Study on thrombocytopenia occurring in *P. vivax* malaria at a tertiary centre in Southern India

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Abstract

**Background:** Malaria caused by *P. vivax* is endemic to most of the tropical nations and are associated with various hematological abnormalities. Complications were more common among *P. falciparum infections as compared to P. vivax infections*. Recent literature suggests more severe forms of *P. vivax* infections including cases with severe thrombocytopenia. Objectives: To study the occurrence of thrombocytopenia in *P. vivax* malaria at a tertiary centre in Southern India. **Materials and Methods:** This retrospective cohort study was done among in-patients with *P. vivax* malaria at a tertiary care center in Southern India over a period of 18 months from October 2012. A total of 200 patients with positive peripheral smear for *P. vivax* malaria and negative for HRP-2 test were included in the study. The thrombocytopenia was graded as per the protocol and results were analyzed by frequency, percentage, mean, standard deviation and chi-square tests. **Results:** among the 200 patients males (74.5%) were affected than females. Mean platelet count at admission was 85,277.78 /cmm. We observed grades of thrombocytopenia were grade -1 in 16.5%, grade -2 in 28.5%, grade -3 in 36.5% and grade -4 in 16.5% of these patients. Complications like ARDS (1%) and acute renal failure (1%) were seen in patients with severe thrombocytopenia. **Conclusions:** In this study, we found severe thrombocytopenia to occur in *P. vivax* mono-infection. We felt *P. vivax* should no longer be considered benign and thrombocytopenia could be an early feature of *P. vivax* mono-infection.

**Key Words:** Malaria, *P. vivax*, severe thrombocytopenia, Southern India.

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INTRODUCTION

Malaria poses a great socioeconomic burden on the general population. According to World Malaria Report 2011, in the South East Asian (SEA) region, both the highest number of confirmed cases (1,495,817) and the highest number of deaths (1023) were reported from India*. In endemic areas, malaria has been considered as the major cause of thrombocytopenia and thereby, it is used as an indicator in patients presenting with fever. Platelet counts of less than 150,000/mm³ increases the likelihood of malaria by 12-15 times *(2, 3)*. Both non-immunological and immunological destruction of platelets have been implicated for the cause of thrombocytopenia. The mechanisms include coagulation disturbances, sequestration in spleen, antibody mediated platelet destruction and oxidative stress. Abnormalities in platelet structure and function can be seen in malaria as the parasites invade the platelets *(4)*. A typical attack of malaria is characterized by paroxysms of fever alternating with periods of fatigue, associated with chills, rigors, sweats, headache, myalgia, back pain, abdominal pain, nausea, vomiting, diarrhoea, pallor and jaundice *(5)*. Infections due to *Plasmodium vivax* were earlier thought to follow a benign course. Haematological abnormalities are very common in malaria, but severe thrombocytopenias were rarely associated with *Plasmodium vivax*. In the last decade, there are increasing reports of changing trends in the presentation of the disease caused by *Plasmodium vivax*. Increasing reports
of fatal complications such as adult respiratory distress syndrome, severe anaemia, acute renal failure and cerebral malaria in Plasmodium vivax mono-infections makes it a global concern (6).

OBJECTIVE OF THE STUDY
To study the occurrence of thrombocytopenia in *P. vivax* malaria infected patients at a tertiary centre in South India.

MATERIALS AND METHODS

Source of Data: The data was collected from patients admitted to a tertiary care center in Southern India with *P. vivax* mono-infection who were positive for Plasmodium vivax by peripheral smear and negative for Histidine rich protein-2 (HRP-2) test.

Study design: This is a retrospective study done over a period of 18 months from October 2012. A total of 200 in-patients with positive peripheral smear for *P. vivax* and negative for HRP-2 test were selected using purposive sampling techniques. They were followed from admission till recovery, discharge or death whichever was earlier.

The following investigations were done in all cases:
1. Haemoglobin estimation, total blood count, differential leucocyte count and platelet count
2. Peripheral smear for malarial parasite-both thick and thin smears stained with JSB stain and seen under oil immersion
3. Histidine rich protein-2 test to rule out *P. falciparum*
4. Liver and renal function tests.

Inclusion criteria:
1. Those admitted with positive peripheral smear for *P. vivax* malaria and negative for HRP-2 test.
2. Age more than 18 years.

Exclusion criteria:
1. Patients with *P. falciparum* infection.
2. Those with chronic kidney disease, chronic liver disease, haematologic malignancies, undergoing chemotherapy and radiotherapy.

Data Analysis: Data collected was analyzed by frequency, percentage, mean, standard deviation and chi-square test. Grading of thrombocytopenia was carried according to NCI Common Terminology - Criteria for Adverse Events Version 3.0 (7). Based on these patients with thrombocytopenia have been divided into following five grades:
- Grade 0: Within normal limit, platelet count 1,50,000 or above
- Grade 1: Platelet count between 75,000 and 1,50,000
- Grade 2: Platelet count between 50,000 and 75,000
- Grade 3: Platelet count between 25,000 and 50,000
- Grade 4: Platelet count less than 25,000.

RESULTS

In the present study, 200 patients positive for *P. vivax* fulfilling the selection criteria were included. Out of 200 patients, 149 (74.5 %) were males and 51 (22.5 %) were females. Ratio of male to female = 2.9:1. Patients included were aged between 17 - 82 years and maximum incidence was seen in the age group of 21-40 yrs with the mean age in this study being 37.32 years. The mean haemoglobin in the study population was 12.46 ± 1.9 g% and mean white blood cell count was 5777.5± 4452.6 (ranging between 1000 - 6200). Mean platelet count was 85277.8± 49207.3 (ranging between 7000 - 2, 73, 000).

As depicted in table -1; fever was the presenting complaint in all the patients (100 %) followed by headache (68.0%), vomiting (27.5% %), jaundice (28.5%), pain abdomen (9.0%), body pain (17.5%) and bleeding tendencies (2.0%).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Headache</td>
<td>136</td>
<td>68</td>
</tr>
<tr>
<td>Jaundice</td>
<td>59</td>
<td>28.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>55</td>
<td>27.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Body pain</td>
<td>35</td>
<td>17.5</td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13</td>
<td>6.5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Oliguria</td>
<td>1</td>
</tr>
</tbody>
</table>

Most common sign was anaemia (29.5%), followed by hepatomegaly (18%), splenomegaly (16.5%) and jaundice (13%) as seen in table 2.

<table>
<thead>
<tr>
<th>Sign</th>
<th>No. of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>37</td>
<td>18.5%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>32</td>
<td>16.0%</td>
</tr>
<tr>
<td>Icterus</td>
<td>26</td>
<td>13.0%</td>
</tr>
<tr>
<td>Signs of dehydration</td>
<td>21</td>
<td>11.0%</td>
</tr>
<tr>
<td>Pallor</td>
<td>17</td>
<td>8.5%</td>
</tr>
<tr>
<td>CNS manifestations</td>
<td>15</td>
<td>7.5%</td>
</tr>
<tr>
<td>Respiratory signs</td>
<td>2</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Among the study group, 195 (93.5%) subjects had thrombocytopenia; with Grade 1 in 16.5%, grade -2 in 28.5%, grade - 3 in 36.5% and grade 4 in 16.5% of these subjects (table -3).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Platelet count</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;150,000/mm³</td>
<td>5</td>
<td>2.5%</td>
</tr>
<tr>
<td>1</td>
<td>75,000-150,000/mm³</td>
<td>33</td>
<td>16.5%</td>
</tr>
<tr>
<td>2</td>
<td>50,000-75,000/mm³</td>
<td>57</td>
<td>28.5%</td>
</tr>
<tr>
<td>3</td>
<td>25,000-50,000/mm³</td>
<td>72</td>
<td>36%</td>
</tr>
<tr>
<td>4</td>
<td>&lt;25,000/mm³</td>
<td>33</td>
<td>33%</td>
</tr>
</tbody>
</table>
Leucocytosis was observed among the patients in our study, of which most of the patients had neutrophilia (68.1%), lymphopenia in 23.9%, monocytosis in 3% and eosinophilia in 5% of the study population. A complication such as hepatic dysfunction (5%), ARDS (1%) and acute renal failure (1%) was seen in patients with severe thrombocytopenia.

**DISCUSSION**

Malaria caused by P. vivax is prevalent in most parts of India. Malaria can produce a variety of haematological variation, especially the thrombocytes and can mimic any haematological disorder. Anaemia and thrombocytopenia are important complications seen frequently in P. vivax malaria. In endemic areas, malaria has been considered as the most important cause for febrile thrombocytopenia. In endemic areas there is 12-15 times chance of identifying malaria in a febrile patient with less than 1, 50,000/mm³ of platelets (2,3,8). In current study, 93.5% patients had thrombocytopenia. Colonel et al. (9) reported thrombocytopenia in 72% of the patients having malaria. Jamal et al. (10) in their study on paediatric population reported 72% of patients to have platelets less than 150000 mm³. While certain studies reported slightly lower incidence of thrombocytopenia (11, 12). The mechanism of thrombocytopenia in malaria is uncertain and various theories have been postulated. Immune mediated lysis of platelets, bone marrow suppression and splenic sequestration are considered to be the cause for thrombocytopenia in malaria (14, 15). There can also be abnormalities in the platelet structure and function due to immune response or from invasion of the platelets by the parasite (15). In acute malarial infection platelets are found to be hypersensitive and there is increased concentrations of platelet-specific proteins such as beta thromboglobulin (B-TG), platelet factor - 4 (PF-4), thromboxane - A2 and prostacyclin (15). The activated platelet has reduced sialic acid in their membrane resulting in its intravascular lysis and thus thrombocytopenia. During malarial infection, two major changes in the platelet function were demonstrated: platelet hyperactivity followed by platelet hypoactivity. The hyperactive platelets induce hemostatic responses which possibly prevent bleeding episodes, a rarity in malaria (15, 16). Thrombopoetin is required for platelet production and hence is elevated when there are low platelet counts (17). Metanat M (18) observed that patients with malaria had low levels of platelet superoxide dismutase and glutathione peroxidase activity from oxidative damage of platelets, resulting in severe thrombocytopenia. In this study, we found significant thrombocytopenia. Metanat M and Sharifi-Mood from Iran demonstrated a new genotype of P. vivax as a cause for severe thrombocytopenia (18). Recent studies done by George P in South India (19) and Gonzalez B et al (20) in Venezuela have shown thrombocytopenia is more common among P. vivax mono-infection in contrast to past observations in P. falciparum.

**CONCLUSION**

In current study, we found severe thrombocytopenia in P. vivax malaria patients. Severe complicated P. vivax malaria cases are increasingly seen world over and no longer considered to be benign. Thrombocytopenia could be an early feature of P. vivax mono-infection. Early suspicion, recognition and prompt treatment of the disease can reduce associated morbidity and mortality.

**REFERENCES**