Clinical spectrum and outcome of severe malaria in pediatric age group in North-West part of Rajasthan

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Abstract

Background: Malaria is a Life- threatening blood disease caused by parasites and influenced the human population and human history to a great extent. This study aims to describe the clinical spectrum, outcome of severe Malaria and compare the severity of plasmodium species.

Methods: This prospective study was conducted in Department of Pediatrics, PBM and Associated Group of Hospitals, Bikaner from June 2012 to December 2012. Only those patients having severe malaria as per WHO 2010 guidelines were included in this study. The diagnosis was made by peripheral blood examination &/or RDT.

Results: 30.37% (130 patients) were categorized as severe malaria according to WHO guidelines. Maximum cases of severe malaria 53.07% presented in 0-5 year age group. The preponderance of male sex in all species of severe malaria. The major complication encountered in severe malaria was severe anemia (78.5%). Plsmodium falciparum infection was found to be more serious to cause significant mortality as comparison to Plasmodiium vivax infection and mixed infection.

Conclusion: we should further give a second thought before labelling P.vivax as benign infection and should consider the chances of complications seriously in P.vivax because it has greater burden in society.

Keywords: Malaria, Plasmodium falciparum, Plasmodium vivax, Severe, Bikaner

Access this article online
Website: www.innovativepublication.com
DOI: 10.5958/2455-6807.2016.00017.9

Introduction

Malaria has influenced the human population and human history to a great extent. Malaria occurs through most of the tropical regions of the world. P.falciparum is predominant in Africa, New Guinea. P.vivax is more common in Central America and Asian countries. The prevalence of these two species is equal in South America, India & Eastern Asia.[1]

According to the World Malaria Report 2012, there were about 219 million cases of malaria and an estimated 660,000 malaria deaths in 2010.[2] Most deaths occur among children living in Africa where a child dies every minute from malaria. India contributes 77% of the total malaria in south East Asia.[3] About 88%of malaria cases and 97% of deaths due to malaria is reported from north western states.[4] There are major differences in the clinical manifestation of the malaria according to age and endemicity. Children between few months of life to five years are more prone to develop severe malaria. This is evident from fact that 75% of malaria deaths occur in this age group. Children are more susceptible to develop cerebral malaria, severe anemia, low blood sugar [hypoglycaemia], raised lactate level in the blood causing blood to become acidic [acidosis], respiratory distress and multi-organ dysfunction.[5,6.7] Severe malaria has been associated with infection due to P.falciparum. P.Vivax is traditionally known to cause benign tertian malaria, although recent studies from south east Asia had highlighted P.vivax malaria as the major cause of morbidity and mortality in infants and children.[8,9] In parallel to this, Kaushik J.S. and colleagues, in a study from east Delhi demonstrated that clinical feature of sever malaria in children caused by P.vivax were similar to those caused by P.falciparum.[10] There has been a recent surge of cases of cerebral malaria caused by P.vivax, as cited from recent Indian studies.[11,12,13]

Thus, with the above background, it is clear that there is a great difference in the spectrum of epidemiology, clinical, presentation and severity of malaria by P.vivax, P. falciparum and mixed infection in various parts of the world. Also there is evidence of recent increase in P.vivax infection and severity of infection in India and south East Asia. But WHO still considers P.vivax as benign infection and continues focusing its attention towards P.falciparum. So a study is planned to clear the picture and evaluate the risk of severe malaria especially in desert area [BIKANER] which is either due to P.vivax *or* P.falciparum or mixed infection.

Material and Methods

This prospective study was conducted in Department of Pediatrics, PBM and Associated Group of Hospitals, Bikaner from June 2012 to December 2012. Only those patients having severe malaria as per WHO 2010 guidelines were included in this study.[14]

The study was approved by the hospital research ethical committee and a written consent, of patient/relative was taken mandatorily.

The Study criteria includes: pediatric patients of malaria with severe manifestation & evidence of asexual phase of malaria parasite in peripheral blood examination and/or positive RDT. Hospital guidelines required detailed study of peripheral blood film examination for malaria parasite for all the patient present with history of fever. Other causes of concomitant illness were ruled out by relevant & significant laboratory investigations and an Exclusion criterion includes: Refusal by parents/relatives for written consent and presence of evidence of other concurrent illness. The diagnosis was made by peripheral blood examination &/or RDT. After thorough clinical & laboratory examination the categorization of severe malaria was done according to WHO guidelines (2010). Further details of all the patients were collected on a study Performa. All the collected data were tabulated and statically analyzed by using SPSS software.

Results

The prospective study on severe malaria was conducted from June 2012 to Dec. 2012 among the admitted patients in department of Pediatrics, PBM & Associated Group of Hospitals, Bikaner. 428 patients diagnosed with malaria were 72.2% (309) cases were due to P. vivax, 14% (60) due to P. falciparum and 13.8% (59) were due to mixed infection. Out of all 30.37% (130 patients) were categorized as severe malaria according to WHO guidelines, and contributing 68% P.vivax, 16.9% *P.falciparum,* 14.6% mixed infection. So *P.vivax* had more burden than *P.falciparum* & mixed infection. Maximum cases of severe malaria 53.07% presented in 0-5 year age group. The preponderance of male sex in all species of severe malaria. The major complication encountered in severe malaria was severe anemia (78.5%), thrombocytopenia (63.3%), cerebral dysfunction (23.8%), shock (20.8%), abnormal bleeding (16.5%), hepatitis (15.4%), metabolic acidosis (14.6%) and acute renal failure (11.5%). Severe anemia (i.e. Hb<5 gm%) was the most common presentation having a burden of 90.09%) in *P.falciparum*, 75.28%) in *P.vivax* and 78.94% in mixed infection in their species. Multiorgan dysfunction was observed in 80.77%) patients of severe *P.falciparum* malaria & in mixed 78.9% as compared to 73% patients of severe *P.vivax* malaria. Severe *P.vivax* malaria was responsible for 6.74% mortality as comparison to 13.63%) mortality attributed to severe *P.falciparum* malaria in this study. Thus, *P.falciparum* infection was found to be more serious to cause significant mortality as comparison to *P.vivax* infection and mixed infection.

Table 1: Clinical Manifestations according to species in Severe Malaria

Clinical Manifestations	Total severe malaria (n=130)	Severe *P.vivax* Malaria (n=89)	Severe *P.falciparum* Malaria (n=22)	Mixed malaria (n = 19)
Severe anemia (Hb<5gm%)	102 (78.5%)	67 (75.28%)	20 (90.09%)	15 (78.94%)
Thrombocytopenia	83 (63.8%)	52 (58.43%)	17 (77.27%)	14 (73.68%)
Hepatitis (S.bilirubin >3mg o/,,	20 (15.4%)	14 (15.73%)	4 (18.18%)	2 (10.52%)
Cerebral dysfunction (BCS*<2) '	31 (23.8%)	18 (20.22%)	8 (36.36%)	5 (26.31%)
Acute renal failure (S.Creatinine >3 mg	15 (11.5%)	11 (12.36%)	2 (9.09%)	2 (10.52%)
Abnormal bleeding	19 (14.5%)	15 (16.85%)	4 (18.18%)	-
Metabolic Acidosis (pH<7.25)	19 (14.6%)	15 (16.85%)	3 (13.64%)	1 (5.26%)
Shock	27 (20.8%)	18 (20.22%)	7 (31.81%)	2 (10.52%)
Hemoglobinuria	11 (8.4%)	4 (4.49%)	4 (18.18%)	3 (15.79%)
Pulmonary Edema	6 (4.6%)	5 (5.62%)	1 (4.54%)	-

Discussion

Malaria is a protozoal disease. The changing clinical manifestations with multi-organ involvement in *P. falciparum*, emerging trends of complications in *P. vivax* malaria, and burden of malaria in children are other important issues that merit attention and formulation of suitable intervention strategies. Study group comprised of 428 patients of pediatric age having diagnosis of malaria. Total no. of P. vivax patients were 309 (72.2%) while total P. falciparum patients were 60 (14%), besides 59 (13.8%) patients of mixed plasmodia infection. The number of complicated P. falciparum patients were 36.7%(22/60) and severe P.vivax patients were 28.8% (89/309) and mixed (both PV and PF) 32.2%(19/59).

The total number of patients with severe malaria as described by the WHO (2010) was 130 in which *P.vivax* accounted for 89 (68.46%) patients while *P.falciparum* was responsible for 22 (16.9%) patients and mixed infection 19 (14.62%) patients. All of them were confirmed by peripheral blood smear examination and/or OptiMAL test. These observations are similar to the findings by Kaushik JS et al. [10] WHO reported majority (88.8%) of severe malaria cases due to P.vivax associated infection in children from Delhi and adjoining districts of Uttar Pradesh. Out of total 130 severe malaria cases, maximum cases 69(53.07%) belonged to 0-5year age group followed by 43(33.07%) patients in 6-10year age group and 18(13.84%)patients in more than 10 year age group. These data on severe malaria are in line with the observations of Tripathy et al.[15] Achidi et al found that children <5 year carried greater malaria than older.[16] Residents of malaria-endemic areas have long periods of malaria parasitaemia punctuated by episodic clinical attacks that decrease in frequency with age. This pattern has been explained by the acquisition of anti-disease/anti-toxic immunity in early childhood and later anti-parasitic immunity following repeated exposure to malaria. In our study out of total severe malaria, 66%(86) were male children while 34%(44)were female with predominance of male child. Although no cause for difference in sex (predominance of male) has been reported in severe malaria in available in literature but slight male predominance in our study may be due to increased health care seeking attitude of parents towards male child in comparison to female child.

The most common presentations were severe anemia (78.5%), Thrombocytopenia (63.8%), Cerebral dysfunction (23.8), shock (20.8%), abnormal bleeding(16.5%), hepatitis(15.4%)&acute renal failure(11.5%). Out of the total 130 patients of severe malaria, most common severe manifestations were severe anemia78.46%[P.vivax75.28%(67/89) *P.falciparum* 90.09% (20/22); Mixed malaria 78.94% (15/19)], thrombocytopenia 64% [P. vivax 58.43%(52/89); P. falciparum 77.27%(17/22); Mixed malaria 73.68%(14/19)], cerebral dysfunction 23% *[P.vivax* 20.22%(18/89); *P.falciparum* 36.36%(8/22); Mixed malaria 26.31%(5/19), abnormal bleedingl6.5% (P. vivax 19.10%; P. falciparum 18.18%), shock20% (P. vivax 20.22%; P. falciparum 22.5 %; Mixed malaria 10.52%), hepatic dysfunction 15.4% (P. vivax 15.73%; P. falciparum 18.18%; Mixed malaria 10.52%), acute renal failurell.5% (P.vivax 12.36%; P. falciparum 9.09%; Mixed malaria 10.52%), metabolic acidosis 14% (P. vivax 16.85%; P. falciparum 13.64%; Mixed malaria 5.26%), hemoglobinuria 8% (P. vivax 4.49%; P. falciparum 18.18%; Mixed malaria 15.79%), pulmonary edema (P. vivax 5.62%; P. falciparum 4.54%). P. falciparum exhibited severe anemia, multiorgan failure, shock and cerebral malaria predominantly while severe anemia, thrombocytopenia, and hepatic dysfunction were most common severe manifestation in P. vivax malaria. It is evident from these figures that *P.vivax* malaria is also capable of causing various severe complications like *P.falciparum* malaria. These finding were similar to observation of Kocher et.al that P. vivax can cause both sequestration related and non-sequestration related complication of severe malaria including cerebral malaria, renal failure, circulatory collapse, severe anaemia, abnormal bleeding, ARDS, jaundice, all of which are commonly associated with *P. falciparum* infections.[17,18] Severe anemia was found to be a major manifestation of severe malaria in our study. The major burden (52.94%) of severe anemia is borne by the age group of below 5 year. In Southern Papua, Indonesia, Tjitra E et al reported that 70% of severe anemia (Hb < 5g/dl) in children can be attributed to infections with *P. vivax*, a rate almost 3-fold higher than that for *P. falciparum.*[19] In this study out of 67 patients (76.5%) of severe anemia caused by *P.vivax* malaria, the mean hemoglobin level was 4.39 gm% and mean reticulocyte count was 1.3%. In present study, thrombocytopenia was present in 63.8% among (P.vivax 58.43%, 77.27% in *P.falciparum* and mixed 73.68%).The decrease in platelet count is an important clue to the diagnosis of malaria as quoted by patel et al. In the present study 25 cases (48%) of *P.vivax* malaria had platelet count < 50,000/uL and 27(52%) cases had platelet count>50,000 to 150,000. These figures were similar to study conducted by Sheraz Jamal Khan et al[20] Although total 63% (83/130) patients in this study had thrombocytopenia but abnormal bleeding occurred only in 23%(19/83) patients in which platelet count below <50,000 was 41.46%(17/41) had bleeding. Both non-immunological destruction as well as immune mechanisms involving specific platelet-associated IgG antibodies that bind directly to the malarial antigen in the platelets has been recently reported to play a role in the lysis of platelets and the development of thrombocytopenia.[21] Liver abnormalities are a relatively common finding in severe falciparum

malaria, but also reported with severe vivax malaria although transient derangement of liver function is a common feature of childhood malaria. In this study out of total 130 severe malaria 15.4% of *(P.vivax* 15.73%, *P.falciparum* 18.2% and in mixed infection 10.5%) patients had hepatic dysfunction. Many studies reported that malarial hepatitis as a common finding in children during the course of severe infection and the incidence is reported to vary from 8% to as high as 32%. In vivax malaria jaundice was predominantly conjugated type with mean level of conjugated bilirubin of 2.6 mg/dl. These findings suggested that besides hemolysis, cholestasis and hepatocellular injury is an important factor causing malarial hepatitis.[22,23] In this study we observed that the patients with severe malarial hepatitis also had significantly higher liver enzymes level (AST, ALT and SAP). In our study that mean level of AST (SGOT) & SGPT was lower in vivax &higher in *P.falciparum*. In this study we found that multiorgan dysfunction was present in 80% of hepatic dysfunction patients. In recent years many reports with definite evidence of hepatic encephalopathy have been reported from different parts of the world, including India. In our study out of 20 patients of hepatic dysfunction, 4 (20%) patients were in hepatic encephalopathy, three of them in grade II and rest one in grade I.

Out of total severe *P.vivax* malaria, 73.03% (65/89) patients had multiorgan dysfunction while *P.falciparum* had 90% (20/22) patients had multi organ dysfunction. In mixed malaria 78.9%(15/19) had multiorgan involment. Although multiorgan involvement was more common in *P.falciparum* malaria (90%) but P.vivax malaria also caused multi organ involvement in as many as 73% patients. Recently, Kumar et.al described that a general shift in the clinical profile of patients with complicated malaria as multiple organ dysfunction/failure is becoming a common feature.[3] Mostly the deaths were due to delayed diagnosis and comatose conditions were the main determinants of death. Overall mortality was 6.9%(9/130). No death was reported among mixed infection. Thus, *P.vivax* infection was found to be almost equally serious to cause significant mortality in comparison to *P.falciparum* but mortality occurred in mixed infection which is in concordance with the study of Joseph et al.[24] So we can concluded that mixed infection tends to have a more benign course as compared to *P. falciparum* monoinfection. Acute renal failure commonly occurs in P. falciparum malaria although its rare occurrence has been reported in *P. vivax* malaria. Out of total severe malaria 11 % (15/130) had renal failure. S.creatinine was elevated in renal failure varying from 3 to 10 mg/dl in PV&PF cases while in mixed infection S.creatinine was observed below3-5mg/dl was found in 100% patients. Cerebral malaria is most lethal entity of severe malaria causing most of the mortality in malaria. Children are more prone to this severe manifestation than other susceptible groups.[25] We had 23% (31/130) patients of cerebral malaria. In out of total *P.vivax* infection was 20%, *P.falciparumin* 36% and 26% had mixed infection. Although most of cases of cerebral malaria are caused by P. falciparum, but recently *P.vivax* is also reported as an emerging pathogen to cause this severe disease. Various cases of cerebral malaria in children due to this benign pathogen were reported by Nurleila S (2012).[26] Possible suggested pathophysiology of cerebral dysfunction in P. vivax malaria is related to ischemic hypoxia causing detrimental nitricoxide generation through enhancement of cytokine (TNFa) induced - nitric oxide synthetase activity. In this study out of total 14.6%(19/130) patients of metabolic acidosis due to severe malaria among these 16.85%,13.6% and 5.26% in P. vivax, *P.falciparum* and mixed infection respectively. Metabolic acidosis is commonly associated with hypoglycemia, severe anemia, acute renal failure and refractory circulatory failure. Out of total 130 cases 27(20.8%) had shock in which *P.falciparum 22.5%* and P.vivax, mixed were 20.22&10.5% respectively. Shock was observed in maximum number of patients with severe *P.falciparum* infection. In our study 8.4 % (11/130) patients of severe malaria had hemoglobinuria. Our study out of total 6 (4.6%>) case of severe malaria had pulmonary edema in which P.vivax, and *P.falciparum* had 5.6%, 4.54% respectively. Nayak et. al described that pulmonary involvement with 10% patient infected with *P. vivax.*[27] If these clinical presentations are ignored, it may lead to delay in diagnosis and can alter the outcome and prognosis of the disease. Therefore, early may reduce the mortality rate associated with this complication.

Thus, we have observed that severe malaria is not only the paradigm of *P.falciparum* but it can be equally important in P.vivax. The complications which occur in severe malaria are not species specific and *P.vivax* can also cause cerebral malaria, thrmbocytopenia, multiorgan dysfunction and mortality. So we should further give a second thought before labelling *P.vivax* as benign infection and should consider the chances of complications seriously in *P.vivax* because it has greater burden in society.

Conclusion

In the last, we can conclude from the study that the *P.vivax* was responsible for the major burden of malaria in North West Rajasthan(Bikaner) area. The incidence of complications in severe malaria was more in *P.falciparum,* however all the complications were also-reported in *P.vivax* and due to its greater burden, the number of patients suffering from complications was *quite* large as compared to *P.falciparum.* In case of mixed species infection, severity and mortality was *significantly* less when *compared with P.falciparum* monoinfection. As thrombocytopenia was common in severe malaria its presence in endemic area should suspect the diagnosis of malaria.

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How to cite this article: Nagaraj N, Berwal PK, Sharma M. Clinical spectrum and outcome of severe malaria in pediatric age group in North-West Part of Rajasthan. International Journal of Medical Microbiology and Tropical Diseases 2016;2(3):107-111.