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Profile of Acute Kidney Injury in Plasmodium Vivax Malaria

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ABSTRACT
Background: *Malaria due to plasmodium vivax(P. vivax) increased now days. Acute Kidney Injury (AKI) is one of the serious complications of P. vivax malaria, worsening its prognosis.*
Objectives: *To describe prevalence, clinical characteristics, mortality predictor, outcome and need of renal replacement therapy in patients of AKI associated with P. vivax malaria.*
Materials & Methods: *This is the prospective observational study conducted in Sarojini Naidu Medical College, Agra between November 2015 and October 2016. It included all cases presented with fever with evidence of AKI. Diagnosis of malaria was confirmed by thick and thin blood films stained with Leishman's stain for malaria parasite and P. vivax cases underwent for OPTIMAL malarial antigen test to rule out mixed malarial infection.*
Result: *AKI occurred in 37 patients (33.03%)out of 112 patients of P. vivax malaria. The clinical feature of P. vivax malaria associated with AKI includes fever (100%), jaundice (62.1%), pallor (56.7%), hypotension (45.94%), hemolysis (51.35%), disseminated intravascular coagulation (DIC) (35.1%), sepsis (29.7%), thrombocytopenia (78..37%), cerebral malaria (2.7%), nausea and vomiting (100%), oliguria (67.56%), acute respiratory distress syndrome(ARDS) (2.7%). All 37 patients with AKI received artesunate. Mortality in P. vivax malaria cases was found 7 (6.25%) out of 112 patients. Out of 7 mortality, 6 patients were suffered from AKI with other complications. Mortality in AKI cases 6 (16.21%), seven patients underwent for hemodialysis. Oliguria on admission, hyperbilirubinemia, hyponatremia, hypotension, metabolic acidosis, DIC, cerebral anaemia and ARDS were main predictor of mortality in our study.*
Conclusion: *AKI is now common in P. vivax malaria and has significant mortality and morbidity. Its early recognition and management can improve the outcome.*
Keywords: *Plasmodium vivax, acute kidney injury, dialysis.*

INTRODUCTION

Malaria remains an extremely destroying global health problem.It is the common cause of mortality in various tropical and subtropical regions. Approximately half of the world population is prone to malaria.Majority of the malarial infected cases as well as deaths occur in sub-Saharan Africa, the disease is seen in about 100 countries, Indian subcontinent and Brazil contributing nearly two thirds of these cases[1].

The WHO estimates that in 2010 there were 219 million cases of malaria resulting in 660,000 deaths[2], equivalent to roughly 2000 deaths every day[3].Using a different set of predictive models the number of documented and undocumented deaths in 2010 was estimated at 1.24 million[4]. This is up from an estimated 1.0 million deaths in 1990[5].

Almost all complications and deaths from malaria are caused by plasmodium falciparum[6]. Recently a changing trend has been observed not only in the clinical manifestations but also the pattern of complication in malaria. Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria, whereas today the combination of jaundice and renal failure are more common[7].

Prevalence of acute renal failure (ARF) in malaria all over the world has been reported as 0.57% to 60%[15]. In south-east Asia there is an up surge in the overall incidence of malarial ARF and has been reported in between 13% to 17.8%[8].ARF occurs commonly in plasmodium falciparum malaria, although its rare occurrence has been reported in P. vivax malaria[9]. Established ARF is usually oliguric,but urine output may also be normal or even increased in the presence of increasing serum creatinine value.

Jaundice is the most common association with malarial ARF (MARF), occurring in more than 75% of cases[10]. ARF usually associated with intravascular hemolysis or heavy parasitaemia[11].

MATERIALS AND METHODS

The present study is a hospital based prospective observational study carried out between November 2015 and October 2016 in Sarojini Naidu Medical College, Agra. The study were done among patients admitted in the P.G. Department of Medicine, the cases of fever suspected to have malaria were evaluated by thick and thin smear stained with Leishman's stainfor malaria parasite and P. vivax cases underwent for OPTIMAL malarial antigen test to rule out mixed malarial infection. A total of 112 patients of P. vivax were taken for study

INCLUSION CRITERIA

1. Patient willing to give consent
2. Older than 14 years of age and of either sex
3. Thick and thin peripheral smear positive for P. vivax

EXCLUSION CRITERIA

1. Patients with mixed malarial infection and dengue
2. Pregnant female
3. Age below 14 years
4. Other causes of fever

METHODOLOGY

All the patients were subjected to renal function test including blood urea and serum creatinine, urine microscopy, complete hemogram, serum electrolytes, plasma blood sugar, liver function test and ultrasonography of abdomen.coagulation profile for disseminated intravascular coagulation, arterial blood gas analysis, Serum leptospira antibody, HIV, HBsAg and anti HCV were carried out when indicated. Further all patients were subjected to peripheral smear examination. Thick and thin smears were prepared and examined.

The management of plasmodium vivax with malaria included use of antimalarials (parentralartesunate), fluid and electrolyte management, adequate supportive therapy, avoidance of nephrotoxic drugs and renal replacement therapy[12].

Patients were followed until discharge or death.

AKI was defined as serum creatinine $\geq$ 3 mg/dl and urine output < 400 ml/day with normal kidney sizeon ultrasonography, as per the definition by World Health Organization(WHO)[13].

Statistical test was performed using 't' test. The statistical significance of association between of AKI and mortality or dialysis requirement was assessed by chi square test. The degree of association was estimated using odd's ratio with 95% confidence interval.

(1) Distribution of Non-AKI & AKI P.vivax malaria patient

Total no. of P.Vivax Malaria	112
Total no. of non AKI cases in patients with P.Vivax Malaria	75
Total no. of AKI cases in patients with P.Vivax Malaria	37
Prevalence of AKI in P.Vivax Malaria	33.03%

(2) Age-Sex wise prevalence of AKI in patients of P.vivax malaria

		Non- AKI	AKI
Age (years)	<30	49	23(62.16%)
	31-45	15	7 (18.91%)
	46-60	8	5 (13.51%)
	>60	3	2 (5.40%)
Sex	Male	47	11(29.7%)
	Female	28	26(70.3%)

(3) Clinical Features of patients with Vivax malaria

Clinical Features	Non-AKI N=75	AKI N=37
Fever	75(100%)	37(100%)
Jaundice	15(20%)	23(62.1%)
Pallor	26(34.6%)	21(56.7%)
Hypotension	5(6.6%)	17(45.94%)
Hemolysis	5(6.6%)	19(51.35%)
DIC	7(9.3%)	13(35.1%)
Splenomegaly	16(21.3%)	13(35%)
Hepatomegaly	10(13%)	8(21%)
Sepsis	7(9.3%)	11(29.7%)
10.Thrombocytopenia	55(73.3%)	29(78.37%)
11.Altered sensorium	Nil	1(2.7%)
12.Nausea & vomiting	3(17.3%)	37(100%)
13.Oliguria	Nil	25(67.56%)
14.ARDS	Nil	1(2.7%)

(4) Possible features causing AKI in patients of P.vivax Malaria (n=37)

Etiological Factors	No.(%)
Heavy parasitemia	17(45.94%)
Hypotension	15(40.54%)
Hyperbiliruminemia	23(62.16%)
Intravascular Hemolysis	19(51.35%)
DIC	13(35.13%)
Volume Depletion	17(45.94%)
Sepsis	11(29.72%)

(5) Renal manifestation in patients of P.vivax Malaria associated Acute kidney Injury (n=37)

Renal manifestations	No.(%)
Oliguria	17(45.94%)
Uremic complications	
-Encephalopathy	1(2.7%)
-Pericarditis	2(5.40%)
Hyponatremia	11(29.72%)
Hyperkalemia	3(8.1%)
Metabolic acidosis	5(13.51%)
Urinary sediments	6(16.21%)
Proteinuria(<1gm/day)	3(8.1%)
Volume overload	3(8%)

(6) Indicators of Mortality in P.vivax Malaria associated with acute kidney injury

Parameters	No. of cases (37)	Survived (31)	Expired (6)
Oliguria/Anuria on admission	17	13(41.9%)	4(66.6%)
Hyperbilirubinemia	23	18(58.00%)	5(83.30%)
Hyponatremia	11	09(29.00%)	2(33.30%)
Hypotension	17	14(45.10%)	3(50.00%)
Metabolic acidosis	5	04(12.90%)	1(16.60%)
DIC	13	10(32.25%)	3(50.00%)
Cerebral malaria	1	Nil	1(16.60%)
Anaemia	21	17(54.80%)	4(66.60%)
ARDS	1	Nil	1(16.60%)

(7) Requirement of dialysis

Dialysis	Non AKI	AKI
Not done	75	30
done	0	7

RESULT

A total of 112 cases of P. vivax malaria were studied between November 2015 to October 2016 and 33 (33.03%) (11 male and 26 females) patients developed acute kidney injury (AKI). This data suggests that females were more commonly developed AKI. The prevalence of AKI was more common in younger age group shown in table 2. The clinical presentation of patients with P. vivax malaria associated with AKI shown in table 3. Fever, jaundice, pallor, hypotension, hemolysis, DIC, thrombocytopenia, oliguria were observed on 100%, 62.1%, 56.7%, 45.94%, 51.35%, 35.1%, 78.37%, and 67.56% of cases respectively, reflecting majority patients had severe malarial infection. The several factors contributing AKI were shown in table 4. The various renal manifestations in patients of P. vivax

malaria associated AKI shown in table 5. The various indicators of mortality in P. vivax malaria associated with AKI includes oliguria/anuria on admission, hyperbilirubinemia, hyponatremia, hypotension, metabolic acidosis, DIC, cerebral malaria, and ARDS which are shown in table 6.

DISCUSSION

The objective of this endeavour was to study the prevalence of acute kidney injury in m,alaria caused by plasmodium vivax, need of renal replacement therapy and mortality in AKI caused by plasmodium vivax malaria in the population of Agra region.

In the last few years many cases of severe malaria were seen and some resulted in death. The reported severe manifestations in plasmodium vivax malaria include cerebral malaria, acute kidney injury, hepatic dysfunction, acute respiratory distress syndrome, multiple organ dysfunction. Malaria continues to be a huge social, economical health problem, particularly in tropical countries. Complicated Plasmodium vivax malaria is a common cause of mortality and morbidity. Early diagnosis and prompt treatment of complications reduces global burden of malaria. The prevalence of acute kidney injury has been vastly studied in malaria caused by plasmodium falciparum but very few studies are available in the context of P. vivax malaria.

A total of 112 plasmodium vivax malaria cases were studied of which 37 (33%) patients developed AKI which is about to similar to the study of Kuashik R et al[14].

Several hypothesis including mechanical obstruction caused by cytoadherence and sequestration of infected erythrocytes, immune mediated glomerular pathology, release of cytokines, reactive oxygen intermediates and nitric oxide by activated mononuclear cells, and alterations in the renal and systemic hemody-namics have been proposed as the mechanisms for renal failure in falciparum malaria[15,16,17,18]. However the cause of renal damage in P. vivax malaria still remains unclear. Descriptions of vivax associated with thrombotic microangiopathy and haemolytic uremic syndrome indicate that in some circumstances, P. vivax might cause microvascular thrombosis, endothelial injury and thrombocytopenia similar to thrombotic thrombocytopenic purpura[19,20]. Another hypothesis states that although of lesser magnitude, the phenomena of cytoadherence and/or sequestration commonly described with falciparum, but can also occur in vivax malaria. The phenomenon of rosettinghas also been described ex vivo in vivax malaria; however, its role in pathophysiology is unknown[21]. In addition to the above, restricted blood flow to the kidneys due to low intake of fluids and loss of fluids due to vomiting and pyrexial sweating can cause dehydration and renal ischemia[18].

Vomiting was present in all the malarial cases with acute kidney injury.

Naqvi R et al[16]male: female ratio was 4: 1 but in our study out of 37 AKI cases 11(29.8%) were male and 26(70.2%) were female. Male: female ratio is 1 :2.36 which is different from previous study due to unknown reason.

Barsoum R S et al[19]malarial AKI is more common in younger age group and non-immune adult population. In our study maximum patients belong to 15-30 years of age. Out of 37 AKI patients 23(62%) belong to 15-30 years of age which is similar to previous study.

Presence of hyperbilirubinemia in malaria can act as a predisposing factor for ARF. Naqvi et al have found that all patients of ARF with jaundice had conjugated hyperbilirubinemia with cholestasis[16]. This well defined association may contribute to the reduction of glomerular filtration rate or development of acute tubular necrosis[8,22]. ARF associated with jaundice had high mortality in comparison to no jaundiced ARF patients[23,24]. Similar findings were noted when ARF was associated cerebral malaria. Mishra et al[1] 28.9% cases of cerebral malaria had ARF. Kaushik et al found that 41% patients of malarial AKI have hyperbilirubinemia[14]. Hyperbilirubinemia was present in 23(62.16%) out of 37% cases with AKI.

In previous study dialysis was needed in 78% AKI patients[25]. In our study 7(19%) patients out of 37 AKI cases needed renal replacement therapy, most of them were oliguric. Among these 6(85.7%) female and 1(14.28%) male.

Sarkar D et al found that 64% of the patients have hepatomegaly and 84% patients have splenomegaly. In our study 16.07% patients have hepatomegaly and 25.8% patients have splenomegaly which is somewhat different, cause may be smaller study group.

Thrombocytopenia is a well documented feature of plasmodium vivax malaria[25]. Sarkar D et al thrombocytopenia is found in 60% cases out of 900 cases. In our study thrombocytopenia (<100000/µl) is found in 75% patients (84 cases out of 112) the result is about to similar.

Mortality in P. vivax malarial ARF is 15.7%[9]. Mortality increases with increase in complications. Mortality in cerebral malaria with ARF is 39.5%[1]. Mortality in P. vivax malaria cases was found 7(6.25%) out of 112 patients. Out of these, 6 patients were suffered from AKI with other complications. Mortality in AKI cases was 6 (16.21%). Hyperbilirubinemia was present in 6 cases out of 7 mortality and thrombocytopenia was found in all cases. In our study multiple complications were present with AKI in expired patients.

Hyperbilirubinemia was present in 42(37.5%) patients out of 112 patients of plasmodium vivax malaria.

Anuria, refractory metabolic acidosis, refractory hyperkalemia, rising trend of serum creatinine, uremic encephalopathy and uremic pericarditis were indication for renal replacement therapy.

Renal replacement therapy was given in the form of hemodialysis technique in our patients.the serum creatinine level significantly decreased after three sessions of hemodialysis. Most of our patients required 3-5 sessions of hemodialysis. The prognosis of malarial AKI depends on the severity of condition, associated non renal complications, and early institution of antimalarial therapy along with dialysis support. Availability of renal replacement therapy malarial AKI has been shown to improve outcome. However effective dialysis or ultrafiltration might further reduce the mortality rate[26].

Although peritoneal dialysis has been used in the treatment of of malarial AKI, its effectiveness in severe case is limited because of peritoneal dysfunction and low clearance due to microcirculation[27].

Renal replacement therapy continued until the patient's kidney function improved in the form of increase in urine output or progressive decline in serum creatinine level.

CONCLUSION

The study concluded that P.vivax malaria is an important cause of AKI in India, and particularly in tropical areas.Malarial AKI most commonly occurs in infection by P.falciparum but it is not uncommon by P.vivax malaria.

Prolonged disease duration, low haemoglobin counts, oliguria or anuria on admission, hyponatremia, hypotension, metabolic acidosis, acute respiratory distress syndrome were the more predictors of mortality in our study.Haemodialysis is an effective treatment for malarial AKI.Early referral of malarial AKI patients to dialysis facility unit,and early institution of haemodialysis in complicated P.vivax malaria may further reduce mortality and enhance recovery of kidney functions.

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