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RESEARCH ARTICLE

PROFILE OF HEPATO-RENAL DYSFUNCTION IN MALARIA.

Dr. Sumitsawhney.

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Abstract

Introduction: Severe malaria infection is increasingly observed now a days in this region of Rohilkhand. Organ failure is caused by mechanism of inflammation as well as sequestration. In this study we have tried to explore the hepato-renal dysfunction in malaria.

Material and Methods: Fifty adult malaria proved cases over the period of one and half year were included in this study. Malaria was detected with smear or rapid diagnostic test for malarial parasite or malaria antigen (LDH) spot test. They were subjected to detailed history, physical examination, course of the disease, hepatic and renal function test along with routine investigations.

Result: 38% were of mixed infection, 28% *P. vivax* and 34% *P. falciparum*. Amongst organomegaly the spleen was enlarged in 44% of cases and hepatosplenomegaly in 24% of cases. Icterus was seen in 52% of cases with hyperbilirubinaemia (S.bilirubin>2.5mg) in 62% and raised transaminases more than two folds in 62% of cases. Patients with renal dysfunction presented with electrolyte abnormality (S.sodium<135meq/l in 30% cases, S.potassium>5.5 meq/l in 12% cases) abnormal urinary sediments in 54% cases with increased protein excretion (>500 mg/day) in 36% of cases. Blood urea was raised (> 80 mg %) in 28% and serum creatinine in 20% of cases (>2.6 mg%).

Conclusion: Malarial infection i.e. *P. vivax*, *P. falciparum* and mixed infection is an important cause of hepato-renal dysfunction which usually lead to acute renal failure and/or hepato-renal failure. Fatality of *P.vivax* is equally important in comparision to *P.falciparum* and mixed infection.

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Introduction:-

Malaria is a disease of tropical and subtropical climates and has been enriched in India for countless year. Recent studies suggest the burden of disease may actually be increasing with increase in mortality and morbidity. Complications in severe malaria are seen as either sequestration (cytoadherence and rosetting) related such

as cerebral malaria or non-sequestration related such as anemia and thrombocytopenia. Sequestration has not been thought to be part of pathophysiology of *P.vivax* infection but with mentioned complications that assumption must now be challenged. Laboratory and clinical studies has suggested equal parasite load *P.vivax* excites greater inflammatory response that does *P. falciparum*.^{1,2}

The presentation of malaria in India varies from febrile illness to various systemic manifestation which are characterised by severe anemia, jaundice, acute renal failure, coma, adult respiratory distress, Disseminated intravascular coagulation (DIC) and eventually a fatal circulatory failure. The clinical spectrum of hepato-renal involvement in malaria varies widely from urinary sediment abnormality, mild proteinuria, jaundice and fluid electrolyte changes to hepato-renal or acute renal failure. The overall incidence varies from 4-17.2% or even more.^{3,6}

This study is to evaluate the frequency and severity of hepato-renal dysfunction in malaria in this region of Rohilkhand, U.P.

Methodology:-

This is a hospital based descriptive study conducted at tertiary care teaching hospital of Rohilkhand (SRMS-IMS, Bareilly) from January 2012 – June 2013. The diagnosed malarial patients admitted in the medical unit of hospital were recruited in this study. The study was designed to include the demographic (age, sex, residence and history of travel) clinical information, biochemical and haematological changes observed in the patients. The blood sample was obtained at the time of admission to confirm the malaria by thick and thin blood film and rapid diagnostic test for malaria (RDT). Parasite count has been made from the peripheral blood smear. Parasite counts were expressed as number of asexual parasite per microlitre of blood and were calculated from the number of parasitized cells per 200 leukocytes in a thick film stain with Giemsa stain i.e. number of parasite X Total Leukocyte Count/200.⁷ This procedure was followed for each species. Gametocyte counts are made from thick films.

Laboratory investigations included full blood count, hemoglobin, liver function test, blood urea, serum creatinine and electrolyte levels, blood sugar level, Ultrasonography abdomen was also performed wherever is needed. Patients with hepato-renal dysfunction the liver function and renal function test were again performed every third day. Patients with clinical history and/or findings suggestive of chronic hepatic or renal disease, drug induced hepatitis, reactivity to hepatitis B surface antigen. Hepatitis C antibodies and Hepatitis A and E, IgM were excluded from the study. Management was done as per standard guidelines for malaria and supportive management for complications. Patients were discharged from the hospital after significant improvement in clinical as well as haematological and biochemical parameters.

Results:-

Fifty diagnosed patients of malaria were enrolled in this study out of which, 32% of cases were from 3rd decade of life, with mean \pm SD - 38.98 ± 17.05 years, and male to female ratio of 1.08:1. Thirty eight percent were of mixed infection and quite a good number of cases (28%) were of *P. vivax* infection (Table 1). Intermittent fever was the most common (98%) clinical presentation with its typical paroxysm whereas continuous fever was present in 4% of cases (Table 2). In addition to fever, complaints like, headache, bodyache (64%), nausea and/or vomiting (44%), and generalized weakness (84%) were seen. Amongst organomegaly, splenomegaly was present in 44% of cases and hepatosplenomegaly in 24% of cases (Table 3). Icterus was present in 52% of cases. Thirty nine cases were anemic (hemoglobin <12 gm%) and 8 of them were severely anemic having haemoglobin less than 5 gm%. Systolic BP less than 100 mm of Hg was noted in 24 % of cases (Table 3).

Routine investigation (Table 4) revealed anemia (Hb less than 12 gm%) in 39 (78%) of cases. Leukocytosis (TLC > 10,000/ cubic mm) was seen in 60% of cases while leukopenia (TLC < 5000/ cubic mm) in 12 % of cases. Thrombocytopenia (platelets \leq 40,000/ cubic mm) was present in 20 % of cases with bleeding tendency in 10% of cases (Table 4). Ten cases had parasitemia of 20-30% with fulminant parasitemia > 30%, was in 10% of cases. CNS involvement in the form of semi consciousness and meningeal irritation signs were present in four and two cases respectively who had parasitemia of more than 30% i.e. fulminant type and amongst them two cases expired who had multi organ failure with fulminant type malaria.

Abnormal liver function test manifested as (Table 5) hyperbilirubinemia (serum bilirubin > 2.5 mg%) in 31 or 62% of cases with frank jaundice in 26 cases. The serum transaminases raised more than two folds in 35 cases (raised SGPT- 62%, raised SGOT- 70%). Abnormal liver function test was more in mixed infection 14 cases.

Renal dysfunction was seen in the form of urine changes (Table 6) as proteinuria >500 mg/day (36%) and raised specific gravity > 1.020 (40%). Biochemical changes revealed as contributory factors to renal dysfunction, the raised serum creatinine (>2.6 mg%), hyponatremia (<135 meq/l) and hyperkalemia (>5.5 meq/l) in 20 %, 30% and 12 % of cases respectively.

Renal biopsy could be done in one case, whose histopathological finding was suggestive of proliferative glomerulonephritis.

All patients were managed with standard course of anti-malarial drugs (chloroquine, artesunate and mefloquine), and conservative management with special attention to maintain fluid electrolyte balance, normoglycemia and combat hepatic and renal dysfunction. Hemodialysis was performed in six cases who had oliguria, anuria and two of them expired. All these six cases had severe parasitemia with hypovolemia and hypotension with septicemia. Two patients who expired, one of them had mixed infection and the other had vivax infection.

Discussion:-

Malaria is a major public health problem in India including other countries of South East Asia, Vietnam and Africa, which is now becoming endemic. The situation is more alarming with increasing incidence of falciparum, as well as vivax and mixed infection, in this region of Rohilkhand. Early identification of malaria and related condition and their management is extremely important to prevent morbidity and mortality related to it. Most of the studies reveal the predominance of males^{2,7,8} but present study revealed no difference in sex, with male to female ratio of 1.08:1. As reported by most of the studies we also observed that many of the patients were between the age group of 21-50 years (68%) with high incidence in age group of 21-30 years (32%). Most of the studies revealed seasonal variation and noted the increase in number of malaria with the onset of rainy season and present in whole rainy season, later on decline.⁸⁻¹⁰ Our study is in confirmity of the reported seasonal variation.

In the present series of cases there were almost equal number of cases of *P. vivax* (14 cases), *P. falciparum* (17 cases) and mixed infection (19 cases). Vivax malaria was always described as a benign disease. However in the past few years, many cases of severe vivax malaria were seen with fatal outcome.¹¹ There were two deaths in this series and one of them was of severe vivax malaria and other mixed infection. They were above 51 yrs of age (i.e. 56 yrs and 64 yrs males). The exact causes of changes in the clinical profile of vivax malaria is uncertain. They may include genetic alteration of the parasite or change in vector and its biting habit.

The mechanisms of organ involvement especially in vivax malaria are debatable. As a whole the enhanced inflammatory responses as well as the sequestration of parasitized red cells in micro circulation were thought to be the possible mechanism.^{1,11} Audrade et al¹² found a strong linear trend between increased level of C-reactive protein, TNF-alpha, IFN- gamma, IFN-gamma:IL-10 ratio and the disease severity of malaria. Price et al¹³ reported that the plasma concentration of TNF alpha are higher in vivax malaria as compared to falciparum malaria with similar degree of parasitemia.

According to World Health Organisation (WHO), apart from jaundice, signs of hepatic dysfunction are unusual. In recent years there has been increasing number of reports favouring existence of the malarial hepatopathy, from Asian countries especially from India.¹⁴ The majority of the cases have either isolated infection with *P. falciparum* or a mixed infection with both *P. falciparum* and *P. vivax*.¹⁵⁻¹⁷ In the present series quite a good number of cases had hepatopathy which was in association with renal involvement but few of them had hepatopathy only. Jaundice was seen in 52% of cases even though hyperbilirubinemia (S. bilirubin > 2.5 mg/dl) in 62 % of cases with raised serum transaminases more than two fold increase indicating towards hepatic involvement in malaria. Jaundice seems to result from either hemolysis or/and hepatic involvement. Hemolysis significantly contributes to the rising bilirubin in severe malarial infection. Parasites infect a large number of cells which are then destroyed in the spleen, resulting in hemolytic anemia and hyperbilirubinemia. Quite a good number of cases with *P. vivax* (20%) had hepatic involvement even though most studies revealed incidence is less in *P. vivax* as compared to *P. falciparum* malaria.¹⁴⁻¹⁷

There are two major renal syndromes associated with malaria¹⁸.

1. A chronic and progressive glomerulopathy that mainly affects African children, classically complicating quartan malaria.
2. Acute renal failure (ARF) associated mainly with falciparum malaria in South East Asia, India and Sub Saharan Africa.

Renal dysfunction (ARF) complication mainly falciparum malaria is fewer than 1 to 4.8% of native patients in endemic areas and it is much more frequent in non immune persons and reported figures usually are 15-33%.^{4,7,8,18,19} Present series revealed renal dysfunction (ARF) in 20% of cases as evidenced by raised serum creatinine with oliguria, anuria (28%) and anemia.

Acute renal failure i.e. renal dysfunction in malaria is multifactorial and two mechanisms are involved in the pathogenesis of nephropathy in malaria^{4,20,21} i.e., impaired microcirculation due to parasitized RBC which resulted in renal ischemia and non specific effects of infection like hypovolemia, hypotension, jaundice, intravascular hemolysis, coagulation and endotoxemia. Hypovolemia is supposed to be common cause of acute renal failure which was seen in 44% of cases as a result of nausea and/or vomiting and loose motions. Volume depletion is the commonest cause of ARF in present study. Evidence of volume depletion was present in as much as 72% of cases which may result from nausea, vomiting, less fluid intake, pyrexia and increased vascular permeability as a result of release of catecholamines in severe infection.^{4,18,20}

Renal involvement in the form of electrolyte abnormalities has also been seen during malarial infection.^{4,18,20,22} In the present series electrolyte abnormalities were seen in form of hyponatremia (30%) and hyperkalemia (12%). Hyponatremia might be due to internal dilution and true sodium wastage that occurs before the onset of oliguria has been reported. Hyperkalemia¹² is striking and often fatal (4%). It is attributed to hemolysis, rhabdomyolysis and acidosis, particularly in the presence of impaired renal function. Lactic acidosis is common, reflecting the degree of tissue hypoxia. This will result in kidney damage in the form of acute tubular necrosis, interstitial nephritis and glomerulonephritis. This kidney damage will result in various urinary findings in form of proteinuria (>500mg – 1g/day, 36% of cases). Proteinuria is usually transient. Urinary protein consists of albumin and both micro and macro molecules of proteins. Urinary sediments revealed hematuria (12%), granular cast (10%) and pus cells (20%).

Malarial infection both *P. vivax* and *P. falciparum* alone or mixed is an important cause of hepatorenal dysfunction which usually lead to acute renal failure and/or hepato-renal failure. Renal involvement varies widely from mild proteinuria in association with urinary sediment changes in acute renal failure. Hepatic involvement will result in jaundice with raised levels of serum transaminases and rarely hepatic failure but may continue with renal failure leading to hepato renal syndrome.

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