Influence of ABO Blood Group Homozygous and Heterozygous Alpha Thalassemia on the Severity of Falciparum Malaria in India

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ABSTRACT

BACKGROUND

Malaria is a global health burden. About 300 - 500 million people suffer from the disease every year, out of whom, about 1 million succumb.[1] This study was undertaken, as there has been no such study regarding the possible effect of α-thalassemia and ABO blood group in Indian population on falciparum malarial infection.

METHODS

This is an observational study carried on in all malarial patients admitted in the Department of General Medicine, VSS Medical College & Hospital, Burla, between October 2008 - September 2010. Inclusion criteria: (i) Fever with positive asexual forms of *falciparum* malarial parasites [thick smear, thin smear, positive quantitative buffy coat (QBC), ICT test]. (ii) WHO criteria for severe *falciparum* malaria[2]. "Controls": Healthy persons of about same age, sex, ethnicity and locality. Exclusion Criteria: Blood transfusion within 3 months, cases of DM, CKD, hepatitis, SCD, tuberculosis, HIV, chronic liver disease, and COPD.

RESULTS

128 cases of malaria, between 15 - 75 years, both sexes, pregnant / non-pregnant were included in the study. For control, the gene frequencies were $\alpha\alpha$ / $\alpha\alpha$ 29 (45.3 %), α 3.7 / $\alpha\alpha$ 27 (42.2 %) and α3.7 / α3.7 8 (12.5 %). For cases, it was found 33 (51.56 %), 25 (39.1 %) and 6 (9.4 %) respectively. In HPLC, HbA0 values of α3.7 / α3.7 (81.83 $\pm$ 10) were > $\alpha\alpha$ / $\alpha\alpha$ (77.11 $\pm$ 21.6) > α 3.7 / $\alpha\alpha$, (64.8 ± 32.42), HbA2 values of $\alpha\alpha$ / $\alpha\alpha$ (2.1 $\pm$ 1.4) > α 3.7 / $\alpha\alpha$ (1.8 ± 0.8) > α3.7 / α3.7 (1.43 $\pm$ 0.27). In HbF, there were nearly same number of cases in all three variants and were negligible in HbS. Anaemia, jaundice, oliguria were the predominant causes of morbidity in alpha thalassaemic patients with severe *falciparum* malaria. Blood group A patients had significantly higher morbidity than blood group B, AB and O.

CONCLUSIONS

The percentage of anaemia, coma, convulsion and death was significantly less in homozygous alpha thalassemia cases in comparison to normal alpha thalassemia and heterozygous alpha thalassemia. Above features were also found to be significantly less in blood group O patients, and significantly high in blood group A patients, when compared to other blood groups. Prevalence of heterozygous and homozygous α-thalassemia was lower in cases in comparison to controls. MCV was significantly lower in homozygous alpha thalassemia patients in comparison to other genotypes of alpha thalassemia. Anaemia, jaundice, coma, shock, oliguria, being the major co-morbidity conditions, should be detected and treated early.

KEYWORDS

Severe *falciparum* Malaria, ABO Blood Group, Homozygous & Heterozygous, α-Thalassemia

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BACKGROUND

Malaria is a global health burden. Every year, worldwide 300-500 million people experience acute case of malaria, out of which about 1 million succumb.[1] The problem has been widespread by chloroquine and mefloquine resistance in plasmodium and pyrethroid insecticide resistance in the Anopheles insect vector. In India, about 27 % population live in malaria high transmission areas (≥ 1 case per 1000 population) and about 58 per cent in low transmission areas (0 - 1 case per 1000 population)[1]. The most affected states are North-Eastern states, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Andhra Pradesh, Maharashtra, Gujarat, Rajasthan, West Bengal, and Karnataka. (Joshi et al 2008)[3] Within Orissa, the bulk of Malaria cases (70 %) are found in the tribal areas.[4,5] The state contributed about 23.58 % of malaria cases, 23.32 % of malaria deaths and 41.57 % of plasmodium *falciparum* malaria cases to the nation in 2008.

Mutation	Country	Origin	Reference
α –thalassaemia	India	Indian	Chouhan et al. (1970) J. Indian Med. Assoc., 54(8): 364-367.
HbKoya Dora	East Godaveri district, Andhra Pradesh	Tribal	Nayudu et al. (1988)
α -thalassaemia	Assam India	Kachari Population	Hundrieser et al. (1987) Hemoglobin, 11 (5): 517-519
α -thalassaemia	Andhra Pradesh	Tribal	Fodde et al. (1988) Hum. Genet., 80(2):157-60
Genetic heterogeneity and population structure	Vidarbha region, Maharastra	Gond related tribes	Rao et al. (1992) Hum Biol., 64(6): 903-917
α -thalassaemia determinants - 60 %	Central India	Indian	Curuk et al. (1993) Br. J. Haematol., 85 (1): 148- 152
An IVS 1-117 (G→A) acceptor site mutation population in the a -2 globin gene A non-deletional α-2 determinant	Central India	Indian	Tribal Curuk et al. (1993) Br. J Haematol., 85 (1): 148- 152
Mutation in polyadenylation signal of α2 gene (AATAAA - - ® AATA - -)	India	Asian	Hall et al. (1994) Br. J. Haematol. 88 (1):225-227
Triplication of a globin gene	Punjab	Punjabi	Garewall et al. (1994) Br. J. Haematol.,86(2): 372-6.
Deletional a+ thalassaemia	Central India	Baiga tribe	Reddy et al. (1995)' Eur. J. Haematol., 55(2):103-109
α -thalassaemia with Sickle cell disease	Indian Subcontinent	Indian	Mukherjee et al. (1997a) Blood, 89(2): 732.
α- thalassaemia gene (3.7 α& - 4.2 αdeletion)	Orissa, India	Orissa	Kulozik et al. (1998) Blood 71 (2): 467-472
A novel α3.5 deletion removing the alpha 1 globin gene with some of its flanking sequences.	Orissa, India	Orissa	Kulozik et al. (1998) Blood 71 (2): 467-472
Reports of α-Thalassaemia: India (1970-2005), Dastidar and Talukder et al.[6]			

Plasmodium falciparum malaria is a common health problem in Western Orissa, which is endemic region for malaria. Highest numbers of *falciparum* malaria (21 %) cases in India are reported from the state of Orissa with maximum number of death.[7] In a study conducted by Sickle Cell Clinic and Research Center, V.S.S.M.C.H, Burla, Orissa, it was found that, out of 80 patients of Sickle Cell Disease 20 (25 %) were found to have alpha thalassemia. (Patel et al).[8] In our hospital V.S.S. Medical College, Burla, a tertiary care hospital the number of *falciparum* malaria cases admitted per year is more than 600 with about 50 % of them being complicated malaria. It is clear that, genetic factors contribute significantly to the variability in malaria. Identifying such parasites and host factors, including the interactions between them will be critical for understanding the basis for protective immunity and to possibly develop novel therapeutic avenues in this disease.

Author / Country	Alpha Thal. (Homozygous)	Alpha Thal. (Heterozygous)
Allen et al 1997 (Papua New Guinea, Melanesia)	↓ risk severe malaria. No effect on cerebral malaria & death. ↑ Incidence mild malaria.	Non-Significant reduction malaria
Lell B et. al. 1999 (Gambia, Africa)	- No protection	- No protection
Mockenhaupt et al, 1999 (Nigeria)	↓ severity of malarial anaemia	- No protection
Mockenhaupt et al, 2004 (Ghana, Africa)	No protection against severe malaria.	↓ severity of malaria only in children below 5 years of age
William et al, 2005 (Kenya, Africa)	Protective against severe malaria	Protective against severe malaria
Wambua et al 2006 (Kenya Africa)	No protection uncomplicated malaria & asymptomatic parasitaemia. Protective to severe malarial anaemia. No protection cerebral malaria.	
Williams et al, 2005 (Kenya, Africa)	Coinheritance of Alpha Thalassemia & sickle gene – No protection against malaria.	
INDIA	Limited study undertaken	
Interaction of Alpha Thalassemia & Malaria Direct Evidence: Few studies with Conflicting Results		

The genetic component of susceptibility to malaria is complex and multigenic with varieties of genetic polymorphisms reported to influence both pathogenesis and different aspects of host response to malaria.[9] The most common best characterized protective polymorphisms involved are the erythrocyte specific structural proteins and enzymes.[10] These polymorphisms include various thalassaemias and ABO blood group, associated with protection against higher parasitaemia. There are limited studies regarding the possible protective effect of alpha thalassemia & ABO blood group in Indian population of *falciparum* malaria infection, for which we undertook this study.

Objectives

To evaluate prevalence of ABO Blood Group, Homozygous and Heterozygous *α*-thalassemia on the severity of *falciparum* Malaria in India, correlates percentage of different clinical presenting features and detect morbidity and mortality amongst different Thalassemia genotypes in comparison to normal variants.

METHODS

This observational study was carried out in the Department of General Medicine VIMSAR, Burla, Sambalpur, Orissa. The duration of study was from October 2008 to Sept 2010.

Inclusion Criteria

- All patients admitted to Department of General Medicine, V.S.S.MCH, Burla, with fever, positive asexual forms of *P. falciparum* in thick smear, thin smear or positive QBC[11] or I.C.T.[12] test with one or more of the WHO's criteria for severe *falciparum* malaria admitted to the hospital were included as a case.
- Age 15 - 70 years**.**
- Both sexes.

Exclusion Criteria

- Received blood transfusion within 3 months of admission.
- Cases of CKD, DM, chronic liver disease, hepatitis, sickle cell disease, COPD, HIV and tuberculosis. Healthy persons of about same age, sex, ethnicity and locality were taken as controls.

Outcome Measures

The clinical and laboratory parameters at day 0 (on day of admission), day 3 and day 5 were taken into account. Morbidity and mortality were recorded by death during hospitalisations, duration of hospital stay > 7 days, and need for blood transfusion. In confirmed cases of *falciparum* malaria, detailed clinical examination and relevant investigations were done to know whether it is uncomplicated infection or complicated malaria with cerebral, renal, haematological, or respiratory involvement.

Alpha thalassemia was diagnosed in these patients with multiplex PCR [13]. It will be determined whether it is (*αα* / *αα*) or heterozygous (*-α* / *αα*) or homozygous (*-α* / *-α*) alpha thalassaemic forms. The incidence of alpha thalassemia genotypes in the cases and controls were determined respectively, and severity of *falciparum* malaria in the different alpha thalassemia genotypes among cases were recorded and studied further with respect to age, sex, and locality.

ABO blood grouping of all severe malaria cases was taken into account, and the severity of malaria among individual blood groups were compared. All patients with positive asexual forms of *P. falciparum* in thick smear, thin smear or positive QBC or ICT test with one or more of the WHO's criteria for severe *falciparum* malaria admitted to the hospital were included in the study. Each case was evaluated by taking a detailed clinical history (including age, sex, chief complaint, history of past and present illness, family history, personal history, presence of risk factors, treatment history) and performing detailed general and systemic examination (cardiovascular system, respiratory system, central and peripheral nervous system)

On admissions, the investigations included were M.P. (QBC), and M.P. (I.C.T.), thick and thin blood smears, complete blood count, sickling test, (H.P.L.C.),[14] (P.C.R.), plasma glucose, blood urea nitrogen (BUN), serum creatinine, electrolytes, total bilirubin, aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and alkaline phosphatase. Chest X-ray, U.S.G. of abdomen& pelvis, C.T. scan of brain, comment on peripheral blood smear are done, if indicated. The history and clinical findings were recorded on standard hospital forms, before therapy, after 24 - 48 hours and after 5 - 7 days of treatment. Blood cultures were done prior to antimicrobial therapy in patients who remained febrile after more than 5 days of antimalarial drug treatment and were suspected of having an associated bacterial infection.

Statistical Analysis

Statistical analysis done at ($p > 0.9999$), by one-way analysis of variance (ANOVA) test, Tukey-Kramer multiple comparison test. Statistical calculations were done through Epi Info 7 for windows.

RESULTS

Our study included 64 cases of severe *falciparum* malaria and 64 controls taken from the same ethnicity and localities from nine different districts of Orissa and Chhattisgarh. It was found that, cases of < 60 years (92.2 %) were affected more than > 60 years of age. The distribution of severe malarial cases and their controls were more in Sambalpur district (23.43 %) and least in Nayagarh district (1.54 %), Odisha, as evident in Figure 1.

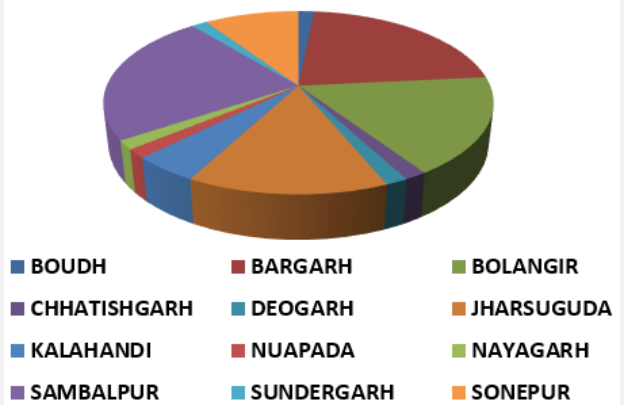

Figure 1. Showing the Distribution of Severe Malaria Cases and Controls from Different Districts of Orissa and Chhattisgarh

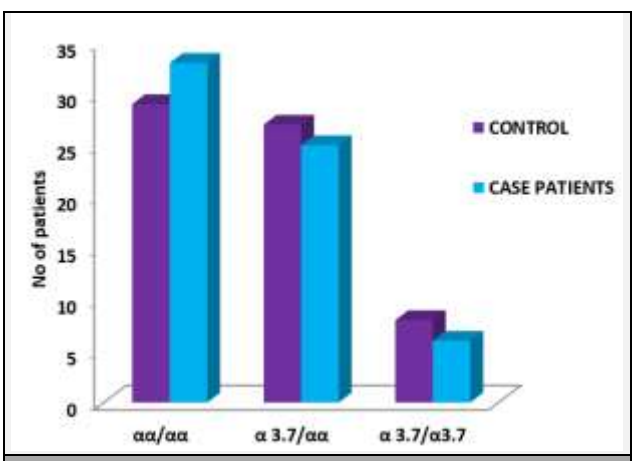

Figure 2. Alpha Thalassemia Frequencies in Case Patients and Controls.

Clinical Features	αα/ αα (33)	α 3.7/ αα (25)	a 3.7/ α3.7 (6)	Total (64)
Anaemia	19 (57.5)	10 (40)	2 (33.3)	31 (48.4)
Jaundice	16 (48.8)	13 (52)	3 (30)	32 (50)
Coma	6 (18.8)	1 (4)	0	7 (10.93)
Shock	11 (33.3)	10 (40)	1 (16.6)	22 (34.3)
Convulsion	5 (15.1)	2 (8)	0	7 (10.93)
Respiratory Distress	4 (12.1)	3 (12)	1 (16.6)	8 (12.5)
Hypoglycaemia	2 (6)	0	0	2 (3)
Bleeding Manifestation	1 (3)	1 (4)	0	2 (3)
Oliguria	32 (96.9)	25 (100)	5 (83)	62 (96.87)
Morbidity (> 7 days)	9 (27.2)	5 (20)	0	14 (21.8)
Mortality	4 (12.1)	0	0	4 (6)

Table 1. Clinical Characteristics of Cases. No. (%)

	αα /αα	α 3.7 / αα	α 3.7 / α3.7
Hb	8.01 ± 1.85	8.11 ± 1.9	9.98 ± 2.5
MCV	81.92 ± 10.6	78.32 ± 12.8	74.2 ± 3.06
PLT	1.86 ± 0.36	1.85 ± 0.41	2.06 ± 0.36
S-Creat	6.46 ± 3.9	5.32 ± 2.4	3.73 ± 0.89
S-BIL	4.07 ± 3.84	3.61 ± 3.4	0.96 ± 0.13
RBS	102.15 ± 24.8	100.8 ± 22.37	87 ± 28.9
MCH	26.99 ± 1.38	25.78 ± 5.3	26.96 ± 1.1
HPLC Values of Cases			
HPLC	*αα* / *αα* (33)	*α* 3.7 / *αα* (25)	*α* 3.7 / *α*3.7 (6)
HbA0	77.11 ± 21.16	64.8 ± 32.42	81.83 ± 10
HbA2	2.1 ± 1.14	1.8 ± 0.8	1.43 ± 0.27
HbF	1.4 ± 0.42	1.4 ± 0.32	1.2 ± 0.41
HbS	0	0	0

Table 2. Laboratory Parameter & HPLC Values of α-Thalassaemic Malaria Cases

Clinical Features	A+	AB+	B+	O+	From Total
Jaundice	81 %	28.50 %	61.10 %	38 %	50 %
Coma	9 %	0 %	27.75 %	4.70 %	10.93 %
Convulsion	9 %	7 %	22.20 %	4.70 %	10.93 %
Shock	54 %	21 %	50 %	19.04 %	34.37 %
Dic	0 %	0 %	11.10 %	0 %	3.12 %
Pallor	54 %	28 %	55.50 %	52.38 %	48.43 %
Hepatomegaly	54 %	28 %	50.00 %	42.85 %	43.45 %
Splenomegaly	63.60 %	28 %	61.10 %	33.30 %	48.33 %
Pulm. oedema / ARDS	9 %	7 %	27.75 %	4.70 %	12.50 %
Oliguria	100 %	92.80 %	94.40 %	100 %	96.87 %

Table 3. Comparative Study of ABO Blood Groups in Relation to Severe Falciparum Malaria

Figure 2 shows the gene frequencies in *αα* / *αα*, *α*3.7 / *αα* and *α*3.7 / *α*3.7 are found to be 29 (45.3 %), 27 (42.2 %) and 8 (12.5 %) respectively. From the above findings it was observed that the prevalence of heterozygous and homozygous *αα*-thalassemia was lower in case patients than in controls. Oliguria, jaundice, anaemia, shock was common clinical characteristics in descending order as evident in Table 1. Morbidity was more than mortality.

The major parameters and HPLC values are given in Table 2. As evident, there is no significant difference found among three genotypes of α-thalassemia in regard to laboratory parameters with the exception of MCV, which is significantly lower in homozygous α-thalassemia. Observation of HPLC values, shows that, there is no significant differences among three genotypes of α-thalassemia. Table 3 shows comparative study of ABO blood groups in relation to severe *falciparum* malaria; reveal that the incidence of severe malaria is significantly less in blood group O patients.

DISCUSSION

In the present study "Influence of ABO blood group, homozygous and heterozygous α-thalassemia on the severity of *falciparum* malaria in India", 64 cases of severe *falciparum* Malaria diagnosed clinically and confirmed by biochemical parameters, admitted to V.S.S. Medical College and Hospital, Burla, Orissa and their 64 controls taken from the same ethnicity and localities were included, more number of cases were found in age < 60 years (93.75 %), and in age > 60 years (6.25 %).

This might be due to the fact that young person's spending more of their time in outdoor activities and are not dressed adequately, exposing them to increasing number of mosquito bites (Park J.E. 1994). The percentage of males (48.4 %) and female (51.56 %) for both controls and cases. The distribution of severe malaria cases and their controls were more in Sambalpur district (23.43 %), Bargarh (21.87 %) and least in Nayagarh District (1.54 %).

For control and cases, the αα / αα variants were 29 (57.3 %) and 33 (51.56 %), the *α* 3.7 / *αα* variants were found to be 27 (42.2 %) and 25 (39.1 %), and the α3.7 / α3.7 variants were found to be 8 (12.5 %) and 6 (9.4 %) respectively. The prevalence observed in both heterozygous and homozygous α-thalassemia were lower in cases in comparison to the controls.

Fever was the most common presentation found in all the severe malaria cases (100 %) (Trumpuz et al, 2003, > 92 % cases of fever).[15] Renal failure, presented with oliguria (< 400 ml of urination / 24 hrs.) was the common complication, which was found in 96 % patients with severe malaria, but in a study by Dash B.S., 2008, (70 %) of cases.[16] About 11 % patients, presented with repeated convulsions and coma.[15] According to (TRAN et al 1996)[17] about 50 % cases, but in a study by (LALLOO et al 1996)[18] only 17 % had cerebral malaria. This might be due to highly selective nature of the study.

Anaemia, a common feature, found in 48 %. Philips et al, 1986[19] (described 10 % are anaemic), Sharma et al 1992[20] reported (86.7 %). Our observation corroborates with their reports. Jaundice, due to heavy parasitaemia and acute haemolysis, is common in adult patients (Warrel and Francis 1991)[21] found 16 % patients with jaundice (total serum Bilirubin > 3 mg %). In our study, we found jaundice in about 50 % malaria patients. DIC (Disseminated Intravascular Coagulation) with bleeding manifestation was found about 3 % of cases. Phillips et al 1986,[19] found < 10 cases that corroborates our study.

Western Odisha, being an endemic region for malaria, many patients were found to have hepatomegaly (43 %) and splenomegaly (48 %) in our study, due to sub clinical malaria infection. Wilson S al[22] detected (29.5 %) cases with hepatosplenomegaly. Death was found in 6 % of cases and all normal alpha thalassaemic patients (αα / αα). No death was found among the heterozygous or homozygous alpha thalassemia cases taken in our study.

From our study, the differences in the clinical features, morbidity and mortality among different α-thalassemia genotypes for anaemia, coma, convulsion and mortality was found to be significant by Tukey-Kramer Multiple Comparison Test at P < 0.009.

The corresponding values are as follows: For Anaemia 19 (57.5 %), 10 (40 %), and 2 (33.3 %), for Coma 6 (18.8 %), 1 (4 %) and 0 %, for Convulsion 5 (15.15), 2 (8 %) and 0 %, for mortality 4 (12.1 %), 0 % and 0 %, in the αα / αα, (normal alpha thalassemia) α3.7 / αα (heterozygous) and α3.7 / α3.7 (homozygous) type of alpha thalassemia patients respectively.

From the different laboratory parameters of the different variants of alpha thalassemia cases, it was observed that, there is no significant difference found among three genotypes of α-thalassemia in regard to laboratory parameters with the exception of MCV, which is significantly lower in Homozygous alpha thalassemia (α3.7 / α3.7) at P < 0.05 by Kruskal-Wallis test. The value of MCV found to be 81.92 ± 3.0678, 32 ± 12.8, and 74.2 ± 3.06 in αα / αα, α3.7 / αα and α3.7 / α3.7 patients respectively.

Observation of high-pressure liquid chromatography findings of the different variants of α-Thalassemia patients, it was noticed that, there is no significant differences among three genotypes of α-thalassemia mentioned above in regards to HPLC values of cases at p > 0.9999 by One Way Analysis of Variance (ANOVA) test.

The comparative study of ABO blood groups in relation to severe *falciparum* malaria revealed that the incidence of severe *falciparum* malaria is significantly less in Blood Group O patient.[23,24] Coma (4 %), convulsion (4 %), shock (19 %) and death (0 %) were significantly less in blood group O patients with severe malaria in comparison to A, B and AB blood groups. In contrast, the incidence of coma (9 %), convulsion (9 %), shock (19 %) and death (16 %) in blood group A was found to be significantly higher in comparison to other blood groups.

So, for final outcome as severity, there is no significant difference between the *αα* / *αα* and *α*3.7 / *αα* at p > 0.05, but there is a significant difference between the *αα* / *αα* and *α* 3.7 / *α*3.7 at p < 0.001, showing the incidence and severity of *falciparum* malaria is significantly lower in homozygous alpha thalassemia patients in comparison to normal alpha thalassemia (*αα* / *αα*) cases. Thomas NW et al, 2005.[25]

There is significant difference between heterozygous alpha thalassemia patients (*α* 3.7 / *αα*) and homozygous deletion type alpha thalassemia patients (*α* 3.7 / *α*3.7) at p < 0.05 by Tukey-Kramer Multiple Comparison Test.

CONCLUSIONS

In the older age group, the incidence of malaria was relatively low (7 %) and there was no significant difference with respect to sex. Cases of severe malaria cases were more in Sambalpur District (23.43 %), Bargarh (21.87 %) and least in Nayagarh (1.54 %) district, Orissa. Prevalence of both heterozygous and homozygous *α*-thalassemia was lower in cases compared to controls. Percentages of anaemia, coma, convulsion and death were significantly less in homozygous alpha & heterozygous alpha thalassemia cases in comparison to normal alpha thalassemia cases with severe malaria. There were no significant differences among three genotypes of *α*-thalassemia with regard to laboratory parameters with the exception of MCV which is lower in homozygous alpha thalassemia patients (*α* 3.7 / *α*3.7) at p < 0.05 by Kruskal-Wallis test. The incidence of severe *falciparum* malaria is significantly less in blood group O patient. The incidence of coma (9 %), convulsion (9 %), shock (19 %) and death (16 %) in blood group A was found to be significantly high in comparison to other blood groups.

Abbreviations

MP - Malaria parasite, QBC - Quantitative Buffy Coat, HPLC - High Pressure Liquid Chromatography, ICT - Immunochromatographic Test, PCR - Polymerase chain reaction, DM - Diabetes Mellitus, CKD - Chronic Kidney Disease, CLD - Chronic Liver Disease, UTI - Urinary Tract Infection, SCD - Sickle Cell Disease, COPD - Chronic Obstructive Pulmonary Disease, TB - Tuberculosis, HIV-Human Immune Deficiency Virus. WHO - World Health Organization, HbF - Fetal Hemoglobin, HbS - Sickle Hemoglobin, DIC - Disseminated Intravascular Coagulation, MCV – Mean Corpuscular Volume, HbA - Normal Hemoglobin, BUN- Blood Urea Nitrogen, SGOT - Serum Glutamic Oxaloacetic Transaminase, SGPT – Serum Glutamic Pyruvate Transaminase.

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REFERENCES

[1] World malaria report 2009. World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. WHO Press 2009.
[2] Sarkar PK, Aluwalia G, Vijayan VK, et al. Critical care aspects of malaria. Journal of Intensive Care Medicine 2009;25(2):93-103.
[3] Joshi H, Prajapati SK, Verma A, et al. Plasmodium Vivax in India. Trends Parasitol 2008;24(5):228-235.
[4] An analysis of health status of Orissa in specific reference to health equity. Feb 24, 2009: p. 20. nrhmodisha.gov.in.
[5] Sharma SK, Pradhan P, Padhi DM. Socio-economic factors associated with malaria in a tribal areas of Orissa, India. Indian J Public Health 2001;45(3):93-98.
[6] Dastidar R, Talukdar G. The molecular basis of *α* thalassaemia in India - a review. Reports of *α* thalassaemia in India (1970-2005), 2006: p. 352.
[7] Malaria in India. Malaria site: National Vector Borne Disease Control. http//nvbdcp.gov.in/malarianew.html.
[8] Dash P, Patel DK, Patel S, et al. Molecular characterization of *α α*/- *α* 3.7 deletion on

haematological and clinical heterogeneity of sickle-Beta0 thalassemia in western Orissa, India. Ind J Haemat Blood Transf 2009;25:140.
[9] Rowe AJ, Opi HD, Williams TN. Blood groups and malaria: fresh insights into pathogenesis and identification of targets for intervention. Curr Opin Haematol 2009;16(6):480-487.
[10] Fowkes FJI, Allen SJ, Allen A, et al. Increased micro erythrocyte count in homozygous alpha (+)-thalassemia contributes to protection against severe malarial anemia. PLoS Med 2008;5(3):e56.
[11] Bhandari PL, Raghuveer CV, Rajeev A, et al. Comparative study of peripheral blood smear, quantitative buffy coat (QBC) and modified cetnrifused blood smear in Malaria diagnosis. Indian J Pathol Microbial 2008;51(1):108-112.
[12] Mishra MN, Mishra RN. Immunochromatographic methods in malaria diagnosis. Med J Armed Forces India 2007;63(2):127-129.
[13] Brown AE, Kain KC, Pipithkul J, et al. Demonstration by the polymerase chain reaction of mixed plasmodium *falciparum* and P. vivax infection undetected by conventional microscopy. Trans R Soc Trop Med Hyg 1992;86(6):609-612.
[14] Head CE, Conroy M, Jarvis M, et al. Some observation on the measurement of haemoglobin A2 and S percentages by high performance liquid Chromatography in the presence and absence of *α* thalassaemia. J Clinical Pathology 2004;57(3):276-280.
[15] Trampuz A, Jereb M, Muzlovic M, et al. Clinical review: severe malaria. Critical Care 2003;7(4):315-323.
[16] Dash BS. Renal failure in Malaria. J Vector Borne Disease 2008;45(2):83-97.
[17] Tran TH, Day NP, Nguyen HP, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe *falciparum* malaria. N Engl J Med 1996;335(2):76-83.
[18] Lalloo DG, Trevett AJ, Paul M, et al. Severe and complicated *falciparum* malaria in Melanesian adults in Papua New Guinea. Am J Trop Med Hyg 1996;55(2):119-124.
[19] Philips RE, Looareesuwan S, Warrell DA, et al. The importance of anemia in cerebral and uncomplicated *falciparum* malaria: role of complications, dyserythropoiesis and iron sequestration. Q J Med 1986;58(227):305-323.
[20] Sharma SK, Das RK, Das BK, et al. Haematological and coagulation profile in acute *falciparum* malaria. J Assoc Physicians India 1992;40(9):581-583.
[21] Warrell DA, Francis N. Malaria. In: McIntyre N, Benhamou JP, Bircher J, et al. eds. Oxford Text Book of Clinical Hepatology. Oxford University Press 1991: p. 701-706.
[22] Wilson S, Jones FM, Mwatha JK, et al. Hepatosplenomegaly associated with chronic malaria exposure: evidence for a pro-inflammatory mechanism exacerbated by schistosomiasis. Parasite Immunol 2009;31(2):64-71.
[23] Pathirana SL, Alles HK, Bandara S, et al. ABO blood group types and protection against severe, plasmodium *falciparum* malaria. Ann Trop Med Parasitol 2005;99(2):119-124.
[24] Cserti CM, Dzik WH. The ABO blood group system and plasmodium *falciparum* malaria. Blood 2007;110(7):2250-2258.
[25] Thomas NW, Sammy W, Sophie U, et al. Both heterozygous and homozygous alpha+ thalassemias protect against severe and fatal plasmodium *falciparum* malaria on the coast of Kenya. Blood 2005;106(1):368-371.