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Clinical assessment of patients of malaria with renal involvement in patients from West Bengal

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Abstract
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 [8]. 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 µM (3 mg/dl) or blood urea >20 mM. Renal involvement varies from mild proteinuria to severe azotemia associated with metabolic acidosis.
The present study was planned in Department of General Medicine, ICARE Institute of Medical Science and Research and Dr Bidhan Chandra Roy Hospital, Haldia. All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study. Total 50 cases of the malarial infections diagnosed in our hospital were evaluated. The study was planned from September 2013 to July 2014.
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 antimalarial 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.

Keywords: acute renal failure, falciparum malaria, nephropathy, etc.

Introduction
Malaria is a potentially life-threatening disease caused by infection with Plasmodium protozoa transmitted by an infective female Anopheles mosquito. Plasmodium falciparum infection carries a poor prognosis with a high mortality if untreated, but it has an excellent prognosis if diagnosed early and treated appropriately.
Malaria, which predominantly occurs in tropical areas, is a potentially life-threatening disease caused by infection with Plasmodium protozoa transmitted by an infective female Anopheles mosquito vector. Individuals with malaria may present with fever and a wide range of symptoms.
The 5 Plasmodium species known to cause malaria in humans are P falciparum, P vivax, P ovale, P malariae, and P knowlesi. [1-3] Timely identification of the infecting species is extremely important, as P falciparum infection can be fatal and is often resistant to standard chloroquine treatment. P falciparum and P vivax are responsible for most new infections. The Plasmodium species can usually be distinguished by morphology on a blood smear. P falciparum is distinguished from the rest of the plasmodia by its high level of parasitemia and the banana shape of its gametocytes. Among patients with malaria, 5-7% are infected with more than a single Plasmodium species. Co-infection with different Plasmodium species has also been described in the parasites' mosquito vectors. [2]
Each Plasmodium species has a defined area of endemicity, although geographic overlap is common. At risk for contraction of malaria are persons living in or traveling to areas of Central America, South America, Hispaniola, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. Among these regions, sub-Saharan Africa has the highest occurrence of P falciparum transmission to travelers from the United States.
After a mosquito takes a blood meal, the malarial sporozoites enter hepatocytes (liver phase) within minutes and then emerge in the bloodstream after a few weeks. These merozoites rapidly enter erythrocytes, where they develop into trophozoites and then into schizonts over a period of days (during the erythrocytic phase of the life cycle). Rupture of infected erythrocytes containing the schizont results in fever and merozoite release. The merozoites enter new red cells, and the process is repeated, resulting in a logarithmic increase in parasite burden.
P falciparum can cause cerebral malaria, pulmonary edema, rapidly developing anemia, and renal problems. An important reason that the consequences of P falciparum infection are so severe is that, due to its ability to adhere to endothelial cell walls, the species causes vascular obstruction. When a red blood cell (RBC) becomes infected with P falciparum, the organism produces proteinaceous knobs that bind to endothelial cells. The adherence of these infected RBCs causes them to clump together in the blood vessels in many areas of the body, causing microvascular damage and leading to much of the damage incurred by the parasite.
Individuals traveling to malarial regions must be provided with adequate information regarding prevention strategies, as well as tailored and effective antiprotozoal medications. For patient education information, see Malaria, Foreign Travel, and Insect Bites.
Individuals with malaria typically acquired the infection in

an endemic area following a mosquito bite. Cases of infection secondary to transfusion of infected blood are extremely rare. The risk of infection depends on the intensity of malaria transmission and the use of precautions, such as bed nets, diethyl-meta-toluamide (DEET), and malaria prophylaxis.

The outcome of infection depends on host immunity. Individuals with immunity can spontaneously clear the parasites. In those without immunity, the parasites continue to expand the infection. P falciparum infection can result in death. A small percentage of parasites become gametocytes, which undergo sexual reproduction when taken up by the mosquito. These can develop into infective sporozoites, which continue the transmission cycle after a blood meal in a new host.

The mechanisms that underlie immunity remain poorly defined. Additionally, individuals who develop immunity to malaria who then leave the endemic area may lose protection. Travelers who return to an endemic area should be warned that waning of immunity may increase their risk of developing several malaria if reinfected. These travelers returning to endemic areas are a special population, sometimes termed visiting friends and relatives (VFRs).

Each Plasmodium species has a specific incubation period. Reviews of travelers returning from endemic areas have reported that P falciparum infection typically develops within one month of exposure, thereby establishing the basis for continuing antimalarial prophylaxis for 4 weeks upon return from an endemic area. This should be emphasized to the patient to enhance posttravel compliance.

Rarely, P falciparum causes initial infection up to a year later. P vivax and P ovale may emerge weeks to months after the initial infection. In addition, P vivax and P ovale have a hypnozoite form, during which the parasite can linger in the liver for months before emerging and inducing recurrence after the initial infection. In addition to treating the organism in infected blood, treating the hypnozoite form with a second agent (primaquine) is critical to prevent relapse from this latent liver stage.

When P vivax and P ovale are transmitted via blood rather than by mosquito, no latent hypnozoite phase occurs and treatment with primaquine is not necessary, as it is the sporozoites that form hypnozoites in infected hepatocytes.

The vector, the Anopheles species mosquito, transmits plasmodia, which are contained in its saliva, into its host while obtaining a blood meal. Plasmodia enter circulating erythrocytes (red blood cells, or RBCs) and feed on the hemoglobin and other proteins within the cells. One brood of parasites becomes dominant and is responsible for the synchronous nature of the clinical symptoms of malaria. Malaria-carrying female Anopheles species mosquitoes tend to bite only between dusk and dawn.

The protozoan brood replicates inside the cell and induces RBC cytolysis, causing the release of toxic metabolic byproducts into the bloodstream that the host experiences as flulike symptoms. These symptoms include chills, headache, myalgias, and malaise, and they occur in a cyclic pattern. The parasite may also cause jaundice and anemia due to the lysis of the RBCs. P falciparum, the most malignant of the 5 species of Plasmodium discussed here, may induce renal failure, coma, and death. Malaria-induced death is preventable if the proper treatment is sought and implemented.

P vivax and P ovale may produce a dormant form that persists in the liver of infected individuals and emerges at a later time. Therefore, infection by these species requires treatment to kill any dormant protozoan as well as the actively infecting organisms. This dormant infection is caused by the hypnozoite phase of the life cycle, which involves a quiescent liver phase. (During this phase, the infection is not typically eradicated by normal courses of antimalarials and requires treatment with primaquine to prevent further episodes of disease.)

Malaria-causing Plasmodium species metabolize hemoglobin and other RBC proteins to create a toxic pigment called hemozoin.

The most malignant form of malaria is caused by this species. P falciparum is able to infect RBCs of all ages, resulting in high levels of parasitemia (>5% RBCs infected). In contrast, P vivax and P ovale infect only young RBCs and thus cause a lower level of parasitemia (usually < 2%). Hemoglobinuria (blackwater fever), a darkening of the urine seen with severe RBC hemolysis, results from high parasitemia and is often a sign of impending renal failure and clinical decline.

Sequestration is a specific property of P falciparum. As it develops through its 48-hour life cycle, the organism demonstrates adherence properties, which result in the sequestration of the parasite in small postcapillary vessels. For this reason, only early forms are observed in the peripheral blood before the sequestration develops; this is an important diagnostic clue that a patient is infected with P falciparum.

Sequestration of parasites may contribute to mental-status changes and coma, observed exclusively in P falciparum infection. In addition, cytokines and a high burden of parasites contribute to end-organ disease. End-organ disease may develop rapidly in patients with P falciparum infection, and it specifically involves the central nervous system (CNS), lungs, and kidneys.

Other manifestations of P falciparum infection include hypoglycemia, lactic acidosis, severe anemia, and multiorgan dysfunction due to hypoxia. These severe manifestations may occur in travelers without immunity or in young children who live in endemic areas.

Malarial nephropathy is renal failure attributed to malarial infection. Among various complications due to infection, renal-related disorders are often the most life-threatening [4]. Including malaria-induced renal lesions, infection may lead to both tubulointerstitial damage and glomerulonephritis. In addition, malarial acute renal failure has emerged as a serious problem due to its high mortality rate in non-immune adult patients [5-6].

Due to the complex malarial syndrome, there are many pathogenic interactions leading to acute renal failure, such as hypovolemia, intravascular hemolysis and disseminated intravascular coagulation. Malarial acute renal failure prevents the kidneys from efficiently removing excess fluid, electrolytes and waste material from the blood. The accumulation of these fluids and material will cause adverse consequences for the patient including, electrolyte abnormality and increased urinary protein excretion [7].

Untreated patients often face a large number of physical complications, but early diagnosis and effective treatment can reduce the high risk of mortality in patients.[1, 2, 3] A three-pronged approach against infection is regularly needed for successful treatment. antimalarial drug therapy (e.g., artemisinin derivatives), fluid replacement (e.g., oral

rehydration therapy), and if needed, renal replacement therapy.

Malarial nephropathies are reported in endemic areas, such as Southeast Asia, India, and Sub-Saharan Africa. The pathogenesis of acute renal failure in severe malaria is unspecific and multifactorial—it affects fewer than 4.8 percent of cases, but reports a high risk of mortality (15 to 45 percent). Histologic evidence shows a large combination of pathogenic mechanisms at play—acute tubular necrosis, interstitial nephritis and glomerulonephritis. Risk factors for malarial acute renal failure include delayed diagnosis, high parasitemia, and clinical presentation of oliguria, low blood pressure, severe anemia, and jaundice. In addition, patients already suffering from diarrhea, hepatitis, or respiratory distress have a worse prognosis.

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 [8]. 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 µM (3 mg/dl) or blood urea >20 mM [9]. Renal involvement varies from mild proteinuria to severe azotemia associated with metabolic acidosis.

Methodology

The present study was planned in Department of General Medicine, ICARE Institute of Medical Science and Research and Dr Bidhan Chandra Roy Hospital, Haldia. All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study. Total 50 cases of the malarial infections diagnosed in our hospital were evaluated. The study was planned from September 2013 to July 2014.

Following was the inclusion and exclusion criteria for the present study.

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).

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

Results and Discussion

Malaria reemerged once again as a major public health problem of India in the late 1970s after a significant decline in the 60's, affecting 2–2.5 million cases usually. Thus malaria is a parasitic diseases of great epidemiological importance, and malarial renal involvement is emerging as an important problem in tropical countries. Renal involvement in malaria displays the full spectrum of interaction between red-cell abnormalities and TH1 and TH2 activation. At one extreme is a slowly progressive immune-complex mediated glomerulopathy that supervenes in a setting of TH2 predominance, classically associated with P. malaria infection. At the other extreme is a severe disease dominated by the hemodynamic consequences of massive red-cell parasitization, eventually leading to acute tubular necrosis. This is mostly seen with P. falciparum infection. In between lay two syndromes, namely, acute interstitial nephritis and acute proliferative glomerulonephritis.

Malaria can affect any age group. However, young persons are more prone to get infected with malaria as compared to elderly [10-12]. The young age group is more affected due to their greater mobility and greater risk of exposure due to more outdoor activity [13].

Malaria causes numerous haematological 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.

Table 1: Type of Malarial Infection and Renal Involvement

Sex	**No. of Cases**	
Males Females	35 15	
Type of Malarial Infection	No. of Cases	Renal Involvement
P. Falciparum	27	8
P. Falciparum + P. Vivax	5	2
P. Vivax	11	1
Serum Positive malaria cases	7	1
Total	50	12

Table 2: Presenting Symptoms in Malarial Nephropathy Cases

Symptoms	**No. of Cases**
Fever	40
Body ache, Myalgia, Headache	34
Hypothermia (Temp. <36.50c)	1
Nausea, Vomiting	7
Oliguria	9
Anuria	0
Bleeding	1
CNS symptoms	4
Convulsion	1
Dehydration or hypovolumia	6
Jaundice	5
Hepatosplenomegaly	3
Splenomegaly	4

Oedema Over Feet & Face	3
Respiratory distress	2
Hypotension (Systolic B.P. <90 mmHg)	3

Table 3: Urinary Findings

Urinary Findings	No. of Cases
Specific gravity > 1.020	6
Proteinura:	
< 500mg / day	5
> 500mg / day	3
Haematuria (RBC>10/HPF)	5
Pus Cells(above 25 cells/HP)	2
Hyaline Cast	1
Granular Cast	1
Cylinduria	2

Table 4: Biochemical Parameters in Renal Patients

Biochemical Parameters	No. of Cases
Blood Sugar < 60 mg / dL	5
Blood Urea –	
up to 80 mg / dL	5
> 80 mg / dL	7
Serum Creatinine –	
up to 2.6 mg / dL	8
> 2.6 mg / dL	4
Serum Bilirubin –	
2.0 – 5.0 mg / dL	7
> 5 mg / dL	5
SGPT or ALT, above two fold increase	6
SGOT or AST, above two fold increase	4
Serum Sodium <130 meq / L	6
Serum Potassium > 5.5 meq / L	4
LDH > 500 IU / L	5

Men were more affected in our study as compared with women, similar to observations of other groups. [14-15] This could be explained by the fact that men are more mobile and moving about, including the swampy areas as com-pared with women in Asian countries, since women are more confined to their homes and near cooking fire, which offers them protec-tion from biting mosquitoes.

Malaria infection caused by P. malariae or P. falciparum is recognized as an important cause of acute kidney injury (AKI) and other renal-related disorders in infected patients. AKI is seen mostly in P. falciparum infection, but P. vivax and P. malariae can occasionally contribute for renal impairment [16], the same is also evident in our study. Children with cerebral malaria have a higher rate and more severe course of AKI than children with mild malaria. [20] Presence of associated cerebral malaria, jaundice and disseminated intravascular coagulopathy (DIC) are poor prognostic factors and predictors of mortality. [21] Malarial hepatopathy is associated with a higher incidence of complications like renal failure, shock, acute respiratory distress syndrome and hypoglycemia [17] and patients with combination of liver and kidney dysfunction have poorer prognosis than either of them singly as was seen in our study. Almost all complications and death from malaria are caused by P. falciparum [18] either singly or as a mixed infection with P.vivax. Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria, where as today the combination of jaundice (hepatopathy) and renal failure (nephropathy) is more common. [19]

The incidence of jaundice in falciparum malaria has been reported to be between 2 and 57%. [22-23] AKI associated with jaundice had high mortality in comparison with nonjaundiced AKI patients. [24] Jaundice is probably associated with toxicity to tubular cells with more risk of development of acute tubular necrosis. In patients with falciparum malaria with jaundice, 40% succumbed to the disease. [25] Indirect hyperbilirubinemia from RBC destruction is the most common form of jaundice reported in malaria. [25-26] Some patients with falciparum malaria have direct hyperbilirubinemia and elevated hepatic enzymes [27].

Conclusion

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 antimalarial 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.

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