Plasmodium vivax malaria: Is it actually benign?

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Received 12 December 2010; received in revised form 7 March 2011; accepted 9 March 2011

KEYWORDS
Children; Plasmodium vivax; Severe malaria

Summary Plasmodium vivax (Pv) malaria is being increasingly recognized as a cause of severe malaria in children.

Objectives: To describe the various severe manifestations associated with vivax malaria by retrospective analysis of records.

Methods: Children between the ages of 0 and 18 years with a confirmed diagnosis of Pv malaria monoinfection done by peripheral blood film (PBF) and/or rapid diagnostic test (RDT) admitted between June and September 2009 were included. Their clinical, hematological and biochemical manifestations were analyzed.

Results: Twenty-three patients of Pv malaria were retrospectively analyzed. Thrombocytopenia was present in 22 (96%) patients with counts less than 50,000/µL in 9 patients. Severe anemia (hb < 5 mg/dl) was present in 8 (34%) patients. Cerebral malaria was present in 3 patients. Liver enzymes were elevated (>3 times normal) in 4 (17.3%) patients while jaundice (bilirubin > 2.5 mg/dl) was present in 2 patients (total bilirubin 5.2 mg/dl and 14.3 mg/dl). Renal dysfunction (creatinine > 3 mg/dl) was present in 6 (26%) patients with 2 patients showing severely deranged renal functions (blood urea 168 mg/dl, 222 mg/dl and serum creatinine 5.0 mg/dl, 5.6 mg/dl, respectively). Hypernatremia was present in one patient. One patient expired within 12 h of presentation because of severely deranged hepatic and renal dysfunction.

Conclusion: Pv malaria can lead to unusual and fatal complications. All new guidelines should include "Severe Vivax malaria" as a clinical entity. Further research into the etiopathogenesis and treatment would be important.

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Introduction

Plasmodium vivax (Pv) also called as benign tertian malaria accounts for more than 50% of infection in South East Asia region [1]. Although it is usually associated with benign course recent literature suggests that Pv can lead to serious manifestations [2-12] similar to Plasmodium Falciparum (Pf). The present report highlights the serious manifestation of Pv malaria in children from India.

Methods

Case records of children between 0 and 18 years of age with diagnosis of Pv malaria between June and September 2009 were retrospectively analyzed. Children with mixed infection with Pf/any other malarial species or any other associated infection were excluded. Diagnosis of Pv was confirmed by peripheral blood film (PBF) examination and/or rapid diagnostic test (RDT). Severe manifestations of malaria [13] like seizure, jaundice, coma, severe pallor, bleeding, oliguria, hypoglycemia, acidosis and ARDS were reviewed. Routine hematological and biochemical investigations were done in all patients.

Results

Among 232 patients of malaria infection presented to our hospital during study period, 110 (47%) were of Pf monoinfection, 108 (46%) of Pv monoinfection and 14 (6%) of mixed infection. Thirty-two patients of Pf monoinfection, 23 patients of Pv monoinfection and 5 patients of mixed (Pf and Pv) infection presented with severe manifestation were admitted. The record of these 23 patients of Pv monoinfection was retrospectively analyzed. Ten (44%) of these patients were female and mean age of presentation was 5.4 years (±3.67) with range from 1 month to 12 years [<1 year 4 (17%); 1-5 years 9 (39%); 5-10 years 7 (30%); >10 years 3 (14%)]. Seventy percent of the children had moderate malnutrition (as per World Health Organization classification) but there was no child with severe malnutrition. In four patients PBF was negative but RDT was positive while one patient had positive PBF but negative RDT.

Gastrointestinal symptoms (diarrhea, vomiting) were present in significant number (43.4%) of patients while seizures presented in 4 (17.3%) patients. Three patients with seizures had cerebral malaria but in fourth patient it was because of hypernatremia (173 meq/L). Hepatosplenomegaly was present in all patients with mean size of liver and spleen being 2.7 cm (SD ± 1.19 cm) and 2.4 cm (SD ± 1.6 cm) below costal margins, respectively. Various severe manifestations of vivax malaria have been described in Table 1. Severe anemia (<5 mg/dl) was present in 8 (34%) cases. Thrombocytopenia (less than 150 × 10^3/μL) was a very common (95.6%) manifestation while severe thrombocytopenia (<50 × 10^3/μL) was present in 9 (39%) patients. Three patients who had platelet counts less than 10 × 10^3/μL presented with bleeding manifestation in the form of petechiae and purpura which improved after platelet transfusion. Five (21%) patients presented with pancytopenia. Two patients presented with jaundice. One of those had indirect hyperbilirubinemia (total bil. 6.2 mg/dl, indirect bil. 5.1 mg/dl) with normal liver enzymes (AST 35 IU/L, ALT 18 IU/L, ALP 240 IU/L) who improved subsequently. This patient had no feature suggestive of hemolytic anemia in the form of increased reticulocyte count, hemoglobinuria or decreased haptoglobin. The one with direct hyperbilirubinemia (total bil. 14.3 mg/dl, direct bil.

<table>
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<tr>
<th>S. no.</th>
<th>Manifestation</th>
<th>No. (%) of patients (n = 23)</th>
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<tbody>
<tr>
<td>1</td>
<td>Severe anemia (&lt;5 mg/dl)</td>
<td>8 (34.7)</td>
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<tr>
<td>2</td>
<td>Thrombocytopenia (&lt;150 × 10^3/μL)</td>
<td>22 (95.6)</td>
</tr>
<tr>
<td>3</td>
<td>Jaundice (bilirubin &gt; 2.5 mg/dl)</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>4</td>
<td>Renal failure (creatinine &gt; 3 mg/dl)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>5</td>
<td>Cerebral malaria (Glasgow coma score &lt; 9/14)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>6</td>
<td>Disseminated intravascular coagulation</td>
<td>1 (4)</td>
</tr>
<tr>
<td>7</td>
<td>Deranged liver enzymes (&gt;3 fold elevation)</td>
<td>4 (17.3)</td>
</tr>
<tr>
<td>8</td>
<td>Leucocytosis (&gt;12,000/cumm)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>9</td>
<td>Persistent vomiting</td>
<td>4 (17.3)</td>
</tr>
<tr>
<td>10</td>
<td>Multi organ dysfunction</td>
<td>1 (4)</td>
</tr>
<tr>
<td>11</td>
<td>Repeated generalized convulsions</td>
<td>4 (17.3)</td>
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</tbody>
</table>
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9.3 mg/dl) had severely deranged liver and renal parameters. Liver enzymes were elevated (>3 fold of normal) in 4 (17.3%) patients. Deranged coagulation parameters were present in two patients. In one patient (INR-1.8, aPTT – 78 s) it improved conservatively while in other (INR – 3.2, aPTT – 140 s) it required FFP (fresh frozen plasma) transfusion. Deranged renal functions (serum creatinine >2.5 mg/dl) were present in 6 patients. One of these had complete renal shutdown (urine output <0.1 ml/kg/h, serum creatinine –5.6 mg/dl) and required peritoneal dialysis while other (urine output – 0.3 ml/kg/h, serum creatinine – 5.0 mg/dl) improved conservatively in 5 days. None of these patients with renal involvement had albuminuria, hematuria or hypertension. In one neonate cold antibody Coomb Test positive hemolytic anemia, with the peripheral smear showing Red blood cells (RBC) agglutinates around the parasitized RBC was present. We found no patient with hypoglycemia, acidosis and acute respiratory distress syndrome (ARDS). Three patients presented with cerebral malaria had seizures and altered sensorium without any focal neurological deficit. Their cerebrospinal fluid examination findings were normal. Neuroimaging (CECT Scan) showed diffuse cerebral edema without any focal infarct or hypoattenuation.

All patients were treated with intravenous quinine and supportive care as per standard guidelines. Repeat PBF after 2 days showed clearance of parasite. Follow up which is routinely done in severe malaria patients, showed no residual neurological deficit in any patient with cerebral malaria.

One nine-year-old boy expired with complication of Pv. This boy presented with severe pallor, GI bleeding and oliguria who had severely deranged hepatic (AST 288 U/L, 340 U/L, total bil. 14.3 mg/dl, direct bil. 6.7 mg/dl) and renal functions (urea 222 mg/dl, creatinine 5.6 mg/dl) with abnormal coagulation profile. The child developed disseminated intravascular coagulation (platelet count 20 × 10^3/μL, INR – 3.2, aPTT – 140 s, D dimer – positive) and expired within 12 h of presentation.

Discussion

Pv which was initially thought to cause a mild infection with a benign course is now increasingly being recognized as a cause of severe malaria similar to Pf in adults and children including infants [14] and neonates [15]. Serious complications like severe anemia [2], thrombocytopenia [3,4], bleeding, jaundice, hepatic dysfunction [5–7], renal dysfunction [8,9], cerebral malaria [10], ARDS [11], severe neutropenia, hydrocephalus [12] and multi-organ dysfunction [16,17] also have been reported in children. All patients fulfilled the criteria of severe malaria [13] except that the parasites seen on PBS examination were of Pv and parasite load was not determined.

Our clinical data strongly indicate that Pv malaria can cause sequestration related complication of severe malaria like cerebral malaria, hepatic dysfunction, renal dysfunction, all of which usually associated with Pf malaria. Other non-sequestration related complications like severe anemia, thrombocytopenia, DIC are multifactorial, were more commonly seen. Possible mechanism underlying the anemia includes hemolytic effect of parasites, decreased deforming capacity of parasitized cells and parasite product mediated effect on erythropoisis. Newer mechanisms like invasion of erythroblasts by parasites have also been reported [18]. Thrombocytopenia has been attributed to increased splenic clearance, reduction of platelet survival, decreased platelet production and increased splenic uptake of platelet. Immunological reaction [19] and oxidative stress [20] are also suggested mechanisms of thrombocytopenia.

Although derangement of liver enzymes was a common finding, severe malarial hepatitis was found in only one child. Malarial hepatitis is known to be caused by direct injury to hepatocytes by the parasite [5–7]. There may be a wide variety of renal manifestation associated with malaria but these are more common with Pf infection. Acute renal failure, electrolyte abnormality, increased urinary protein excretion and abnormal urinary sediments have been reported in patient with Pv malaria [8,9]. We also observed deranged renal functions in significant number of patients however severe renal failure was seen in only two patients.

Our results are similar to other published data from Indonesia, Pakistan and other studies from India. In a large study from Papua New Guinea, Indonesia which included both inpatient and outpatients of malaria found that risk of severe disease in the terms of severe anemia, respiratory distress and coma were more common in Pv (23%) as compared to Pf (20%) [21]. Another prospective study conducted in two rural health facilities in Papua New Guinea reported 9537 cases of malaria, the risk of severe malaria was comparable in Pv and Pf especially in children less than 5 years of age [22]. One more study from Indonesia which included 1560 infants of less than 3 months of age of malaria. In these young infants, infection with Pv was associated with a greater risk of severe anemia (odds ratio, 2.4; 95% CI 1.03–5.91) and severe
severe vivax malaria (odds ratio, 3.3; 95% CI 1.07—10.6) compared to PF [23]. A retrospective analysis of 221 patients of Pv malaria from India by Sharma et al. [24] found thrombocytopenia, hepatic dysfunction, renal dysfunction in significant number of patients (96%, 27% and 7%, respectively). Three maternal deaths occurred due to ARDS. In another study from Bikaner (India) of 456 adult Pv malaria patients, 40 showed severe manifestations. Complications observed were hepatic dysfunction and jaundice in 23 (57.5%) patients, renal failure in 18 (45%) patients, severe anemia in 13 (32.5%) patients, cerebral malaria in 5 patients (12.5%), acute respiratory distress syndrome in 4 patients (10%), shock in 3 patients (7.5%) and multi-organ dysfunction was detected in 19 (47.5%) patients [16]. A study on young adult females comparing the severe manifestations of Pv malaria among pregnant (n = 25) and non-pregnant (n = 144) groups found complications like severe anemia (60% vs. 27%), hepatic failure (12% vs. 7.6%), renal failure (8% vs. 3.4%), ARDS (4% vs. 2.7%) and multiorgan dysfunction (4% vs. 3.4%) more common in pregnant females [17]. There is no larger study on pediatric patients regarding severe manifestation of Pv malaria. A case series by Parakh et al. of Pv malaria (n = 6) have shown severe anemia (2 patients), altered renal functions (2 patients) and cerebral malaria (3 patients) in pediatric patients [25].

Our study highlights the fact that Pv can lead to serious fatal complications similar to Pf. All national and international guidelines should incorporate the term “severe vivax malaria” and describe it further.

Conflicts of interest

Nothing to disclose.

Acknowledgements

We thank Dr. Praveen Kumar for his involvement towards patient’s management and critical review of the manuscript.

Funding: None.

Competing interests: None.

Contributions: HS collected the data, performed the statistical analysis and wrote the manuscript; AP conceptualized the idea, contributed toward writing and statistical analysis and would act as guarantor. All other authors were involved in patient management.


