ORIGINAL ARTICLE

SPECTRUM OF CLINICAL AND BIOCHEMICAL PROFILE IN CHILDREN WITH MALARIAL NEPHROPATHY

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Abstract

Aim: To assess the factors, clinical presentations and complications associated with malarial nephropathy.

Methods: This prospective study was conducted in the period from July 2009 to January 2013 and included malarial children with nephropathy, aged between 6 months to 14 years. Malaria was confirmed by microscopic examination of blood smear. Detailed clinical evaluation and investigations were carried out to find multi-organ afflictions with special emphasis on renal involvement. Acute Kidney Injury (AKI) staging was done as per Acute Kidney Injury Network Staging into three groups which is modified RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) staging.

Results: Out of 168 cases with malaria, 82 (48.8%) cases had nephropathy. One hundred and two (60.7%) were between 5-10 years age group. Renal involvement was seen with P. falciparum malaria in 58 (48.3%) patients. Oligo-anuria was present in 48 (58.5%) cases and generalized edema was present in 27 (32.9%) cases at the onset. Proteinuria was present in 66 (80.5%) cases. Hyponatremia was seen in 29 (35.3%) patients. Twenty (62.5%) cases presented in Stage III of AKI, 9 (28.1%) in stage II and remaining 3 (9.4%) cases in stage I. Fourteen cases (17.1%) were treated with peritoneal dialysis and six cases were shifted to hemodialysis unit requiring prolonged renal supportive care. Of them, thirteen cases had P. falciparum malaria. Sixteen patients out of 168 cases (9.5%) died. Nine children out of 16 (56.2%) who died were associated with malarial nephropathy of which seven cases (77.7%) had Stage III AKI among which 5 (71.4%) children had P. falciparum malaria and remaining cases had mixed infection.

Conclusion: The spectrum of malarial nephropathy in children is highly variable ranging from asymptomatic proteinuria to advanced stage of AKI. Renal involvement is more common and severe in P.falciparum. Children aged between 5-10 years along with oligo-anuria, symptomatic azotemia, electrolyte abnormalities and hepatopathy are more likely to develop advanced stage AKI and subsequently have an increased risk of mortality.

Keywords: AKI, Children, Malarial Nephropathy, Plasmodium falciparum, Hyponatremia

Introduction

Malaria remains a serious health problem in many parts of the world. It causes high morbidity and claims many lives in developing countries each year. Humans are generally infected by four species of malaria parasites (1), although infections with a fifth parasite P. Knowlesi are known to occur in humans on the islands of Borneo and peninsular Malaysia. (2) Malarial acute kidney injury (AKI) is commonly found in non-immune adults and older children with falciparum malaria. Occurrence of AKI in severe falciparum malaria is quite common in Southeast Asia and Indian subcontinent where intensity of malaria transmission is usually low with occasional micro-foci of intense transmission. (3) In India, maximum malaria cases are contributed by the state of Odisha. Although Odisha has a population of 36.7 million (3.5%), it contributes 25% of total 1.5 to 2 million reported annual malaria incidence, 39.5% of P. falciparum malaria and 30% of deaths due to malaria in India (4) Major manifestations of severe falciparum malaria in children are cerebral malaria, severe anemia, metabolic acidosis, but renal failure is not commonly encountered. (5,6) Although there are studies describing the association of AKI with malaria in adults, very few have been reported in children. (7-9)

This study aims to find out the current incidence, clinical profile, biochemical abnormalities and outcome of malarial nephropathy in children attending a tertiary care referral hospital of the state with maximum malaria cases in the country.

Methods & Materials

This prospective study was conducted from July 2009 to January 2013 in the department of Pediatrics at SVPPGIP and SCB Medical College, Cuttack, Odisha, India in children aged between 6 months to 14 years. During this period, a total of 168 cases were admitted with malaria (confirmed by microscopic blood smear examination). Other causes like sepsis, sickle cell disease were ruled out in them by relevant tests. Out of them, 82 children who met the definition of malarial nephropathy (10) were included in the study. Malarial Nephropathy was determined if there were deranged renal function tests (serum creatinine >1.5mg/dl) or proteinuria ≥2+ by dipstick method or abnormal cast in the urine. Hepatopathy was defined as rise in serum bilirubin along with the rise in serum ALT levels to more than three times the upper limit of normal. 10) Acute Kidney Injury (AKI) Staging was done as per Acute Kidney Injury Network (AKIN) staging into 3 groups i.e.; Stage I, II and III which is a modification of RIFLE (Risk, Injury, Failure, Loss, End stage renal disease) criteria. (11) Their demographic, clinical, and laboratory data at the time of presentation were documented and analyzed. Detailed clinical evaluation and investigations were carried out to detect multi-organ dysfunction with special emphasis on renal involvement. The data was stored and analyzed by Microsoft Excel software.

All the patients were treated according to National Vector Borne Disease Control Programme guidelines. (15) Complications were managed according to the existing hospital guidelines. Patients were followed up after 3 months of discharge for resolution of nephropathy. During follow up, their clinical status and renal function tests were noted.

Table 1: Age-wise distribution of our cases (n=168)

Age group	Malarial nephropathy N= 82 (48.8%)	No nephropathy N= 86 (51.2%)	TOTAL
6 months-1 year	1 (25%)	3 (75%)	4 (2.4%)
1-5 years	3 (25%)	9 (75%)	12 (7.1%)
5-10 years	54 (52.9%)	48 (47.1%)	102 (60.7%)
10-14 years	24 (48%)	26 (52%)	50 (29.8%)

Table 2: Manifestations of Renal Involvement

Clinical Features and Laboratory Finding	No. of cases (n=82)
Oligo-anuria	48 (58.5%)
Edema	27 (32.9%)
Proteinuria (>2+ by dipstick)	66 (80.5%)
Raised serum creatinine (>3mg/dl)	26 (31.7%)
Raised serum creatinine (>1.5 - < 3.0mg/dl)	13 (15.8)
Abnormal urinary cast/cellular component	42 (51.2%)
Hemoglobinuria	7 (8.5%)
Hyponatremia	29 (35.4%)
Hypernatremia	12 (14.6%)
Hypokalemia	12 (14.6%)
Hyperkalemia	13 (15.9%)

Results

Out of 168 cases of malaria, 82 (48.8%) cases had malarial nephropathy. Male to female ratio was 1.4:1. Age distribution is given in table 1. Clinical and laboratory abnormalities seen with malarial nephropathy are depicted in Table 2. Twenty (62.5%) cases presented in Stage III of AKI, 9 (28.1%) in stage II and remaining 3 (9.4%) cases in stage I. Renal involvement was seen in 58 (48.3%) patients with P. falciparum malaria, 14 (17.1%%) patients with mixed P.falciparum and P.vivax infections and 10 (12.2%) patients with P.vivax infection. Fourteen cases needed peritoneal dialysis and six others needed to be shifted to hemodialysis unit requiring prolonged renal supportive care. Out of 20 cases requiring dialysis, 13 (65%) cases had P. falciparum malaria, 7 (35%) cases had mixed infection, whereas none of the children with P. vivax malaria needed dialysis. Out of 20 cases dialyzed, five cases died (four cases due to multi organ dysfunction and one case had sepsis with DIC) and remaining 15 cases survived with no major adverse outcome. Out of 168 cases, 82 (48.8%) cases had malarial nephropathy and 32 (19%) had malarial hepatopathy. Thirteen (15.8%) cases had malarial hepatopathy with nephropathy, of which five cases (38.4%) died. Malarial hepatopathy plus nephropathy in malaria has a higher risk of death than nephropathy (n=4) alone (p=0.0005). Overall mortality in children with malaria was 16 (19.5%) and 9 out of those 16 had malarial nephropathy. Seven of those cases had Stage III AKI whereas two cases were in Stage II AKI. Amongst Stage III AKI cases, 5 (71.4%) children had P. falciparum malaria and remaining 2 cases had mixed malaria infection. On follow up, all cases had normal creatinine, but 12 (14.6%) cases had persistent proteinuria (>2+) and/or microscopic hematuria at the end of 3 months.

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. (1) AKI is seen mostly in P. falciparum infection, but P. vivax and P. malariae can occasionally contribute for renal impairment (3), 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. (16) Presence of associated cerebral malaria, jaundice and disseminated intravascular coagulopathy (DIC) are poor prognostic factors and predictors of mortality. (17)

Malarial hepatopathy is associated with a higher incidence of complications like renal failure, shock, acute respiratory distress syndrome and hypoglycemia (4) 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 (5) 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. (6) The global prevalence of AKI in malaria has been reported to be 0.57%-60%. In developing countries such as India, the incidence of AKI varies from 13% to 17.8%. (9) In our study, it was 39%. This can be attributed to the fact that there are very few centers in Odisha that have the facility of renal dialysis and hence many cases are referred to our hospital. It was also found in many studies on children with severe malaria that the presence of associated DIC increased the mortality rate (18) but the same was not seen in our study.

The spectrum of malarial nephropathy in children is very wide ranging from asymptomatic

proteinuria to advanced stage of AKI requiring renal replacement therapy (RRT). The pathogenesis of the 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. (12)

The histopathology of malarial nephropathy may show a variable mixture of acute tubular necrosis (ATN), interstitial nephritis, and glomerulonephritis. (12) Acute tubular necrosis is the most consistent histological finding. Renal vasoconstriction, acute tubular necrosis presumably results from renal microvascular obstruction and cellular injury consequent upon sequestration of P.falciparum and the filtration of nephrotoxins such as free hemoglobin, myoglobin and other cellular material in the kidney. (12)

Hyponatremia is the most common dys-electrolytemia in our study and it is a typical biochemical finding in malarial nephropathy being reported in up to 55% of cases. (12) Although internal dilution is the usual mechanism of hyponatremia, true sodium wastage that occurs before the onset of oliguria has been reported. (12) Proteinuria, usually resolves completely with recovery from ARF. (12) Most of the patients in our cohort were oligo-anuric and 20 children underwent renal replacement therapy (RRT) because of hyperkalemia and symptomatic azotemia with 5 (25%) deaths among them.

Conclusion

Children aged between 5-10 years along with oligo-anuria, symptomatic azotemia, electrolyte abnormalities and hepatopathy are more likely to develop advanced stage AKI. Transient proteinuria and disturbances of fluid and electrolytes may be found in majority cases of malarial nephropathy. P. falciparum malaria is associated with advanced stage AKI (Stage III) and hence needs 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. However, a larger cohort with longer duration of study is required to know the long term outcome of malarial nephropathy.

Contributor Statement

SKP- conception and manuscript review, PM - literature search and data acquisition, LD - design and drafting of manuscript, SKS - approval of the data to be published, DT - data acquisition and drafting

Funding: None

Conflict of Interest : None

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DOI No. 10.7199/ped.oncall.2014.70