Retrospective analysis of vivax malaria patients presenting to tertiary referral centre of Uttarakhand

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ABSTRACT

Introduction: Despite the high prevalence of Plasmodium vivax (P vivax) malaria, research into its complications has lagged disproportionately as compared to Plasmodium falciparum (P falciparum) malaria.

Material and methods: The present retrospective observational study was conducted on cases with P vivax mono-infection presenting with severe malaria on the basis of one or more criteria as per the World Health Organization guidelines being used for severe falciparum malaria in children, as well as other manifestations been classified as complicated malaria, during an outbreak of malaria in a single tertiary referral hospital of north India.

Results: Seventy-four patients of acute malaria presented during the outbreak, of which 50 cases with P vivax mono-infection were included for the study. Complicated malaria was diagnosed in 41/50 cases, with thrombocytopenia being the commonest manifestation. Other presentations of severe malaria in our patients were liver dysfunction (with or without jaundice) 31/50 cases, respiratory involvement 14/50 cases, renal impairment 11/50 cases, circulatory collapse (Shock) 8/50 cases, severe anaemia 3/50 cases and central nervous system (CNS) involvement 2/50 cases.

Conclusion: The term “benign tertian malaria” no longer holds true for P vivax mono-infection. The authors wish to open a new front for researches on the possible genotypic abnormalities that the parasite or its carrier might have acquired over decades and has transformed into a species with the malignant potential of P falciparum.

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2. Material and methods

The current observational study was performed at the Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun during an outbreak of malaria between the months of April and August in the year 2008. All the patients over the age of 18 years who tested positive for malarial parasite—P. vivax [both by blood smear examination (thick and thin) and rapid malaria test] and underwent treatment at the Department of Medicine, either as in-patients or out-patients, were included in the study. As this is a retrospective observational study we were not able to perform PCR to rule out co-infection; however the patients found to be having co-infection by above methods were excluded. A thorough general and systemic examination was performed and the blood samples were examined for haemoglobin, total leucocyte count, platelets, red cell indices (packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin concentration), liver function test (serum total bilirubin, direct bilirubin, alanine amino transferase, aspartate amino transferase, alkaline phosphatase), renal function tests (blood urea nitrogen, serum creatinine), blood gas and arterial pH estimation wherever indicated. Liver function test and renal function test was done with Beckman Coulter CX 9 auto-analyzer and hemogram was done with MSS-3sH-build 84 HD Consortium auto-analyzer.

The patients presenting with clinical features mimicking malaria were excluded if they tested negative for malarial parasite tests but treated empirically for malaria; tested positive for Plasmodium falciparum; were co-infected with Plasmodium falciparum; or had other infections proven either by serology or culture studies of blood and body fluids. The patients who had positive peripheral blood smears or positive rapid malaria test alone were also excluded. Rapid malaria test was performed by DiaMed OptiMAL kit with detection ability for parasitemia of 0.002%. The kit detects the API was <2 in most regions of India [Kumar et al., 2000]. The annual parasite incidence (API) is a malariometric index to express malaria cases per thousand population. As per the National Vector Borne Disease Control Programme (NVBDCP) incidence records, the API was <2 in most regions of India.

The mean platelet count in our study group was 52 × 10^9/l [range: 15–223 × 10^9/l]. In our study group were 56 ± 0.6 × 10^9/l (range: 1.1–3.4 gm/dl). The mean BUN levels of the study group were 24.4 mg/dl (range: 1.1–3.4 gm/dl). The mean blood glucose level of the study group was 111.40 ± 2.8 mg/dl (range: 111.40 ± 12.52 mmHg, respectively. The circulatory collapse observed in 8/50 cases responded to fluid resuscitation alone; however, vasopressors and steroids were required in 2 cases after fluid resuscitation failed.

Hyperbilirubinemia was observed in 31/50 cases with a mean bilirubin level of 2.6 ± 2.8 mg/dl in the study group. Mean alanine amino transaminase (ALT) and aspartate amino transaminase (AST) levels of the study group were 43.8 ± 5.6 IU/l and 48.5 ± 46.6 IU/l, respectively. Elevated serum transaminases (twofold or higher) were observed in 5/50 cases having normal bilirubin levels. The serum albumin levels were also decreased with a mean of 2.8 ± 0.6 gm/dl (range: 1.1–3.4 gm/dl).

The mean BUN levels of the study group were 28.5 ± 24.4 mg/dl and mean serum creatinine levels were 1.2 ± 0.6 mg/dl. The mean blood glucose level of the study group was 115.5 ± 40.4 mg/dl. We encountered high ESR in all patients with a range of 45–110 mm/1st hour.

The parasite clearance time as indicated by negative rapid malaria test as well as negative smear examination was 4.06 ± 1.67 days and fever clearance time was 4.98 ± 1.92 days. The duration of follow-up was one month. On follow-up all the biochemical and haematological parameters that were deranged during hospitalization were retested and found to be in normal range confirming the absence of chronic disease process as well as acute nature of illness.

A striking feature was the absence of hypoglycemia either at presentation or throughout the course of hospitalisation; moreover, we did not encounter any mortality.

3. Results

A total of 74 patients of acute malaria presented to our institute during the outbreak, of which 50 patients had P. vivax mono-infection, 21 patients had P. falciparum mono-infection and 3 had P. vivax and P. falciparum co-infection. Both in-patients as well as out-patients with P. vivax mono-infection were included for the study. Of these 50 patients 34 were in-patient and 16 were out-patient. The average age of the patients in the study group was 38.5 ± 20.8 years; the male to female ratio being 3:2. The mean duration of fever prior to presentation to our centre was 8 ± 1.4 days, duration of admission was between 5 and 12 days and the patients with severe malaria were treated with artemisinin compounds plus doxycline; while patients with non-severe malaria were treated with chloroquine. All the patients who were G6PD sufficient were given primaquine for radical cure.

Although, pulmonary and renal systems were predominantly affected (14/50 and 11/50 cases, respectively) either in isolation or in combination, multi-organ dysfunction was noted in 6/50 cases. The mean platelet count in our study group was 56 ± 0.6 × 10^9/l (15–223 × 10^9/l) and thrombocytopenia was the commonest abnormality in those with complicated malaria (41/50 cases). The mean systolic and diastolic blood pressures in the study group were 111.40 ± 20.80 and 69.40 ± 12.52 mmHg, respectively. The circulatory collapse observed in 8/50 cases responded to fluid resuscitation alone; however, vasopressors and steroids were required in 2 cases after fluid resuscitation failed.

4. Discussion

Given the tremendous morbidity and mortality associated with malaria, WHO has issued guidelines defining the potentially fatal severe malaria in children [World Health Organization, 2000]. Traditionally, severe malaria is synonymous with P. falciparum; the burden and virulence of vivax malaria has been under-rated. It is only recently that severe disease due to P. vivax was reported in 36 out of 1135 P. vivax infected patients (3.2%) from a hospital in north-east Indonesian New Guinea (Papua) [Barcus et al., 2007]. Some manifestations of vivax malaria, not classified under severe malaria are thrombocytopenia and mild to moderate anaemia. In our study we have maximum number of patients with these complications; hence we are classifying these patients as having complicated malaria.

The annual parasite incidence (API) is a malarialometric index to express malaria cases per thousand population. As per the National Vector Borne Disease Control Programme (NVBDCP) incidence records, the API was <2 in most regions of India [Kumar et
A total of 1059 cases of malaria were reported in the year 2008 from the state of Uttarakhand of which only 47 were due to *P falciparum*; the overall mortality was nil (NVBDCP data).

Anaemia was observed in 41/50 cases with complicated malaria which was further classified into severe and non-severe anaemia. We were not able to find any representative study for the prevalence of anaemia from this region. Moreover, the correction of anaemia without hematinics on follow up suggests that anaemia could be attributed to malaria.

Destruction of parasitized red cells, complement-mediated lysis and phagocytosis of non-parasitized red blood cells might be responsible for the development of anaemia in malaria [Claire et al., 2004]. Increased splenic clearance of parasitized as well as non-parasitized red cells, reduction of red cell survival even after disappearance of parasitemia, dyserythropoiesis in the bone marrow and drug-induced hemolysis might also be other contributory factors (Table 1).

Thrombocytopenia was the most common manifestation of our study with 41/50 cases having platelet counts of less than 150 × 10⁹/L. Thrombocytopenia has also been described as the most common manifestation of malaria in the WHO report. The study by Jadhav et al. (2004) also showed presence of thrombocytopenia in cases with vivax malaria, with a mean platelet count 115 × 10⁹/L (range of 8–573 × 10⁹/L). The mechanism of thrombocytopenia in vivax malaria remains uncertain; however, immune-mediated lysis, sequestration in the spleen, dyspoietic process in the marrow and diminished platelet production might be the possible mechanisms.

Liver dysfunction has been described in the WHO review as the most common abnormality of the adult population in severe malaria. Similar results of liver dysfunction have been observed in another study from an Asian country [Noppadon et al., 2006]. Hyperbilirubinemia observed in cases of vivax malaria can be attributed to increased hemolysis of both parasitized and non-parasitized erythrocytes as well as to hepatic injury, as has been observed in cases with *P falciparum* malaria [Wilairatana et al., 1994]. Similar to *falciparum* malaria, dilitated hepatic sinusoids containing hypertrophied kupffer cells and parasitized red cells may also be contributory to hepatic injury in *P vivax* infection [Mishra et al., 1992].

Respiratory involvement was observed in 14/50 patients at presentation. Two patients had clinical and radiological evidence of pleural effusion while three had acute respiratory distress syndrome (ARDS) and required ventilatory support. ARDS has not been commonly described in patients with vivax malaria; however, there are a few isolated case reports of ARDS in vivax malaria. The postulated mechanism of respiratory distress in *P vivax* infection is sequestration of infected erythrocytes within the pulmonary microvasculature causing alveolar-capillary dysfunction [Nicholas et al., 2007] secondary to the changes in red blood cells and microcirculation. Other possible mechanisms might be packing of pulmonary capillaries and venules with inflammatory cells and parasitized red cells, oedematous vascular endothelium causing narrowing of the lumen, interstitial oedema and hyaline membrane formation.

Renal involvement was found in 11/50 cases. None of them required dialysis and improved with conservative management. There is no representative study showing the prevalence of renal disease in India; but two isolated community based studies from India put the figure between 0.79% and 0.16% [Agarwal, 2005; Mani, 2003]. Renal impairment is known to occur with *falciparum* malaria but is rare in patients of *vivax* malaria. The pathogenetic mechanisms of renal failure in *falciparum* malaria namely microcirculatory disorders, anoxia, subsequent necrosis of the glomeruli and renal tubules, disseminated intravascular coagulation and possibly acute diffuse malarial nephritis may be implicated in vivax infection [Das, 2004].

Circulatory collapse was encountered in 8/50 patients. Presence of shock can be explained by intravascular hemolysis and fluid loss due to vomiting and bleeding episodes. Involvement of splanchnic microcirculation can lead to ischemia of the gut, mucosal edema, necrosis and ulceration leading to gastrointestinal bleeding; further these changes in the gut may also lead to absorption of toxins, precipitating septic shock. A possibility of direct involvement of adrenal gland by the malarial parasite causing addisonian like illness can also be considered, as a few patients (2/50) responded to steroids and vaspressors, after failure of fluid resuscitation.

Central nervous system involvement is not common in *vivax* malaria but was observed in 2/50 cases. It might have been due to heavy parasitemia and sequestration of parasitized red cells in cerebral circulation or due to malarial encephalitis and meningoencephalitis, as in cases of *falciparum* malaria.

Other common findings in all our patients were a high ESR and a low serum albumin. Prolonged malarial infection and severe anaemia are usually associated with a higher ESR. Decreased albumin levels may be a reflection of variable contribution of liver and renal disease besides gastrointestinal ischemia.

### 5. Implications

It may be concluded from this observational study that there is a major burden of *vivax* malaria in north India. Our study is probably the largest case series ever reported, however, it might be just the tip of the iceberg because many of the cases might have been treated successfully in the periphery by the practitioners. Although, there was no mortality, which is concordant with the NVBDCP data but the presentation in some of our cases was potentially fatal. Our data cannot be extrapolated to the whole population but this may call for a larger population based study and the term “benign tertian malaria” should be reconsidered as *vivax* malaria no longer appears to be a benign disease.

Our study may also prove to be an initiator for further research into possible genotypic abnormalities that the parasite or its carrier may have acquired over decades of aggression of insecticides, injudicious usage of conventional antimalarials, ecological transformations due to industrialization and possible co-infection with certain viruses. Another possibility is the co-infection with newer...
plasmodial species that may have occurred and went unrecognized by conventional testing techniques.

References


