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 αα / αα 29 (45.3 %), α3.7 / αα 27 (42.2 %) and αα / αα 7 (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 / αα 81.83 ± 10 were > αα / αα 77.11 ± 21.6 > α3.7 / αα, (64.8 ± 32.42), HbA2 values of αα / αα 2.1 ± 1.4 > α3.7 / αα (1.8 ± 0.8) > αα / αα 1.43 ± 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. The problem has been widespread by chloroquine and mefloquine resistance in Plasmodium species 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). 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)

Within Orissa, the bulk of Malaria cases (70%) are found in the tribal areas. 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) |
| HbKoya Dora | East Godawari district, Andhra Pradesh | Tribal | Nayudu et al. (1988) |
| α-thalassaemia | Assam India | Kachari Population | Hundrieser et al. (1987) |
| α-thalassaemia | Andhra Pradesh | Tribal | Fodde et al. (1988) |
| Genetic heterogeneity and population structure | Vizianagaram region, Vizianagaram, India | Gond related tribes | Curuk et al. (1993) |
| α-thalassaemia determinants | Central India | Indian | Br. J. Haematol., 85 (1): 148-152 |
| An IVS 1-17 (G→A) acceptor site mutation population in the α-2 globin gene A non-deleterious α-2 determinant | Central India | Indian | Br. J. Haematol., 85 (1): 148-152 |
| Mutation in polyadenylation signal of α2 gene (AATAAA → 8, AATAA → 8) | India | Asian | Hall et al. (1994) |
| Triplication of a globin gene | Punjab | Punjabi | Garewall et al. (1994) |
| Deletional α+ globin gene | Central India | Baiga tribe | Reddy et al. (1995) |
| α-thalassaemia with Sickle cell disease | Indian Subcontinent | Indian | Mukherjee et al. (1997a) |
| α-thalassaemia gene (3.7 αB 4.2 deletion) | Orissa, India | Orissa | Kulozik et al. (1998) |
| A novel α3.5 deletion removing the alpha 1 globin gene with some of its flanking sequences | Orissa, India | Orissa | Kulozik et al. (1998) |

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. 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.).

The genetic component of susceptibility to malaria is complex and multifactorial with various of genetic polymorphisms reported to influence both pathogenesis and different aspects of host response to malaria. These best characterized protective polymorphisms are the erythrocyte specific structural proteins and enzymes. These polymorphisms include various thalassemias and ABO blood group, associated with protection against higher parasitaemia. There are limited studies regarding the possible protective effect of α-thalassaemia & 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\(^1\) or I.C.T.\(^2\) 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 \(^3\). It will be determined whether it is *(αA/αA)* or heterozygous *(αA/αα)* or homozygous *(αα/αα)* alpha thalassemic 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.),\(^4\) (P.C.R.), plasma 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

| Boudh | Bargarh | Bolangir |
|-------|--------|--------|
| Chhatishgarh | Deogarh | Jharsuguda |
| Kalahandi | Nuapada | Nayagarh |
| Sambalpur | Sundergarh | Sonepur |

Figure 2. Alpha Thalassemia Frequencies in Case Patients and Controls.
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 %), Barghar (21.87 %) and least in Nayagarh District (1.54 %).

For control and cases, the αA / αA Variants were 29 (57.3 %) and 33 (51.56 %), the αA / αA variants were found to be 27 (42.2 %) and 25 (39.1 %), and the αA / αA 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). Renal failure, presented with oligaemia (< 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. About 11 % patients, presented with repeated convulsions and coma. According to (TRAN et al 1996) about 50 % cases, but in a study by (LALLOO et al 1996) only 17 % had cerebral malaria. This might be due to highly selective nature of the study.

Anaemia, a common feature, found in 48 %. Phillips et al, 1986 (described 10 % are anaemic), Sharma et al 1992 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) 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, 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 et al detected (29.5 %) cases with hepatosplenomegaly. Death was found in 6 % of cases and all normal alpha thalassaemic patients (αA / αA). No death was found among the heterozygous or homozygous alpha thalassemia cases taken in our study.

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

| Clinical Features | αA / αA | αA / α3.7 | α3.7 / αA3.7 | Total No |
|------------------|---------|-----------|-------------|----------|
| Haemoglobin (Hb) | 80.1 ± 1.85 | 81.11 ± 1.9 | 81.67 ± 1.9 | 81.11 ± 1.9 |
| MCV              | 81.92 ± 10.6 | 78.32 ± 12.8 | 74.2 ± 3.06 | 77.11 ± 21.16 |
| PLT              | 1.86 ± 0.36 | 1.85 ± 0.41 | 2.06 ± 0.36 | 2.06 ± 0.36 |
| S-Creat          | 6.46 ± 3.9 | 5.32 ± 2.4 | 3.73 ± 0.89 | 4.23 ± 0.89 |
| S-Bil            | 4.07 ± 3.84 | 3.61 ± 3.4 | 3.96 ± 0.13 | 3.61 ± 3.4 |
| RBS              | 102.15 ± 24.8 | 100.8 ± 22.37 | 87 ± 28.9 | 91.12 ± 23.4 |
| MCH              | 26.99 ± 1.38 | 25.78 ± 5.3 | 26.96 ± 1.1 | 26.99 ± 1.38 |
| HPLC Values of Cases |       |           |             |          |
| HPLC αA / αA3.7 | α3.7 / αA3.7 | αA3.7 / αA |          |          |
| HbA0             | 77.11 ± 21.16 | 64.8 ± 32.4 | 81.13 ± 10 | 81.13 ± 10 |
| HbA2             | 2.1 ± 1.14 | 1.8 ± 0.8 | 1.43 ± 0.27 | 1.8 ± 0.8 |
| HbF              | 1.4 ± 0.42 | 1.4 ± 0.32 | 1.2 ± 0.41 | 1.4 ± 0.42 |
| HbS              | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 |

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

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

| Clinical Features | αA / αA | αA / α3.7 | α3.7 / αA3.7 | Total No |
|------------------|---------|-----------|-------------|----------|
| Jaundice         | 81 %    | 28.50 %   | 61.10 %     | 50 %     |
| Coma             | 9 %     | 0 %       | 27.25 %     | 47.0 %   |
| Convulsion       | 9 %     | 7 %       | 22.20 %     | 47.0 %   |
| Shock            | 54 %    | 21 %      | 50 %        | 19.04 %  |
| Dic              | 0 %     | 0 %       | 11.10 %     | 3.12 %   |
| Pallor           | 54 %    | 28 %      | 55.50 %     | 42.43 %  |
| Hepatomegaly     | 54 %    | 28 %      | 50.00 %     | 42.45 %  |
| Splenomegaly     | 63.60 % | 28 %      | 61.10 %     | 48.33 %  |
| Pulm. oedema / ARDS | 9 %    | 7 %       | 27.75 %     | 47.0 %   |
| Oliguria         | 100 %   | 92.80 %   | 94.40 %     | 96.87 %  |

Figure 2 shows the gene frequencies in αA / αA, αA3.7 / αA and α3.7 / αA3.7 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 αA-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.
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 %), 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 %), 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 α3.7 / αα at p > 0.05, but there is a significant difference between the αα / αα and α3.7 / α3.7 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 / α3.7) 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 / α3.7) 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 %), 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.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com. Financial or other competing interests: None. Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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