Diagnostic Value of Low Platelets in Malaria

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Abstract

Objective: To study the incidence of thrombocytopenia in adults with Plasmodium vivax infection.

Method: An observational study comprising 84 consenting individuals with Plasmodium vivax infection was undertaken. All the individuals belong to armed forces who are from different parts of the country. Everyone had normal platelet count prior to admission to the hospital. After admission, they were subjected to routine hematological and biochemical investigations comprising complete blood count including platelet counts, urine routine, liver function test, renal function test, serum electrolytes and Chest X-ray after ruling out Dengue, concomitant sepsis and possibility of recent viral infection. Grading of thrombocytopenia was done according to NCI common terminology criteria for adverse events Version 3.0. Results were analysed and tabulated.

Result: A total of 84 patients were studied. 82 (97.6%) patients had thrombocytopenia. Majority (68.3%) of the patients had their lowest platelet count on the 5th and 6th day of fever. There was no associated increase in risk of complication with the increase in grade of thrombocytopenia. But with increase in severity of thrombocytopenia, it took more time for the platelets to recover to normal level.

Conclusion: Thrombocytopenia is widely present in P. vivax malaria of adults. However, the severity of thrombocytopenia does not correlate with the likely progression to complication. The chance of progressing to complicated malaria is equal among all adults of P.vivax malaria irrespective of the platelet levels. Hence, in a resource limited rural Indian set-up where the expertise to diagnose and detect malaria microscopically or reliable antigen detection method is not available, thrombocytopenia in an acute febrile illness especially on Day 5 to Day 6 of fever onset could be considered as P. vivax malarial infection with good amount of diagnostic accuracy (sensitivity of 97.6%) and empirical anti-malarial therapy could be started as per the existing treatment guidelines.

Introduction

Malaria, the disease known to have altered the course of humanity in the past has killed millions and many more have suffered from it. In the last 100 years of civilization, nearly 150 million to 300 million people have died of malaria, accounting for nearly 2% to 5% of all deaths.¹ Ever since Sir Ronald Ross made his landmark discovery in 1897 at Secunderabad, India, the disease still remains unconquered. Even with definitive treatment available, malaria continues to kill thousands across the globe.

It is no more a fact that complicated malaria is caused by Plasmodium falciparum (P. falciparum) alone as Plasmodium vivax (P. vivax) can also lead to severe complicated malaria [2]. P. vivax infection is indicated in multiple organ failures as seen with P. falciparum.

The clinical profile of malaria varies widely and certain aspects are yet to be studied extensively. Thrombocytopenia in malaria is a known complication. However, there are not many studies done regarding thrombocytopenia in P. vivax especially in adults of Indian population. The percentage of people having low platelets in P. vivax according to various studies done across the globe varies from 40% to 78%.³,⁴ Many Indian studies are however carried out in paediatric population.

In this study, we analysed the extent of thrombocytopenia in P. vivax in Indian adult population. Also, we carried out the study to find any co-relation between the severity of thrombocytopenia and complicated malaria.

Material and Methods

Place of study

The study was conducted in the Department of Medicine, 15 Air Force Hospital from 01 Jun 2017 to 31 Dec 2017.

Study design

An observational study was undertaken.

Sample size

A total of 84 patients with P. vivax malaria were evaluated.

Inclusion criteria

1. The study comprised of all consenting individuals above the age of 18 years diagnosed to have P. vivax malaria by peripheral blood smear.
2. All individuals with prior normal platelet count.

Exclusion criteria

1. Patients less than 18 years of age.
2. Patients having either mixed infection with P. vivax and P. falciparum or mono-infection with P. falciparum alone.
3. Patients with concomitant sepsis, Dengue or any other undiagnosed

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Table 1: Frequency distribution of grades of thrombocytopenia

<table>
<thead>
<tr>
<th>Thrombocytopenia grade</th>
<th>Platelet count/mm³ of blood</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>≥150,000</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Grade I</td>
<td>75,000 - 150,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade II</td>
<td>50,000 - 75,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade III</td>
<td>25,000 - 50,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade IV</td>
<td>≤25,000</td>
<td>4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

4. All non-consenting individuals and individuals who withdrew consent during any part of the course of the study.

Study Design

A total of 108 patients were enrolled in the study. 12 patients were detected to have mixed malaria and hence excluded from the study. 03 patients had concomitant sepsis while presenting to the hospital and were also excluded from the study. Of the 95 individuals who were selected for the study after analysing the inclusion and exclusion criteria mentioned above, 11 individuals were not willing to participate after explaining the course of the study in the language they best understand.

All the individuals belong to armed forces who are from different parts of the country. Since it is mandatory to undergo initial medical examination in armed forces prior to recruitment which includes a complete blood count and also every individual undergoes annual medical examination which also includes complete blood count, it is clear that everyone had normal platelet count prior to admission to the hospital.

All eligible patients who have consented to the study were subjected to routine hematological and biochemical investigations comprising complete blood count including platelet counts, urine routine, liver function test, renal function test, serum electrolytes and Chest X-ray. All patients were also checked for Dengue infection using NS1 antigen based card test. Patients requiring specialized investigation like ultrasound abdomen, CT scan of brain and arterial blood gas analysis (ABG) were done as per requirement.

Diagnosis of malaria was done through detection of malaria parasite (P. vivax) in peripheral blood smear.

Complete blood count including platelet counts were done using 5 part Sysmax Hematology analyser.

Grading of thrombocytopenia was done according to NCI common terminology criteria for adverse events Version 3.0. Results were analysed and tabulated.

Result

A total of 108 patients were enrolled in the study. After analyzing the inclusion and exclusion criteria, 84 eligible patients consented for the study.

The mean age of the study population was 34.2 ± 9.10 years with 78.6% of them being under 40 years of age.

Of the 84 patients, 82 patients (97.62%) had thrombocytopenia (platelets less than 1.5 lakhs per mm³ as per NCI common terminology criteria for adverse events Version 3.0). Frequency distribution of grades of thrombocytopenia in the study population is depicted in Figure 1/ Table 1. Lowest platelet count observed among the study population showed negatively skewed distribution, with the median platelet count being 58,500 cells/mm³ of blood.

About 39% of the patients were admitted on the 4th day of fever while 21% were admitted on 3rd day, 20% on 5th day, 11% on 6th day, 5% on 7th day, 2% on 8th day and 1% on 10th day of fever. Majority (68.3%) of the patients had their lowest platelet count on the 5th and 6th day of fever with 37.8% and another 30.5% of the patients were found to have lowest platelet count on 5th and 6th day of fever respectively. 12.2% of the patients had their lowest platelets on the 4th and 7th day each while only 6.1% of them had on the 8th day. A meager 2.4% were found to have the lowest platelet count on the 3rd day and only 1.2% on the 10th day of fever. The distribution of lowest platelets in respect to the day of fever onset is shown in Figure 2.
In 76.9% of patients with Grade I Thrombocytopenia, platelets returned to normal level between Day 8 to Day 11 while in Grade II thrombocytopenia, 80.7% patients recovered between Day 10 to Day 12 while a similar trend is seen in Grade III thrombocytopenia where 76.9% patients recovered between Day 10 to Day 12. In Grade IV Thrombocytopenia, normal platelets were seen between Day 11 to Day 13. The graph depicting time period for platelet recovery in various grades of Thrombocytopenia is depicted in Figure 3.

Total leukocyte count (TLC) dropped to less than normal in 42.9% of the patients. The drop is seen between 4<sup>th</sup> to 8<sup>th</sup> day of fever in 82% of the patients. The TLC was also found minimum on 3<sup>rd</sup> day of fever in 9.5%, 4<sup>th</sup> day in 18%, 5<sup>th</sup> day in 26%, 6<sup>th</sup> and 7<sup>th</sup> day in 13% each, 8<sup>th</sup> day in 12%, 9<sup>th</sup> day in 5% and 10<sup>th</sup> day in 4% of the patients. The frequency distribution of total leukocyte count is depicted in Table 2.

Mean haemoglobin on the day of lowest platelet count was observed to be 13.17±1.30 g/dl which was within the normal limits for adult males.

A significant proportion of patients had hyperbilirubinemia with normal serum aminotransferases. 38.1% (32/84 patients) had hyperbilirubinemia. The percentage of people with hyperbilirubinemia increased with the severity of thrombocytopenia. While none in grade 0 had hyperbilirubinemia, only 12.0% (03/25) had in grade I. On the contrast, 44.4% (12/27) in grade II, 57.7% (15/26) in grade III and 50.0% (02/04) in grade IV had hyperbilirubinemia with normal serum aminotransferases (Table 3).

### Discussion

Malaria is a true hematologic disease and affects all blood cell lines. Anemia and thrombocytopenia are the most common hematologic complications associated with malaria. Thrombocytopenia in malaria is a known complication. However, there are not many studies done regarding thrombocytopenia in P. vivax especially in adults of Indian population. The percentage of people having low platelets in P. vivax according to various studies done across the globe varies from 40% to 78%.<sup>3,4</sup> Also, the conducted studies implicate that the likelihood of the febrile illness being malaria is 12 to 15 times higher if the platelet count is less than 1.5 lakhs/mm<sup>3</sup>.<sup>3,4,7</sup>

Our study analysed the association between thrombocytopenia and P. vivax infection in which low platelets (platelets less than 1.5 lakhs/mm<sup>3</sup>) was seen in 97.6% cases Figure/Table 1. Other studies done by Colonel et al,<sup>8</sup> Jamal et al,<sup>9</sup> and NK Gupta et al reported thrombocytopenia in a significantly lesser proportion of 72%, 72% and 78% respectively. However, NK Gupta et al and Colonel et al conducted their study in paediatric population. There are also few worldwide studies conducted in children who reported much lower incidence of thrombocytopenia in malaria like 40%<sup>7</sup> and 59%.<sup>10</sup>

The precise mechanism by which thrombocytopenia occurs in malaria is unknown. The fact that P. vivax is no less serious than P. falciparum is well established after the advent of molecular diagnosis.<sup>2</sup> The possible explanations for the occurrence of low platelets in malaria are due to direct lytic effect of the parasite on the platelets,<sup>11</sup> immune mediated mechanisms involving platelet specific antibodies<sup>12</sup> and damage due to oxidative stress.<sup>13</sup> Though the possibility exists that thrombocytopenia may be due to decreased thrombopoiesis, the presence of normal megakaryocytes in the bone marrow literally rules out this possibility. Our study showed an incidence of thrombocytopenia in 97.6% cases (82 out of 84 cases). Few studies done recently in adults also showed that thrombocytopenia is more common in P. vivax malaria.<sup>15,16</sup> The results are contrary to the conventional notion that P. falciparum malaria causes severe thrombocytopenia than P. vivax malaria.

In our study, though thrombocytopenia was noted in 97.6% cases, there is no associated increase in risk of complication with the grade of thrombocytopenia. None of the 82 patients who had thrombocytopenia developed any bleeding complication. While 02 cases of complicated malaria had low platelets, 02 cases with normal platelets also progressed on to complicated malaria showing no relation to the extent of thrombocytopenia and risk of complication. The most commonly observed complication was hypotension. This result is contrary to the findings exhibited by George P et al,<sup>17</sup> Bhatia V et al,<sup>18</sup> Harish R et al,<sup>19</sup> Kakar A et al<sup>20</sup> and Arti Muley et al<sup>21</sup> where low platelets were associated with increased complication. However, majority of these studies have reported the complications occurring in children and our study comprises of adult Indian population in their second and third decade of life with mean age 34.2 ± 9.10 years.

In our study, majority of the patients were admitted on Day 3 and Day 4 of onset of fever. After confirmation of diagnosis by peripheral blood smear, Chloroquine was started to all on the same day of admission to the hospital. Similar studies conducted did not mention about the day of onset of fever in context to treatment.

The study showed that a majority (68.3%) of the patients had their lowest...
platelet count on the 5th and 6th day of fever. The distribution of lowest platelets in respect to the day of fever onset is shown in Figure/Table 2. This is in contrast to the findings of Arif M et al where thrombocytopenia was common among the initial days (Day 1 to Day 4). Also, comparing various similar studies, there were no conclusions drawn about the relation of onset of fever to the day of lowest platelets which is a novelty of our study.

We observed in our study that the time period for platelets to return to normal levels (>1,50,000/mm³) varied with the degree of thrombocytopenia. With increase in severity of thrombocytopenia, it took more time for the platelets to recover to normal level. While in about 80% of patients with Grade 1 Thrombocytopenia platelets returned to normal level between Day 8 to Day 11, a similar proportion in Grade II and Grade III thrombocytopenia recovered between Day 10 to Day 12 whereas in Grade IV Thrombocytopenia, it was between Day 11 to Day 13. The results are no surprise since it takes longer time for lowest levels of platelets to return to normal.

In our study, Chloroquine was started very early in the disease course (majority on Day 3 and Day 4 of onset of fever). Whether the time period for platelet recovery is related to early starting of Chloroquine treatment requires further elaborate studies since none of our patients presented after Day 10 of onset of fever.

There is a significant association between low platelets and high bilirubin levels with normal transaminases observed in our study. While 02 cases with normal platelets had no liver function abnormality, 38% of cases with low platelets had elevated bilirubin with normal transaminases. This is consistent with the results of Arti Muley et where 35.7% had hyperbilirubinemia. Further, the percentage of people with hyperbilirubinemia increased with the severity of thrombocytopenia. The rise in bilirubin was transient with none progressing to acute liver cell failure and normal serum bilirubin was observed after four to six days of febrile period. However, whether an increase in bilirubin alone with normal transaminases is associated with risk of complication cannot be commented upon by our study.

Conclusion

Thrombocytopenia is widely present in P. vivax malaria of adults. However, the severity of thrombocytopenia does not correlate with the likely progression to complication. Our study shows no co-relation between the grade of thrombocytopenia and complication. The chances of progressing to complicated malaria is equal among all adults of P.vivax malaria irrespective of the platelet levels. Rightly so, thrombocytopenia is not a criteria to define complicated malaria. Also, platelet value tends to reach the lowest on Day 5 to Day 6 of onset of fever.

Even in the modern era of medicine, we are heavily dependent on slide method to detect malaria since none of the antigen based malaria detection kits are reliable. Slide detection method requires hands of well trained and experienced lab technicians. The HRP-2 and pLDH based rapid detection kits failed to detect malaria in blood samples with parasite load more than 5000 per microlitre. Hence, in a resource limited rural Indian set-up where the expertise to diagnose malaria microscopically or reliable antigen detection method is not available, thrombocytopenia in an acute febrile illness especially on Day 5 to Day 6 of fever onset could be considered as P. vivax malarial infection with good amount of diagnostic accuracy (sensitivity of 97.6%) and empirical anti-malarial therapy could be started as per the existing treatment guidelines. Though the presence of thrombocytopenia is not a specific finding to malaria, the endemicity of malaria in the region with the presence of thrombocytopenia could be a guiding factor for treatment.

But the presence of thrombocytopenia in P. vivax malaria in different Indian geographical locations needs to be studied extensively before formulating a treatment guideline for starting to treat malaria based on thrombocytopenia.

References