Original Article

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Paediatrics Section

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

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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 thrombocytopaenia, 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 *P.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 thrombocytopaenia (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 *P.vivax* with various complications like thrombocytopaenia, cerebral malaria, a disseminated intravascular coagulation (DIC), the acute respiratory distress syndrome (ARDS), hepatic dysfunction and renal involvement [8–11]. Most of the case reports are from the adult or mixed population, with a few paediatric cases. The objective of this study was to highlight the severe manifestations in *P.vivax* malaria, in children who were admitted in the malaria transmission season of 2011, at a tertiary care hospital.

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 line list 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 presence 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 (38.9%) 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].

Age Group (Years)	Males No. (%)	Females No. (%)	Total No. (%)
< 5 years	13 (39.4)	9 (42.9)	22 (40.7)
6– 10	13 (39.4)	8 (38.1)	21 (38.9)
> 10	7 (21.2)	4 (19.0)	11 (20.4)
Total	33 (100.0)	21 (100)	54 (100.0)

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

All the cases presented with fever as the chief complaint, with a median duration of two days and the duration ranged from 1–3 days prior to their admissions. Hepatomegaly was present in 44 (81.5%) cases, with a mean size of 3.27±1.8 cm below costal margin (which ranged between 1 to 10 cm), while splenomegaly was present in 39 (72.2%) cases, with a mean size of 3.27 ± 1.8 cm (which ranged between 1 to 9 cm). Among the study cases,the most common atypical presentations which were seen were severe thrombocytopaenia (platelet count < 20,000/ cumm) in 20 (37.0%) cases and jaundice with deranged liver functions in 14 (25.9%) cases. The other atypical presentations were abnormal bleeding in 10(18.5%) cases, impaired consciousness (GCS ≤ 9) in 10 (18.5%) cases and severe anaemia in 8 (14.8%) cases. 6 (11.1%) children presented with hypotension, 4 (7.6%) with repeated convulsions, 3 (5.6%) with pulmonary oedema/ARDS and 3 (5.6%) with ascites. One case each showed haemoglobinuria, and pleural effusion [Table/Fig-2].

Clinical Manifestations*	Number	Percentage
1. Severe Thrombocytopenia (platelet count < 20,000)	20	37.0
2. Jaundice	14	25.9
3. Abnormal Bleeding	10	18.5
5. Impaired consciousness (GCS ≤ 9)	10	18.5
4. Severe anaemia	8	14.8
5. Hypotension	6	11.1
6. Convulsions	4	7.4
7. Pulmonary oedema/ARDS	3	5.6
8. Ascitis	3	5.6
9. Haemoglobinuria	1	1.9
10. Pleural effusion	1	1.9

[Table/Fig-2]: Clinical manifestations of malaria among the study subjects (n = 54).
* Some patients presented with multiple manifestations

Thrombocytopaenia 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-5]. 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	Age Group (Years)			Total	p value*
	0 – 5 No. (%)	6 – 10 No. (%)	> 10 No. (%)		
1. Severe Thrombocytopenia	7 (31.8)	10 (47.6)	3 (27.3)	20 (37.0)	.424
2. Jaundice	3 (13.6)	8 (38.1)	3 (27.3)	14 (25.9)	.186
3. Abnormal Bleeding	5 (22.7)	3 (14.3)	2 (18.2)	10 (18.5)	.776
4. Impaired consciousness	5 (22.7)	4 (19.0)	1 (9.1)	10 (18.5)	.634
5. Severe anaemia	4 (18.2)	1 (4.8)	3 (27.3)	8 (14.8)	.198
6. Hypotension	3 (13.6)	2 (9.5)	1 (9.1)	6 (11.1)	.886
7. Convulsions	3 (13.6)	0 (0.0)	1 (9.1)	4 (7.4)	.227
Total	22 (100.0)	21 (100.0)	11 (100.0)	54 (100.0)	

[Table/Fig-3]: Distribution of clinical manifestations of *P.vivax* malaria in relation to age group of the study subjects.

Clinical Manifestations	Sex		Total	p value*
	Males No. (%)	Females No. (%)		
1.Severe Thrombocytopenia	11 (33.3)	9 (42.9)	20 (37.0)	.480
2. Jaundice	9 (27.3)	5 (23.8)	14 (25.9)	.777
3. Abnormal Bleeding	5 (15.2)	5 (23.8)	10 (18.5)	.486
4. Impaired consciousness	3 (9.1)	7 (33.3)	10 (18.5)	.035
5. Severe anaemia	7 (21.2)	1 (4.8)	8 (14.8)	.131
6. Hypotension	3 (9.1)	3 (14.3)	6 (11.1)	.667
7. Convulsions	2 (6.1)	2 (9.5)	4 (7.4)	.638
Total	**33 (100.0)**	**21 (100.0)**	**54 (100.0)**	

[Table/Fig-4]: Distribution of clinical manifestations of malaria in relation to sex of the study subjects

Clinical Manifestations	Place of residence		Total	p value*
	Delhi No. (%)	Outside Delhi No. (%)		
1. Severe Thrombocytopenia	12 (32.4)	8 (47.1)	20 (37.0)	.301
2. Jaundice	9 (24.3)	5 (29.4)	14 (25.9)	.745
3. Abnormal Bleeding	7 (18.9)	3 (17.6)	10 (18.5)	1.000
4. Impaired consciousness	6 (16.2)	4 (23.5)	10 (18.5)	.707
5. Severe anaemia	5 (13.5)	3 (17.6)	8 (14.8)	.696
6. Hypotension	6 (16.2)	0 (0.0)	6 (11.1)	.161
7. Convulsions	3 (8.1)	1 (5.9)	4 (7.4)	1.000
Total	37 (100.0)	17 (100.0)	54 (100.0)	

[Table/Fig-5]: Distribution of clinical manifestations of malaria in relation to place of residence of the study subjects

in the cases of . Only scarce literature is available on the *P.vivax* infection which presents as severe complicated malaria, less so in the paediatric age group. A recent study which was done in Bikaner [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 thrombocytopaenia, which was reported in 90.2% of the cases and in about 37.0% children, severe thrombocytopaenia (<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 thrombocytopaenia 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 malena, haemetemesis, 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,

except one, which showed an encephalitis like picture. Thapa et al., reported 2 cases of *P.vivax* cerebral malaria in 12 year old children at Calcutta, India [24]. Parakh et al., reported 6 children who were aged 1.5-11 years, who presented with severe *P.vivax* malaria. Among them, 3 had presented with cerebral malaria (), 2 with severe anaemia and 2 with abnormal KFT [25]. The altered sensorium in *P.vivax* malaria has been postulated to occur due to the occult mixed plasmodium infections, the metabolic changes, the reversible local microvascular dysfunction, endothelial activation and injury, and the microvascularthrombo-inflammatory responses. Besides these factors, age, the geographical profile, social factors and the genetics of the host play important roles in the pathogenesis of severe *P.vivax* malaria.

Severe anaemia was reported in 14.8% (8) cases, which may be due to recurrent bouts of haemolysis and dyserythropoiesis [26]. Besides, in vivax malaria, more number of non-infected RBCs are cleared from the circulation as compared to those in in falciparum malaria [27, 28]. The exact mechanism is not clear, but it has been postulated to be caused by the host immune mechanisms and the oxidative damage [29].

7.6% (4) cases had repeated convulsions. Hypoglycaemia was ruled out in all the cases as the cause of the seizures or the altered sensorium. Ozen et al., reported a case of *P.vivax* malaria which presented as status epilepticus [30]. Hypotension was observed in 11.1% (6) of the cases. None of the patients presented with ARF or multiorgan failure. Kaur and Gulati reported a case of *P.vivax* malaria which presented with fever, rash, a progressive deterioration of the renal function and uraemic encephalopathy [31].

Few patients (5.6%) presented with ARDS/ pulmonary oedema. The ARDS in vivax malaria probably results from the cytokine-related increases in the alveolar permeability and from the altered alveolar fluid clearance [32].

The exact pathophysiology of severe *P.vivax* malaria is not clear till date. The inflammatory response which occurs during the *P.vivax* infection is greater than that which is seen in the *P. falciparum* infection, with a similar or a greater parasite load [33]. The cytokine production which occurs during the infection is higher than that which is seen in the *P. falciparum* infection [34]. We could not draw comparisons between the proportions of se vere malaria and *P.vivax* malaria, as only the sick vivax malaria cases were studied. Moreover, ours was a retrospective, record based study, which nevertheless highlighted the occurrence of the severe manifestations 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.

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