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A study on the clinical profile of complicated *Plasmodium vivax* mono-infections

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ABSTRACT

Objective: To identify cases of severe *Plasmodium vivax (P. vivax)* mono-infections among adults. **Methods:** In this retrospective study, 30 adult patients admitted to medical wards of a tertiary hospital in a malaria endemic urban area from March 2010 to April 2010 were included. The diagnosis of *P. vivax* malaria was established by peripheral blood film (PBF) examination, and severe malaria was categorized as per World Health Organization guidelines. **Results:** Complications observed were thrombocytopenia in 28 (93.3%), hepatic dysfunction and jaundice in 13 (43.3%), renal dysfunction in 8 (26.7%), severe anaemia in 3 (10.0%), cerebral malaria in 2 (6.7%), and acute respiratory distress syndrome (ARDS) in 1 (3.3%) of 30 patients. **Conclusions:** *P. vivax* malaria with severe complications is common in the investigated area, and an intensive and large-scale study of the disease is necessary.

1. Introduction

The usual cases of *Plasmodium vivax (P. vivax)* malaria have a relatively benign clinical course as compared with *Plasmodium falciparum (P. falciparum)* malaria[1]. However, some reported complicated *P. vivax* mono-infections recently. They pointed to a spectrum of severe diseases that had been possibly mistaken as *P. falciparum* malarial infections in the past. In past, whenever complications were noticed among patients with *P. vivax* infections, they were attributed to undetected associated *P. falciparum* malaria. But co-infection of *P. vivax* and *P. falciparum* cause mutual suppression of each other *in vivo* and tends to be benign[2]. *P. vivax* as the sole cause for severe complicated malaria is well proven and accepted by WHO as well in its treatment schedule.

The *P. vivax* malaria has been reported to result in cerebral malaria, hepatic dysfunction with severe jaundice, acute lung injury, acute respiratory distress syndrome, pulmonary oedema, shock, renal failure, splenic rupture, severe thrombocytopenia, haemorrhage and severe anaemia[3,4].

The appearance of chloroquine resistance in *P. vivax* parasites, the lack of primaquine alternatives to attack the dormant liver-stage hypnozoites, documentation of cases of severe disease, and increasing temperature caused by climate change increase the concern of this disease and its spread.

2. Materials and methods

This was a retrospective study with data collected from case records of patients admitted to a tertiary hospital in a malaria endemic urban area with severe *P. vivax* mono-infection. Patients with evidence of *P. falciparum* or mixed malarial infections were excluded. A total of 30 adult patients were recruited for the study. None of the female patients were pregnant or were in a puerperal period. The age of patients ranged from 18-66 years, and the average was 42 years.

The data were assessed by using the clinical parameters, including patient's history and clinical examination. To detect malaria parasites, conventional thick and thin peripheral blood flows (PBFs) stained with Giemsa were examined under oil immersion and confirmed by immune-fluorescent smear study. Slides were considered negative when there were no parasites in 100 high-power fields.

Furthermore, malaria patients with one of the following

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parameters were defined as severe[1,4]: 1) severe malaria in the form of cerebral malaria, 2) severe anaemia with haemoglobin level (Hb) < 5 mg/dL, 3) severe thrombocytopenia with platelet count < 50 000 /mm^3), 4) pancytopenia, 5) jaundice with serum bilirubin > 3 mg/dL, 6) splenic rupture, 7) acute renal failure with serum creatinine >3 mg/dL, 8) acute respiratory distress syndrome.

3. Results

Hepatic dysfunction with jaundice was present in 13 (43.3%) patients, and the mean serum bilirubin was 3.3 mg/dL (maximum=16.8 mg/dL) with predominant conjugated hyperbilirubinemia. Mean±SD of aspartate aminotransferase (AST) level was (59.3±41.7) IU/L (maximum=189.0 IU/L), mean±SD of alanine aminotransferase (ALT) level was (49.8 ±47.0) IU/L (maximum=136.0 IU/L). Renal dysfunction was present in 8 patients (26.7%). Mean±SD of blood urea level was (44.9±18.9) mg/dL (maximum=108.0 mg/dL) and the mean±SD of serum creatinine level was (1.8±1.1) mg/dL (maximum=4.2 mg/dL). Other causes of renal dysfunction such as hypertension, diabetes mellitus, septicaemia, hypotension, and shock were ruled out by appropriate investigations. Haemodialysis (2-8 dialyses in a patient) was not required for any patient.

Severe anaemia was present in 3 (10.0%) patients, and the mean±SD of haemoglobin level was (10.3±3.6) mg/dL (minimum=2.5 mg/dL). Thrombocytopenia with a mean±SD of platelet count (63 640.0±12 402.9)/mm^3 was observed in 28 patients of whom had bleeding manifestations (minimum=15 000.0/mm^3).

Cerebral malaria was present in 2 patients, both of whom had associated seizures. A Glasgow coma score 5 was observed in these two patients. Other causes of altered sensorium and seizures were ruled out by detailed CSF examination, CT scan of head, fundus examination, and serum electrolytes. Acute respiratory distress syndrome (ARDS) was seen in 1 (3.3%) patient.

Two (6.7%) patients died, of which one had ARDS, jaundice and renal failure, and another had cerebral malaria, jaundice and renal failure.

4. Discussion

Severe and complicated malaria is usually caused by *P. falciparum* but it has been increasingly observed that *P. vivax* malaria can present with severe sequestration and non sequestration related complications.

In the present study, severe thrombocytopenia is the most common manifestation followed by hepatic dysfunction. Among the 30 patients in the study 28 patients (93.3%) had severe thrombocytopenia of whom none had bleeding manifestations. Makkar *et al*[5] and Kakar *et al*[6] have reported cases of *P. vivax* mono-infections presenting with severe thrombocytopenia. The mechanism of severe thrombocytopenia in severe *P. vivax* malaria is poorly understood. Some of the postulated mechanisms of thrombocytopenia are anti-platelet antibody mediated immune destruction of platelets[7], oxidative stress, alterations in splenic functions and a direct interaction between the Plasmodium and platelets[8,9].

Thirteen (43.3%) of the 30 patients presented hepatic dysfunction with jaundice, which was the second most common complication observed in our study. In a prospective study conducted by Kochar in Bikaner, India, among 1 091 admitted adult patients of malaria, 40 patients had severe *P. vivax* malaria[10]. The most common complications observed in that study were jaundice with hepatic dysfunction; followed by acute kidney injury. A clinical study of 110 patients done by Mohapatra *et al*[11] reported severe manifestations rates as jaundice (7.2%), cerebral involvement(0.9%), severe anaemia (7.2%), thrombocytopenia (3.6%) and pancytopenia (0.9%). Hepatic dysfunction or malarial hepatitis was postulated to be due to direct hepatic injury[12].

One patient in our study had ARDS and did not survive. In 2001, Tanios *et al*[13] had reported a similar case of vivax associated ARDS in a 42 year old woman who travelled to Papa New Guinea. *P. vivax* is widely believed not to cause cyto-adherence and micro-vascular sequestration and therefore is unable to cause organ dysfunction[14]. In a prospective study done in Papau on 1 570 cases of severe vivax malaria 78 patients presented with respiratory distress[15]. Studies have shown evidence of sequestration of parasites in lung vasculature during evaluation of lung injury due to *P. vivax* malaria[16].

Severe anaemia as a complication was found in three (10.0%) patients, in our study. In the study done in Papua, Indonesia[15], severe anaemia was the major complication associated with *P. vivax* malaria accounting for 87% of severe disease compared to 73.% (1 144/1 570) of severe manifestations with *P. falciparum* malaria. Severe anemia and hemostatic complications are attributed to cytokines and leukotrienes[7].

Two cases were diagnosed as cerebral malaria in our study. In a study done in Papua[15], 42 among 1 570 severe *P. vivax* infected patients presented with coma. In anther study by Mohapatra[11], 0.9% of cases presented with cerebral malaria. A Japanese case report published in 2003[17], reports *P. vivax* malaria presenting as acute postinfection encephalomyelitis (ADEM). The mechanism behind cerebral malaria in *P. vivax* mono-infections also is not fully understood. Cerebral dysfunction in *P. vivax* malaria may occur through nitric oxide[18,19].

Renal ischemia is the dominant pathogenic mechanism that results in acute tubular necrosis and renal dysfunction in severe malaria[20]. Renal dysfunction was present in 8 (26.6%) patients in our study. The study in Bikaner by Kocher *et al*[10], renal dysfunction was the second most common complication of severe *P. vivax* malaria after hepatic dysfunction.

Microrheologic research that analyzed malaria severity in *P. vivax* infection clearly demonstrated enhanced aggregation, erythrocyte clumping, and reduced deformability affecting microcirculation[21]. Drug resistance has been implicated as a contributor to severity together

with the particularly high regional malaria transmission force[22].

Nucleic acid detection using nested, multiplex or multiplex real-time PCR can detect parasites down to a level of 1 to 5 parasites/μL of blood. PCR can also detect mixed-species infections, since the 18S (small subunit) rRNA genes of *Plasmodium* species are conserved with no cross-reactivity[23]. Rapid diagnostic tests (RDTs) for malaria generally employ immune chromatographic lateral flow technology, in which a blood sample migrates across the surface of a nitrocellulose membrane containing stripes of antibodies specific for different epitopes of a target antigen along with a control antibody[24].

In conclusion, a large-scale study examining pathogenesis of severe disease, clinical spectrum and burden of *P. vivax* malaria in our country is needed. Newer diagnostic tools like PCR, FISH techniques must be practised in confirming the *P. vivax* mono-infections in the large scale studies which are to be done. There is also an urgent need to re-examine control measures that can be implemented against this emerging but neglected aspect of the disease.

Conflict of interest statement

We declare that we have no conflict of interest.

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