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Study of acute kidney injury in severe falciparum malaria

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Abstract
The contribution of malaria to overall hospital admissions for AKI varies from 2% to 39%2 Majority of the cases were due to severe falciparum malaria, however recently few cases of plasmodium vivax causing renal dysfunction have been reported. Acute kidney injury is an important cause of morbidity and mortality in severe falciparum malaria. All patients were treated with inj Artesunate 2.4 mg/kg b/w at 0 hrs., 12 hrs., 24 hrs. then once daily for 7 days or continued until they were able to tolerate drugs orally. Then ACT (artemether plus lumefanterne or Artesunate plus sulfadoxine-pyrimethamine) was given orally for a course of 3 days. Supportive treatments such as fluid replacement, urine output and plasma glucose were monitored closely during the period of admission. Patients with convulsion were treated with inj phenytoin 100 mg i.v 8hrly till they were able to take oral phenytoin with the same dose. Group A patients had mean urine output of 349m1112hrs. This group of majority were oliguric fulfilling failure criteria of RIFLE. Only 3 patients of group B were oliguric and hence the mean urine output of group was in nonoliguric range. Group C patients were without complications. With the use of serum cystatin C as a early renal injury marker, early recognition of renal dysfunction and with prompt antimalarial therapy, judicious fluid management and avoidance of nephrotoxic drugs, further impairment in renal function can be reduced.

Keywords: acute kidney injury, severe falciparum malaria, Cystatin C

Introduction

Malaria is the most important parasitic disease of humans caused by Protozoa of the genus plasmodium. The malarial parasite is transmitted by the mosquito vector of the Anopheles family. Although primarily a disease of the tropics, it is transmitted in 107 countries causing 1 to 3 million deaths each year. India harbours both P. vivax (50-55%) and P Falciparum (45-50%) and contributes 70% of malarial cases in south east Asia region. The prevalence of these two species is approximately equal in Indian subcontinent. There is an estimated 70 to 100 million cases each year, but only 1.6 to 1.8 million cases are reported by the National vector Borne Disease control Programme (NVBDCP).

According to NVBDCP report Odisha contributed 200958 cases of malaria in the year 2011. Out of which 183400 were falciparum malaria. In 2012, till August the number of cases of malaria were 575349 cases out of which 296121 were due to P. falciparum [1].

V.S.S. Medical College and Hospital is a tertiary care referral hospital in Western Odisha catering to the health needs of 6-8 million populations.

Approximately 2000 cases of malaria were admitted during the year 2011, falciparum malaria contributed to the majority of the cases 1470 of 2000 (78%) resulting mortality in 15% of the cases. 97% of all the deaths were due to complicated malaria resulting from multiorgan dysfunction.

The contribution of malaria to overall hospital admissions for AKI varies from 2% to 39% [2] Majority of the cases were due to severe falciparum malaria, however recently few cases of plasmodium vivax causing renal dysfunction have been reported [3, 4]. Acute kidney injury is an important cause of morbidity and mortality in severe falciparum malaria.

In the absence of a universally accepted definition of acute renal failure and recognition that ARF as previously defined includes a spectrum of clinical conditions, the term acute kidney injury has been proposed to reflect the entire spectrum of the syndrome, hence RIFLE [5] and AKIN [6] criteria were born to define the Acute Kidney injury

Several low molecular weight (LMW) proteins have been evaluated as endogenous markers of GFR with cystatin C commanding the most attention. cystatin C is a 13-KD basic protein of the cystatin superfamiy of cysteine protease inhibitors. It is synthesised by all nucleated cells at a constant rate. The principal mode of excretion of cystatin C is renal. Cystatin C is freely filtered by the glumerulus and is then metabolized after being reabsorbed in proximal tubule.

Studies in a number of patients have shown that serum cystatin C may be more sensitive and specific than serum creatinine value in determining renal dysfunction. In addition small reductions in GFR appears to be detected more easily using cystatin C measurement than with creatinine determination [7, 8, 9]. Other studies have indicated that cystatin C determination has a greater ability to detect subclinical kidney dysfunction than using creatinine measurement 10.

Renal involvement is frequent and serious complication contributing to the morbidity and mortality of the patients with severe falciparum malaria.

Hence the present study has been undertaken with the aim to study Acute Kidney Injury in severe falciparum malaria, with the objectives of knowing the incidence of AKI in malaria, association of other organ dysfunction with AKI, outcome of AKI and to know the subclinical renal dysfunction using serum cystatin C as a renal injury marker in patients with severe falciparum malaria.

Methodology

All Adults patients (>14 yrs.) with positive asexual forms of malaria in thick smear, thin smear or positive QBC/ICT test admitted to the hospital were included in the study.

Severe malaria' was defined according to the World Health Organization criteria (WHO 1990 modified in 2000). 5 In contrast to the WHO criteria; however, we used a practical definition of cerebral malaria: any impairment of consciousness or convulsions.

The diagnosis of plasmodium falciparum will be done by either Microscopy, QBC or lOT.

Criteria to diagnose AKI: Patients fulfilling the RISK criteria of RIFLE i.e. decreased urine output <0.5m1/kg/hr. for 6 hrs., increased s creatinine x 1.5 or INJURY criteria as increase in serum creatinine x2 or UO <0.5m1/kg/hr. for l2hrs. AKIN criteria of acute kidney injury as increase in serum creatinine of 0.3mg/dI or >50% developing over <48hrs., or a urine output of <0.5m1/kg/hr for >6 hrs.

All patients were treated with inj Artesunate 2.4 mg/kg b/w at 0 hrs., 12 hrs., 24 hrs. Then once daily for 7 days or continued until they were able to tolerate drugs orally. Then ACT (artemether plus lumefanterne or Artesunate plus sulfadoxine-pyrimethamine) was given orally for a course of 3 days. Supportive treatments such as fluid replacement, urine output and plasma glucose were monitored closely during the period of admission. pts with convulsion were treated with inj phenytoin 100 mg i.v. 8hrly till they were able to take oral phenytoin with the same dose. Hypoglycaemia was treated with an intravenous injection of 50% dextrose followed by a continuous infusion of 10% dextrose. Oliguric acute renal failure (ARF) i.e. urine output < 400 ml! 24 h associated with rising serum creatinine despite rehydration and a trial of diuretics; was treated with haemodialysis. Patients who developed severe tachypnea or adult respiratory distress syndrome (ARDS) were intubated and ventilated with positive end expiratory pressure if indicated.

The history, clinical findings and investigations were recorded on standardized hospital forms. All these data during admission, after 24-48 hours and after 5-7 days were recorded accordingly and summarized.

Results

Based on the serum creatinine and serum cystatin C levels on the first day of admission patients are grouped accordingly.

Table 1: Group Classification

	Day 1	Day 1	Total	%age
Group-A	Increased Creatinine	Increased Cystatin C	21	35%
Group-B	Normal Creatinine	Increased Cystatin C	17	28.3%
Group-C	Normal Creatinine	Normal Cystatin C	22	36.66%

Group A patients had increased creatinine and increased cystatin C, it consisted of 21 nos. of patients (35%).

Group B patients had normal serum creatinine and increased serum cystatin C. This group included 17 patients (28.3%).

Group C patients had normal serum creatinine & normal serum cystatin C levels on the first day of admission. This group consisted of 22 patietns (36.66%).

Table 2: Mean s. creatinine, s. cystatin c and urine output

	Mean	SD	SEM	N	90%CI	95% CI	99%CI
S.creatinine mg/dl	1.62	1.22	0.15	60	1.36 to1.89	1.30 to 1.94	1.20 to 2.04
S. Cystatin C mg/L	1.53	1.17	0.15	60	1.28 to 1.78	1.22 to 1.83	1.12 to 1.93
UO (ml/12hr)	456	190.8	23.14	60	417.4 to 492	409.8 to 502	394.6 to 517.3

The above table is showing the mean creatinine, cystatin C and urine output in all the 60 patients.

Table 3: Renal parameters in different groups

S.creatinine (mg/dl)	<.14	1.5-2.0	2.1-2.5	2.6-3.0	>3.0	Mean	SD	SEM	N	90%CI	95%CI	99%CI
Group A	0	7	3	4	7	2.83	1.42	0.31	21	2.29 to 3.36	2.18 to 3.48	1.95 to 3.71
Group B Day 1	17	0	0	0	0	1.02	0.15	0.03	17	0.96 to 1.09	0.94 to 1.11	0.91 to 1.14
Day 2	7	7	2	1	0	1.60	0.54	0.13	17	1.37 to 1.83	1.32 to 1.88	1.21 to 1.99
Group C Day 1	22	0	0	0	0	0.93	0.21	0.01	22	0.85 to 1.01	0.83 to 1.02	0.80 to 1.06
Day	22	0	0	0	0	0.91	0.22	0.42	22	0.81 to 1.02	0.82 to 1.01	0.81 to 1.15

Table 4: Renal parameters in different groups

S.creatinine (mg/dl)	<.14	1.5-2.0	2.1-2.5	2.6-3.0	>3.0	Mean	SD	SEM	N	90%CI	95%CI	99%CI
Group A	0	5	4	5	7	2.49	1.50	0.32	21	1.9 to 3.06	1.81 to 3.18	1.56 to 3.43
Group B Day 1	0	12	4	1	0	1.33	0.29	0.07	17	1.20 to 1.46	1.18 to 1.49	1.12 to 1.54
Group C Day 1	22	0	0	0	0	0.74	0.06	0.01	22	0.71 to 0.76	0.71 to 0.77	0.70 to 0.76

Table 5: Urine out put

Urine output (ml/12 h)	<500	500-1000	>1000	Mean
Group A	15	3	3	349.05
Group B – Day 1	6	11	0	736.08
Day 2	8	9	0	544.36
Group C-Day 1	0	6	16	1106.52
Day 2	0	4	18	1243.80

Group A patients had mean urine output of 349m1112hrs. This group of majority were oliguric fulfilling failure criteria of RIFLE. Only 3 patients of group B were oliguric and hence the mean urine output of group was in nonoliguric range. Group C patients were without complications.

Discussion

Raised serum creatinine was observed in 51.6% of cases hyperbilirubinemia in 38.33% and Hypoglycemia in 6.66%.

Maheshwan A *et al*. [10] proposed that renal involvement in falciparum malaria can present as electrocyte abnormality, abnormal urinary sediments and increased urinary protein excretion.

In our study Hyponatremia is observed in 8.33%, Hypolkalemia in 3.23% of cases. Urine microalbuminurta, microscopic hematuria were seen in 21 66% and 10% cases respectively

Okwara EN *et al*, [11] reported upto 13.3% prevalence of UTI in patients (aged 3 months to 12 years) of malaria.

P 0 Okunola *et al* [12] reported UTI as a silent comorbidity in children less than 5 years with malaria The prevalence was upto 9%

The uropathogens isolated included staphycococus (55.6%), E. coli (29.6%) and K pneumonia (14.8%).

In our study we had 11.66% of patients with presence of significant urine pus cells. The prevalence of bacterial coinfection may be ascribed to pronounced immunosuppression, which could be more marked in severe malaria, and may be due to bladder catheterization inducing UTI in patients with complicated malaria.

Renal impairment is a common complication of severe falciparum malaria. Quartan malarial nephropathy associated with chronic or repeated infections with plasmodium malaria is well known and few reports have described an association of AKI with plasmodium vivax infection. However majority of the cases are due to falciparum malaria.

Precise mechanism of renal failure in falciparum malaria is not clearly known. Independent studies done by Elam- Ong S, Sitprijav and Barsoum Rs. [13] Hypothesized that mechanical obstruction by infected erythcocytes, immune mediated glomerular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation, etc. as possible mechanisms of renal dysfunction.

The contribution of malaria to overall hospital admission for renal dysfunction vacres from 20% to 39%.

Gilles HM, Handrichse RG reported that the incidence of ARF is as high as CM.

Eiam-Ong S49 reported that ARE is a frequent and serious complication of falciparum malaria in non-immune adults and older children.

In our study we found the incidence of Acute Kidney injury in 51.6% of the cases.

Dash RK, Mishra K, *et al*, [14] reported 35% cases of severe P. falciparum malaria having ARE. The study also indicated an increase in incidence of malarial ARE.

High incidence of malarial ARE, both the children and adults has been reported from several centers across the country. Tran TH *et al*, [15] reported severe malaria in Vietnamese adults is usually a multisystem disease where more than 40% of severe malaria patients had ARE, and more than 55% of fatal cases had ARE on admission that rose to 70% by the time they died.

In our study incidence of renal impairment was associated most commonly with hepatopathy (55%), followed by cerebral malaria (39.47%).

As a component of multiorgan dysfunction acute kidney injury was associated with cerebral malaria and hepatopathy (20.6%).

Sural S. *et al* studied acute renal failure associated with liver disease in India concluded that hyperbilirubinemia in falciparum malaria possibly predisposes for ARE, which may remain unnoticed.

Dash et al showed that malarial ARE was significantly associted with liver dysfunction. Independent studies done by mukherji AP, Wilairatna P, and Marshk also confirmed the association

Our study is compatible with the above mentioned studies 21 out of 31 cases (67 7%) of acute kidney injury had liver dysfunction

We found that association of cerebral malaria with AKI was (48.3%), and three organ involvement of cerebral malaria, hepatopathy and AKI as 20.6%. The findings are in agreement with the above mentioned study.

Renal involvement in malaria can be oliguric or nonoliguric Honda N, Hishoda A studied pathophysiology of experimental nonoliguric acute renal failure in animal models have shown that there is less morphologic and functional damage in nonoliguric as compared to oliguric acute renal failure. There is also evidence in humans suggesting that the absence of oliguria in ATN generally reflects less severe disease.

Rubina Naqvi *et al*, [16] DOW medical college and civil hospital, Karachi studied the outcome in severe acute renal failure associated with malaria. 68% of the patients were oliguric and rest were non oliguric 78 8% required renal replacement therapy, However number of dialysis sessions did not differ significantly between the oliguric and nonoliguric groups.

Dr. Junejo Abdul manon [17] *et al* studied acute renal failure associated with malaria, they had 76.09% patients had oliguric ARE, 78 26% required dialysis and 76 06% recovered

completely while 23.9% died in early dialysis.

In our study is in agreement with the above studies 23 of 31 patietns with acute kidney injury had oliguria (74.19%) with mean creatinine of 2.74mg/dI. 8 of 31(25.8%) underwent hemodialysis 6 of them were oliguric and two were non oliguric. 3 out of 31 died within 48 hours of hospitalization (9 6%) All the three patients had multiorgan daysfunction and were oliguric. 83.87% recovered completely with treatment, with conversion of oliguric renal failure to non oiguric in a mean of 5 days. 2 patients were lost in the follow up.

Several low molecular weight (LMW) proteins have been evaluated as endogenous markers of GFR with cystatin C commanding the most attention. Cystatin C is a 13-KD basic protein of the cystatin superfamily of cystene protease inhibitors. It is synthesized by all the nucleated cells at a constant rate. The principal mode of excretion of cystatin C is renal. Cystatin C is freely filtered by the glumerulus and is then metabolized after being reabsorbed in proximal tubule.

Studies in a number of patients have shown that serum cystatin C may be more sensitive and specific than serum creatinine value. In addition small reluctions in GFR appeal to be detected more easily using cystatin C measurement than with creatinine determination

Other studies have indicated that cystatin C determination has a greater ability, to detect subclinical kidney dysfunction than using creatinine measurement.

We estimated the serum levels of cystatin C in all the 60 patients on the first day of admission. Total incidence of acute kidney injury was 51.6% with mean serum creatinine of 2.57mg/dI, mean cystatin C was 2.l8mgIL and mean urine output was 456.3ml/l2hrs. It consisted of 61.5% of males and 38.5% female patients. Majority of the patients were in their second and third decade of life. The mean duration of fever before the detection AKI was 6 days. The incidence oliguric AKI was 74.19% (23 of 31), and rest i.e. 25.8% were nonoliguric. Based on the serum levels of cystatin C and S. creatinine levels patients were classified into 3 groups. Group A patients were admitted with renal injury, incidence of hospitalization with acute kidney injury was 35%, out of which 66 6% were male and 73 3% were female patients. Mean serum creatinine was 2.83mg/dI, mean cystatin C was 2.49mgIL, mean urine output was 349m1/l2hr. Majority of the patient were oliguric (71.4%).

All the 17 patients of Group B had their serum cystatin C elevated (mean 1 33 mg/L) and normal serum creatinine (mean 1.02mg/dI) on first day of admission. 52.9 patients were oliguric and 47.1% patient were non oliguric. 10 patients developed increase in serum creatinine on second day of admission mean creatinine 1600mg/d1 ($p<0$ 0001) Majority of the patients were oliguric (80%)

Remaining seven patients had their serum in creatinine within normal range on second day ($p=0.7882$) and throughout the duration of admission, indicating these patients had minimal impairement in renal function which was detected by raised cystatin C.

Group C patients had normal cystatin C (mean 0.74mg/dl) and normal serum creatinine (mean 0.93). Serum creatinine remained within normal range on second day mean creatinine 0.9lmg/di ($p=0.698$) and throughout the duration of admission. All 22 patients of this group were without any complications and hence were also considered as controls to compare with patients with subclinical renal dysfunction

Most common single organ dysfunction associated with AKI was with Hepatopathy 55%, followed by cerebral malaria 39.47%, Hypotension 15.7%, ARDS 7.9%, anemia 2.63%. 4 patients (10%) had only acute kidney injury as their complication.

Gunthur A *et al*. did a retrospective study of stored sera and patient files of falciparum malaria in Germany It showed that elevated cystatin C was more frequent (54.6%) than the serum creatinine (20 4%), indicating cyst C detected patients with mild impairment in renal function.

CoIIE, Botey A, Alvarez et al showed that cystatin C determination has a greater ability to detect subclinical kidney dysfunction than the creatinine-measurement.

In our study we had 7 patients in Group A who had raised serum cystatin and normal creatinine. Hence indicating minor impairment of renal function. Majority of these patients 6 out of 7 were nonoliguric.

In a mixed critical care population, determination of serum cystatin C level enabled a diagnosis of AKI 1.5 days earlier than the plasma creatinine concentration.

Herget Rosenthal and associates analyzed data for 85 patients in ICU who were at risk of developing AKI and used RIFLE classification to define AKI In that study authors reported that serum cystatin C level detected AKI I to 2 days before changes in serum creatinine level

In our study we had ten patients in group B who had elevated serum cystatin C and normal serum creatinine on the day of admission and elevated serum creatinine on the second day of admission ($p<0.0001$), indicating serum cystatin C had predicted the acute kidney injury I day earlier than serum creatinine

Overall elevation of cystatin C was more frequent than elevated serum creatinine ($p<0$ 0001) with serum cystatin C as a renal injury marker the incidence of acute kidney injury raised to 63.3%.

Conclusion

We conclude that incidence of acute kidney injury is high, minor of renal function occurs in severe faluiparum malaria which cannot be detected by serum creatinine Serum Cystatin C detects renal dysfunction one day earlier than the serum creatinine, outcome of acute kidney injury is poor when associated with multiorgan dysfunction. Overall recovery is good with early administration of antimalarials, fluid replacement and renal replacement therapy.

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