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Spectrum of renal dysfunction in malaria

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Abstract

Out of 19053 fever cases screened for malaria, 509 cases were found positive for malaria and 284 cases were selected for the present study. Total 31 patients had renal failure. 70.97% of renal failure patient had *P. vivax* mono-infection. Thrombocytopenia was the most common hematological abnormality. 7 (22.58% of malarial renal failure) patients required hemodialysis. All patients had vivax malaria. 5 patients' health improved after hemodialysis while 2 patients died during the course of illness. 5 patients (1.76%) died during the hospitalization, out of which, 4 patients had renal failure. Previously vivax malaria was considered as a benign disease, but now all sort of complications of malaria also have been observed with *P. vivax* infection. Although the significant number of patients were improved conservatively with anti-malarial drugs but the availability of renal replacement therapy for malarial renal failure has been shown to improve outcome.

Keywords: malaria, renal failure, hemodialysis.

1. Introduction

Malaria remains a devastating global health problem. It is the major cause of mortality in various tropical and subtropical regions [1]. Generally, it is regarded as the benign disease and has been neglected but it can cause severe infection and mortality. It has been suggested that the malaria incidence is between 9 and 50 times greater than reported, with a 13-fold underestimation of malaria-related mortality [2-4]. In India, an estimated 95% population lives in areas where malaria transmission has been reported or climatic conditions favor transmission [5]. In quite a few states of India, like Rajasthan, *P. vivax* is the dominating malaria parasite [6]. Recently there is a changing trend not only in the clinical manifestations but also the pattern of complications in malaria. Up to the last decade of 20th century cerebral malaria was the predominant manifestation of severe malaria, whereas, with the beginning of 21st century, jaundice and renal failure become more common complication [7].

Renal involvement has been reported in *P. falciparum*, *P. malariae*, and recently in *P. vivax* infections. Malarial acute renal failure is diagnosed when plasma or serum creatinine >265 μ M (3 mg/dl) or blood urea >20 mM [8]. Renal involvement varies from mild proteinuria to severe azotemia associated with metabolic acidosis.

The present study was conducted to determine the incidence of acute renal failure among the patients of malaria, and its association with renal replacement therapy as well mortality in North West Rajasthan, India.

2. Material and Method

This prospective observational study was conducted in Department of Medicine, S.P. Medical College and associated groups of hospitals, Bikaner, Rajasthan, North West India, Near Indo-Pak border, on hospitalized cases of malaria during the study period from June 2014 to December 2015, fulfilling the inclusion and exclusion criteria.

2.1 Inclusion Criteria The following patients were included in the study:

Patients of fever found positive for malaria parasite with peripheral smear and/or rapid diagnostic test (RDT).

2.2 Exclusion Criteria The following patients were excluded from present study:

- With prolonged dehydration
- Patients receiving Non-steroidal Anti-Inflammatory Drugs for a long period
- The presence of any other disease which can lead to renal dysfunction or diagnosed case of the renal disease

The Institutional research board of S. P. Medical College, Bikaner gave clearance for proposed work, vide order no. (Acad)SPMC/2014/3634.

The present study was conducted on 19053 cases of fever screened for malarial parasite, out of which 509 cases were detected as malaria by Peripheral blood film (PBF) and/or Rapid diagnostic test. Before enrolment, details about nature and utility of present study were explained to all patients and informed consent was taken. After enrolment, all patients were subjected to detailed history, clinical examination and relevant investigations. After implication of inclusion and exclusion criteria, and on the basis of consent, 284 cases were included in the study.

Data for proposed study were recorded in pre-defined proforma which includes various parameters like socio-demographic profile, history, investigations, treatment, and outcome.

Complete Blood count (CBC), biochemical assay (urea, creatinine, glucose, serum protein, albumin, globulin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and urine examination were carried in all patients. Other investigations viz. dengue serology, test

for typhoid fever, Ultra Sonography, X-ray chest, computerized tomography scan (CT scan), magnetic resonance imaging (MRI), etc. were carried out as and when required. All patients received anti-malarial treatment and hemodialysis was carried in renal failure patients on the basis of indications and contraindications. Hematological and the biochemical assay were repeated during the hospital stay as and when required. All patients were followed until discharge or death.

Data entry and statistical analysis were performed with the help of Microsoft Excel and SPSS version 16. Continuous variables were presented as mean and standard deviations while categorical variables were presented as number and percentage. The χ^2 test was used to compare differences in categorical variables and independent t-test and z-test for continuous variables. P value <0.05 (at 95% confidence interval) was considered to indicate statistical significance.

3. Results

Among 284 of malaria cases in this study, 174 (61.27%) had non-severe and 110 (38.73%) had severe malaria amongst them while 31 (10.92%) had renal failure.

Table 1: Comparison of renal failure patients with other patients of malaria

Clinical variables		Number of patients		
		Renal failure (n=31)	Non renal failure (n=253)	Total (n=284)
Age group (years)	≤20	6 (19.35%)	64 (25.30%)	70 (24.65%)
	21-30	7 (22.58%)	99 (39.13%)	106 (37.32%)
	31-40	4 (12.90%)	48 (18.97%)	52 (18.31%)
	41-50	5 (16.13%)	18 (7.11%)	23 (8.10%)
	>50	9 (29.03%)	24 (9.49%)	33 (11.62%)
	Mean age	38.68±17.52	30.52±13.51	31.41±14.19
Gender	Male	23 (74.19%)	178 (70.36%)	201 (70.77%)
	Female	8 (25.81%)	75 (29.64%)	83 (29.23%)
Residential area	Rural	27 (87.10%)	154 (60.87%)	181 (63.73%)
	Urban	4 (12.90%)	99 (39.13%)	103 (36.27%)
Type of malaria	<i>Plasmodium vivax</i>	22 (70.97%)	203 (80.24%)	225 (79.23%)
	<i>Plasmodium falciparum</i>	5 (16.13%)	37 (14.62%)	42 (14.79%)
	Mixed	4 (12.90%)	13 (5.14%)	17 (5.99%)
Other complications	Anemia	17 (54.84%)	51 (20.16%)	68 (23.94%)
	Thrombocytopenia	27 (87.10%)	221 (87.35%)	248 (87.32%)
	Jaundice	13 (41.94%)	30 (11.86%)	43 (15.14%)
	Proteinuria	29 (93.55%)	117 (46.25%)	146 (51.41%)
	Shock	1 (3.23%)	4 (1.58%)	5 (1.76%)
	Cerebral malaria	1 (3.23%)	4 (1.58%)	5 (1.76%)
	Acute Respiratory Distress Syndrome	1 (3.23%)	2 (0.79%)	3 (1.06%)
Outcome	Improved	27 (87.10%)	252 (99.60%)	279 (98.24%)
	Death	4 (12.90%)	1 (0.40%)	5 (1.76%)
Mean duration of hospitalization (days)		8.09±4.53	5.02±2.49	5.36±2.94

Table 1 Shows that elderly, male and rural population were at more risk to develop malarial renal failure. Other complications of malaria like anemia, jaundice, shock, cerebral malaria, and Acute Respiratory Distress Syndrome (ARDS) were more commonly found with renal failure. Proteinuria was commonly associated with renal failure. The mortality was greater in renal failure patients than non-renal failure patients. The mean age of malarial renal failure patients was 38.68±17.52 years. 23 (74.19%) patients were male and 8 (25.81%) were female. 27 (87.10%) patients belongs to rural area and 4 (12.90%) from urban area. Anemia was found in 17 (54.84%), thrombocytopenia in 27 (87.10%), jaundice in 13 (41.94%), shock in 1 (3.23%), ARDS in 1 (3.23%), and cerebral malaria in 1 (3.23%) patient(s) of malarial renal failure. The mean duration of hospitalization in

renal failure patients was 8.09±4.53 days. 27 (87.10%) were improved and 4 (12.90%) patients died during the course of illness.

Table 2: Other organ dysfunction associated with malarial renal failure (n=31)

Organ dysfunction		Number of patients
Only renal dysfunction		8 (25.81%)
Two organ dysfunction	Anemia	8 (25.81%)
	Jaundice	5 (16.13%)
	Cerebral malaria	1 (3.22%)
Three organ dysfunction	Anemia and Jaundice	7 (22.58%)
	Anemia and shock	1 (3.22%)
Multi organ dysfunction	Anemia, Jaundice and ARDS	1 (3.22%)

Table 2 shows that among the renal failure patients, 8 (25.81%) patients had only renal failure. Other single organ involvement was present found in 14 (45.61%) patients, among them anemia was present in 8 (25.81%) cases, jaundice in 5 (16.13%), and cerebral malaria in 1 (3.22%). Three organ dysfunction found in 8 (25.81%) patients, among them anemia with jaundice in 7 (22.58%), and anemia with shock in 1 (3.22%) patient(s). 1 (3.22%) patient had multi organ dysfunction (anemia, jaundice, and ARDS with renal failure).

Fever was the most common presenting symptom (100% in the non-severe case and 97.27% in severe cases), followed by vomiting, headache and body ache, which was recorded in about half of patients. Weakness and pain abdomen were found in about in one-third of cases while breathlessness was found mainly in severe cases. Altered sensorium, delirium, convulsion, diplopia, gangrene of foot, splenic infarct, pleural effusion, G 6 PD deficiency were observed in few cases of severe manifestations.

Table 3: Correlation between socio-demographic & clinical profile and type of malaria in renal failure patients

Clinical variables		Type of malaria		
		Plasmodium vivax (n=22)	Plasmodium falciparum (n=5)	Mixed (n=4)
Mean age (years)		39.64±19.60	38.6±12.34	33.5±11.68
Gender	Male	15 (68.18%)	4 (80%)	4 (100%)
	Female	7 (31.82%)	1 (20%)	0
Residential area	Rural	18 (81.82%)	5 (100%)	4 (100%)
	Urban	4 (18.18%)	0	0
Other associated complications	Anemia	12 (54.55%)	1 (20%)	3 (75%)
	Thrombocytopenia	18 (81.82%)	5 (100%)	4 (100%)
	Jaundice	9 (40.91%)	2 (40%)	2 (50%)
	Proteinuria	22 (100%)	4 (80%)	3 (75%)
	Shock	1 (4.55%)	0	0
	Cerebral malaria	1 (4.55%)	0	0
Outcome	ARDS	0	1 (20%)	0
	Improved	19 (86.36%)	4 (80%)	4 (100%)
	Death	3 (13.64%)	1 (20%)	0
Hemodialysis		7 (31.82%)	0	0

As shown in table 3 Shows thrombocytopenia (platelet <150,000 per mm³) was the most common hematological abnormality in all type of malaria. The most of the renal failure patients had vivax malaria. All other complications were also found in vivax malaria.

After implication of indication and contraindication 7 patients required hemodialysis [9]. All were infected with PV and were from rural area. 3 patients required only 1 hemodialysis, 1 patient required 3 hemodialysis, 1 patient required 4 hemodialysis, and 2 patients required 5 hemodialysis. 5 patients got improved after hemodialysis while 2 patients died during the course of illness. Among the two expired, one underwent 5 hemodialysis while another had only 1 hemodialysis before death.

The overall mortality in our study was 5 (1.76%). 4 patients had vivax malaria and 1 had falciparum malaria. All were from rural area. Among those who died, renal failure was most common organ dysfunction (4 out of 5).

4. Discussion

Many parts of India are endemic to malaria. Rajasthan region has always been regarded as a hypoendemic area for malaria¹⁰. Although our study does not reflect the true prevalence of malaria in the community as most of our patients were from Bikaner city and others were serious and complicated cases referred from primary health centers situated in rural areas with semi-developed medical facilities. In the different geographical area, different species of malaria is predominant. In India, vivax is the most common species encountered followed by falciparum [6]. In our study 42 (14.79%) cases were due to *P. falciparum*, 225 (79.22%) cases were of *P. vivax*, and 17 (5.99%) were due to mixed infection of malaria.

Malaria can affect any age group. However, young persons

are more prone to get infected with malaria as compared to elderly [11-13]. The young age group is more affected due to their greater mobility and greater risk of exposure due to more outdoor activity [14]. The present study had 201 (70.78%) males as compared to females 83 (29.23%). In this area, tradition and social customs require women to clothe her selves completely and remain in the confines of her house whereas men are engaged in outdoor and agricultural activities and are not fully clothed most of the time providing ample opportunity for mosquitoes to bite.

Malaria causes numerous hematological alterations of which anemia and thrombocytopenia are the most important. In India where the population has already reduced hemoglobin concentration due to inadequate dietary intake, the burden of other infections especially in children, malaria adds to the already fragile health status of the population. Anemia is a frequent finding in malaria cases, particularly in developing nations. Thrombocytopenia is most common hematological finding in this study. In the present study the percentage of patients showing thrombocytopenia (<1.5 lacs) were 87.67% of total cases, 90.48% of falciparum cases, 86.67% of vivax cases and 94.11% of mixed infection. Thrombocytopenia is the most common finding, irrespective of the type of malaria. The presence of thrombocytopenia in a patient with acute febrile illness in the tropics increases the probability of malaria and can be a helpful clinical indicator for malaria. Thrombocytopenia is a common finding in cases of malaria both vivax and falciparum as shown by most of the previous studies conducted [13, 15], but in the present study thrombocytopenia commonly associated with mixed infection of malaria as in the study conducted by Kochar DK *et al* [16].

Over last many years, jaundice and renal failure are increasingly being noticed in patients with malaria. In the present study, the occurrence of liver dysfunction, as

measured by s. bilirubin >3 mg%, were found in 43 (15.14%) cases.

Acute renal failure is one of the dreaded complications of malaria. Acute renal failure is mediated by several mechanisms. These may be due to the effect of the parasitized RBC (pRBC) on the microcirculation, hypovolemic shock, non-specific effects of inflammation, immune-mediated glomerular pathology, alterations in the renal microcirculation, increased plasma viscosity due to infection, release of chemical mediators, hyperbilirubinemia, etc [17-19].

In our study renal failure was present in 31 (10.92%) cases of malaria who were admitted to the hospital, out of which 22 (70.97%) were of *P. vivax*, 5 (16.13%) were of *P. falciparum*, and 4 (12.90%) were of mixed malaria. Although this does not show the true incidence of ARF in malaria as this study involved only those cases of malaria who were admitted to our tertiary care hospital referred from periphery because of the severity of illness or intolerance of drugs. But it clearly shows that significant numbers of malarial renal failure patients had PV mono-infection.

In the present study renal failure were found in 9.78% of vivax malaria, 11.90% of falciparum malaria and 23.53% of mixed malaria. This indicates that mixed infection of malaria would be more severe than mono-infection and more prone to develop renal failure.

Among the renal failure patients, 27 (87.10%) patients belong to the rural area while 4 (12.90%) were from the urban area. Rural persons are more prone to develop renal failure. It may be due to lack of awareness, ignorance about the disease, difficult to approach to medical facilities and thus delay in diagnosis & initiation of treatment, and marked apathy to a specific treatment.

In our study, proteinuria was found in 146 (51.41%) cases while among the renal failure patients proteinuria was found in 29 (93.55%) cases. Proteinuria was found in significant number of patients with malaria, whereas renal failure patients were more commonly associated with proteinuria.

Although anti-malarial therapy was the mainstay of treatment of malaria-associated acute renal failure along with symptomatic treatment but some patients need hemodialysis. Dialysis was required in various studies ranges from 10 to 80% of renal failure patients. Studies conducted by Naqvi R *et al* [20], Maheshwari A *et al* [21], Gupta BK *et al* [22], Nayak KC *et al* [23] have showed that 79.8%, 43.2%, 10.81% and 10.61% of renal failure patients required dialysis respectively. In our study 7 (22.58% of malarial renal failure) patients required hemodialysis. Hemodialysis could not be done in other patients because of no indication (like a good response to conservative treatment, no serial rapid rise in serum creatinine and improvement in urine output) or contraindication (like hypotension or bleeding manifestations) or very short stay in the hospital. In the present study, all patients which required hemodialysis were *P. vivax* malaria. Improvement in the treatment of malaria require hemodialysis in fewer patients compare to previous studies.

Previously mortality with renal failure patients were ranged from 20 to 30% [22-25] while in present study mortality was 12.90% in renal failure patients and overall mortality was 1.76%. Overall mortality was higher in female (2.41%) than male (1.79%) because of specific neglect in getting rapid treatment. Reduction in mortality in the current study may be due to early approach to medical facilities, early diagnosis of illness and improvement in treatment as well as the easy availability of dialysis.

Our study has several limitations. The study was based at a single academic center and our experience may be quite different from the other parts of the world.

A major limitation of the study is that the renal biopsy was not obtained because patients did not give consent to undergo renal biopsy, some had other morbid conditions and some were recovered early in the course of the disease.

Another limitation of our study is all analysis required for renal involvement could not be possible to perform in every case.

5. Conclusion

Previously vivax malaria was considered as a benign disease, but now all sort of complications of malaria also have been observed with *P. vivax* infection for last more than 1 decade. Timely better treatment is required because the delay in treatment could be fatal. The patients presenting with fever, anemia, thrombocytopenia, renal failure and jaundice provide a high index of suspicion for malaria. Renal failure due to malaria is a most common severe manifestation and usually associated with other manifestations of severe malaria. Renal dysfunction is the major cause of death. Although significant number of patients were improved conservatively with anti-malarial drugs but the availability of renal replacement therapy for malarial ARF has been shown to improve outcome. Early initiation of anti-malarial therapy and renal replacement therapy, if required, could further reduce mortality and enhance recovery of renal function.

Recommendation

As this study had some limitation we recommend a multicentric study for the longer duration of time to overcome the seasonal and regional effect on the study. For the exact pathological changes in the kidney, renal biopsy (antemortem as well as postmortem) will be of great help.

Abbreviations

ALT: Alanine aminotransferase
 ARDS: Acute Respiratory Distress Syndrome
 ARF: Acute Renal Failure
 AST: Aspartate aminotransferase
 CBC: Complete Blood Count
 CT: Computerized Tomography
 G 6 PD: Glucose 6 Phosphate Dehydrogenase
 HD: Hemodialysis
 MRI: Magnetic Resonance Imaging
 NVBDCP: National Vector Borne Disease Control Programme
 PF: *Plasmodium falciparum*
 PV: *Plasmodium vivax*
 RDT: Rapid Diagnostic test
 SD: Standard Deviation
 WHO: World Health Organization

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