PLASMODIUM VIVAX: IS IT CHANGING COURSE?

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ABSTRACT

Objective: To determine the haematological parameters in patients with *Plasmodium vivax* malaria.

Study Design: Descriptive study.

Place and Duration of Study: The study was carried out at the Department of Medicine and Department of Pathology, Military Hospital Rawalpindi, Pakistan from 1st June 2010 to 30th September 2010.

Methodology: Two hundred and sixteen patients were with confirmed *Plasmodium vivax* (*P.vivax*) infection. Demographic and malariometric data of all patients suffering from *P.vivax* was collected on a patient data form. The diagnosis of *P.vivax* malaria was established by peripheral blood film (PBF) and Rapid diagnostic test (RDT). All haematological parameters e.g. white blood cells (WBCs), platelet count, bilirubin levels were noted.

Results: The mean age was 25.10 ± 5.35 years. Out of 216 patients 183 patients (84.7%) were males and thirty three patients (15.3%) were females. Thrombocytopenia was found in 186 patients (86.1%). Leucopoenia was noted in 37 patients (17.1%). Anaemia was found in 17 patients (7.8%). Increased bilrubin levels were noted in 65 patients (30%). Increased alanine transaminase levels were present in 32 patients (14.8%). Nine patients had serum creatinine levels more than 1.2 mg/dl (4.1%).

Conclusion: *Plasmodium vivax* malaria although considered benign has the potential to cause serious haematological derangements in affected individuals

Keywords: Benign tertian, thrombocytopenia, hepatic dysfunction.

INTRODUCTION

Malaria is a devastating parasitic disease deeply associated with socioeconomic burden in many temperate and most tropical countries. Infections with *Plasmodium falciparum* (*P. falciparum*), is associated with the greatest morbidity and mortality (of the four species of malaria parasite that commonly infect humans) and therefore appropriately remained focus of interest for majority of malaria related research. In contrast infection with *P. vivax*, the most frequent and widely distributed cause of recurring (tertian) malaria in humans' is considered a "benign" infection receiving lower priority from researchers, policy makers, and funding bodies[1,2]. Although the emphasis on *P. falciparum* is appropriate, the burden of vivax malaria should not be under appreciated and exacts a significant toll on almost 40% of the world's population[3]. A new evidence based global distribution map of *P. vivax* estimates that 2.85 billion people lived at risk of infection with this parasite in 2009, predominantly in east and central Asia[5]. However, in the absence of a denominator, the true incidence of severe vivax malaria is unknown. Centre for Disease Control (CDC) maintain a National Malaria Surveillance System (NMSS) to collect epidemiological and clinical information on malaria cases diagnosed in the United States. In 2005 the most recent year for which NMSS data are available, 1,528 cases of malaria were reported, of which 337 (22.1%) resulted from *P. vivax infection*[6]. In Pakistan *P. vivax* accounts for 75%, while *P. falciparum* accounts for 25% of the malaria burden[7]. In Punjab; DG Khan, Rajanpur and Muzaffarghar have hotspots for both falciparum and vivax: in Sindh; Tharparkar, Jamshoro and Umerkot have mostly vivax cases: in Baluchistan; Jhal Magsi, Sibi and Jafferabad are continuing to report a considerable number of vivax malaria cases[9]. The

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risk of *P. vivax* thus is cosmopolitan and it is endemic to tropical and subtropical areas of Asia, North and South America, the Middle East, North Africa, and the South Pacific. It has placed huge burdens on the health, longevity, and general prosperity of large sections of the human population. There have also been increasing numbers of case reports describing severe manifestations of vivax malaria in recent years[4]. In this prospective study incidence of various complications in the study population due to *Plasmodium vivax* malaria have been under statistical microscope.

METHODOLOGY

This prospective study was conducted on 216 admitted adult patients presenting in Military Hospital Rawalpindi, Pakistan from 1st June 2010 to 30th September 2010. Malaria was defined as a symptomatic illness associated with any peripheral parasitemia or a positive RDT.

Selection Criteria

Adult patients of both genders presenting with *Plasmodium vivax* infection were enrolled in the study by consecutive sampling. Informed written consent was taken from all patients.

Inclusion Criteria

Both male and female (above 18 years of age) confirmed cases (on PBF and RDT) of *Plasmodium vivax* infection were included in the study.

Exclusion Criteria

Patients who refused to give the written consent, those less than 18 years of age, those with *Plasmodium falciparum* and mixed infection, those who have taken any treatment before presenting to hospital and those with inter-current illness (dengue fever, enteric fever) were not included in the study.

Operational Definitions

- *Plasmodium vivax* malaria was defined as history of fever with demonstration of *Plasmodium vivax* in PBF (Peripheral blood film)/RDT (Rapid Diagnostic Tests).
- Thrombocytopenia was defined as platelet count of less than 1, 50,000 /mcl.
- Leucopenia was defined as total leukocyte count less than 4000/mcl.
- Anemia was defined as hemoglobin of less than 12 g/dl.
- Diagnostic methods used to detect malaria parasites.

Conventional thick and thin peripheral blood films (PBFs) stained with Giemsa were examined under oil immersion. Slides were considered negative when there were no parasites in 100 high power fields. Rapid Detection Test (RDT) was conducted in patients to confirm diagnosis of *P. vivax* when required.

Apart from PBF, laboratory investigations included complete blood count, platelet count, bleeding time, blood glucose, blood urea, serum creatinine, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum electrolytes, complete urine analysis, electrocardiogram, x-ray chest, and appropriate blood test to rule out typhoid fever, hepatitis B and C, leptospirosis, dengue, and infection with human immunodeficiency virus in selected patients.

Data Analysis

All the data was recorded on preformed patient data collection form. Variables recorded included each patient's age, gender and presence of haematological dysfunction.

RESULTS

A total of 216 patients with *Plasmodium vivax* malaria presented in this hospital during the study period. Age group varied from 16 to 40 years. The mean age was 25.10 ± 5.35 years. Males outnumbered females. Out of 216 patients 183 patients (84.7%) were males and 33 patients (15.3%) were females. Thrombocytopenia was the most common finding. Thrombocytopenia was present in 186 patients (86.1%). Severe thrombocytopenia as defined by platelets less than 50,000/mcl was present in 24 patients (11.1%). Leucopoenia as defined by TLC count of

less than 4000 /mcl was present in 37 patients (17.1%). Anaemia defined by Hb% less than 12 g/dl was present in 17 patients (7.8%). Increased bilirubin levels were present in 65 patients (30%). Increased alanine transaminase levels were present in 32 patients (14.8%). Nine patients had serum creatinine levels more than 1.2 mg/dl (4.1%). All the patients survived.

DISCUSSION

Malaria is an extremely common disease caused by four species of *Plasmodium* with the addition of *P. Knowlesi* as a fifth one, causing malaria in some parts of South East Asia[1]. *P. vivax* has long been neglected and mistakenly considered inconsequential. It is now entering strategic debates on malaria epidemiology, control, drug resistance, pathogenesis and vaccines[2]. Medical community world over is now getting aware and concerned about the widespread reports of the illness and death caused by 300 million cases of vivax malaria every year[2,3]. While more attention is focused on more prevalent and more deadly of the human malarial parasite i.e. *P. falciparum*, it is increasingly been realized that benign designation associated with vivax malaria might be a misnomer. Most certainly it is inappropriate to call it a benign parasite. It has a propensity to significant anaemia, thrombocytopenia and violent fevers[4-6]. Uncomplicated vivax malaria is associated with significant morbidity. Furthermore, recent publications of several well documented studies have highlighted and validated that like *P. falciparum*, *P. vivax* malaria can frequently cause severe and complicated clinical syndromes that may result in death[4,6,9].

Profound thrombocytopenia is a well recognized complication of falciparum malaria but there have been reports regarding thrombocytopenia in vivax malaria[3,6]. In our study thrombocytopenia was a common finding in patients suffering from Vivax malaria. Direct lytic effect, immunological reactions, splenic sequestration and oxidative stress are some of the suggested mechanisms of thrombocytopenia[7]. Although 86.1% of the patients in this study had low platelet counts none of them had any bleeding complications and none of the patients required transfusion of platelets. Lowest count observed in our study was 14,000/ul. Severe thrombocytopenia as defined by platelet count of less than 50,000/ul was observed in 24 patients (11.1%). In a recent Indian study thrombocytopenia was observed in 96% of the patients of which 6% had platelet of less than

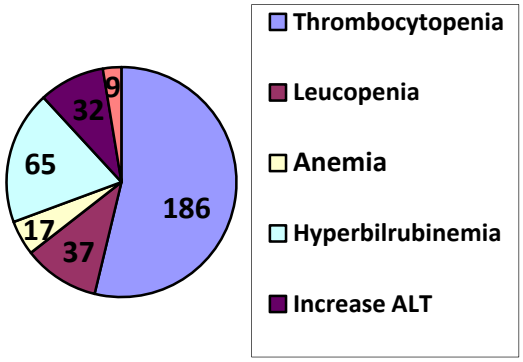

Figure-1: Hematological parameters in patients with *P. vivax* infection.

20,000/ul .

It is uncommon to have hepatic dysfunction in vivax malaria although malarial hepatitis has been well described in falciparum malaria[8]. In our study 30% of patients had indirect hyper bilirubinimia and 14.8% had raised liver enzymes indicating liver injury by the parasite. There is a wide spectrum of renal involvement in malaria which is certainly more common in falciparum infections. There are reports of acute renal failure, electrolyte imbalance, active urinary sediment and proteinuria in vivax malaria[9]. A total of 9 patients (4.1%) had raised serum creatinine in our study. No patient went into acute renal failure. Intriguingly, 37 of our patients (17.1%) showed evidence of leucopenia as defined by a total leucocyte count of less than 4000. Although changes in leucocyte count have been reported in other studies from Papua New Guinea. However,

this is a not a very frequently observation of *Plasmodium vivax* malaria.

Complications in severe malaria are either sequestration related such as cerebral malaria, renal dysfunction, hepatic dysfunction and ARDS or non sequestration related including anemia or thrombocytopenia[9-11]. Non sequestrations related are known to occur in *Plasmodium vivax* malaria quiet frequently. Anaemia as defined by Hb% of less than 12 g/dl was present in 17 patients (7.8%) in our study. In an Indian study by Kochar and others, 40 patients with severe vivax malaria were reported[8]. Most common complication was hepatic dysfunction followed by renal failure. Cerebral malaria was observed in 5 patients. Severe anaemia was observed in 13 patients. A recent study from Indonesia shows severe anaemia to be the most common complication[12]. Cerebral malaria has been reported in one patient from Pakistan.

The mechanism of thrombocytopenia in malaria is not clearly known[3]. Fajardo and Tallent in 1974 demonstrated *P. vivax* within platelets by electron microscopy and suggested a direct lytic effect of the parasite on the platelets[5]. Both non immunological associated IgG antibodies that bind directly to the malarial antigens in the platelets have been recently reported to play a role in the lysis of platelets and development of the thrombocytopenia. There were 37 patients in our study (11.1%) who had severe thrombocytopenia. Of 173 cases of malaria in U.S solders reported by Martelo et al in 1969, 93% had *P. vivax* but only 15% had thrombocytopenia with no documentation of lowest platelet count. In Horstmann's series the lowest platelet count in 39 cases of vivax malaria was 44,000/uL. Pukrittayakamee et al. describes a case of volunteer experimentally infected with the Chesson's strain of *P. vivax* with a platelet count of 20,000/uL[3]. Recently a case of vivax malaria associated with an initial platelet count 5,000/uL was reported from Pakistan[13].

Exact pathogenesis of *P. vivax* remains partly understood because of paucity of research in the area. *P. vivax* was considered incapable of micro vascular sequestration and cytoadherence. However recent observations are pointing to the contrary. Recently it has been clearly demonstrated that in severe vivax infection, there is enhanced aggregation, erythrocyte clumping and reduced deformability effecting microcirculation.

A parasite considered historically benign seems to be changing course and behaviour. The reasons for these changes are subject of debate and further research regarding the host response and the pathobiology of the parasite. Thrombocytopenia is an almost invariable association with vivax malaria as shown in our study and supported by other studies in India, Indonesia and Papua New Guinea. Although there was no mortality observed in our study, a significant number of patients had evidence of multi organ involvement. There are numerous reports of a severe and complicated course associated with vivax malaria. Vigilance and close monitoring is required in a disease which has the potential for malignant transformation from benignity.

CONCLUSION

Our prospective study supports and *P. adds* further weight to the body of evidence highlighting that infection due to *P. vivax* is not always benign. Benign tertian malaria generally has an uncomplicated course but sporadically, all complications usually associated with *P. falciparum* malaria have also been reported in vivax malaria. There is frequent association with deranged parameters like anaemia, thrombocytopnia and derange renal and liver functions.

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