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Study of Severe Malaria Caused by Plasmodium Vivax in Comparison to Plasmodium Falciparum and Mixed Malarial Infections in Children

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Malaria alone is responsible for major proportion of morbidity and mortality in children. Most cases of malaria are due to P.vivax. P.vivax has always been considered benign but recent studies and molecular studies are giving evidences towards increasing virulence and severity of P.vivax. Aim of this study was to observe severe malaria caused by P.vivax in comparison to Falciparum and mixed malarial infections. Other added aim was to observe for concomitant bacterial infections, how it affects clinical outcome and role of antibiotics in such cases of severe malaria. This was a hospital based study conducted in a tertiary care center in Uttar Pradesh. Patients were tested for malaria using Peripheral blood smear and Rapid malaria antigen test. Total of 200 cases of severe malaria were enrolled in study. Patients were categorized as severe malaria on basis of WHO guidelines. Of 200 cases of severe malaria, 130 (65%) had P.vivax infection, 31 (15.5%) had falciparum infection and 39 (19.5%) had mixed infection with both the species. Noteworthy results observed in cases of severe malaria with P.vivax infections were cerebral malaria (29.2%), severe anemia (26.9 %), severe thrombocytopenia (7.6%) and mortality (13%). Almost 15 % of total patients had concomitant bacterial infections that contributed significantly towards morbidity and prolonged hospitalization. From our study we observed that P.vivax cannot more be considered benign and needs quick diagnosis, prompt treatment and should be observed for complications. Antibiotics use should be considered in severe malaria.

Keywords: Bacterial co-infections; Plasmodium vivax; Severe Malaria.

Malaria is a life threatening disease that has been known since ancient times to human kind. Though many rigorous efforts have been taken towards eliminating malaria, it still remains a Global health problem. It is one of major disease having significant impact on human race in terms of morbidity and mortality.[1,2] Malaria is endemic in India and many of South East Asia as well as other countries of world. Recent World Malaria Report states that India alone contributes to 4% of World malaria Cases[3] Worldwide 2.85 billion populations is at risk of getting P.vivax infection.[4]. P.vivax has always been assumed to cause benign tertian malaria. It was in 2013 only when P.vivax case estimates were included by WHO in its World malaria report. World Malaria Report (WMR) 2013 documented 11.9 to 22 million P.vivax cases per year[5].

P.vivax because of its prevalence and increasing severity is now considered as major

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obstacle in malaria elimination[6]. A total of 0.84 million cases and around 194 deaths were attributed to malaria on 2017 in India[7]. In Endemic countries like India malaria is a major factor affecting morbidity and mortality of pediatric age group. There are few studies that show increasing severity of P.vivax in adults. However, such studies dedicated to pediatric age group are very few. There are case reports and small case series reporting severe vivax malaria in children. Therefore, this study was carried out with larger sample size to determine the proportion of disease severity, the spectrum of complications and alterations in laboratory parameters of P.vivax and to compare it with that of P.falciparum and mixed malarial infections .Hence, Aim of our study was to study various complications caused by P.vivax in pediatric age group and to compare it with complications caused by P.falciparum or mixed malarial infections. Another added aim of our study was to look for presence of concomitant bacterial infections in cases of severe malaria and its effect on final outcome of such cases.

MATERIAL AND METHODS

A prospective observational analytical hospital based study was done over Pediatric ward of a Tertiary care hospital situated in Kanpur, India. A total of 200 patients under age of 18 years were enrolled in the study by convenient sampling. Written informed consent was taken from parents. Study was approved by institutional ethical committee. Severe malaria was defined as per WHO guidelines[8].

Inclusion criteria

1. Children in age group of 6month to18 years of age
2. Peripheral smear or rapid malaria antigen test (RMAT) positive for malaria.

Exclusion criteria

Patient presenting with fever and treated empirically like malaria but malarial parasite 'negative on peripheral smear and RMAT.

Diagnosis

The diagnosis and confirmation of species of P.falciparum and P.vivax malaria were established by thin and thick blood smear .Whereas RMAT (Rapid malaria antigen test) were based on detection of specific Plasmodium spp .lactate dehydrogenase and histidine rich protein 2. RMAT or peripheral blood smear positive for both P.vivax and P.falciparum were labeled as mixed malarial infections.

Data Collection and Analysis

Data regarding patient clinical presentation, investigations and outcome were recorded. Prevalence of symptoms, signs, severity criteria, lab parameters and their relation to mortality were studied. Appropriate tests were applied to test statistical significance of results.

RESULTS

As depicted in table 1, in our study out of 200 cases of malaria, 100% were positive by rapid card test which includes 130 cases of P.vivax (65 %), 19.5 % cases of mixed malaria and 15.5% cases of Falciparum while only 22% cases of malaria were positive by both card and PBS which included 16 % cases of P.vivax, 2 % cases of mixed malaria and 4 % cases of P.falciparum. (Table 1)

Further, as shown in table 2, total of 84 patients (42%) had thrombocytopenia of varying degree. Patients were further classified into

Table 1. Distribution of cases as per positivity in rapid card test (RCT) or peripheral blood Smear (n=200).

Type of malaria parasite	Malaria antigen positive by card test No. (%)	Malaria positive by both card and peripheral blood smear NO. (%)
P.vivax (n=130)	130 (65%)	32(16%)
P.falciparum(n=31)	31(15.5%)	4 (2%)
Mixed malaria(n=39)	39(19.5%)	8 (4%)
Total(n=200)	200(100%)	44(22%)

mild (platelet count: 1.5 lakh to 50,000/mm^3), Moderate (platelet counts: 50,000 to 20,000/mm^3) and severe (platelet counts <20,000/mm^3) thrombocytopenia. Moderate thrombocytopenia was most common degree of thrombocytopenia found in all three types of malaria. 7% of malarial cases in our study had severe thrombocytopenia. Severe thrombocytopenia cases were highest in P.vivax (7.7%) followed by mixed malaria (7.6%) and P.falciparum (3.2%). P.vivax had statistically significant (p=0.049 by z proportion test) higher cases of severe thrombocytopenia when compared to falciparum group. As shown in table2 occurrence of moderate anemia (Hb 5- 10 gm/dl) was more common than mild (>10gm/dl but less than normal reference for that age and gender) and severe anemia (<5gm/dl) in all three species groups. Severe anemia was present in 25% of patient and that all three species groups were causing almost similar percentage of severe anemia with no statistically significant difference (p=0.40517 by Z proportion test)

We also made an observation whether all thrombocytopenia or severe thrombocytopenia alone had significant clinical bleeding. In our study as shown by table 3, out of 84 cases of malaria with thrombocytopenia of varying degree clinical bleeding was seen in 40.4 % cases only and 59.5% cases were not associated with bleeding. Thus clinical bleeding in thrombocytopenia was not that frequent as is generally assumed of. However, 71.4% children with severe thrombocytopenia had significant clinical bleeding. Statistical analysis revealed that there was significant

Table 2. Distribution of cases according to degree of thrombocytopenia and anemia

	P.vivax (n=130)	P.falciparum (n=31)	Mixed Malaria (n=39)	Total (n=200)
Mild thrombocytopenia	18(13.8%)	7(22.5%)	5(12.8%)	30(15%)
ModerateThrombocytopenia	23(17.6%)	6(19.5%)	11(28.2%)	40(20%)
Severe thrombocytopenia	10(7.69%)	1(3.2%)	3(7.6%)	14(7%)
Mild anemia	35(26.9%)	6(19.3%)	9(23.1%)	50(25%)
Moderate anemia	60(46.1%)	16(51.6%)	19 (48.7%)	95(47.5%)
Severe anemia	35(26.9%)	9(29%)	11(28.2%)	55(27.5%)

Table 3. Distribution of cases according to clinical bleeding and deranged PT/aPTT in cases of thrombocytopenia

Degree of thrombocytopenia	Bleeding			Gross bleeding with/ without deranged PT/aPTT	
	Total	Mild	Gross	Deranged PT /aPTT	Normal PT/aPTT
Mild(n=30)	6(20%)	3	3	3	0
Moderate(n=40)	18(45%)	4	14	14	0
Severe(n=14)	10(71.4%)	3	7	2	5
Total (n=84)	34(40.4%)	10	24	19	5

Table 4. Distribution of cases according to cerebral malaria in different species of malaria

Type of malaria parasite	Total cases of cerebral malaria	P value
P.vivax (n=130)	38(29.2%)	0.62
P.falciparum (n=31)	8(25.8%)	
Mixed malaria(n=39)	14(35.9%)	
Total (n=200)	60(30%)	

co-relation between gross bleeding and severe thrombocytopenia (p=0.017 by chi square test). With above table we further made an analysis which revealed abnormally high PT / aPTT in all the patient 17/17 (100%) who had gross bleed in mild and moderate thrombocytopenia. Thus, stressing that probably thrombocytopenia alone was not responsible for gross bleeding here. Whereas only 2out of 7 cases (28.6%) in severe thrombocytopenia group with gross bleeding had deranged PT /aPTT , bringing in to yet another observation that gross bleeding in this group was mainly due to very low platelet count (<20 thousand/mm^3) than deranged PT/aPTT.

As shown in table 4, in our study cerebral malaria features were present in 38 cases (29.2%) of P.vivax, 8 cases (25.2%) of P. falciparum and 14 cases (35.9%) of mixed malaria. Though mixed malaria had higher cases of cerebral malaria than P.vivax, this difference was insignificant (p=0.62 by chi-square).

Further, as depicted in table 5, Out of 200 patients enrolled in our study 26 patients (13%) died. On analysis we observed that mixed malaria had highest percentage of mortality (23.1%) followed by P. vivax (13.07%) and this difference was statistically significant (p=0.017).No mortality was seen in P.falciparum.

As seen in table 6, 33cases (16.5%) with severe malaria had bacterial co-infections (Pneumonia, UTI, Positive blood culture). Out of 26 mortalities only 3 had bacterial co-infections while rest 23 cases were without bacterial co-infections. There was no significant assosciation between bacterial co-infection and mortality (p=0.39 by independent t-test). Mean duration of hospital stay in cases of severe malaria with bacterial co-infections was 16.75+/- 3.6 days which was significantly higher in comparison to mean duration of hospital stay in cases of severe malaria not associated with bacterial infection where this duration was 8+/-1.2 days (p=0.00000 by independent t-test).

Table 5. Distribution of cases according to mortality

Type of malaria parasite	No. of mortality (%)	P value
P.vivax(n=130)	17 (13.07%)	0.017
P.falciparum(n=31)	0(0%)	
Mixed malaria(n=39)	9(23.1%)	
Total(n=200)	26(13%)	

DISCUSSION

In our study, out of 200 cases of severe malaria maximum cases were of P.vivax followed by mixed malaria group and P.falciparum. All patients were card positive for malaria of which only 44 were positive by both card and Peripheral blood smear examination (PBS). Hence, RDT was more sensitive than PBS but equally specific in detecting malaria and these results were similar to study by Azikiwe et al[9]. This could be due to higher technical skills which are required for smear examination. Other contributing factor for this difference could be higher rates of disappearance of malarial parasites from peripheral blood even after a single dose of antimalarial. Considering these facts and also the grave outcomes of severe malaria, antimalarial treatment was started as soon as RCT for malaria was positive. Through our study we would like to propose same protocol for starting antimalarial in malaria endemic areas.

In our study percentage of severe malaria cases having thrombocytopenia was 42 %.This percentage was lesser as compared to another Indian study on severe malaria in children done in Bikaner where it was 65.3%[10]. Our study also

Table 6. Distribution of cases according to mortality and mean duration of hospital stay in severe malaria cases with bacterial co-infections

Patient of malaria	No (%)	Mortality No (%)	Mean duration of hospital stay	
			Mean	S.D.
With bacterial infection	33(16.5%)	3(9%)	16.75	3.6
Without bacterial infection	171(85.5%)	23(13.45%)	8	1.2
Total	200(100%)	26(13%)	12.37	6.18
p value		0.39		0.00000

observed that P.vivax was responsible for highest cases of severe thrombocytopenia (7.69%). Though this percentage was lesser in comparison to study by Tanwar GS et al where 15.79 % of P.vivax cases had severe thrombocytopenia[10]. These results were in tune with Indonesian study where P.vivax associated severe thrombocytopenia rate was 8.4%[11]. Thus in our study we observed that thrombocytopenia was present in large number of malaria positive patients and P.vivax had highest cases of thrombocytopenia. Our study stresses the importance of thrombocytopenia in acute febrile patient from malaria endemic area as an indicator of acute malaria.

Another important observation of our study was to observe effect of different species of malaria on hemoglobin level. Anemia was defined as Hb < 11 g/dl[12] and further classified as per WHO guidelines for anemia classification in severe malaria[8]. In our study percentage of P.vivax cases with severe anemia was slightly lesser than P.falciparum and mixed malarial infections but this difference was statistically insignificant. In endemic countries like India where there is intense transmission and relapses are frequent younger children are at more risk to develop clinically significant severe anemia due to P.vivax infection.[13] There have been few studies dedicated to observe impact of P.vivax infection on hemoglobin concentration and spectrum of anemia has been found to range from almost insignificant to very dramatic[14].

However how severe anemia due to P.vivax affects clinical outcome in severe malaria is not very well studied domain. Hereby we would like to propose need of separate dedicated study to observe how severe anemia due to P.vivax affects body response to other infectious and non-infectious diseases and thus affecting survival rate in such scenarios. Its need of hour to study how already existing malnutrition, iron deficiency, co-infection with intestinal helminthes and relapses of P.vivax itself are affecting frequency and degree of anemia due to P.vivax.

We also tried to make an observation whether all thrombocytopenia had clinical bleeding or only those with severe thrombocytopenia had. Percentage of significant clinical bleeding in severe malaria was 15% however in study by Tanwar GS et all it was 21%[10].

Statistical analysis revealed clinical bleeding to be significantly higher in patients with severe thrombocytopenia. Till now, WHO has not included thrombocytopenia in criteria of severe malaria. However, on basis of our study we would like to propose severe thrombocytopenia to be included in severe malaria criteria. On further analysis an important observation was made that significant gross bleeding in mild and moderate thrombocytopenia group was mainly due to associated Disseminated Intravascular Coagulation (deranged PT \ a PTT) as compared to severe thrombocytopenia group where it was mainly due to very low platelet counts(< 20,000/ mm^3) .

Other important observation of our study was comparison of cerebral malaria in different species of malaria. There are scanty studies on P.vivax induced cerebral malaria in children's in India .We observed some alarming results. We observed that 38 cases of P.vivax had cerebral malaria. Our cases of P.vivax cerebral malaria were more than Sudanese study where 11.2 % cases of severe malaria in children with P.vivax had cerebral malaria.[15]. Though mixed malaria had highest cases of cerebral malaria followed by P.vivax, this difference was statistically insignificant.

One of the most important observations of our study was mortality rate in different species of malaria. Results of mortality rate alone are alarming and eye opening that P.vivax can no more be considered benign. Though mixed malaria is having maximum mortality we observed that p.vivax also had major contribution to deaths. .Our study results showing high mortality in mixed malaria was similar to other study by Manaskotepui et al[16]. However, it has been shown in few studies that its P.vivax super infection on already existing P.falciparum that makes mixed malaria more severe than P.falciparum super infection on P.vivax[17] Hence again emphasizing the contribution of P.vivax in severe malaria though indirectly here. Other than increasing virulence of P.vivax recent studies have found association between P.vivax and delayed morbidity and indirect mortality. One such study in Papua, Indonesia found that after 30 days of the initial presentation with malaria risk of death was significantly higher in P.vivax as compared to P.falciparum.[18]

Though malaria recurrence was not observed as a cause of increased morbidity and

mortality in our study, we attempted to look for presence of concomitant bacterial infections (Pneumonia, UTI or sepsis) and its effect on final outcome of severe malaria. In malaria endemic areas like India there is co-circulation of various disease agents. Hence there remains high probability that malaria may be acquired along with other bacterial, viral, fungal, parasitic or other malaria parasite itself (mixed malarial infection). Few studies have shown that severe malaria predisposes to bacterial co-infections[19-23]. Bacterial co-infections (pneumonia, UTI, positive blood culture) were present in 16.5% cases. These results were in tune with studies done on bacterial infections in severe malaria in African countries where prevalence of bacterial co-infection was around 12%.[19,25-27]. Pneumonia was predominant bacterial co-infection in our study affecting in total 20 cases (10%). Studies on respiratory manifestations of severe malaria in pediatric age group are very scanty till now. Therefore we made an attempt to document the same. . Diagnosis of pneumonia was made on basis of clinical findings, radiological findings like infiltrates or consolidation and laboratory parameters like elevated CRP, deviation in white blood cell count and positive blood culture if any. Our study showed that 14 cases (10.7%) of P.vivax presented with pneumonia which was more than 3cases (9.6%) of P.falciparum with pneumonia 3 cases (7.6%) of mixed group with pneumonia but this co-relation was statistically insignificant in both. However, this result was surprisingly a major deviation from other studies till now which showed P.falciparum causing significantly more cases of pneumonia than P.vivax.

Positive blood culture was seen in 5(2.5%) of cases of severe malaria, it included 4 (3.07%) cases of P.vivax, 1 case (3.02%) of P.falciparum. However, none of severe malaria cases due to mixed malaria had bacterial co-infection in our study.

In our study mortality was observed in 10.34% cases of severe malaria associated with bacterial infections as against 13.45% cases not associated with bacterial infection. This difference was not statistically significant. Hence cases associated with bacterial infection were not showing higher mortality. This result is in contrast to other studies where bacterial co-infection has significantly contributed to mortality.[19, 24-27]

However other important observation in our study was that mean duration of hospital stay in cases of severe malaria associated with bacterial infection was 16.75 +-3.6 days which was significantly higher as compared to mean duration of hospital stay in cases of severe malaria not associated with bacterial infections that was 8+-1.2 days. These results are similar to other study showing prolonged hospitalization in cases of malaria with bacterial co-infections[28].

Therefore, bacterial co-infection was contributing significantly towards morbidity and prolonged hospitalisation, thereby causing physical and mental sufferings and loss of productive days of their parents. In view of risk of concomitant bacterial infection in severe malaria WHO and national guidelines have kept low threshold to start antibiotics.[29, 30]

On basis of major observation of our study that showed bacterial co-infection in severe malaria quite significant and almost as high as that of African study[19,24,25,27,31] we would like to advocate use of broad spectrum antibiotics in severe malaria or at least to keep low threshold for same and to be guided by severity of malaria, CRP levels, WBC levels , x-ray findings in decision making even though if blood ,urine, stool cultures are negative.

CONCLUSION

In our study we found P.vivax as underlying cause of mortality and life threatening morbidities in children. Severe vivax malaria is an emerging entity and demands further clinical and molecular research to understand its increasing virulence .We also found that concomitant bacterial infections in severe malaria that contributed significantly towards morbidity and prolonged hospitalisation. Therefore, recommendation on prophylactic use of antibiotics in cases of severe malaria needs to be studied.

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Conflicts of Interest

The authors declare no conflict of interest.

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