Clinical and Hematological Changes in Childhood Malaria in India

Ritika Chhawchharia¹, Shital Kolhe², Riya George³, Keya R. Lahiri⁴

¹(Postgraduate Student, Department Of Pediatrics, D Y Patil Medical College, Navi Mumbai, India)
²(Associate Professor, Department Of Pediatrics, D Y Patil Medical College, Navi Mumbai, India)
³(Assistant Professor, Department Of Pediatrics, D Y Patil Medical College, Navi Mumbai, India)
⁴(Professor And Head, Department Of Pediatrics, D Y Patil Medical College, Navi Mumbai, India)

Abstract: Malaria caused by Plasmodium species is a disease with high morbidity and mortality, especially in children. The changing clinical and blood manifestations of P.falciparum, emerging trends of complications with P.vivax are some of the important issues that merit attention at present in India. The prospective cross-sectional study conducted on 170 patients of malaria in Mumbai aimed at studying the clinico-haematological alterations in the disease. Fever and splenomegaly were critical findings in majority of patients so that they may be used for clinical diagnosis of malaria and early institution of therapy. P.vivax was the predominant species with severe thrombocytopenia however anemia was common in P.falciparum infection. Older children were affected more severely than infants with hematological complications, namely anemia and thrombocytopenia. Anemia and thrombocytopenia were common observations while leucocyte count was normal in most patients. After 48 hours of antimalarial treatment, platelet count improved with restoration to normal in majority of patients while anemia worsened in most cases. There was a negative correlation between platelet count and hyperparasitemia. Despite availability of extensive literature on various manifestations of malaria, the evolving nature of the disease mandates continuous revision of existing data.

Keywords: childhood malaria, clinical, hematological

I. Introduction

"Malaria" derived its name from the Italian language (mala – bad; aria – air) as it was believed to be caused by foul air near marshy areas. Malaria is a global health problem, imposing the biggest socio-economic burdens on humanity. Despite the early success of malaria eradication programme in 1950-60, there was an upsurge of cases in 1970s when the disease comeback with a vengeance. New malaria ecotypes developed from environmental impact and were followed by epidemics in the 1990s [1]. At present, official figures for malaria in India indicate 0.7–1.6 million confirmed cases and 400-1,000 deaths annually [2]. According to the World Malaria Report 2014, 22% of Indian population live in high transmission (> 1 case per 1000 population) areas, 67% live in low transmission (0–1 cases per 1000 population) areas and 11% live in malaria-free areas. In 2013, 0.88 million cases have been recorded, with P.falciparum causing 53% and P.vivax causing 47% of the infections [3].

Haematological alterations like anemia, qualitative and quantitative changes in platelets, leukocytosis or leucopenia are well known in malaria. Most of these findings are more pronounced in P.falciparum as compared to P.vivax. However, there is no unanimity in the findings with some studies showing minimal differences and others showing significant haematological alteration in P.falciparum as compared to P.vivax.

Clinical diagnosis of malaria is important especially in the tropical countries due to lack of credible diagnostic facilities and scarce health care in these areas. Timely upgradation of previous data is necessary to be adept with the course of the disease to facilitate early diagnosis and prompt treatment.

II. Methods and Materials

A prospective cross-sectional study was conducted in a tertiary care centre for a total duration of 2 years, including inpatients of age <12 years, with P.vivax or P.falciparum malaria, confirmed on peripheral smear examination or a positive rapid malaria antigen test. Patients >12 years or who had received empirical therapy with anti-malarials were excluded from the study. A self-constructed semi-structured case record form was used to record the clinical features, and laboratory parameters like complete hemogram, peripheral smear and rapid antigen test for malaria. Daily hemograms were recorded after initiation of therapy with anti-malarial drugs, as per WHO guidelines 2010. Institutional ethics committee approval was taken and an informed consent was obtained before enrolling patients for the study.
Data was collected from 170 patients and statistical analysis was done using SPSS software (version 22). Data was analysed using the chi-square test, Spearman’s Rho Correlation ratio and z-test of proportion. A p value<0.05 was considered statistically significant.

Hemoglobin <10gm% was considered as anemia and those with <5gm% were considered severely anemic. Total white blood cell (WBC) count between 5,000-16,000cells/cu.mm was considered normal. Platelet count less than 1,50,000 was considered thrombocytopenia, which was divided into mild (1,00,000-1,50,000 cells/cu.mm), moderate (50,000-1,00,000 cells/cu.mm,) and severe categories (<50,000 cells/cu.mm). Restoration of platelet count to >1,50,000cells/cu.mm was considered end point in serial hemograms.

### III. Results

Our study consisted of 170 cases, with 57.6% males and 42.4% females. P. vivax was the predominant species causing malaria in 69.4% cases while only 9.4% cases had P. falciparum malaria. Mixed infections with P. falciparum and P. vivax were found in 21.2% cases. Malaria was commoner in older children (41.8%, 46.2% of 1-5 years and >5 years age group respectively) as compared to 11.9% of infants, which is also a sizeable amount.

Fever was a universal finding with vomiting second in line, observed in 38.2% patients, followed by abdominal pain, nausea and headache. Convulsions and altered sensorium were seen in 10.5% and 5.2% patients, respectively. There were no patients with bleeding manifestations, despite thrombocytopenia. Hepatomegaly and splenomegaly were common, as observed in 78.3% and 95.2% of cases.

#### Hematological Profile of Malaria

Anemia with mean hemoglobin of 9.54gm/dL was a common finding. Mean leucocyte count and platelet count were 7.15 x 10³ and 110 x 10³ respectively. Mean hemoglobin, leucocyte count and platelet count in different age groups are shown in (Table 1), which suggests that infants were more anemic as compared to older children while thrombocytopenia was commoner in older children. Leucocyte count was normal in majority of cases. Mean hemoglobin was lowest in children with P. falciparum malaria while thrombocytopenia was observed in mixed malaria more often than P. falciparum or P. vivax malaria alone. (Table 2)

#### Anemia in Malaria

Anemia was a common manifestation of malaria, observed in 54.1% cases, out of which, 2.9% cases suffered from severe anemia. Infants and children between 1-5 years were highly susceptible to develop anemia, constituting 80% and 67.6% of cases in each group respectively (p<0.05). Anemia was found to be associated with 50.8% of P. vivax cases, 56.3% of P. falciparum and 63.8% of mixed malaria cases (Table 3). A negative correlation was observed between hemoglobin and duration of fever, and hemoglobin and hyperparasitemia; however, these results did not reach statistical significance. After 48 hours of treatment with anti-malarial drugs, a further drop in hemoglobin was observed in 54.7% of cases.

#### Leucocyte Counts in Malaria

Majority of patients had a normal leucocyte count while 42.9% cases demonstrated leucopenia.

#### Thrombocytopenia in Malaria

Thrombocytopenia was observed in 74.2% cases, and 12.9% cases had severe thrombocytopenia. Thrombocytopenia was more rampant in older children with 78.9% of 1-5 year olds and 70.9% of >5 year olds affected with it. P. vivax, P. falciparum and mixed infections were responsible for thrombocytopenia in 71.1%, 68.7% and 86.1% cases respectively. Proportion of severe, moderate and mild thrombocytopenia was significantly higher in P.vivax infection than P.falciparum or mixed infection (p<0.05)(Table 4). A negative correlation was observed between platelet count and hyperparasitemia, measured by parasitic index on peripheral smears (p<0.05). Platelet count and duration of fever prior to treatment were also studied and a negative correlation was found. Majority of patients (89.5%) responded well to anti-malarial treatment in terms of rise in platelet count after 48 hours of treatment. Remaining 10.5% patients with thrombocytopenia showed a further fall in platelet count, however, the counts were recovered by the end of treatment. Normal platelet count i.e., >1,50,000 cells/cu.mm was restored within 48 hours of treatment in 51/104 patents. Only one patient required 7 days while 10 patients restored normal platelet count within 24 hours.

### IV. DISCUSSION

Malaria poses a significant health burden in India, with its widespread upsurge in rural as well as urban areas. In spite of various eradicative measures taken around the world, it remains the most notorious protozoal infection amongst humans. Hematological changes are the hallmark of malaria and their meticulous analysis can be instrumental in prompt and accurate diagnosis of the disease.
In this study, 69.4% cases were P. vivax, followed by 21.9% mixed and 9.4% P. falciparum infection. It can be proposed that P. vivax cases are on a rising trend amongst children with greater morbidities (4,5,6). Under-fives were more affected than infants in this study, which is in accordance with previous explanations that, fetal hemoglobin and maternal IgG confer immunity to infants (7,8). However, as many as 11.9% of affected infants is an example of poor disease control and changing epidemiology of malaria.

Fever has been described as one of the cardinal symptoms in malaria and is of historical importance. Other common symptoms observed were vomiting, pain in abdomen, headache, and nausea. None of the cases presented with bleeding manifestations, despite thrombocytopenia. Expression of tissue factor (TF) on the endothelium, and pro-coagulant role of parasitized RBC and activated platelets can explain absence of bleeding manifestation in malaria (9). Complications like ARDS, cerebral malaria and prerenal shutdown were observed more with P. vivax. This perspective is alarming while considering drug resistance in malaria.

Splenomegaly was described as a characteristic feature, by Hippocrates in the 5th century BC(10). Splenomegaly was a critical diagnostic feature in our study. With the above observations, it can be safely inferred that fever with splenomegaly in a child should compel us to strongly suspect malaria.

Anemia is a common feature of malaria, as exemplified by mean hemoglobin level of 9.54g/dL in our study and similar values in a study from Kenya and Karnataka (11,4). Out of the 54.1% cases with anemia, 2.9% cases of severe malaria indicate high morbidity of the disease. In the developing countries, nutritional deficiencies and parasitic infestations aggravate anemia leading to dimorphic patterns (12). Under-fives are more prone to develop anemia, which can be explained by the smaller red cell mass and relatively lower immunity to malarial parasite as opposed to older children who acquire immunity due to repeated exposure to the parasite (13). Severe anemia was observed in patients with longer duration of fever and hyperparasitemia. Even after receiving treatment for 48 hours, 54.7% patients demonstrated a further fall in hemoglobin. This observation is also reported by Price et al and Das et al in their studies (14,15). Malaria causes dyserythropoiesis and depressed reticulocytosis, along with increased destruction of parasitized and unparasitized erythrocytes that causes a slow recovery even after decreased parasitemia (16). Early treatment with antimalarials can truncate the impending anemia and accelerate recovery (17). Hyperparasitemia is associated with increased risk of anemia in malaria (11,12,18,19).

Although mean leucocyte count was normal, leucopenia was observed in 42.9% of cases. This observation is supported by other studies that have demonstrated leucopenia (17,20,21) and in contrast with another study that have demonstrated leukocytosis (11).

Thrombocytopenia is a consistent finding in both P. vivax and P. falciparum malaria in various studies conducted all over the world (5,11,22,23,24). Around 74.2% of cases in our study had thrombocytopenia which was also observed in various studies conducted in Thailand, USA and Australia (17,25,26). Children more than 5 years were susceptible to thrombocytopenia as also demonstrated in another study by Ladhani et al (27). Although thrombocytopenia was rampant amongst cases of P. vivax malaria, severe thrombocytopenia was seen in P. falciparum cases. Over the years, more studies report increasing incidence of thrombocytopenia with P. vivax malaria (4,28). More the parasitemia more was the occurrence of thrombocytopenia in our study. Rojansthein et al and Horstmann et al also presented similar results in their respective studies (29,30). Complete recovery of thrombocytopenia occurred rapidly within 48-72 hours without any bleeding manifestations in majority of cases and only one patient required 7 days. Joshi et al in India obtained similar result in their study with 92 patients(31).

V. Figures and Tables

Figure 1: Clinical features of malaria: Fever was a universal finding present in 100% cases. Bleeding manifestations were not observed in any patient despite thrombocytopenia.
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Table 1: Mean hemoglobin, leucocyte and platelet counts in different age groups - Anemia, thrombocytopenia were common findings with infants being more susceptible to anemia.

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>TLC (cells/cu.mm.)</th>
<th>PLATELETS (cells/cu.mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 years</td>
<td>8.52</td>
<td>7.88 x 10^3</td>
<td>124 x 10^3</td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>9.14</td>
<td>7.9 x 10^3</td>
<td>108 x 10^3</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>10.07</td>
<td>6.51 x 10^3</td>
<td>107 x 10^3</td>
</tr>
</tbody>
</table>

Table 2: Mean hemoglobin, leucocyte and platelet counts in different Plasmodium species - Anemia was more common with P.falciparum infection while mixed infections were more prone to thrombocytopenia.

<table>
<thead>
<tr>
<th>Parasete</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>TLC (cells/cu.mm.)</th>
<th>PLATELETS (cells/cu.mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Malaria</td>
<td>9.19</td>
<td>7.84 x 10^3</td>
<td>85 x 10^3</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>8.92</td>
<td>7.94 x 10^3</td>
<td>117 x 10^3</td>
</tr>
<tr>
<td>Plasmodium vivax</td>
<td>9.72</td>
<td>6.84 x 10^3</td>
<td>116 x 10^3</td>
</tr>
</tbody>
</table>

Table 3: Distribution of Anemia in different age groups and species of Plasmodium - Infants and falciparum malaria were more severely affected with anemia.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Species</th>
<th>Severe anemia (&lt;5g%)</th>
<th>Anemia (5-10g%)</th>
<th>Normal (&gt;10g%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 yrs</td>
<td>P. vivax</td>
<td>1 (5.0%)</td>
<td>15 (75.0%)</td>
<td>4 (20.0%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>1- 5 yrs</td>
<td>P. falciparum</td>
<td>1 (1.4%)</td>
<td>47 (66.2%)</td>
<td>23 (32.4%)</td>
<td>71 (100%)</td>
</tr>
<tr>
<td>&gt;5 yrs</td>
<td>Mixed</td>
<td>3 (3.8%)</td>
<td>25 (31.6%)</td>
<td>79 (100%)</td>
<td>79 (100%)</td>
</tr>
</tbody>
</table>

Table 4: Distribution of Thrombocytopenia in different age groups and species of Plasmodium – Older children 1-5 years and mixed malaria cases were more severely affected with thrombocytopenia.

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>0 – 1 years</th>
<th>1- 5 yrs</th>
<th>&gt;5 years</th>
<th>P. vivax</th>
<th>P. falciparum</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>2 (10.0%)</td>
<td>16 (22.5%)</td>
<td>20 (25.4%)</td>
<td>22 (18.6%)</td>
<td>7 (43.7%)</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>10 (50.0%)</td>
<td>31 (44.7%)</td>
<td>25 (31.6%)</td>
<td>47 (39.8%)</td>
<td>1 (6.3%)</td>
<td>18 (50%)</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (10.0%)</td>
<td>9 (12.7%)</td>
<td>11 (13.9%)</td>
<td>15 (12.7%)</td>
<td>3 (18.8%)</td>
<td>4 (11.2%)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (30.0%)</td>
<td>15 (21.1%)</td>
<td>23 (29.1%)</td>
<td>34 (28.9%)</td>
<td>5 (31.2%)</td>
<td>5 (13.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (100%)</td>
<td>71 (100%)</td>
<td>79 (100%)</td>
<td>118 (100%)</td>
<td>16 (100%)</td>
<td>36 (100%)</td>
</tr>
</tbody>
</table>

VI. Conclusions

Infection with P.vivax is on a rise with increasing morbidities even in infants. Fever with chills and splenomegaly are significant clinical indicators for suspecting malaria. Anemia and thrombocytopenia are common manifestations with little effect on leucocyte count. As against previous knowledge, P.vivax is emerging out as an equally notorious parasite, if not more than P.falciparum. Morbidity in terms of thrombocytopenia and anemia are related to hyperparasitemia. With treatment, anemia tends to worsen initially. This study alerts us towards the increasing occurrence of complicated malarias in different age groups and with different species.

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References


