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Original Article

The clinical and biochemical features of complicated falciparum malarial nephropathy

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الملخص

أهداف البحث: تهدف هذه الدراسة إلى استكشاف تأثر الكلى من مضاعفات الملاريا المنجلية كما لوحظ على الأطفال المنومين بالمستشفى.

طرق البحث: أجريت هذه الدراسة خلال أربعة أعوام متتالية على الأطفال المصابين باعتلال الكلى نتيجة الملاريا من عمر ٦ أشهر إلى ١٤عاما. وتم التأكد من الملاريا عن طريق الفحص المجهري لمسحة الدم. وتم عمل تقييم سريري مفصل وفحوصات لمعرفة تعدد الأعضاء المتضررة مع التركيز بشكل خاص على تضرر الكلى. كما رصد التدرج لحصول قصور كلوي حاد وفقا لشبكة تدرج القصور الكلوي الحاد المعطى من ثلاث مجموعات من المرضى، التي تم أيضا تعديلها بواسطة التدرج التالي: خطورة, وضرر, وفشل, وفقدان, والمرحلة النهائية لمرض الكلى.

النتائج: من بين ٣٥٠ مصابا بالملاريا, وجد لدى ٥٦ (١٦%) تضرر كلوي. وكانت أعمار ١٤٠ (٤٠%) مصابا ما بين ٥-١٠ أعوام. كما لوحظ ضرر كلوي خطير لدى ١٤ (٢٥%) من الأطفال أعمارهم بين ١٠-١٤ عاما. ووجد قلة/انقطاع البول عند ٤٠ (٤,٧١%) من المصابين، ووذمة عامة عند ٣٣ (٩,٥٨%) من الأطفال من بداية الإصابة بالملاريا. وظهر لدى ٤٧ من الحالات اختلالا في وظائف عدد من الأعضاء, بينما ٩ حالات كان لديها فشل كلوي فقط. كما وجد أن المصابين بالملاريا المسببة لاعتلال الكبد والكلى أكثر عرضة للوفاة من المصابين باعتلال الكلى فقط.

الاستنتاجات: تختلف أطياف اعتلال الكلى بسبب الملاريا عند الأطفال بدرجة كبيرة تتراوح من وجود بروتين بالبول بدون أعراض إلى مراحل متقدمة من القصور الكلوي الحاد. وتأثر الكلى أكثر شيوعا وخطورة في الملاريا المنجلية. الأطفال الذين تتراوح أعمارهم بين ٥-١٤ عاما مع قلة/انقطاع البول, وأعراض آزوتيمية, وتغيرات بالمعادن واعتلال كبدي هم أكثر عرضة لمراحل متقدمة من القصور الكلوي الحاد وبالتالي زيادة خطر الوفاة.

الكلمات المفتاحية: قصور كلوي حاد؛ نقص صوديوم الدم؛ الملاريا المسببة لاعتلال الكلى؛ الملاريا المنجلية.

Abstract

Objective: This study aimed to explore renal involvement in complicated falciparum malaria as observed in hospitalized children.

Methods: This prospective study was conducted for four consecutive years with children 6 months to 14 years old who were affected by malarial nephropathy. Malaria was confirmed by microscopic examination of a blood smear. Detailed clinical evaluation and investigations were carried out to determine multi-organ involvement with special emphasis on renal functions. The staging for Acute Kidney Injury (AKI) was carried out as per Acute Kidney Injury Network Staging, which provided three groups of patients who were further modified by Risk, Injury, Failure, Loss, End stage renal disease (RIFLE) staging.

Results: Out of 350 cases with malaria, 56 (16%) cases had nephropathy. One-hundred-forty cases (40%) were aged between 5 and 10 years. Serious renal involvement was observed in 14 (25%) children who were 10–14 years old. Oligo-anuria was found in 40 (71.4%) cases, and generalized oedema was found in 33 (58.9%) children from the onset of malaria. Approximately 47 cases showed associated multi-organ dysfunction, and 9 cases had isolated renal failure. Malaria-induced hepatopathy and nephropathy had a higher risk of death than nephropathy alone.

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Conclusion: The spectrum of malarial nephropathy in children is highly variable, ranging from asymptomatic proteinuria to advanced stages of AKI. Renal involvement is more common and severe in *P. falciparum*. Children aged between 5 and 14 years and those with oligo-anuria, symptomatic azotaemia, electrolyte abnormalities and hepatopathy are more likely to develop advanced stage AKI and subsequently have an increased risk of mortality.

Keywords: AKI; Children; Hyponatremia; Malarial nephropathy; *Plasmodium falciparum*

Introduction

Malaria remains a serious health problem in many parts of the world. It causes high morbidity and threatens many lives in developing countries each year. Humans are generally infected by four species of malaria parasites.[1] In India, 60−75% of infections are due to *Plasmodium vivax* and 35−40% of infections are due to *Plasmodium falciparum*. Only a few cases of *Plasmodium malariae* have been reported from Orissa and Karnataka, although infections with a fifth parasite, *Plasmodium Knowlesi*, are known to occur in humans on the islands of Borneo and peninsular Malaysia.[2,3] Malarial acute renal failure is commonly found in non-immune adults and older children with falciparum malaria. The occurrence of acute kidney injury (AKI) in severe falciparum malaria is quite common in Southeast Asia and the Indian subcontinent where the intensity of malaria transmission is usually low, with occasional micro-foci of intense transmission.[4] In India, most malaria cases are contributed by the state of Odisha. Although Odisha has a population of 36.7 million (3.5%), it contributes 25% of the total 1.5 to 2 million annual malaria case reports, 39.5% of *P. falciparum* malaria and 30% of deaths due to malaria in India. The five major manifestations of severe falciparum malaria in children are cerebral malaria, severe anaemia and metabolic acidosis, but renal failure is not commonly encountered.[5−7] Although there have been studies describing the association of AKI with malaria in adults, very few have been reported in children.[8] *P. falciparum* is responsible for the most severe, complicated and fatal form of the disease. AKI commonly occurs in *P. falciparum* malaria, although it is rare in *P. vivax* malaria. The incidence in India includes 13% in northeast (NE) India, 17.2% in Orissa and 17.8% in Delhi. Previously, ARF was rare in children but has been increasing in older children. AKI is multifactorial and has a high mortality rate, especially for late referrals or if renal transplant therapy is not available. The resurgence of malaria in Orissa provided us an opportunity to study the changing trends in malarial AKI and its correlation with the parasite species, severity of infection, clinical course and prognostic factors.

Materials and Methods

The present study is prospective, and the incidence of malarial nephropathy along with the clinical features, lab parameters, treatment and outcome were documented. A study of renal involvement in complicated falciparum malaria in hospitalized children was undertaken for 3 years. All children 6 months to 14 years old who were admitted with severe falciparum malaria were subjected to a blood smear examination (thick and thin) for malaria parasites. Smear examination was performed every sixth hour for the first 72 h. Among those admitted, 56 children who met the definition of malarial nephropathy[9,10] were included in this study. A detailed history was taken, and a detailed examination performed with special focus on blood pressure and urine output (<1 ml/kg/h). All patients were investigated for serum urea, creatinine (>1.5 mg/dl) and proteinuria ≥2+ by the dipstick method or abnormal cast in the urine. Hepatopathy was defined as a rise in serum bilirubin along with a rise in serum ALT levels to more than three times the upper limit of normal.

Acute Kidney Injury (AKI) was defined as an increase in serum creatinine (≥0.3 mg/dl) within 48 h or an increase in serum creatinine >1.5 times baseline, which is presumed or known to have occurred with 7 days or UO <0.5 ml/kg/hr for 6 h. AKI Staging was recorded as per Acute Kidney Injury Network (AKIN) staging into 3 groups: Stage I, II and III, which is a modification of the Risk, Injury, Failure, Loss, End (RIFLE) stage renal disease criteria. The RIFLE criteria are based on decreases in estimated creatinine clearance (eccL) and urine output. Risk was defined as an eccL decrease by 25% or urine output <0.5 ml/kg/hr for 8 h. Injury was defined as an eccL decrease by 50% or urine output of <0.5 ml/kg/hr for 16 h. Failure was defined as an eccL decrease by 75% or eccL< 35 ml/min/m2 or urine output <0.5 ml/kg/hr for 24 h or being anuric for 12 h. Loss was defined as persistent ARF, which is complete loss of kidney function for 4 weeks. End stage renal disease was defined as end stage kidney disease for >3 months.

Serum electrolytes, bilirubin and urine analysis were performed. All of the findings, treatment responses and outcomes were recorded. Detailed clinical evaluation and investigations were carried out to detect multi-organ dysfunction with special emphasis on renal involvement. The data were stored and analysed by Microsoft Excel software. Children with severe malaria but who were smear negative, those who died immediately and patients with an ARF other than malaria were excluded from this study. All patients were treated according to the National Vector Borne Disease Control Programme guidelines.[11] Complications were managed according to the existing hospital guidelines. Patients were followed up after 3 months of discharge for the resolution of nephropathy. During follow up, their clinical status and renal function tests were noted.

Results

In this prospective study, 56 (16%) out of 350 malaria patients had renal involvement (Table 1). Out of 56 cases of

Table 1: Age-wise distribution of our cases (n = 350).

Age group	Malarial nephropathy N = 56 (16%)	No nephropathy N = 294 (84%)	Total
6 months–1 year	1 (1.8%)	35 (11.9%)	36 (10.3%)
1–5 years	15 (26.8%)	118 (40.1%)	133 (38%)
5–10 years	26 (46.40%)	114 (38.7%)	140 (40%)
10–14 years	14 (25%)	27 (9.1%)	41 (11.7%)

renal involvement, 29 patients had a history of (h/o) drug intake. From 29 cases of renal involvement, 25 cases (86.2%) survived and 4 cases died. The remaining portion of the 56 patients (27 cases) had no previous h/o drug intake, out of which 14 cases survived (51.85%) and 13 cases (48.1%) died. Therefore, there was a significant relation between drug intake and outcomes. The clinical features of malaria associated with renal involvement showed that most of the patients presented with oligoanuria and proteinuria, and the smallest percentage presented with haemoglobinurea (Table 2). Cases of less than 1 year old who survived were excluded from the table. More deaths occurred among children 10–14 years of age (Table 3). Survival and death from malarial nephropathy are plotted on a bar diagram (Figure 1), and the data from Table 3 were analysed with Kaplan–Meier estimators (Table 4).

Twenty-four (42.8%) cases presented in Stage III of AKI, 26 (46.4%) in stage II and the remaining 6 (10.7%) cases in stage I. Fourteen cases (25%) were treated with peritoneal dialysis, and five cases were shifted to hemodialysis, requiring prolonged renal supportive care. Table 4 shows the predictor of outcomes in renal involvement cases. Approximately 47 out of 56 cases were associated with multi-organ dysfunction, and 9 cases were associated with isolated renal failure. Malarial hepatopathy plus nephropathy in malaria has a higher risk of death than nephropathy alone. There was 100% survival in isolated renal failure, and 36.2% of patients had mortality with multi-organ dysfunction. Major contributors to overall mortality were cerebral malaria (100%), jaundice (58.8%), hypotension (23.5%), hypoglycaemia (17.6%), DIC (23.6%) and hyperkalaemia (17.6%). On follow up, all cases had normal creatinine, but 6 (10.7%) cases had persistent proteinuria (>2+) and/or microscopic haematuria at the end of 3 months. The probability p-values are also noted (Table 5). A positive correlation among regressors was found from the predictors of malarial nephropathy (Figure 2).

Table 2: Manifestations of renal involvement.

Clinical features and laboratory finding	No. of cases (n = 56)
Oligo-anuria	40 (71.4%)
Oedema	33 (58.9%)
Proteinuria (>2+ by dipstick)	42 (75%)
Raised serum creatinine (>3 mg/dl)	21 (37.5%)
Raised serum creatinine (>1.5 – < 3.0 mg/dl)	35 (62.5%)
Abnormal urinary cast/cellular component	29 (51.7%)
Haemoglobinuria	4 (7.1%)
Hyponatremia	19 (33.9%)
Hypernatremia	5 (8.9%)
Hyperkalaemia	7 (12.5%)

Table 3: Age-wise mortality with renal involvement.

Age in years	Total no	Survived	Percentage	Death	Percentage
1–5	15	10	66.7	5	33.3
5–10	26	20	76.9	7	25.93
10–14	14	9	64.3	5	35.7

Discussion

Malaria infection caused by *P. malariae* or *P. falciparum* is recognized as an important cause of AKI and other renal-related disorders in infected patients.[12] AKI is mostly seen in *P. falciparum* infection, but *P. vivax* and *P. malariae* can occasionally contribute to renal impairment,[4] and similar results were also evident in our study. Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria. However, the combination of jaundice (hepatopathy) and renal failure (nephropathy) is more common today.[7] The global prevalence of AKI in malaria has been reported to be 0.57–60%. The spectrum of malarial nephropathy in children is very wide ranging, from asymptomatic proteinuria to advanced stages of AKI, which require renal replacement therapy (RRT). The pathogenesis of renal involvement is nonspecific, multifactorial and associated with high mortality. There are two major renal syndromes associated with malaria: chronic and progressive malarial nephropathy that mainly affects African children, classically complicating quartan malaria and acute malarial nephropathy associated with falciparum malaria in Southeast Asia, India, and sub-Saharan Africa.[5] The histopathology of malarial nephropathy may show a variable mixture of acute tubular necrosis (ATN), interstitial nephritis and glomerulonephritis. ATN is the most consistent histological finding. Renal vasoconstriction and ATN presumably result from renal microvascular obstruction and cellular injury consequent with the sequestration of *P. falciparum* and filtration of nephrotoxins, such as free haemoglobin,

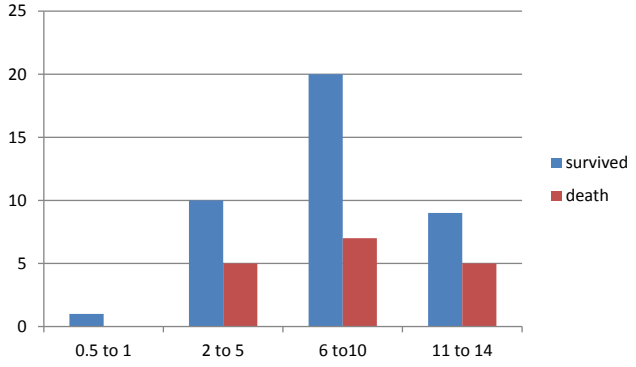

Figure 1: Bar diagram of survival and death of malarial nephropathy patients.

Table 4: Kaplan–Meier estimators from Table 3.

Time period	At risk (%)	Became unavailable Censored	Died (Failed) (Succeeded)	Survival probability estimate	95% Confidence interval	
					Lower limit	Upper limit
3	100	0	0	1	0.953899	1
3	100	0	5	0.95	0.881701	0.981447
3	95	0	7	0.88	0.796023	0.933748
3	88	0	5	0.83	0.738913	0.895066
3	83	0	0	0.83	0.738913	0.895066

Table 5: Predictor of outcome in renal involvement cases.

Clinical syndrome	Prevalence	CFR	Overall mortality %	P value
Cerebral malaria	45 (80.3%)	17 (37.8%)	100	<.001
Jaundice	29 (51.8%)	10 (34.4%)	58.8	<.001
Hypotension	11 (19.6%)	4 (36.3%)	23.5	<.14
Hypoglycaemia	8 (14.3%)	3 (37.3%)	17.6	<.001
DIC	8 (14.3)	4 (50%)	23.6	<.001
Hyperkalaemia	7 (21.4%)	3 (10.2%)	17.64	<.001

myoglobin and other cellular material in the kidney. Hyponatremia is the most common dys-electrolytemia in our study, and it is a typical biochemical finding in malarial nephropathy that is reported in up to 33.9% of cases.[13] Although internal dilution is the usual mechanism of hyponatremia, true sodium wastage before the onset of oliguria has been reported.[13] Proteinuria usually resolves completely with recovery from ARF.[13] Most of the patients in our cohort were oligo-anuric, and 19 children underwent RRT because of hyperkalaemia and symptomatic azotemia.[14] Children with cerebral malaria have a higher rate and more severe course of ARF than children with mild malaria.[13] The presence of associated cerebral malaria, jaundice and disseminated intravascular coagulopathy (DIC) are poor prognostic factors and predictors of mortality.[15] Malarial hepatopathy is associated with a higher incidence of complications, such as renal failure, shock, acute respiratory distress syndrome and hypoglycaemia, and patients with a combination of liver and kidney dysfunction have poorer prognosis than either of them singly, as was seen in our study. It has also been found in many studies on children with severe malaria that

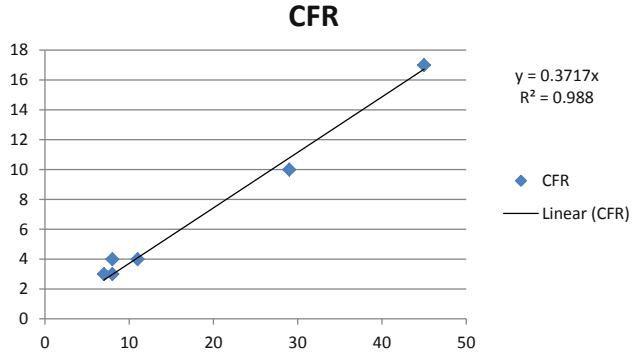

Figure 2: Predictors of malarial nephropathy with regression analysis.

the presence of associated DIC increased the mortality rate,[16] but the same was not seen in our study.

Mosquito control

Initial vector control strategies in this area involved limiting the mosquito population through the draining of wetlands, removal of potential breeding habitats, installation of house screens, and use of larvivorous fish. The use of less toxic and more eco-friendly larvicidal agents point to the potential usefulness of such agents as an alternative, cost-effective strategy in certain urban and peri-urban areas. Currently, insecticide use still plays a significant role in malaria control programs involving the use of insecticide-treated bednets and indoor residual spraying. A recent strategy that is considered to be an environmentally friendly alternative for insect control, but is not currently being applied to mosquitoes, is the sterile insect technique (SIT). SIT involves the mass rearing and release of sterile males which, upon mating with the native population, are unable to produce viable offspring and thereby drive the native population into decline or eradication Sterilization of insects has been accomplished by irradiation or chemosterilization. The Kochi Corporation in Kerala tried out a novel and cost effective method of reducing the mosquito population at the larvae stage itself, in which the salinity of water in canals and stagnant pools is increased by adding sea water.

Challenges in mosquito control

The development and spread of parasite resistance to certain anti-malarial agents has presented a major barrier to successful disease management in malaria-endemic areas and has probably contributed to the resurgence of infection and increase in malaria-related deaths in recent years. The Anopheles mosquito, the mosquito responsible for spreading most cases of *P. falciparum* malaria, can develop resistance to insecticides after prolonged exposure. This reality can severely undermine existing interventions, such as indoor residual spraying of insecticides and widespread use of insecticide-treated bed nets. For all of these reasons, it is critically important to create new tools that allow scientists to continually stay one step ahead of the parasite and mosquito at all times, which is a very difficult task.[17]

Conclusion

Children aged between 5 and 14 years with oligo-anuria, symptomatic azotemia, electrolyte abnormalities and

hepatopathy are more likely to develop ARF. Transient proteinuria and disturbances in fluids and electrolytes can be found in the majority of cases of malarial nephropathy. *P. falciparum* malaria is associated with ARF and hence requires dialysis and good supportive management for better outcomes. Malarial nephropathy has an increased risk of mortality, especially when it is associated with *P. falciparum* infection. Early and prompt diagnosis along with aggressive therapy can prevent progression to complicated malaria while we are waiting to combat other factors, such as vector control, administrative shortfalls, financial stringency, and so forth. A new molecular marker needs to be developed that can give early clues about renal involvement before the biochemical abnormalities of renal involvement are detected.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

DR conceived and designed the study, conducted research, provided research materials, and collected and organized data. MCS analyzed and interpreted data. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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