,2]. A number of studies were conducted to investigate the association between ABO blood group system and some disease conditions[3-8]. Some of these studies reported significant associations, suggesting that ABO blood groups have an impact on infection status of the individuals possessing a particular ABO blood group[5-8].

In view of heavy burden placed on human health due to malaria, a good many investigations have been conducted to find out whether or not ABO blood groups antigens are associated with susceptibility, resistance, or severity of malaria. Nonetheless, these studies have reported contradictory results. Some studies reported the absence of significant association between P. falciparum (prevalence, parasitemias or antibody titre) and ABO antigens[4,9-10]. On the other hand, other studies have shown that high frequency of malaria episodes has been observed among blood group 'A' individuals as compared with other blood group individuals. Large numbers of severe malaria cases were also reported among blood group 'A' individuals[11].

Variations in reports on the association of ABO blood groups and disease progression of malaria show the complexity of the interaction between the parasite and host immune responses. In addition studies have shown the impact of other red blood cells (RBC's) polymorphisms including haemoglobin abnormalities such as HbS, HbC, thalassemia and deficiency in erythrocyte complement receptor (CR) or glucose-6-phosphate dehydrogenase deficiency on malaria susceptibility and severity[12,13]. There is a paucity of hospital-based, comparative studies to investigate the relationship between blood group types and severity of malarial infections. This study was undertaken to fill up the lacunae in understanding the relationship between blood group phenotypes and malaria in a hospital environment

MATERIALS AND METHODS

The study was conducted from January 2008 to December 2012 on blood samples from patients who presented with malaria and confirmed as positive in R.L. Jalappa hospital. The diagnosis was based on peripheral smear and malarial card test in a few cases. Blood group was determined by forward and reverse method.

Hematological parameters which included haemoglobin, total leukocyte count, differential leucocyte count and platelet count of each patient were done on automated cell counter. The demographic details of the patients and clinical details were obtained from case records of the patients. Malarial species and the severity of clinical course were correlated with blood groups. The clinical course between the different groups was compared using the following parameters for severe infection[14]:

- parasite load of >10/1000 RBC's
- severe anemia with haemoglobin <6g%
- platelet count of <10,000/mm^3
- hepato or splenomegaly
- clinical signs of severe malaria such as fever >101^0 F
- and other organ involvement

RESULTS

Over a period of 4 years 205 patients turned out to be positive for malaria and all the samples were evaluated by thick and thin smears. The species of malarial parasites were *P. falciparum(Pf)*(123%); *P. vivax(Pv)* (78%) and 4 patients had mixed infection of both *Pv* and *Pf.*

Among 205 patients, 33 were 'A' positive, 84'B' positive, 70 'O' positive and18 'AB' positive (Table 1). Irrespective of the blood group, the number of patients affected by *P. falciparum* was more than *P. vivax*. Among the patients who had mixed infection, 2 had 'A' group and 2 'O' group.

Malaria affected all age groups and the age ranged from 6 months to 82 years (M:F 3:1). The number of adults affected was more (n= 129) than the children (n=76) (Table 2 & 3).Majority of cases were inpatients, 2 were pregnant women with *Pf* infestation, recovered with subsequent therapy. Diagnosis of cerebral malaria was made in two young adults, who died due to complication, irrespective of efficient management.

Table 1 Frequency of ABO blood groups among parasite species

Parasite species	Blood groups				Total
	A	B	O	AB	
Pf	20	56	36	11	123
Pv	11	28	32	7	78
Mixed	02	0	2	0	4
Total	33	84	70	18	**205**

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Table 2 Prevalence of malaria by age among adults

Parasite species	Blood groups				Total
	A	B	O	AB	
Pf	10	35	21	6	72
Pv	7	23	18	6	54
Mixed	1	0	2	0	3
Total	18	58	41	12	**129**

Table 3 Prevalence of malaria by age among children <18 years

Parasite species	Blood groups				Total
	A	B	O	AB	
Pf	10	21	15	5	51
Pv	4	5	14	1	24
Mixed	1	0	0	0	1
Total	15	26	29	6	76

The laboratory investigations are summarized in Table 4

Table 4 Summary of salient laboratory features

Parameters	Parasite species	Blood groups			
		A	B	O	AB
Hb range (%)	*Pf*	3.1-14	2.4-15.2	4.8-15	3-13.5
	Pv	7.7-14.9	6.4-15.9	4.9-14	8.6-15.2
TLC (per mm^3)	*Pf*	3.9-28.6	2.3-25	2.3-20	3.6-33
	Pv	3.7-23	2.8-13	2.9-17.9	3.2-12.8
Platelet count (per mm^3)	*Pf*	0.23-3.8	0.21-3.23	0.1-3.67	0.2-3.38
	Pv	0.28-2.3	0.21-4.2	0.15-3.9	0.67-2.3
DLC Neutrophils (%)	*Pf*	32-80	30-87	34-85	40-82
	Pv	34-76	26-83	27-87	57-86
Lymphocytes (%)	*Pf*	13-66	10-69	15-62	15-55
	Pv	20-64	3-73	13-70	14-40
Eosinophils (%)	*Pf*	0-23	0-8	0-18	0-6
	Pv	2-4	0-47	0-9	**0-4**

When the clinical severity was compared with blood groups, it was observed that non O group comprised of 43 cases, while only 20 cases was seen in O group (Table 5). By applying chi-square test (Table 6), it was observed that O group and non O group did not differ in clinical severity ($p>0.05$)

Table 5 Comparison of O and non-O blood group with clinical severity

Blood group	Severity of Malaria		Total
	Non Severe malaria	Severe malaria	
Non O	92	43	135
O	50	20	70
Total	142	63	**205**

Table 6 Chi- square tests

	Asymp. Sig (2 sided)	Exact sig (2 sided)
Pearson chi-square	0.629	
Continuity correlation	0.746	
Likelihood ratio	0.628	
Fisher's exact		0.749

DISCUSSION

Malaria has been known since antiquity. Much new information has emerged since a relationship between ABO and malaria was first suggested > 40 years ago[15]. However, the correlation of severity of malarial infection to the patient's blood group has been of recent interest in the quest for the answers to the factors influencing clinical course of the disease. The observation by Miller et al[16]. that human erythrocytes lacking the Duffy blood group antigens are refractory to invasion by P. vivax parasites indicate the usefulness of studying the association of blood group with malaria. In the Indian scenario, the literature relating to malaria and the blood groups are sparse and have mixed results. Thakur and verma[17] in their study concluded that ABO blood groups do not show differential susceptibility to malaria. Joshi et al[18] reported no correlation between ABO blood groups and malaria in Delhi. Other studies indicated a possible relationship[19]. The present study was attempted to correlate the blood groups and the clinical presentations in malaria patients.

Among the adults, this study showed different age groups had no significant correlation with incidence of malaria. All age groups and both genders were affected. However, the course of the disease in children was severe than that among adults. In a cross-sectional study, influence of age and other factors that affect clinical outcome of P. falciparum malaria in non-immune patients was evaluated. In their study of 135 patients with Pf malaria, 84 (62%) were <40 years old, and only 5% developed severe malaria, compared with 18% who were >40 years old (odds ratio, 4.29); moreover, all deaths occurred in the latter group. Male subjects did not differ from female subjects with regard to severity of disease[20]. Similarly, in this study the severity did not differ between males and females.

Red blood cells of children with severe malaria-associated anemia (SMA) have acquired deficiencies in the complement regulatory proteins complement receptor 1 (CR1, CD35) and decay accelerating factor (DAF, CD55). Deficiencies in red blood cell CR1 and CD55 in children with SMA were accompanied by a marked decline in immune complex binding capacity and increased C3b deposition in vivo and ex vivo. Importantly, these changes were specific because they were not seen in red blood cells of children with cerebral malaria or their controls. These data suggest that the decline in red blood cell CR1 and Cd55 seen in children with SMA were of physiologic significance and may predispose erythrocytes to complement-mediated damage and phagocytosis in vivo[14].

All patients presented with fever and chills. The initial presentation of fever and chills was present irrespective of the blood groups. However the number of ICU admissions was more in'B'than other groups, and also associated with P. falciparum infection. Among the hospitalized adult patients, 20% had haemoglobin below 6 g/dl including both *P. falciparum* and *P. vivax* infections. Though the predominant population was adults, in the children who were affected, haemoglobin ranged from 4.0-14 g%. The reason for the anemia was because macrophages not only clear infected erythrocytes but also phagocytes destroyed uninfected red blood cells during malarial infections. It has been observed

in a prospective study conducted in Orissa that the clinical features in Indian children differed from those reported in most studies that involved an African population.
Multiple organ dysfunctions emerged as a important presenting feature and a new predictor of death in childhood malaria though anemia causes morbidity with malaria[21]. Anemia was also seen with *P. vivax* infection. 6 months old baby with *P. vivax* had haemoglobin of 5g% was treated in ICU indicating other factors also played a role.

Areas that cannot afford even simple laboratory diagnostic tests often use only a history of fever which is subjective as the indication for malaria. Using Giemsa stained blood smears from children in Malawi, one study showed that unnecessary treatment for malaria was significantly decreased when clinical predictors including temperature, pallor and splenomegaly were used as treatment indicators (sensitivity increased from 21 to 49%)[22].

Platelet count was decreased in 80% of patients. In P. falciparum infection platelet count dropped to <20,000/mm3 irrespective of the blood group. When correlated with parasitic load, it did not show any correlation. It has been noted that the presence of thrombocytopenia in an endemic area should alert malaria infection. Both non-immunological destruction and immune mechanism are implicated in the pathogenesis of thrombocytopenia[14].

- Specific platelet-associated IgG antibodies that bind directly to the malarial antigen in the platelets play a role in the lysis of platelets.
- Elevated M-CSF levels in malaria, by increasing macrophage activity may mediate platelet destruction
- Oxidative stress damage-decreased platelet superoxide-dismutase and glutathione peroxidase activity and high platelet lipid peroxidation.

Clinical severity, rather than incidence or prevalence of detectable parasitemia, is a more relevant outcome to assess ABO group and survival. Studies reporting clinical features such as cerebral malaria carry more weight than those reporting only laboratory markers such as percentparasitemia, because the latter does not always predict survival. Among those with a well-developed humoral immunity, there is little correlation between high circulating parasitemia and severity of illness. P falciparum infection increases the serum levels of IgM and IgG antibodies, and also IgE in individuals living in endemic areas. The association of high antiPFIgE levels with a reduced risk of developing clinical malaria suggests the involvement of IgE in protection[23].

It was reported favourable outcome for group 'O' individuals compared with group 'A' among 489 patients in Zimbabwe with p. falciparum malaria. They studied 209 outpatients and 280 severely ill inpatients. Coma was 3-times more common among group 'A' individuals compared with non-A persons. Because patients with coma are at a higher risk for death, this study supports the hypothesis that groups 'O' individuals may have a survival advantage in severe malaria. However, the sample size was insufficient to observe an effect of 'ABO' group on survival[24].

In one study 100 cases of severe P. falciparum malaria with 100 cases of mild malaria were studied. Severe malaria was defined as either hyperparasitemia with >0.25x1012 infected red blood cells (RBCs) per L or >10% parasitemia; or severe malaria with Hb<5g/L; or clinical signs of severe malaria. Mild malaria cases had minimal laboratory abnormalities and were treated as outpatients. The ratio of group A to group O in patients with severe malaria was 0.50, but was only 0.17 among those with mild malaria (3-fold relative risk). Among all groups A individuals, 71% had severe malaria and only 29% mild malaria (p<0.01). In contrast, among all group O cases, 46% had severe malaria and 54% mild malaria (p<0.21)[25]. Similar reports have been published in literature to show strong association between ABO and disease severity in malaria[14]. However, in our study all ABO phenotypes had similar clinical severity, which correlates with other study[4,9-10].

There is a strong association between rosette formation and ABO blood group, with group A and group B RBCs (A>B) forming rosettes more than group O cells in each of 8 tested strains (p<0.001)[26]. Most recently it was confirmed that group A targets formed the strongest rosettes. In addition it was reported that RBCs of group A enzymatically converted to RBCs, of group O and Bombay RBCs rosetted minimally and to the same degree. Thus,

potential of resetting appears specific (but not exclusive) to A and B antigens[27].

The adherence of parasitized RBCs to other cells is central to the Pathophysiology of severe malaria syndromes including cerebral malaria, respiratory failure, multiorganfailure, and death. Parasitized RBCs adhere to the vasculature through a process termed "sequestration", closely mimicking inflammatory leukocyte attachment. Furthermore, half of infected RBC isolates form occlusive intravascular aggregates, which consist not only of infected RBCs bound to each other "autoagglutinates" but also infected RBCs bound to uninfected RBCs "homotypic RBC rosettes" and/or to platelets "heterotypic RBC rosettes. It impairs blood flow, causing tissue ischemia and cell death.

Malaria is known to have affected many erythrocyte genes, including those concerned with globin synthesis, membrane proteins, and RBCenzymes. Given the importance of RBCs in malaria, an influence on genes encoding the most abundant antigens on the RBC membrane such as blood groups is expected. It is also difficult to dissociate the role played by ABO sugars from the contribution of other glycosylated adhesion molecules.

The present study only employed parasitemia as a laboratory marker to determine the association of ABO blood groups and malaria. The study also did not consider factors like HbS, HbC, CR, iron status of the host which could affect the nature of malarial infestation. Had more laboratory markers or clinical features been used, more information would have been generated on the associations. Nevertheless, the findings indicate that individuals of blood group A, B are more susceptible to malaria as compared with individuals with the blood type O. Further in-depth studies are required to clearly establish the role of ABO blood groups in the malarial infestation.

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