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Changing trends in the clinical and hematological profile of *Plasmodium vivax* mono infection

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Abstract

Background: Malaria continues to be a major public health problem in South East Asia. *Plasmodium vivax* is the most widely distributed human malaria parasite with an at-risk population of 2.5 billion persons. With the implementation of molecular diagnosis, it has become evident that *P.vivax* mono infection could also result in multiple organ dysfunction and severe life-threatening disease as seen in *P. falciparum* infection.

Objectives: To study the changing trends in the clinical and hematological presentation of the *Plasmodium vivax* malaria and to sensitize the health care provider about the changing presentation of the *Plasmodium vivax* mono infection and to introduce a high index of suspicion against it's potentially life threatening complications hitherto considered not significantly prevalent, by printing and publishing the data thus obtained and circulating it amongst the health care providers in and around Amritsar.

Methods: This is a single center prospective study including 100 children attending thalassemia day care center and on regular blood transfusion therapy for a minimum of 2 years and whose ferritin level is above 1000 µgm/dl. Detailed history and examination were recorded in the proforma. Blood was drawn for thyroid function tests and most recent ferritin value obtained from patients record was used for analysis.

Results: A total of 55 cases of vivax malaria were included in the study. Severe disease was present in 19(34.5%) cases of malaria. In addition to fever, the most common clinical features at presentation in children were: fatigue in 96.4%(53/55), headache in 54% (30/55), myalgia in 54%(30/55), arthralgia in 43%(24/55), vomiting in 64% (35/55) and nausea in 58%(32/55).Hepatosplenomegaly in 51% (28/55) of patients, splenomegaly in 26% (14/55) and hepatomegaly alone in 3% (2/55), varying degrees of icterus in 20% (11/55) and respiratory distress in 12.7% (7/55). Anemia was present in 89.1% (49/55) and thrombocytopenia (platelet count < 1,50,000/µL) was present in 45.5% (25/55) of the children.

Conclusion: In recent years, the clinical pattern of vivax malaria has changed. Severe vivax malaria is now very common with increasing mortality. Not only the number, but also the type of complication influences the outcome of complicated malaria.

Keywords: *Plasmodium vivax*, Clinical, Haematological,Parameters

Introduction

Malaria is a mosquito-borne infectious disease caused by a eukaryotic protist of the genus Plasmodium[1]. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Once nearly-eradicated, the disease now affects more than 300 million and kills more than 3 million people every year the majority of whom are young children in sub-Saharan Africa and south east Asia[2]. Malaria is commonly associated with poverty, and can indeed be a cause of poverty and a major hindrance to economic development[3]. The dreaded disease is difficult to eradicate and its control is possible only with coordinated efforts of the general public, healthcare personnel and government agencies. With changing clinical profiles, widespread drug resistance and global warming threatening to increase mosquito density and the spread of other mosquito borne infections like Dengue and Chikungunya, time has come for all of us to wake up and take note of the imminent danger.

Five species of the plasmodium parasite can infect humans: the most serious forms of the disease are caused by *Plasmodium falciparum*. Malaria caused by *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* causes milder disease in humans that is not generally fatal. A fifth species, *Plasmodium knowlesi*, is a zoonosis that causes malaria in macaques but can also infect humans[4][5].

It is naturally transmitted by the bite of a female Anopheles mosquito. When a mosquito bites an infected person, a small amount of blood is taken, which contains malaria parasites. These develop within the mosquito, and about one week later, when the mosquito takes its next blood meal, the parasites are injected with the mosquito's saliva into the person being bitten. After a period of between two weeks and several months (occasionally years) spent in the liver, the malaria parasites start to multiply within red blood cells, causing symptoms.

Malaria is a febrile illness characterized by fever and related symptoms. However it is very important to remember that malaria is not a simple disease of fever, chills and rigors. In fact, in a malarious area, it can present with such varied and dramatic manifestations that malaria may have to be considered as a differential diagnosis for many clinical problems!

All the clinical features of malaria are caused by the erythrocytic schizogony in the blood. The growing parasite progressively consumes and degrades intracellular proteins, principally hemoglobin, resulting in formation of the 'malarial pigment' and hemolysis of the infected red cell. This also alters the transport properties of the red cell membrane, and the red cell becomes more spherical and less deformable. The rupture of red blood cells by merozoites releases certain factors and toxins (such as red cell membrane lipid, glycosylphosphatidyl inositol anchor of a parasite membrane protein[5]), which could directly induce the release of cytokines such as TNF and interleukin-1[5] from macrophages, resulting in chills and high grade fever. This occurs once in 48 hours, corresponding to the erythrocytic cycle. In the initial stages of the illness, this classical pattern may not be seen because there could be multiple groups (broods) of the parasite developing at different times, and as the disease progresses, these broods synchronize and the classical pattern of alternate day fever is established. It has been observed that in primary attack of malaria, the symptoms may appear with lesser degree of parasitemia or even with submicroscopic parasitemia[5]. However, in subsequent attacks and relapses, a much higher degree of parasitemia is needed for onset of

symptoms. Further, there may be great individual variations with regard to the degree of parasitemia required to induce the symptoms.

While most of the clinical manifestations of malaria are caused by the malarial infection per se, high grade fever as well as the side effects of anti malarial therapy can also contribute to the clinical manifestations. All these may act in unison, further confusing the picture. In some cases, secondary infections like pneumonia or urinary tract infection can add to the woes. All these facts should always be kept in mind.

Materials and Methods

The study was carried out in the Department of Pediatrics, Government Medical College, Amritsar and Civil Hospital Amritsar. The sample was taken from the patients from in and around Amritsar [(31.63°N 74.87°E with an average elevation of 234 meters (768 ft), (semiarid tropical climate typical of northwestern India with peak incidence of malaria from July to September)]. The sample included all the slide positive *Plasmodium vivax* cases (no. of cases 50 or the cases recorded during the duration of study) visiting the outdoor and Indoor Patient Department, conforming to the inclusion criteria described vide infra. After getting an informed consent, the patient was evaluated as per predesigned clinical and laboratory parameters.

Diagnosis and species was determined by Giemsa stained thick and thin blood smears following WHO recommendations[6]. All the slides declared positive for *P. vivax* was counter verified from the Department of Pathology, Government Medical College Amritsar.

After the diagnosis, clinical evaluation was done according to the previously designed protocol and the information recorded in a predesigned Proforma. The evaluation included body weight, assessment of blood pressure, heart and respiratory rates, axillary's temperature, systemic examination and description of the general condition of the patient and the subsequent clinical course during the period of hospitalization.

Laboratory parameters employed in assessment of the hematological profile of the cases, as and when considered relevant according to the clinical picture were regardless of the fasting period, the level of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), direct and indirect bilirubin, creatinine, blood glucose was assessed. Blood cell profile was examined in all cases. Normal reference values of hematology was based on the Wintrobe´s criteria[7].

Appropriate blood test to rule out typhoid fever, hepatitis B and C, dengue, and other infections was done in suspected patients. Depending upon the clinical manifestations, other specific tests undertaken included urine and blood culture, cerebrospinal fluid (CSF) examination, computed tomography (CT) of the head, ultrasonography of whole abdomen, and other relevant examinations as available in the Government Medical College Amritsar.

The cases enrolled for the study were exclusive *P. vivax* infection, permanent residence in the study area and history of fever during the present episode.

Results

During the period of the study, out of all the patients presenting with fever, 59 children had a positive peripheral blood film for malarial parasite *Plasmodium vivax.* Four children were not included in the study because of evidence of concomitant illness in 2 children (one child was on antiretroviral therapy and 1 child had enteric fever). One child was not included in the study as the parents refused admission as well as consent. One patient of cerebral malaria left against medical advice and hence was excluded. The subsequent analysis was done in 55 children. Out of the total children included, 21 were hospitalized. Fever was the chief presenting complaint in all the patients (100%), with a median duration of 6 (range 2-9) days. In addition to fever, the most common clinical features at presentation in children were: fatigue in 96.4%(53/55), headache in 54% (30/55) , myalgia in 54% (30/55), arthralgia in 43% (24/55), vomiting in 64%(35/55) and nausea in 58%(32/55).

The more common clinical signs amongst these patients included hepatosplenomegaly in 51% (28/55) of patients, splenomegaly in 26% (14/55) and hepatomegaly alone in 3% (2/55), varying degrees of icterus in 20% (11/55) and respiratory distress in 12.7% (7/55).

Severe malaria was defined according to the WHO guidelines for classification of malaria. According to that definition 19 children were diagnosed as having severe malaria. This number constituted 34.5% of the total cases.

Anemia is considered one of the cardinal features of malaria. In the present study out of all the patients put together 89.1% (49/55) had some degree of anemia, with 25.5% (14/55) having mild anemia, 25.5% (14/55) having moderate anemia, 16.4%(9/55) having severe anemia and 21.8% (12/55) having very severe anemia. The classification into mild, moderate, severe and very severe anemia was according to the WHO definitions. The mean hemoglobin concentration was 5.92+/-2.60 in children of severe malaria and 9.55+/-2.36 in children of non severe disease .Type of anemia was normocytic normochromic in 61.8 %(34/55), normocytic hypochromic in 23.6 %(13/55) and microcytic hypochromic in 14.5 %(8/55) children. Statistical analysis showed that very severe anemia (cases with hemoglobin less than 5 gm %) was significantly associated with severe malaria at a p value of 0.000(Table 1/Figure 1) and even severe anemia (all cases with hemoglobin <7 gm%) was also significantly associated with severe malaria at a p value of .006 (Table 2/Figure 2).

Table 1: Cross tabulation of very severe anemia with malaria severity

	Very severe anemia	Non severe anemia	Total
Non severe cases	1	35	36
Severe cases	11	8	19
Total	12	43	55

Figure 1: Very severe anemia vs malaria severity

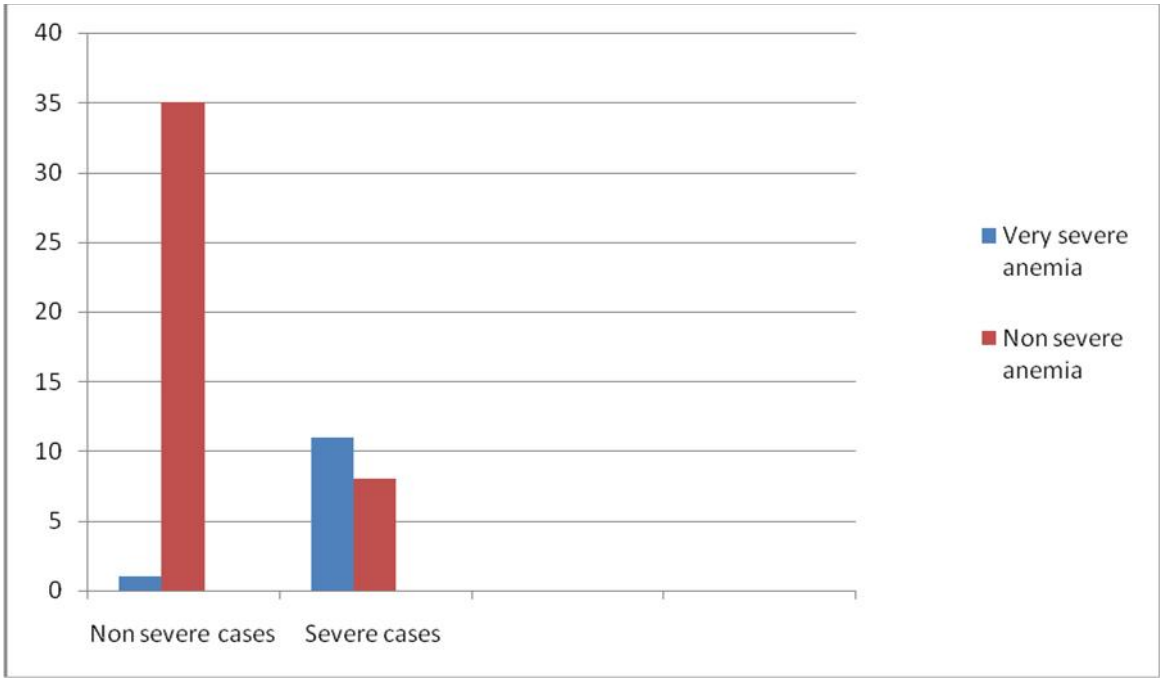
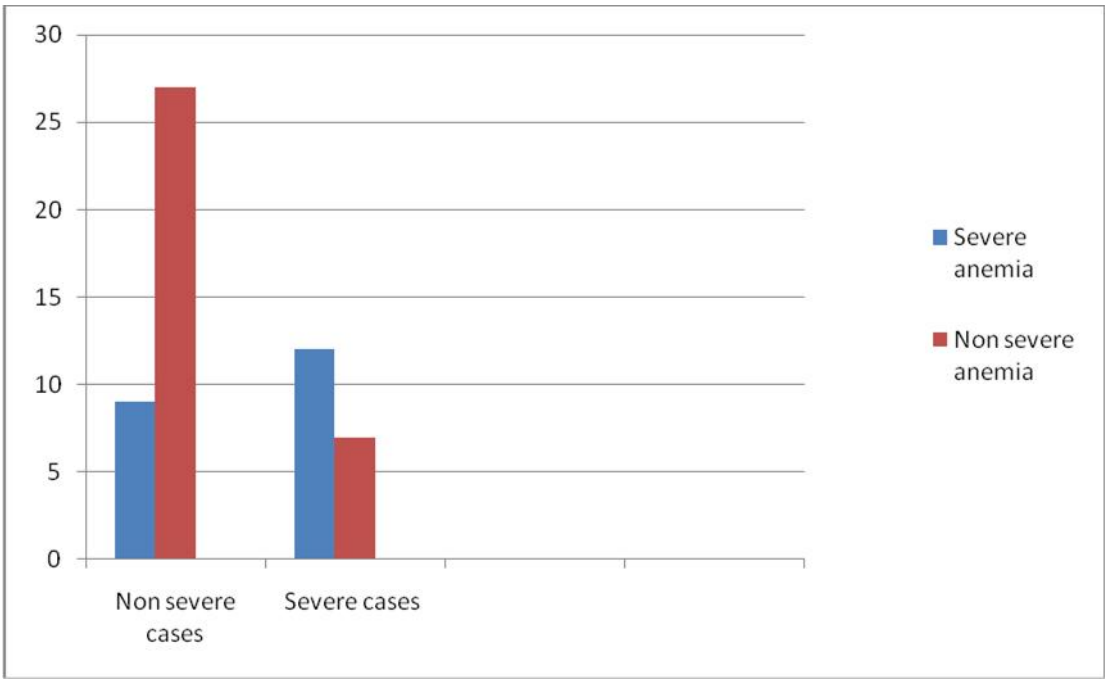


Table 1: cross tabulation of severe anemia with malaria severity

	severe anemia	Non severe anemia	Total
Non severe cases	9	27	36
Severe cases	12	7	19
Total	21	34	55

Figure 2: Severe anemia vs malaria severity

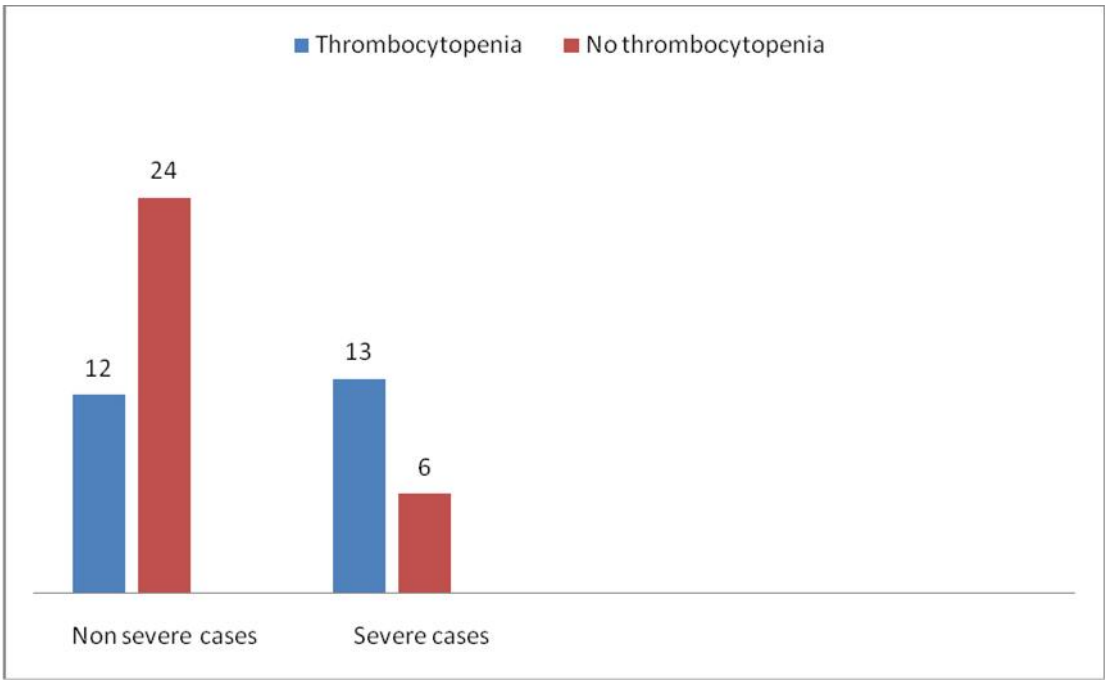


Thrombocytopenia (platelet count < 1,50,000/µL) was present in 45.5% (25/55) of the children. Statistical analysis showed that the association of thrombocytopenia with severity of malaria was significant (p-value for Fisher's two sided test is p=.022) (Table 3/Figure 3).

Table 3: Cross tabulation of severity of malaria with thrombocytopenia

	thrombocytopenia	No Thrombocytopenia	Total
Non severe cases	12	24	36
Severe cases	13	6	19
Total	25	30	55

Figure 3: Severity of malariavs thrombocytopenia



Central Nervous system involvement was present in 12 out of the 55 children (21.8%). The most common form of CNS involvement was as altered sensorium in 83.3% (8/12) of the patients with CNS involvement. Seizures were present in 58.3% (7/12) and motor-sensory weakness of any part of the body in 25% (3/12) of the patients with CNS involvement. Out of the 7 patients with seizures 5 (71% of total) had multiple convulsions with abnormal sensorium in between the seizures and 2 had simple febrile seizures. Out of these 12 children with central nervous system involvement, cerebral malaria (as defined in WHO Guidelines) was diagnosed in 2 children (16%) after ruling out concomitant involvement of the central nervous system by some other disease process. Both children were more than 10 years of age. In both these children cerebral malaria was a part of a Multi Organ Dysfunction Syndrome. Remarkably both survived without any residual neurological deficits. [One 8 year old male child with a definite diagnosis of *P.vivax* cerebral malaria went LAMA later died at a private hospital; had to be excluded from the study].

Hepatic dysfunction was present in 20% (11/55) children having, *P. vivax* infection. Out of the 11 children of hepatic dysfunction in *P. vivax* mono infection mean ± SD level of serum bilirubin was 3.160 ± .848 mg/dL. All children had mild jaundice (3–5 mg/dL). Jaundice was predominantly of the conjugated type (81.4% [9/11]) with mean level of conjugated bilirubin of 2.027 ± 0.808 mg/dL. The mean level of AST was (311.27 ± 173.11 IU/L) and that of ALT (373.45 ± 191.43 IU/L). On clinical examination it was associated with hepatosplenomegaly in 51% (28/55)of patients, splenomegaly in 26% (14/55) and hepatomegaly alone in 3% (2/55).Hence splenic enlargement was absent in 23% of the children. No child had any signs of hepatic encephalopathy. Statistical analysis showed that the association of hepatic involvement with severity of malaria was significant (the p-value for Fisher's two sided test is p=0.035).

Respiratory system involvement in the form of respiratory distress was present in 12.7% (7/55) children. One (2% [1/55]) case had severe respiratory involvement with features suggestive of pulmonary edema with P. vivax malaria presenting with multi organ dysfunction as anemia (Hb 3.1 gm %), thrombocytopenia (platelet 52,000/µL), cyanosis with respiratory distress and shock. The child was managed according to WHO guidelines but expired after 2 days of admission.

Abdominal involvement was present in 76.4% (42/55) of the patients. The most common form of abdominal involvement was vomiting in 63% (35/55) which was associated with nausea in 91% of the cases (32/55), followed by abdominal pain/discomfort in 22% (12/55) and diarrhea in 5.5% (3/55) .Statistical analysis showed that there was no significant association between abdominal involvement and severe malaria (resulting p-value for Fisher's two sided test is p=0.336).

Renal involvement as a part of the disease was present in 12.7% (7/55) of the children .71% (5/7) children had oliguria alone and 29% (2/5) children had co existent edema (without any evidence of malnutrition or cardiovascular involvement).Statistical analysis showed that the association of renal involvement with severity of malaria was significant (the p-value for Fisher's two sided test is p=0.041).

Hypoglycemia was present in 5.4% (3/55) of the children. One of the children presented with altered sensorium which relieved after glycemic correction. The other 2 children had hypoglycemia as an associated symptom with cerebral malaria and multi organ dysfunction.

Discussion

The aim of the present study from Amritsar (northern part of India) was to describe the prevalent clinical spectrum of *Plasmodium vivax* infection in light of the reports of severe and complicated vivax infection from different parts of the world (especially from India) and to document evidence of *P. vivax* as an emerging causative agent for severe malaria, earlier associated with *Plasmodium falciparum* only. This prospective study included 55 patients out of which severe malaria (as defined by WHO Guidelines) was present in 19. This number constituted 34.5 percent of the total cases.

The present study showed a large number of cases of severe malaria caused by *P. vivax* among children residing in Amritsar and neighboring districts of Punjab during the study period. Clinical features of severe malaria caused by *P. vivax* were similar to those caused by *P. falciparum*, which included altered sensorium, severe anemia, and thrombocytopenia. These data on severe vivax malaria are in line with those reported from Papua New Guinea and Indonesia. [8,9].Features of severe vivax malaria in our study were cerebral malaria, severe anemia, thrombocytopenia, bleeding tendencies, hepatic dysfunction, acute renal failure and respiratory failure. Out of the total children (n=55) , the largest number of children affected were in the age group of 6-10 years(40%) , followed by children in the age group of 0-5 years and then children older than 10 years of age. A similar age distribution was found in the severe cases where 36.8% of the cases were in the age group 6-10 years. But the proportion and predilection of infected children developing features of severe malaria was greatest in the age group 0-5 years. This showed that children less than 5 years were at greatest risk of developing severe disease with *P.vivax* infection. Similar distribution observations were made in studies from Papua New Guinea[10] and Rajasthan ,India [11]. Anemia in malaria is due to the destruction of infected erythrocytes and to bone marrow suppression .Anemia is one of the most important signs in malaria and our study confirms what is already known. Severe anemia was the major manifestation of severe malaria in our study.The percentage of children with severe anemia was highest in children less than 5 years of age. This predilection has been reported in numerous studies worldwide and recently in studies from Indonesia[12] and India [11].The type of anemia in *P. vivax* mono infection was predominantly normocytic normochromic type and this observation was also similar to the earlier reports[11]. The proportion of male children involved is more than females in all ages, although the percentage of female children having anemia increases with increasing age. The reasons for this distribution are not clear, though different disease modifying factors like overall resistance to infections in females, socioeconomic factors and onset of menstruation resulting in an increase in prevalence of anemia with increasing age in female age groups can be postulated. We observed thrombocytopenia in 45.5% of the *P.vivax* malarial children, a significantly high proportion, although similar pediatric cases

have been reported earlier [11,13,14]. Profound thrombocytopenia is uncommon in malaria due to *P. vivax*, although it is well-documented in *P. falciparum*-associated malaria. In a study from India, it has been found that platelet count < 20,000/cumm was noted in only 1.5% cases of vivax malaria as against 8.5% cases of falciparum malaria, and none of the subjects with vivax malaria had a platelet count less than 5000/cumm[15]. Similar findings have been found in our patients with only two children having a platelet count below 20,000/cumm .Seventy one percent of the children with thrombocytopenia had a mild thrombocytopenia. The bleeding manifestations were present only in 9% patients and these findings are also consistent with earlier studies[11,13,16].

CNS involvement was present in 12 out of the 55 children (21.8%) excluding 2 children with a typical febrile seizure, rest 10 children had altered sensorium as a part of the presenting complaints. Though malaria with altered sensorium, weakness and seizures was present in a significant proportion of these 10 children, only 2 cases could be assigned a definite diagnosis of cerebral malaria as per the WHO definition of cerebral malaria[17]. This number is 3.6% of the total children, and 10.5% of the children with severe malaria. This is comparable to 13.85% in the study from Bikaner [11] but way less than 50% as reported from Delhi [18].There was no death with cerebral malaria in our study. Similar results have been seen in other studies in which all the patients recovered completely without any neurological sequelae[11,18].

In our study, respiratory system involvement in the form of respiratory distress was present in 12.7% (7/55) children. Among severe disease patients 26.3% had respiratory distress which was commonly associated with severe anemia, acute renal failure, hypoglycemia and shock. All these children had multi organ dysfunction. One child having features of severe ARDS expired while the rest recovered .Similar estimates of mortality and morbidity have also been reported in various other studies. [19,20] Hence P.*vivax* mono infection is also associated with acute respiratory distress syndrome (ARDS)/ non cardiogenic pulmonary edema, a disease process previously thought to occur only in malaria caused by *P. falciparum.*

In our study hepatic dysfunction was present in 20% (11/55) children having, *P. vivax* infection. In the 19 children diagnosed with severe malaria, 36.8% (7/19) had hepatic involvement in the form of jaundice. The hyperbilirubinemia was of predominantly conjugated type (81.4%) and liver enzymes were raised, indicative of "malarial hepatitis". The pattern of biochemical observations in this study is similar to observations in other recent studies [11].These findings suggest that besides hemolysis, cholestasis and hepatocellular injury are important factors for causing jaundice. According to WHO, apart from jaundice, signs of hepatic dysfunction are unusual and clinical signs of liver failure such as asterexis or liver flaps are never seen unless there is concomitant viral hepatitis.[17] However, in recent years, many reports with definite evidence of hepatic encephalopathy with malaria have been reported in patients from different parts of the world, including India.[11,21,22] In our study all patients with hepatic dysfunction recovered completely on supportive treatment and antimalarial drugs and none of them developed any complications especially hepatic encephalopathy.

A total of 2 children with malaria died in which 1 of the deaths occurred within 48 hours and 1 on the 3rd day. The case-fatality rate in children with *P. vivax* mono infection was 3.6%. One of the children was a 12 year old male who presented with Respiratory system involvement in the form of cyanosis and respiratory distress. He later developed multi organ dysfunction and expired within 48 hours of admission. The second child was an 8 year old male child who presented with typical features of malaria but on the third day developed acute abdominal symptoms and a lower gastrointestinal bleeding. The child expired within 8-10 hours before a definite diagnosis for the abdominal catastrophe could be ascertained.

Seven (29.1%) patients with very severe anemia (hemoglobin <5 g/dL) and clinical features of decompensated/poorly compensated anemia required blood transfusion. Five patients of

thrombocytopenia with bleeding required platelet transfusion. All the patients of severe vivax malaria with Central Nervous System involvement responded to quinine. All the cases of uncomplicated malaria were treated with oral chloroquine. There were no residual features or sequelae of disease in all patients who got cured.

Conclusion

The present study highlights the epidemiology of *P. vivax* malaria in pediatric age group. Since *P. vivax* was considered a benign disease, there are scarce reports. The study stresses that Plasmodium vivax can result in severe disease and can no longer be considered a benign condition. Severe Vivax Malaria is now very common with increasing mortality. Thrombocytopaenia is very common manifestation in severe Vivax malaria. Life threatening complications such as ARDS, ARF, Cerebral malaria and MODS were seen in patient infected with severe Vivax malaria in our study. There are certain areas where the results of the present study differ from some existing studies while agreeing with others. More studies are needed, especially at the population level so that we can clearly define the clinical spectrum of *P.vivax* monoinfection.

In addition further research is needed to define role of host genetics (e.g. Duffy genotypes, G6PD deficiency) upon severity. Factors and clinical complications predicting death; contribution of co-morbidities and concurrent infections to severe disease and biomarkers for severity also need to be assessed. Whether all the clinical complications classified as 'severe' share the same mechanisms of disease remains to be seen. Most importantly we need to examine whether the WHO criteria for severe *P. falciparum* malaria also apply for *P. vivax.*

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