AFEBRILE MALARIA

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ABSTRACT

Objective: To study the presentations of afebrile malaria with respect to febrile malaria.
Study Design: Cross sectional descriptive.
Place and Duration of Study: Combined Military Hospital (CMH) Mangla Cantt, from Jan 2015 to Jan 2017.
Material and Methods: A retrospective cross sectional descriptive study was conducted on patients received at CMH Mangla during the study period. Permission from the ethical committee of hospital was obtained for the study. Malaria was diagnosed by exam of peripheral blood film slide on Leishman,s stain. Typing of the parasite was done using ICT immunochromatographic strip test. All consecutively advised malarial parasite (MP) tests on febrile and afebrile patients were included in the study. All repeated MP test on the same patients were excluded from the study. No co-incidental/asymptomatic case was diagnosed or included in the study.
Results: A total of 5372 MP tests of patients were advised out of which total 1120 cases were reported positive for malaria infection during above study period. A total of 205 cases of suspected afebrile malarial patients were advised MP test. Out of which 116 cases of afebrile malaria were confirmed at Lab. The percentage ratio of total positive MP test was 21%. The ratio of positive febrile to afebrile total MP positive cases was 10:1. Among 116 afebrile patients the presentations were refractory anemia in 42 cases, elevated ALT in 35 cases, thrombocytopenia in 3 cases, & jaundice in 8 cases. All presentations of afebrile malarial patients were normalized after antimalarial treatment. Data were analyzed in excel. Descriptive statistics was applied on qualitative variables. Frequency and percentage documented.
Conclusion: Malaria without fever is a statistically significant cause of morbidity among patients. Although simple to diagnose and easy to treat, omission of lab diagnosis leads to accumulation of untreated cases of afebrile malaria who are advised expensive and time wasting investigations burdening the Medicare system.

Keywords: Afebrile, Alanine aminotransferase, Malaria, Refractory anemia, Thrombocytopenia.

INTRODUCTION

Malaria without fever is symptomatic disease caused by plasmodium infection in which fever is absent. Today malaria is the 4th leading cause of disease burden in developing countries[1,2].

Although malaria is recognized as major cause of fever among patients received at military hospitals, yet malaria without fever is a big miss among afebrile chronically ill patients[3]. Among American troops returning from Afghanistan in 2002, the median time to diagnose malaria was nearly 8 months after their home return. Afebrile malaria was observed commonly in pregnancy, plasmodium falciparum malaria, patients at extremes of age, troops on chemoprophylaxis for malaria, recurrent infections of malaria, immune-compromised patients and patients with end stage organ failure[1,5,6].

Malarial plasmodium is parasites of five different species[1,6,7,9].

Plasmodium falciparum malaria can occur without mosquito bite by recrudescence. Plasmodium ovale, malariae & vivax malaria can occur without mosquitoe bite by recurrence. Incubation period of malaria is upto three years. These stated facts undermine the seasonal and expected incubational pattern of disease[10-12].

Afebrile malaria is (premunition), a delayed clinical presentation of acute infection due to partial humoral immunity by IgM, IgG, and IgA antibodies against plasmodium toxins, or

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Received: 14 Apr 2017; revised received: 02 Jul 2017; accepted: 10 Sep 2017

incomplete treatment which results in subcritical parasitemia[10-12].

For *P. falciparum*, the Erythrocyte-binding antigen 175 (EBA-175) is required for erythrocyte adhesion and invasion. For *P. vivax*, this receptor is related to the Duffy blood-group antigen Fya or Fyb.

The disease in human beings is caused by, the direct effects of the asexual parasite, RBC invasion, RBC destruction and by the hosts immune reaction[2,13,14].

During intrahepatic or pre-erythrocytic merogony, the swollen infected liver cells eventually burst, discharging motile merozoites into the bloodstream. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain inert for a period ranging from 3 weeks to ≥1 year before reproduction begins[1,15,16]. These dormant forms, or hypnozoites, are the cause of the relapses that characterize infection with these two species. In *P. Falciparum* sequestration of infected RBCs in brain & kidney is cause of later recrudescence[1,17].

In *P. falciparum* infections, membrane protuberances appear on the erythrocyte's surface after the red cell's invasion. These "knobs" present erythrocyte membrane adhesive protein (PfEMP1) that mediates cytoadherence to receptors on venular and capillary endothelium[17,18]. The processes of RBC cytoadherence, RBC resetting, and RBC agglutination are central to the pathogenesis of falciparum malaria. They result in the sequestration of RBCs containing mature forms of the parasite in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism. Sequestered parasites continue to develop out of reach of the principal host defense mechanism, the splenic processing and filtration. In the other human malarias, sequestration does not occur. Parasites may persist in the blood for months or years (or, in the case of *P. malariae*, for decades) if effective treatment is not given[18-20].

This study was conducted to specifically target segment of afebrile symptomatic malaria patients who had measureable secondary feature which were reversed to normal after effective eradication of plasmodium parasite. Aim is to enlighten the clinicians to advise laboratory diagnostic tests for malaria even in the absence of fever if any of the measureable secondary features is observed in their patients.

MATERIAL AND METHODS

A descriptive cross sectional study was conducted on all cases of laboratory diagnosed malaria at CMH Mangla between Jan 2015 to Jan 2017. Total sample of 1120 cases of malaria were included in the study by non-probability consecutive sampling technique. This sample study included total of 205 suspected cases of afebrile malaria comprising patients with refractory anemia, thrombocytopenia, leukocytosis and elevated alanine transaminase (ALT) or bilirubin with negative viral screen in the study. All these cases were advised MP test. Only thin blood film was examined. A total of 116 cases of afebrile malaria and 1004 cases of febrile malaria were reported positive by laboratory. Repeat MP exam of the same patient were not added to the total count. Coincidental laboratory finding of plasmodium or asymptomatic carrier and patients with intermittent fever were not included in afebrile category. Demographic and clinical data was collected in a predesigned performa. This study was irrespective of sex, race, ethnicity and geographical distribution. Peripheral smear stained by Leishman,s stain were examined under microscope for diagnosis of malaria. All slide negative cases were checked negative on ICT. If positive on smear visual reconfirmation of all cases was done by the author, typing by using ICT (α easy check 4758 Beechnut Street, Houston TX USA 77096) was done for confirmation. ICT is immunochromatographic capture assays with monoclonal antibodies to species-specific antigens (histidine-rich protein2 [PfHRP2]), aldolase of plasmodium falciparum and conserved plasmodium antigens (lactate dehydrogenase). For recording secondary measurable feature following cut off levels were laid. Anemia (Hb<9 gm/dl), Thrombocytopenia

platelet count (<100,000/µL) Jaundice Serum bilirubin >18 micro m/l & raised ALT >55 IU/L, Leukocytosis (>11,000/µL). Haematology counter Sysmex XP-100 & automated chemistry analyzer Selectra Pro-M were used for measurements. Data was analyzed using percentage of ratios.

RESULTS

in this study total number of patients was 5372. Comprising a total of 5167 cases of suspected febrile malaria and 205 cases of suspected afebrile malaria. Among febrile patients 51% were falciparum, 24% were mixed and 25% vivax infection (table-I). Among the afebrile malaria patients 44% were falciparum and 12% mixed and 54% were vivax infections (table-II).

Table-I: Febrile malaria total positive cases 1004/5372.

Secondary analytical features	Number	Percentage Ratio
Anemia	387	38.5%
↑ ALT	325	32.4%
Thrombocytopenia	365	36.4%
Jaundice	12	1.2%
leucocytosis	24	2.4%
Nil	168	17%

Table-II: Afebrile malaria total positive cases 116/205.

Secondary analytical features	Numbers	Percentage ratio
Refractory anemia	42	36.2%
↑ ALT	35	30.2%
Thrombocytopenia	31	26.7%
Jaundice	8	6.8%
leucocytosis	24	20 .7%

DISCUSSION

Common clinical presentations in afebrile malaria were weakness, headache, body ache, back ache, joint pains, jaundice, dizziness, vertigo, altered behavior, acute psychosis. The probable cause of afebrile malaria in this study was pregnancy, drug resistance or malaria chem-oprophylaxis during UN Missions in Africa.

Anemia (Hb <9 gm/dl) pregnancy, 34 out of a total of 42, were the largest segment of refractory anemia patients[21,22] who responded to antimalaria therapy with rapid improvement in Hb and generalized well-being.

Hb<9 gm/dl was taken as positive finding; it results from accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. Splenic immunologic and filtrative clearance functions are augmented in malaria, and the removal of both parasitized and ***uninfected*** erythrocytes is accelerated. The spleen is able to remove damaged ring-form parasites and return the once infected erythrocytes to the circulation, where their survival period is shortened. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures.

Chronic fatigue was the most common complaint made by patients who were later diagnosed with afebrile malaria with or without anemia.

Thrombocytopenia, decreased platelet count (<100,000/µL) is due to increased peripheral platelet sequestration and destruction in reticulo-endothelial tissues. Thrombocytopenia was observed 60% with falciparum infections and 40% with vivax malaria. Thrombocytopenia occurrence rate was 36.4% in febrile and 26.7% in afebrile patients[19,20].

Leukocytosis (>12,000/µL) increase in absolute neutrophil count occurs in acute

response to foreign antigen of plasmodium and bacterial superadded infection. Occurrence rate was 2.4% in febrile and 20.7% in afebrile patients.

Mild jaundice and raised ALT. Jaundice with serum bilirubin >18 µm/l was observed in 6.8% of afebrile patients[19,20]. Hepatocytic injury and cholestatic components of jaundice results when infected hepatocytes are destroyed by hepatic merogony and CD4 + and CD8 + T cells which kill intrahepatic parasites. Hemolytic component of jaundice occur due to shizogony of infected RBCs and by cell-mediated and antibody-dependent cytotoxicity to kill intra-erythocytic parasites.

In this study, four soldiers returning from operational area in Waziristan presented after 3 months with non- viral jaundice which normalized after effective antimalarial treatment. ALT was raised in upto 30.2% of afebrile malaria patients,with and without jaundice. Observed elevation was between 56-200 IU/l. All cases reverted back to < 55 IU/l after anti malarial treatment. ALT elevation was observed most frequently in combination with thrombocytopenia and anemia.

CONCLUSION

Afebrile malaria is prevalent among patients presenting with chronic fatigue and laboratory derangements. More resources should be invested in acquiring better stains and allied facilities for diagnosing plasmodium infection in hospital laboratories.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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