Prevalence of Pancytopenia in Patients of Plasmodium Vivax Malaria in A Tertiary Care Hospital

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Abstract: Background &Objective: To study the prevalence of pancytopenia and hemophagocytic syndrome in Plasmodium Vivax infection in pediatric age group. Methods: In all 53 patients presenting during study period with Plasmodium Vivax (P. vivax) malaria and pancytopenia in our institution were evaluated for clinical features, complete hemogram and serum ferritin. Results & Interpretation: Pancytopenia was present in all 53 patients with increase in serum ferritin level in 36 patients. There was significant change noticed in complete blood picture done at admission and on day 7. Conclusions: Pancytopenia and Hemophagocytic syndrome (HPS) were reportedly associated with P. Falciparum infection, though their presence in P. vivax malaria infection was reported only as isolated case reports. However, this study has found a significant correlation with pancytopenia & HPS with P. Vivax infection as well. Therefore, a high index of suspicion and early treatment is the key to reduce the mortality with this syndrome. [Naveen P NJIRM 2017; 8(2):118-122]

Key Words: Plasmodium vivax Malaria (P. Vivax), Pancytopenia, Hemophagocytic syndrome (HPS), children.

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Introduction: Malaria is a parasitic disease with presence in more than 103 countries. It has become increasingly responsible for associated co morbidities often adversely affecting the outcome in diseased patients. The parasites most often implicated are Plasmodium Falciparum and Plasmodium Vivax. India is co-endemic for both, which are together responsible for 20 % death due to disease and 0.88 million cases (National Vector Borne Disease Control Program – 2013 report).

According to the working group of WHO the presence of parasitemia with severe anemia is one of the criteria for defining severe Malaria. In considerable number of patient anemia is often found in conjunction with thrombocytopenia. The cause for it are multifactorial and are thought to be due to increased hemolysis of both RBCs containing merozoites as well as non-parasitized RBCs, lowered threshold for splenic clearance of abnormal erythrocytes and platelets. In the bone marrow dyserythropoietic changes are prominent.

The patient may consequently develop anemia, when the hemoglobin may fall as much as 2 gm% / day, bleeding gums, epistaxis andpetechia, although significant bleeding in the form of hematemesis and melena occur in < 10% of cases. The association ofpancytopenia and HPS with P. vivax was not widely reported in literature, however in our study we found significant correlation between HPS and P. Vivax infection.

The presence of severe malaria due to plasmodium vivax with its resulting burden on cost of health care and paucity of literature regarding P. Vivax with HPS have led us to undertake this study.

Aims and Objectives:

1. To study the prevalence of pancytopenia associated with P. Vivax Malaria in pediatric patients.
2. The prevalence of HPS in P. Vivax infection.

Methods: Setting and Participants: The study included all vivax malaria positive patients with pancytopenia admitted in PICU / Paediatric ward at Rohilkhand Medical College and Hospital, Bareilly in study period of 5 month (1stJUNE – 31stOCTOBER). A total of 56 children were included in the study, among them 3 patients had mixed infection of – plasmodium vivax with plasmodium falciparum in peripheral blood smear so they were excluded. All the, 53 patients were plasmodium vivax positive by peripheral blood examination and rapid diagnostic test (antigen card test - LDH) and developed pancytopenia during their illness. Approval from ethics committee was obtained prior to commencement of the study.

Inclusion criteria:

1. All patient admitted in paediatric ward with severe plasmodium vivax malaria and pancytopenia during study period
2. Not suffering from any other illness (chronic / serious / malnutrition) accounting for anaemia or

thrombocytopenia based on clinical assessment and investigations.

Exclusion criteria:

1. Fever attributed to other causes.
2. Patient's hospital stay less than 7 days.

Investigations: All patients presenting with complaints of fever with or without chills and rigor and associated symptoms of pain abdomen, vomiting, bleeding with altered sensorium were investigated. Complete hemogram of all the patients was done on the day of admission and at day 7^{th} of hospital stay. Malaria test by Peripheral blood smear (Thick and Thin smear) and Rapid diagnostic test (Antigen Card test- LDH) were done.

In addition, liver function test (LFT), Kidney function test (KFT) with coagulation profile were also done.

Statistical analysis: Data was analyzed by SPSS software (version 23.0, SPSS Inc., Chicago, IL). Paired t-test was used to calculate significance values in categorical variables. Statistical significance was defined as p -value < 0.05.

Results: During the study period 53 patients were admitted to the hospital. Among them 33 (62.2 %) were male and 20 (37.7 %) were female. (Table: 1). the highest number of patients among both males and females belongs to the age group 8- 12 years.

Table 1: Demographic Distribution

Age	Male	%	Female	%
4-7	11	33.3	7	35
8-12	17	51.5	9	45
13-18	5	15.2	4	20

The most prevalent symptoms of malaria were fever with chills and rigor (67.9%) associated with pain abdomen (54.7%) and vomiting (62.2%). Some patients also presented with history of fever without chills and rigor (32.1%). Around 13 patients presented with bleeding (18.8 %) and altered sensorium (5.6%). (Table: 2)

Haemorrhagic manifestation were present in around 10 patients, of which in 7 patients petechias were present alone, and 3 patients had significant bleeding from single site (gastric haemorrhage) along with petechiae all over the body.

Splenomegaly was present in 48 patients and it was marked in every patient at day of admission and regression was monitored in these patients every day.

Table 2: Clinical Features of study population

Symptoms	No. of Cases(53)	%
Fever without chills and rigor	36	68%
Fever with chills and rigor	17	32%
Pain Abdomen	29	55%
Vomiting	33	62%
Bleeding	10	19%
Altered sensorium	03	6%
Splenomegaly	48	90%

Malaria was diagnosed in enrolled patients by peripheral blood smear examination in 25 (47.1%) cases and by rapid diagnostic test in 20 (37.7%) cases. Around 8 patients (15.2%) had both peripheral blood smear and rapid diagnostic test positive. (Table: 3)

Table 3: Distribution of Malaria Investigation

Malaria investigation	No. of cases (53)	%
PBS	25	47.1%
MP by Card	20	37.7%
PBS + MP By Card	08	15.2%

Among the 53 patients presenting with P. Vivax infection and pancytopenia, all had thrombocytopenia; out of which 24 patients had platelet count between 50,000 to 1 lakh, 23 patients had platelet count between 20,000 to 50,000 and 6 patients had platelet count below 20,000. Anaemia was a common finding, being present in 52 patients, however of these only 12 had haemoglobin < 6 gm%, 21 had haemoglobin in between 6 – 8 gm% and 19 had haemoglobin in between 8 – 10 gm%. Among all these patients 17 presented withleucopenia associated with thrombocytopenia and anaemia. (TABLE 4a)

After the initiation of treatment all cell lines shows drastic change, and repeat hemogram done at day 7 showed increase in their count.There was significant rise in values of leucocyte count and platelet count, but no significant rise in haemoglobin. Serum ferritin was also done in these patients which was raised in 36 patients with mean (SD) of 1182 (337.2). (TABLE 4b)

Table 4(a): Complete Hemogram done at admission and at day 7

Thrombocytopenia	DAY-1 (n)	%	DAY-7	%
50000 – 1 Lakh <	24	45.3	48	90.6
20000 – 50000	23	43.4	5	9.4
10000 – 20000	6	11.3	0	
Leucopenia				
>7000	4	7.5	16	30.2
7000-4000	32	60.4	37	69.8
<4000	17	32.1	0	
Haemoglobin				
<6	12	22.6	2	3.8
6 – 8	21	39.6	28	52.8
8 – 10	19	35.8	15	28.3
> 11	1	1.9	8	15.1

Table 4(b): Comparison of Complete Hemogram done at admission and at day 7

	Day – 1 Mean (SD)	Day-7 Mean (SD)	P-Value
Hemoglobin	7.78 (1.67)	9.59 (1.49)	0.00
Leucocyte Count	4308.2 (1089.74)	6558 (803.58)	0.001
Platelet Count	49760 (22493)	167460 (29532.56)	0.041
S. Ferritin	1182 (337.2)	N/A	N/A

Bone marrow examination was not performed in these patient as parental consent was not given.

Discussion: Exhaustive search of literature reveals that this study is the first to examine the association of P. vivax malaria with pancytopenia.Complicated malaria was usually attributed to infection with P. Falciparum (including pancytopenia and HPS), and P. Vivax infection was implicated less often. There are increasing reports that P. vivax can present with both sequestration and non-sequestration related complications, which were commonly associated with p. falciparum infection. But this satudy was essentially undertaken as during this period we found that a very large number of patients admitted in our hospital, presented with pancytopenia.

According to Aouba A et alin P.vivax infection, pancytopenia generally occurs due to microangiopathic haemolyticanaemia or due to hemophagocytic syndrome[1]. Hemophagocytic syndrome usually occur due to inappropriate or excessive immunological responses of T-cells.HPS is a clinicopathological entity characterized by benignproliferation of monocytes or macrophages showing phagocytosisof hematopoietic cells[2]. HPS is commonly associated with blood malignancies, autoimmune conditionsand infections with viruses, bacteria and parasites[2]. The etiological role of P.Vivax infection is suggested bythe absence of other associated disease and also the total clinicaland hematological recovery after chloroquine and artemisinin combination therapy. Asimilar report of HPS has been described by Ohno et al in apatient with Plasmodium falciparum (PF) infection[8]. In addition, erythrophagocytosis of normal andparasitized cells may occasionally be observed in the bonemarrow of patients with malaria, and in one reported caseof PF infection 80% of the blood monocytes showed plateletphagocytosis [2]. HPS is often considered as a T-cell-mediateddisorder with inappropriate and/or excessive production ofcytokines such as tumor necrosis factor a,interferon g and macrophage colony-stimulatingfactor (M-CSF), resulting in monocyte activation[3]. Strikingly high levels ofthese cytokines have been observed in patients with malariaand could trigger HPS initiation[4].

The Histiocyte societytrials, HLH 94 and HLH 2004 have defined the diagnostic criteria for the diagnosis of this syndrome[4,5,6].

Diagnostic criteria for hemophagocytic syndrome:

1) Fever >38.5°C, lasting for more than 7 days
2) Splenomegaly
3) Cytopenia involving at least two cell lines
   a) Hemoglobin < 9 gm% or < 90 g/lit
   b) Platelets < 100,000/µl or < 100 × 109/lit
   c) Absolute neutrophil count <1000/µl or <1 × 109/lit
4) Hemophagocytosis demonstrated on bone marrow
5) Serum Ferritin ≥500 µg/lit
6) As well as other supportive criteria

Hemophagoctyosis may continue independent of the presence of the malarial parasite. Prolonged hemophagocytosis is one of the complications of hemophagocytic syndrome in malaria and results in prolonged anemia and has been reported in falciparum malaria but not yet reported in vivax malaria in children[7,8,9,10].Park et al described vivax malaria complicated by pancytopenia with hemophagocytic syndrome in immunocompetent

servicemen[11]. Yamakawaet al described vivax malaria with pancytopenia secondary to bone marrow hypoplasia in a 39-yr old male who travelled to Southeast Asia and pancytopenia improved with sulphadoxine and pyrimethamine[12]. Aoubaet al described a case of hemophagocytic syndrome associated with P. vivax infection in 41-yr old woman who improved with chloroquine[1]. A case of pancytopenia secondary to hemophagocytic syndrome due to P. vivax in a 37-yr old Nepali woman in Saudi Arabia was reported byAlbaker W etal whereasThapaet al reported a case of pancytopenia complicating cerebral malaria due to P. vivax in a 7-yr old girl child[13,14].Hemophagocytic syndrome in malaria should be suspected in all cases of severe and/or complicated malaria and especially where the anemia does not improve even after receiving antimalarial therapy. We didn't include bone marrow aspiration as diagnostic criteria due to reluctance by the parents to give permission, however maximum patients improved after antimalarial treatment. It is our belief that P. vivax should be listed as one of the causes of secondary HPS especially in children from malaria endemic areas. A regular follow up of such cases should be done even after successful antimalarial therapy as prolonged anemia is one of the serious complications in such cases.

Conclusion: In conclusion, HPS could play a role in the pathogenesisof cytopenia observed during plasmodium infestation. As itsfrequency, has not been systematically studied duringmalaria, it is difficult to assign its role in the outcome of patients with severe complicated malaria specially that due to P. Vivax. However, it could be implicatedin life-threatening complications due to infection byPlasmodium species, justifying further studies. It is generally seen in Plasmodium falciparum malaria but as our study shows it can even occur in Plasmodium vivax malaria. Therefore, a high index of suspicion and early treatment is required to reduce the mortality from this syndrome.

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Conflict of interest: None
Funding: None
Cite this Article as: Naveen P, Alka B. Prevalence of Pancytopenia in Patients of Plasmodium Vivax Malaria in A Tertiary Care Hospital. Natl J Integr Res Med 2017; 8(2):118-122