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ORIGINAL ARTICLE

Acute Kidney Injury Due To Leptospirosis-A Cohort Study

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ABSTRACT
Background & objectives: Acute kidney injury (AKI) is a prominent feature of both mild and severe leptospirosis. Few large series describe in detail clinical and laboratory features of cases with AKI and their outcome. We planned to study the clinical features of acute kidney injury (AKI) in Leptospirosis and factors associated with mortality. Methods: We performed a prospective analysis (between 01.01.2013 to 31.12 2013) of all consecutive, confirmed leptospirosis cases with AKI (n=46, 36 male, age 42.63 with a SD of 13.15years). Results: Of the total 67 cases of fever with AKI, 46 patients (68.66%) were diagnosed as Leptospirosis by modified Faine's criteria. Serovars identified by Microscopic agglutination test (MAT) were L.Icterohaemorrhagiae, L.Australis and L.Autumnalis. Urine output was lower in those who died (Mean urine volume in the non survivors was 500ml (SD-326) and 810ml (SD-427) in the survivors. (p-0.02). The common signs in the 46 patients with AKI due to Leptospirosis include jaundice (76.09%), pedal edema (58.70%), conjunctival suffusion (93.48%) and meningism (65.22%). The signs that are most consistent with the diagnosis of leptospirosis in patients with AKI were conjunctival suffusion (p-0.000019) and meningism (p-0.0039). Multinomial logistic regression showed pulmonary involvement either in the form of cough with expectoration, lung crepitations or dyspnea when taken together is associated with significant increase in mortality (n=29, OR-13.00, 95%CI- 1.52-111.47, 2-5.95, p-0.015). Conclusions: Most common cause of AKI due to AFI in our series was leptospirosis. Urine output and pulmonary involvement are predictors of mortality.
Keywords; *Kerala – leptospirosis; Predictors of mortality; MAT; AKI*

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INTRODUCTION

Leptospirosis is a widespread zoonosis, caused by spirochetes of the genus Leptospira [1]. Clinical manifestations can be acute febrile illness, aseptic meningitis, jaundice, renal failure, pulmonary hemorrhage, and refractory shock [1]. Acute tubular necrosis due to Community-acquired infections is the commonest cause for AKI in the tropics [2]. Incidence of Acute kidney injury (AKI) is between 25% to 80% in the tropics [2] . The incidence of AKI in severe leptospirosis varies from 40% to 60% [3]. Renal insufficiency in severe leptospirosis may be acute oliguric or non-oliguric renal failure. Factors involved in acute kidney injury (AKI) in leptospirosis, are direct nephrotoxic action of the leptospira, hyperbilirubinemia, rhabdomyolysis and hypovolemia(4). The major histological findings are acute interstitial nephritis and acute tubular necrosis [4].

Leptospirosis classically has an initial septicemic phase followed by an immunological phase. Septicemic phase presents with fever, myalgia, conjunctival suffusion and non specific features like cough, rash, vomiting and lymphadenopathy. Immunological phase is often characterized by multi organ failure (MOF), the most common being liver and kidney. Leptospirosis presenting with renal failure frequently has MOF and death occurs in one-third of the patients [5].Severe disease may present as a fulminant monophasic illness with fever progressing to jaundice, oliguric renal failure, pulmonary hemorrhage, refractory shock, and death within days [6].

A study which recognizes the clinical and laboratory profile of acute kidney injury in Leptospirosis may help to prioritize our resources in identifying them and if possible manage them at an earlier stage with prompt intervention.

Aim of the study

The aim of the study was to find the clinical and laboratory profile of acute kidney injury due to Leptospirosis and predictors of mortality.

MATERIALS AND METHODS

The is a cohort study of patients admitted with febrile illness complicated with acute kidney injury in Government Medical College Thrissur, conducted for an year between 01.01.2013 to 31.12 2013.

Patients above 13 years admitted with fever of less than 14 days complicated by acute kidney injury as evidenced by Increase in serum creatinine of more than or equal to 0.3 mg/dl or more than or equal to 150 to 200 percent from baseline or urine output less than 0.5 ml/kg per hour for more than 6 hours were included in the study.

Blood and urine examination, chest x ray, serial monitoring of blood urea serum creatinine ,sodium and potassium, IgM ELISA for Leptospirosis and Dengue virus were done in all patients. In selected patients, urine potassium, Widal test, Weil Felix test, IgM anti hepatitis A, peripheral smear, microscopic agglutination test (MAT) and PCR for Leptospira were also done.

STATISTICAL ANALYSIS

Statistical analysis was done using EPI INFO version 7. Quantitative variables were reported as means+/- SD and the qualitative variables as percentage. The chi square test, student's t test and regression analysis were used in the analysis of risk factors. The descriptive values below 5% (p value < 0.05) were considered statistically significant.

RESULTS

There were 67 patients with fever and AKI during the study period and of this 46 (68.66%) were due to Leptospirosis according to modified Faine's criteria. Serovars identified by Microscopic agglutination test (MAT) included *L. Icterohaemorrhagiae* (n=2), *L. australis* (n=3) and *L. autumnalis* (n=1). Leptospirosis Polymerase chain reaction (PCR) was done in 10 patients (15%). Out of these, six patients were positive.

The mean age of the study population was 42.63 with a SD of 13.15. There were 53 (79.10%) male and 14(20.90%) female patients in the study population .In confirmed cases of Leptospirosis, no of males were 36(78.26%) and females 10(21.74%). Mean age of the males were 42.87 (SD-13.75) and those of females were 41.71(SD-10.94).In confirmed cases of Leptospirosis, mean age was 40.07 (SD-10.73) and in cases other than Leptospirosis, mean age was 48.24 (SD-16.23).

Fever cases showed a peak during the months of June- July and October- November with 37.3% (n=25) and 25.3% (n=17) of the total cases respectively. Similar peaks were seen in confirmed cases of Leptospirosis in the corresponding months, 30.4% (n=14) and 37 %(n=17).

Among patients with AKI due to leptospirosis decreased urine output was seen in 84.78% (n=39). Mean urine volume in the first 24 hours was 715ml (SD-421) in Leptospirosis patients where as it was 500ml (SD-324) in cases other than Leptospirosis. (p-0.04)

Symptoms at the time of presentation of patients with AKI is shown in Table -1

Table 1; Symptoms at the time of presentation in patients with febrile AKI*

Symptoms	AKI due to leptospirosis	%	AKI due to other causes	%	RR	95% CI		Chi square	P
						upper	lower		
Headache	30	65.22	7	33.33	1.52	1.05	2.2	4.71	0.03
Myalgia	44	95.65	11	52.38	4.8	1.35	17.13	15.53	0.0008
Jaundice	31	67.39	8	38.1	1.48	1.01	2.17	3.95	0.0467
Decreased urine output	39	84.78	18	85.71	0.98	0.63	1.52	0.07	0.787
Altered sensorium	10	21.74	7	33.33	0.82	0.53	1.26	0.51	0.478
Loose stools	24	52.17	6	28.57	1.35	0.98	1.85	2.364	0.124
Dyspnea	21	45.65	13	61.9	0.81	0.59	1.13	0.94	0.33
Cough	11	23.91	4	19.05	1.1	0.76	1.56	0.016	0.9
Hemoptysis	4	8.7	0	0	1.5	1.26	1.79	0.013	0.909

*AKI-Acute Kidney Injury

Diabetes Mellitus was present in 16.42% [11] of total cases and 15.22% [7] of Leptospirosis cases and Systemic Hypertension in 11.94% (8) of total cases and 13.04% (6) of Leptospirosis. About one third of

patients gave a history of recent intake of nonsteroidal anti inflammatory drugs. Details of co morbid illnesses are shown in Table; 2.

Table 2; Co morbid conditions in AKI* with fever

History	Leptospirosis		Other causes	
	Number	Percentage	Number	Percentage
Diabetes	7	15.22%	4	19.05%
Hypertension	6	13.04%	2	9.52%
Liver disease	2	4.35%	1	4.76%
COPD	2	4.35%	1	4.76%
NSAID intake	17	36.96%	6	28.57%
Travel history	5	10.87%	4	19.05%
Smoking	23	50%	9	45%
Alcohol	21	45.65%	9	42.86%

*AKI-Acute Kidney Injury

The major clinical signs at the time of presentation included jaundice (68.66%), pedal edema (55.22%), conjunctival suffusion (77.61%), meningism (52.24%) and crepitations (46.27%). [Table 3]

Table 3; Physical signs in patients with AKI* with fever

Signs	Leptospirosis		Other causes		RR	95% CI		Chi square	p value
	Number	Percent	Number	Percent		Lower	Upper		
Pallor	11	23.91%	5	23.81%	1.00	0.69	1.46	0.09	0.76
Jaundice	35	76.09%	11	52.38%	1.45	0.94	2.25	2.74	0.09
Pedal edema	27	58.70%	10	27.03%	1.15	0.82	1.61	0.34	0.56
Conjunctival suffusion	43	93.48%	9	42.86%	4.13	1.49	11.46	18.45	0.000019
Meningism	30	65.22%	5	23.80%	1.71	1.18	2.49	8.32	0.0039
Hepatomegaly	20	43.48%	4	19.05%	1.38	1.02	1.86	2.76	0.10
Splenomegaly	21	45.65%	6	28.57%	1.24	0.91	1.7	1.11	0.29
Crepitations	21	45.65%	10	47.62%	0.96	0.7	1.35	0.01	0.9
Rhonchi	5	10.87%	4	19.05%	0.79	0.43	1.44	0.28	0.60
Temperature >39°C	28	60.87%	9	42.86%	1.26	0.89	1.78	1.23	0.27

*AKI-Acute Kidney Injury

Both hepatomegaly and splenomegaly together was present in 20.90% (n=14) patients. Only one patient with leptospirosis had purpura. The mean respiratory rate was 30 (SD-9) at the time of admission. Most of the cases occurred during the rainy season (71.6%).Other epidemiological parameters of Fever with AKI is shown in Table; 4.

Table 4; Epidemiological parameters of Fever with AKI*

Parameters	Leptospirosis		Others		RR	95% CI		Chi Square/ Fishers' exact	p value
	n	%	n	%		upper	lower		
Contact with contaminated environment	26	56.5	3	14.29	1.70	1.23	2.36	8.827	0.003
Rainfall	36	78.3	12	57.14	1.43	0.9	2.25	2.211	0.13
Animal contact	7	15.2	1	4.76	1.32	0.96	1.82	0.670	0.413

*AKI-Acute Kidney Injury

Mean total leucocyte count was higher than normal in the sample population as well as in patients with Leptospirosis and fever due to other causes. Mean platelet count was lower ((mean-75370, p-0.03) in patients with Leptospirosis (Table 5).

Table 5; Laboratory parameters in patients with AKI* and fever

Parameter	Sample population		Leptospirosis		Other cases		p value
	mean	SD	mean	SD	Mean	SD	
WBC count	13926	6701	12705	6405	16735	6673	0.02
Platelet count	94776	97030	75370	82866	137285	113382	0.014
Total bilirubin	7.53	8.85	8.94	9.74	3.71	3.94	0.004
Direct bilirubin	4.71	5.94	5.56	6.42	2.41	3.6171	0.018
SGOT	187.83	282.55	198.72	309.17	160	4.19	0.6

SGPT	160.61	377.41	181.37	437.35	107.56	132.52	0.5
ALP	212.38	157.21	207.23	142.19	225.25	194.43	0.7
Blood urea	97	47	97	47	97	47	0.95
Serum creatinine	4.22	2.31	4.14	2.08	4.38	2.81	0.7
CPK	1026	885	1095	915	711	706	0.3
Serum sodium	132	17.5	133.8	6.92	127.36	30.72	0.18
Serum potassium	4.32	1.13	4.2	1.12	4.61	1.14	0.2

*AKI-Acute Kidney Injury

Elevated creatinine phosphokinase was seen in majority of patients with leptospirosis with a mean value of 1095 (SD-915). Albuminuria was present almost universally in Leptospirosis patients (97%), but majority of patients showed only trace or 1+ albuminuria (77%).

IgM ELISA for Dengue antigen done in 43 (66%) patients, Widal test in 9 (13%), Weil Felix in 8 (12%) were negative. IgM anti Hepatitis A was done in 13 patients (19%) of which one was positive. He was also positive for IgM ELISA for Leptospirosis and was consistent with the diagnosis of leptospirosis as per modified Faine's criteria. Peripheral smears were negative for malarial parasite.

Hypokalemia was seen in 17.39% (n=8) patients and they had increased renal loss of potassium ranging from 21 to 41 meq. Chest X-ray in 8 patients (12%) showed bilateral interstitial infiltrates suggestive of acute respiratory distress syndrome (ARDS). Three of them expired.

The predictors for mortality that has statistical significance by univariate analysis includes cough with expectoration, pallor, pedal edema, lung crepitations and splenomegaly. (Table 6)

Table 6; Predictors of mortality in leptospirosis with AKI*

Parameters	survivors		Non survivors		RR	95% CI		Chi square	p value
	number	percent	number	percent		lower	upper		
Cough	4	12.5	7	50	3.18	1.43	7.08	5.61	0.017
Dyspnea	12	37.5	9	64.3	2.14	0.85	5.41	1.84	0.17
Pallor	4	12.5	7	50	3.18	1.43	7.08	5.61	0.02
Pedal edema	15	46.88	12	85.71	4.22	1.07	16.73	4.56	0.03
Splenomegaly	9	28.13	12	85.71	7.14	1.80	28.39	10.8	0.001
Crepitations	11	34.38	10	71.43	2.98	1.09	8.12	4.0	0.046

*AKI-Acute Kidney Injury

On multinomial logistic regression, pulmonary involvement either in the form of cough with expectoration, lung crepitations or dyspnea when taken together is associated with significant increase in mortality (n=29, OR-13.00, 95%CI- 1.52-111.47, 2-5.95, p-0.015). Severe pulmonary involvement requiring mechanical ventilation had relative risk of 4.11 on assessing the risk of mortality. (n=9, RR-4.11, 95%CI- 1.94-8.73, 2-9.23, p-0.002)

Acute kidney injury was common in Leptospirosis. However, severe AKI requiring renal replacement therapy in the form of haemodialysis or peritoneal dialysis did not show increase in the risk of mortality.(n=13, OR-1.67, 95%CI- 0.43-6.46, 0.2-0.15, p-0.70).Mean urine volume in the non survivor group was 500ml(SD-326) which is lower than that of survived, that is 810ml(SD-427) (p-0.02).

DISCUSSION

Most common cause of AKI due to AFI in our series was leptospirosis (68.66%). Serovars identified by Microscopic agglutination test (MAT) include *L. Icterohaemorrhagiae*, *L. Australis* and *L. Autumnalis*. Similar serovars were identified by Pappachan et al in a study conducted in midland rural area of Kerala state. In a study conducted by J Navaseelan et al, L.grippotyphosa was the commonest serogroup followed by L.Icterohaemorrhagiae and L.pomona in central Chennai during February 2009 and January 2010.

Leptospiral AKI was seen in relatively younger age group. In a tertiary care centre study conducted by Deodhar et al in Christian medical college, Ludhiana, similar results were obtained with mean age of 38 years [7]. The relatively younger age group of patients with leptospirosis may be attributed to the increased risk of exposure to contaminated environment based on their occupational status.

Males constituted majority of patients with AKI due to leptospirosis (78.26%). Studies by Angnani *et al* also points towards a male preponderance in leptospirosis. Leptospirosis cases showed a peak during the months of June- July and October- November with 30.4% and 37% of the total cases respectively corresponding with the southwest and northeast monsoon prevailing in Kerala. Studies from various parts of the world gives clear data regarding monsoon and post monsoon epidemics associated with leptospirosis. Periods of heavy rain followed by few days of little or no rain seemed to be the setting for leptospirosis epidemics in this part of the world according to Pappachan et al. [8] Similar observations

have been made by studies conducted in Brazil by Miyazato et al which showed an increased incidence during flooding in monsoon season.

Significant predictors for the diagnosis of leptospirosis in patients with AKI were headache (p-0.03), myalgia (p-0.00008) and jaundice (p-0.047). Headache was seen in 30 patients (65.22%) and altered sensorium in 10 (21.74%) indicates the importance of neurological involvement which often is underestimated.

We found diarrhea in 24 (52.17%) patients, not a classical finding in Weil's syndrome. Digestive system involvement is reported in other retrospective series(5),(9). More than one third (36.96%) of patients gave a history of recent intake of non steroidal anti inflammatory drugs. Almost half of the patients gave positive history for high risk behaviors including smoking (50%) and alcohol use (45.65%).

The most common signs associated with AKI due to Leptospirosis include jaundice (76.09%), pedal edema (58.70%), conjunctival suffusion (93.48%) and meningism (65.22%). The signs that are most consistent with the diagnosis in patients with AKI due to leptospirosis were conjunctival suffusion (p-0.000019) and meningism (p-0.0039).

The most important epidemiological determinant for the diagnosis of Leptospirosis is contact with contaminated environment (n-26, 95%CI 1.23-2.36, p-0.003). Most of the cases occurred during the rainy season (71.6%).Only a minority of patients (11.9%) gave a history of animal contact (Table 4). Three epidemiological factors considered by Shivakumar et al for supporting the diagnosis of leptospirosis are rainy season, contact with contaminated environment and animal contact.

Laboratory findings in Leptospirosis include neutrophilic leucocytosis and thrombocytopenia. Mean platelet count was significantly lower (p-0.03) in patients with Leptospirosis (mean-75370).

Abnormal liver function tests were common. The pattern of abnormality commonly involves a disproportionate elevation of conjugated bilirubin with mild elevation in transaminases. Leptospirosis cases showed significant conjugated hyperbilirubinemia than other cases (p-0.018). Similar observations were made by S.Ahmad et al who described a significant rise in bilirubin, with lesser increase in transaminases and marginal increase in alkaline phosphatase levels. The hyperbilirubinemia is generally out of proportion to the other liver function test values.

Among patients with AKI due to leptospirosis decreased urine output was seen in 84.78% (n=39). Mean urine volume in the first 24 hours was 715ml (SD-421) in Leptospirosis patients where as it was 500ml (SD-324) in cases other than Leptospirosis (p-0.04). Albuminuria was present in Leptospirosis patients was mild and majority of patients showed only trace or 1+ albumin (77%).All patients with hypokalemia, showed increased renal loss of potassium with urine potassium ranging from 21 to 41 meq/ day. Hypokalemia as a part of renal involvement in leptospirosis was found in around 41% patients according to Lopes et al. AKI in leptospirosis is primarily non-oliguric, and hypokalemia occurs frequently due to kaliuresis [2]. Another factor that can contribute to hypokalemia in leptospirosis is the inhibition of Na, K-ATPase activity in the renal proximal tubules. This alteration causes an increased distal sodium delivery and consequently an increase in potassium secretion.

Pulmonary involvement in the form of cough with expectoration, dyspnea or crepitations on physical examination had significant increase in the risk of mortality. Severe AKI requiring renal replacement therapy in the form of haemodialysis or peritoneal dialysis did not show statistically significant increase in the risk of mortality.

LIMITATIONS OF THE STUDY

The study was done in patients admitted in a tertiary care centre which serves the population of only three to four districts in Kerala. Epidemiology of acute febrile illness may differ in other places.

SUGGESTIONS

A larger population based study is necessary for better understanding of the disease profile. A study with sufficiently long duration is needed to identify the time dependent trends in the leptospirosis cases.

ETHICAL ASPECTS

Relevant permission was obtained from the institutional ethics committee prior to the beginning of the study

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