The Unusual Presentation of a Usual Organism – the Changing Spectrum of the Clinical Manifestations of Plasmodium Vivax Malaria in Children: A Retrospective Study

SHOBHA SHARMA¹, KAILASH CHANDRA AGGARWAL¹, SHIVANI DESWAL¹, DEEPAK RAUT¹, NEELAM ROY¹, ROHIT KAPOOR¹

ABSTRACT
Background: Malaria is a major public health problem in the south-east Asian region. Among all countries in the SE Asian region the highest number of cases and deaths are reported from India. Children below 14 years of age contribute to approximately 42% of all the deaths. A majority of the deaths are attributed to severe malaria which is caused by Plasmodium falciparum. It is considered that causes a benign causing febrile illness without significant complications. However, in recent years, the spectrum of is shifting from being the cause of benign fever, to more severe complications. There have been case reports of complications like thrombocytopenia, cerebral malaria, a disseminated intravascular coagulation, the acute respiratory distress syndrome, hepatic dysfunction and renal involvement. Most of the case reports are from the adult population, with an occasional occurrence of paediatric cases.

Objective: To highlight the increasing number of severe manifestations in Plasmodium vivax malaria in the children who were admitted in the malaria transmission season of 2011, at a tertiary care hospital.

Design: A descriptive, cross-sectional study.

Material and Methods: Study Subjects: Children with an acute febrile illness of a duration of < 7 days, which was confirmed as Plasmodium vivax positive malaria by testing the peripheral smears and/or by Rapid Diagnostic Testing, who were admitted in the paediatric ward of a tertiary care hospital in New Delhi (India), during May 2011 to October 2011. Case records of context cases were analysed retrospectively.

Statistics: The data was summarised by calculating the rates, ratios, proportions, means, standard deviations and the 95% confidence intervals. The Chi square test was applied to assess the significant difference between two qualitative variables.

Results: Among the case records of 54 patients, 40.7% were below 5 years. 61% were males and 38.9% were females. Besides hepatomegaly and splenomegaly which were the most common symptoms, which were seen in 81.5% and 72.2% children respectively, the various unusual manifestations seen were severe thrombocytopenia (37%), jaundice with deranged LFT values (25.9%), abnormal bleeding (18.5%), impaired consciousness with a GCS of < 9 (18.5%), severe anaemia (14.8%), hypotension (11.1%), repeated convulsions (7.6%), pulmonary oedema/ARDS (5.6%) and ascites (5.6%). One case each showed haemoglobinuria, and pleural effusion.

Conclusion: Plasmodium vivax is emerging as a cause of severe malaria. There is a further need to study the pathophysiology, virulence factors and the molecular mechanisms which are involved in malaria.

Key words: Plasmodium vivax malaria, Children, Complications

BACKGROUND
Malaria, along with six other infectious illnesses i.e. diarrhoea, acute respiratory infections, measles, tuberculosis, HIV/ AIDS and hepatitis B, accounts for 85% of the global infectious disease burden [1,2]. The south east Asian region contributes to about 15.2% of the global malarial burden, with an estimated number of 28-41 million cases of malaria and 49,000 deaths in the year 2010, with the highest number of estimated as well as reported cases and deaths from India [3]. In 2011, India continued to have the maximum number (13M) of reported cases and 753 deaths [4,5]. Among all the deaths which were caused by malaria in a year, children below 14 years of age contributed to approximately 42% of mortality [6]. The distribution of and P. falciparum varies in different parts of India. A majority of the P. vivax cases (approximately 90%) are reported from the Indo-Gangatic plains, the northern hilly areas, Noth-west India including Delhi, India [7].

P. vivax is generally considered as benign and it usually causes febrile illnesses without significant complications. Most of the mortality is attributed to the severe complications seen mainly in P. falciparum species. But in recent years, the spectrum of P. vivax is shifting from being the cause of benign tertian fever, to the cases with more severe complications. There have been case reports of

METHODS
Approval was taken from the ethical committee of the institute to conduct this study.

Design
This was a descriptive, cross-sectional study, in which the discharge records of the children admitted at a tertiary care hospital in New Delhi (India) during May 2011 to October 2011, were examined retrospectively. All the acutely sick children admitted in the paediatric ward with a febrile illness of a duration of < 7 days and confirmed as P. vivax malaria by testing the peripheral smears and/or by rapid malaria antigen testing, were included in the study. However, all the children who were admitted with a febrile illness but were negative
for the malaria test or those who were positive for P.Falciparum or a mixed infection and those who had other associated infections like enteric fever, urinary tract infections or proven meningitis/encephalitis, were excluded from the study. The children from the out patients department with a positive malaria diagnosis were also excluded from the study. The case definition of severe malaria was made according to the WHO criteria.

Data Collection

The test results of P.vivax malaria for the study period of 6 months was collected from the haematology and the parasitology departments of the hospital. Accordingly, the case sheets and the discharge summary of these cases were collected from the Medical Records Department (MRD) by matching with the age and sex as per the laboratory results. The case sheets and the discharge summary sheets were examined in detail, to identify the clinical manifestations and the laboratory findings of these cases which were recorded on them.

Lab Analysis

The confirmation of malaria in these cases was done by using the RDT kit and/or by testing the peripheral smears, which showed the trophozoites/schizonts/gametocytes stages of P.vivax.

Data Analysis

The list line of these identified cases was prepared and it was entered into an MS Excel sheet. The data was validated for its completeness and correctness by randomly checking the case sheets, the line list with the data which was entered in Excel and also the time of the data compilation. The data was summarised by calculating the rates, ratios, proportions, means, standard deviations and the 95% confidence intervals. The Chi square test was applied to assess the significant difference between two qualitative variables.

RESULTS

In the year 2011, the total number of positive cases of malaria at all ages was 456 (inpatients and outpatients) at our study centre, among which, the positive cases were 261 (57.2%), the P. falciparum cases were 192 (42.1%) and 3 cases were of a mixed infection. The case sheet screening of 70 admitted sick children who were positive for malaria was done, out of which 16 were excluded due to the absence of other definitive diagnoses like enteric fever, meningitis, UTIs or an evidence of mixed infections. 54 children were included for a detailed study of the severe manifestations. A majority of the cases were from Delhi, 38 (70.4%) and 16 cases (29.6%) were from the neighbouring states of Haryana, Uttar Pradesh and Bihar. Most of the cases, 22 (40.7%) were under the age of 5 years , while 21 (39.9%) cases were between the ages of 6 to 10 years and 11 (20.4%) children were above the age of 10 years [Table/Fig-1]. The mean age was 6.7 ± 4.1 years with a 95% confidence interval of 5.6–7.8 years. Among the total cases, 33 were boys (61.1%) and 21 were girls (38.9%) [Table/Fig-1].

The confirmation of malaria in these cases was done by using the RDT kit and/or by testing the peripheral smears, which showed the trophozoites/schizonts/gametocytes stages of P.vivax.

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>Males No. (%)</th>
<th>Females No. (%)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>13 (39.4)</td>
<td>9 (42.9)</td>
<td>22 (40.7)</td>
</tr>
<tr>
<td>6– 10</td>
<td>13 (39.4)</td>
<td>8 (38.1)</td>
<td>21 (38.9)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>7 (21.2)</td>
<td>4 (19.0)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (100.0)</td>
<td>21 (100)</td>
<td>54 (100.0)</td>
</tr>
</tbody>
</table>

[Table/Fig-1]: Distribution of the Malaria cases according to age and sex

The clinical manifestations were further assessed to look for other manifestations which are not usually seen. Thrombocytoeaenia was the commonest unusual presentation in all the age groups. The other unusual manifestations were distributed similarly across all the age groups and the difference was not statistically significant [Table/Fig-3]. The pattern of the unusual presentations of P.vivax malaria in children was similar in both girls and boys, except that the proportion of girls (33.3%) with impaired consciousness was significantly (p < 0.05) more than that among boys (9.1%) [Table/Fig-4].

There were similar patterns of presentation amongst the P.vivax malaria cases from Delhi and outside Delhi and the difference was not statistically significant [Table/Fig-3]. Among the 54 patients, all showed positivity when they were tested with the rapid malaria diagnostic kit for P.vivax . Positive peripheral smears which showed various stages of the parasite were present in approximately 40% (22) of the cases. The parasite load was available in 24% (13) of the children, which ranged from 200/µl to 41000/µl, with the highest counts being seen in the children who had multiple complications.

DISCUSSION

In the year 2011, the total number of positive cases of malaria in all ages were 456 (inpatients and outpatients) at our institute, among which the P.vivax positive cases were 261(57.2%), the P.falciparum cases were 192 (42.1%) and 3 cases were of a mixed infection. In India, the percentage of falciparum cases showed a rise from 38% in 1995 to 52% cases in [4], but the situation in different parts of the country vary and there are more number of P.vivax cases in the north-western areas like Delhi and the nearby areas as compared to the P.falciparum cases. Out of the four species, P.vivax and P. falciparum are responsible for most of the cases of malaria and the latter is responsible for the maximum number of cases of severe malaria and thereby, the increased mortality. The P.vivax infection is considered as benign, without much consequences, but there are case reports which have emerged from around the world, which force us to notice the changing pattern in the severity of the P.vivax infection. The clinical profiles of 54 P.vivax positive children were studied, to look for the manifestations which are not usually seen.

**Clinical Manifestations**

<table>
<thead>
<tr>
<th><strong>Number</strong></th>
<th><strong>Percentage</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe Thrombocytoeaenia (platelet count &lt; 20,000)</td>
<td>20 (37.0)</td>
</tr>
<tr>
<td>2. Jaundice</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>3. Abnormal Bleeding</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>4. Severe anaemia</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>5. Impaired consciousness (GCS ≤ 9)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>6. Convulsions</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>7. Pulmonary oedema/ARDS</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>8. Ascites</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>9. Haemoglobinuria</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>10. Pleural effusion</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

*Some patients presented with multiple manifestations*

**Table/Fig-2**: Clinical manifestations of malaria among the study subjects (n = 54).
in the cases of . Only scarce literature is available on the *Plasmodium vivax* infection which presents as severe complicated malaria, less so in the paediatric age group. A recent study which was done in Bilkaner [12], India, a north-western area which is in proximity to our study centre, had a higher proportion of children 63.1% (65/103) who had *P. vivax* severe malaria than the children who had *P. falciparum* malaria 42.7% (79/185).

In the East Asian region, in the largest prospective study which was conducted in Papua, New Guinea and in Indonesia by Genton et al, over a period of 8 years (1997-2004), out of 9537 cases of all age groups with confirmed malaria, 6.2% had severe manifestations, most of them being children who were < 5 years. Among these, the proportion of the children with *P. falciparum* severe malaria was 11.7% and the proportion of severe malaria cases which were caused by *P. vivax* was 8.8%, which concluded that there was an increased number of children with *P. vivax* severe malaria [13].

In our study, the most common manifestation was thrombocytopenia, which was reported in 90.2% of the cases and in about 37.0% children, severe thrombocytopenia (<20,000/cumm) was present, with the lowest platelet count of 6000/cumm, which was probably the lowest count which was recorded among children in the literature [14-18]. There have been occasional reports of thrombocytopenia with *P. vivax* malaria, either as an isolated or a more commonly associated complication [14-18]. Both a non-immunological destruction [19] as well as the immune mechanisms which involve the specific platelet-associated IgG antibodies that bind directly to the malarial antigen in the platelets, have been recently reported to play a role in the lysis of the platelets and in the development of thrombocytopaenia [20]. The elevated M-CSF (macrophage colony stimulating factor) levels in which are seen in malaria, on increasing the macrophage activity, may mediate platelet destruction in some cases [21]. An oxidative stress damage of the thrombocytes has also been implicated in the aetio-pathogenesis, based on the finding of low levels of platelet superoxide-dismutase and glutathione-peroxidase and the high platelet lipid peroxidation levels in malaria patients [22]. A clinically apparent, abnormal bleeding was seen in 18.5% (10) cases in the form of melena, haematemesis, epistaxis, haematuria, petechiae and purpurae.

Icterus with deranged liver functions was present in 25.9% cases in our study, which was similar to the finding of a retrospective study which included all the age groups, which was done by Sharma and Khanduri, who reported deranged liver functions in 27% of the cases [23]. There were 18.5% (10) children who presented with impaired consciousness, with a GCS of ≤9. Out of 10 cases lumbar puncture was done in 80% (8) cases and it was found to be normal in all cases, except one case, which showed pleocytosis of 12 cells with 70% lymphocytes and protein levels of 50 mg/dl. This suggested a probable diffuse encephalopathy in all cases,
Plasmodium vivax was emerging as an important cause of severe complicated malaria and it should no longer be considered entirely benign. There is a need to further study and clarify the pathophysiology, virulence factors and the molecular mechanisms which are involved in P. vivax malaria.

CONCLUSIONS

Plasmodium vivax is emerging as an important cause of severe complicated malaria and it should no longer be considered entirely benign. There is a need to further study and clarify the pathophysiology, virulence factors and the molecular mechanisms which are involved in P. vivax malaria.

REFERENCES


