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RESEARCH ARTICLE

FOCUS INTO THE ROLE OF ACUTE KIDNEY INJURY IN LEPTOSPIROSIS: AN OBSERVATIONAL HOSPITAL BASED STUDY IN NORTH EASTERN INDIA

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ABSTRACT

Background: Leptospirosis is an emerging public health zoonotic disease affecting humans and animals alike. In humans, it can lead to a wide range of presentations, some of which may be mistaken for other diseases commonly occurring in the community. Without treatment, Leptospirosis can be fatal leading to kidney damage, meningitis, liver failure, respiratory distress, and even death. Reports on leptospirosis-induced acute kidney injury (AKI) in this part of country are scant and lacking in detail.

Materials and Methods: A total of 56 patients above the age of 12 with a seropositive leptospira test admitted in Silchar Medical College and Hospital from 1st June 2016 to 31st December 2017 were included in the present study. AKI was defined according to the KDIGO definition. Patients were stratified as oliguric and non-oliguric with the former having a urine output of 0.5 mL/kg/hr.

Results and Observations: Out of 56 patients that fit into our inclusion criteria, 31 (55.35%) of them had developed acute kidney injury. Other than fever, symptoms on presentation included headache 41 (73.21%), myalgia 36(64.28%) and jaundice 35 (62.5%) respectively. Blood urea nitrogen (BUN) and serum creatinine levels were significantly elevated in the oliguric subjects than the non-oliguric patients. Adverse outcome with respect to renal replacement therapy requirement and death were more common in oliguric patients.

Conclusion: The majority of patients who developed AKI following leptospirosis required renal replacement therapy. Non-oliguric forms had better prognosis and oliguria and hyperkalemia have been identified as predictors of a poor outcome.

INTRODUCTION

Leptospirosis is a disease which is prevalent all over the globe and is an important zoonosis caused by pathogenic strain of Leptospira, an obligate aerobic spirochete. The rat is the major reservoir of leptospira, mainly in urban areas. Transmission of the disease to human occurs through direct contact with blood, tissues, organs, or urine of infected animals, or through indirect contact, when injured mucosa or skin is exposed to contaminated water (Bharti *et al.,* 2003). It may also be associated with water sports and recreational exposure at lakes. The outbreak occurs usually in the rainy season with the mean incubation period of 15 days. The clinical course of leptospirosis can be divided into two phases. The initial phase lasts three to seven days and manifests as flu like illness and subsides after four to seven days from symptom onset. In that phase, leptospira can be isolated in the blood. In the second phase, more severe symptoms, such as altered mental status, acute renal failure, respiratory insufficiency, hypotension and arrythmias, can occur (Daher *et al.,* 1999). The clinical manifestation of leptospirosis is varied, non-specific and diverse ranging from a mild acute self-limiting febrile illness to frank liver and kidney failure.

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The classical presentation, referred to as the Weil's syndrome encompasses the triad of hemorrhage, jaundice and acute kidney injury. Global data across all ages reveal that the incidence of AKI in leptospirosis is at 36% (World Health Organization, 2011). The renal involvement in leptospirosis can vary from a subclinical course with mild proteinuria and urinary sediments to overt AKI. The AKI usually presents with a rapid elevation in blood urea and creatinine, and can be associated with jaundice. Acute kidney injury is common in severe disease, presenting after several days of illness and characterized by interstitial and tubular damage. It can be either non oliguric or oliguric renal failure. Factors contributing to renal failure in leptospirosis include infection of the kidney with pathogen, immune mediated renal damage, dehydration, jaundice and rhabdomyolysis (Plank and Dean, 2000). The characteristic presence of normo or hypokalemia in leptospirosis AKI has been attributed to urinary losses due to increased distal potassium secretion caused by increased distal sodium delivery consequent to impaired proximal sodium reabsorption. The presence of non-oliguria can be explained by the inability to concentrate urine in leptospirosis due to inner medullary collecting duct resistance to vasopressin-stimulated water transport. The outcome of AKI if recognized early and managed properly is fair, but a significant proportion of mortality is also associated with it (Kularatne *et al.,* 2011).

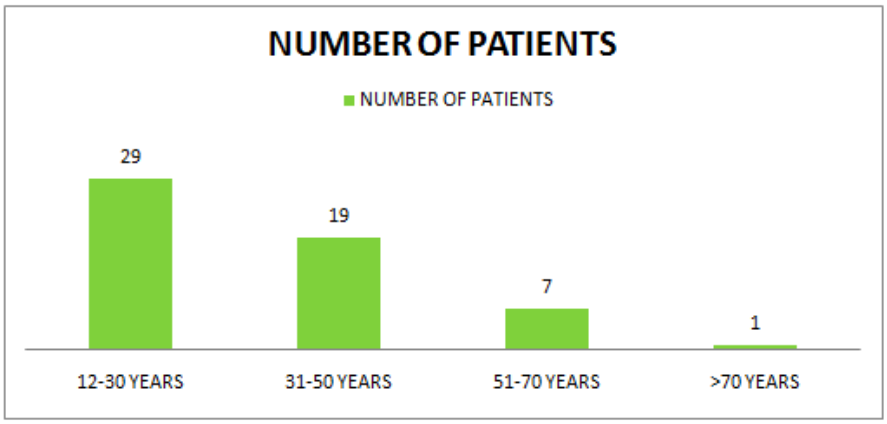

Figure 1. Age distribution of patients

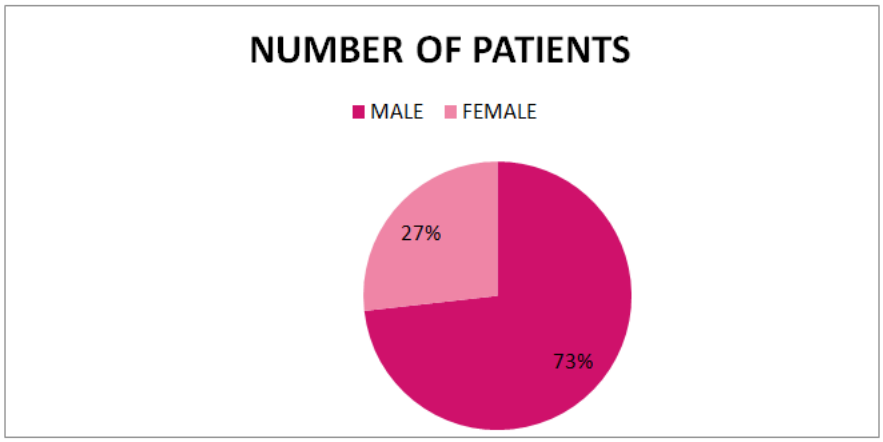

Figure 2. Sex distribution of patients

Aims and Objectives

- To evaluate the clinical spectrum of patients with leptospirosis
- To determine any risk factors towards the development of acute kidney injury (AKI) and subsequent mortality.

MATERIALS AND METHODS

A hospital based observational study was conducted to describe the demographic profile of patients with leptospirosis and to determine any risk factors towards the development of AKI. A total of 56 patients aged more than 12 years, diagnosed to have leptospirosis and admitted in Silchar Medical College and Hospital from 1st June, 2016 to 31st December, 2017 were included in the study. The diagnosis of leptospirosis was confirmed by ELISA for evaluation of leptospira's IgM and MAT. Acute kidney injury was defined according to KDIGO guidelines. Patients with pre-existing kidney diseases concomitant febrile illnesses (dengue, viral hepatitis, HIV infection, malaria, filariasis, typhoid fever, tuberculosis, urinary tract infection) or any concomitant cause leading to AKI (Nephrolithiasis, ureteric calculi, bladder outlet obstruction, hepato-renal syndrome, vasculitis) were excluded from the study. Data were collected for demographic characteristics, and presence or absence of following clinical and laboratory manifestations. Fever and chills, jaundice, echymosis and petechiae, mucosal bleeding, myalgia, arthralgia, lymphadenopathy, cough, pharyngitis, nausea and vomiting, diarrhea, abdominal pain, hepatomegaly, splenomegaly, headache, meningismus and disturbed consciousness were recorded in the history. Laboratory tests including complete blood count and peripheral blood film, serum urea and creatinine, serum electrolytes, total bilirubin, ALT and AST, proteinuria, hematuria, serum amylase and lipase, serum creatine-kinase, random blood glucose, PT-INR were done. In addition, rapid kit test for malaria antigen, blood smear (thick and thin) for malarial parasites, were also done in all the patients. Dengue IgM ELISA and NS1 antigen, Widal test/ IgM antibody for salmonella typhi was screened if indicated. Statistical analysis was performed using SPSS Version 20. Continuous variables were presented as mean (±standard deviation). Univariate statistical analysis was performed by Chi-square test for comparing proportions and ANOVA for comparing means. The value $p < 0.05$ was considered to be statistically significant.

RESULTS

Majority of patients with AKI belonged to the age group of 12-30 years accounting for 51.78% (n =29) of total patients. The median age of the patients was 38.5±8.6 years. AKI was more commonly associated with male sex, 73.21% (n= 41) of the patients were males. The distribution of patients in various age groups is shown in Figure 1.

The predominant symptom was fever, although the length varied between 1-18 days, followed by nausea and vomiting, muscle pain and jaundice.

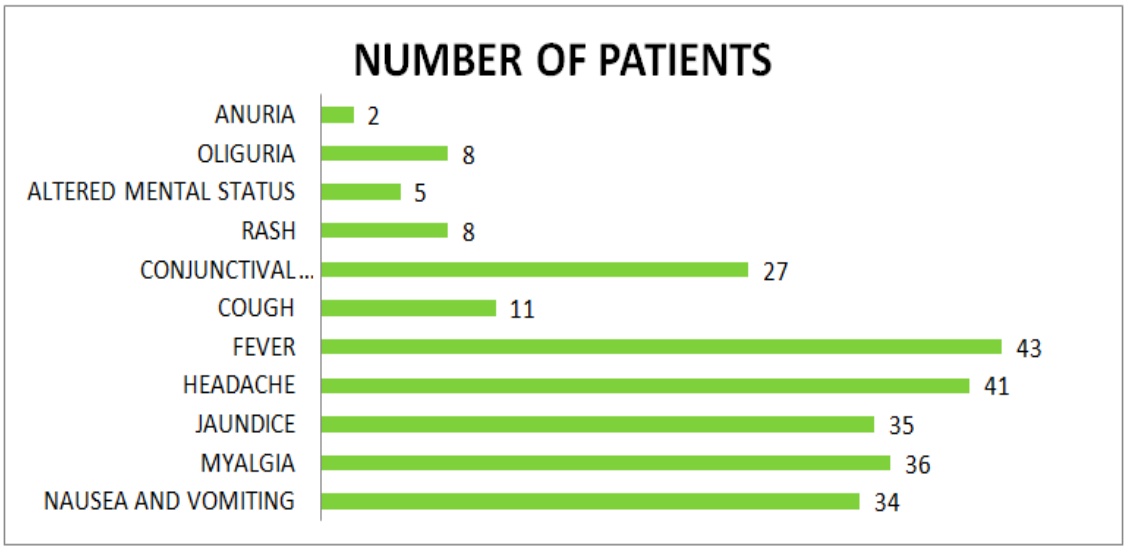

Figure 3.Clinical presentation of patients

Table 1. Comparison of clinical signs and laboratory findings in patients with oliguric and non oliguric renal failure

Sings and laboratory Parameters	Oliguric AKI (10/31)	Non oliguric AKI (21/31)	P Value
Dehydration	8	10	0.8
Icterus	10	7	0.001
Pulse rate(/minute)	112±15	93±10	0.23
Total leucocyte count(/mm^3)	16556±1208	12329±578	0.01
Serum Creatinine(mg/dl)	8.5±6.7	4.3±2	0.001
Blood urea(mg/dl)	187±20	121±12	0.01
Serum Sodium(meq/L)	129±6	130±5	0.28
Serum potassium(meq/L)	5.2±1.7	3.3±1.2	0.11
Serum Alt	141.1±145.3	102.4±122.9	0.05
Serum bilirubin(mg/dl)	6.3±2.1	3±1.1	0.001

Table 2. Treatment modality and mortality of patients with leptospirosis-induced AKI

Parameters	Oliguric AKI (n=10)	Non oliguric AKI (n=21)	P value
Hospital days ≥7 days	8	6	0.2
Dopamine requirement	4	5	0.01
Use of diuretics	5	6	0.01
Rrt requirement	6	2	0.001
Mortality	4	2	0.012

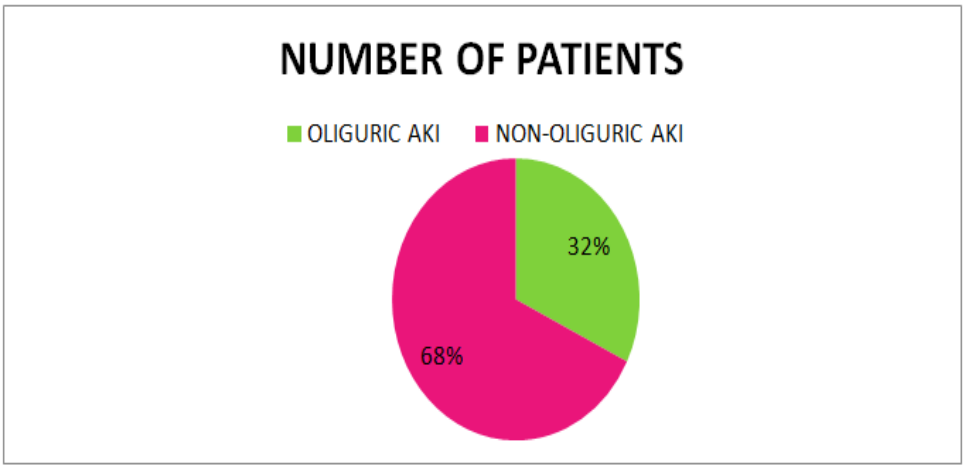

Figure 4. Prevalence of Oliguric AKI vs. non-Oliguric AKI

Clinical presentation of patients with leptospirosis is presented in Figure 3. Out of 56 patients (confirmed cases of leptospirosis) included in the study, 31(55.35%) patients had developed acute kidney injury according to the KDIGO guidelines. Out of 31 patients, 26 were male (83.87%) and 21(67.74%) out of them were younger than 25 years. Out of the patients developing AKI, 10 patients (17.85%) developed oliguric AKI and 21 patients (37.5%) developed non oliguric AKI.

Treatment and Outcome

About 90% of patients were treated with intravenous ceftriaxone. The other antibiotics used included doxycycline, ciprofloxacin and ampicillin in small percentage. Out of 10 patients with oliguric renal failure 6 of them required hemodialysis whereas out of 21 patients with non oliguric renal failure only 2 patients required hemodialysis. There were six (10.7%) deaths wherein one patient died because of respiratory failure due to pneumonia, and the other 5 died because of oliguric renal failure.

DISCUSSION

The clinical manifestations of leptospirosis may vary from subclinical infection to severe and potentially fatal disease. The most severe form is Weil's disease, which is presented by febrile illness with bleeding tendency, hepatic dysfunction and acute kidney injury (AKI). Tubulo-interstitial nephritis is the main cause of acute renal injury in leptospirosis. Among 56 confirmed cases of leptospirosis, 31(55.35%) patients developed acute kidney injury. In developed countries, leptospirosis is an uncommon cause of acute kidney injury (AKI) (Kokudo *et al.,* 2009). However, in tropical countries, where the disease is endemic, leptospirosis is an important cause of AKI. The incidence of AKI varies from 10% to 60%, depending on the severity of the disease, age, and definition of AKI (Sitprija *et al.,* 2003). Renal failure was seen in more than one third of the cases in the study by Seguro AC et al. (1990). In the present study AKI was more common in males, 73.21% (*n*= 41). The incidence of leptospirosis was higher in males that may be attributed to the risk associated with occupational exposure especially farmers who spent most of their working time in rice fields where prolonged water contact is unavoidable. The spreading of leptospirosis occurs during the rainy season every year, starting from June through to November. In another Indian study from Kerala by Pappachan MJ et al. 58.9% was men (2004).

The most common clinical symptoms in the patients were fever and chills, headache, myalgia and jaundice. Most patients in the study population had fever for one week or more before diagnosis, this may impose patients at greater risk of acute kidney injury. Patients developing AKI had significant hepatic involvement with elevated ALT and bilirubin levels (Windpessl *et al.,* 2014). Leptospirosis oliguric AKI primarily occurs due to dehydration (Cerqueira *et al.,* 2008). Leukocytosis was one of the significant risk factors in predicting AKI in this study. Markum also found this correlation in a review of 68 patients with AKI due to leptospirosis (Markum *et al.,* 2016). It may reflect the grade of inflammation in patients with acute tubular injury. Daher et al. found no relationship between leukocytosis and acute renal failure (Daher *et al.,* 2009). But a few studies showed that leukocytosis is an important factor in predicting the outcome of patients. According to Covic's study, there was significant correlation between leukocytosis and deaths. (Covic *et al.,* 2003).In contrast to other studies, hypokalemia was not present with non oliguric AKI. A wasting sodium and potassium defect has been consistently documented by different groups (Seguro *et al.,* 1990). Renal failure due to leptospirosis can be divided into two types viz oliguric and non-oliguric, non oliguric type being more common with creatinine usually less than 4mg/dl and is associated with better prognosis (Windpessl *et al.,* 2014). Oliguria and anuria in severe cases (with creatinine more than 4) are usually accompanied by dehydration, jaundice and severe sepsis. Coexistent hematuria and rhabdomyolysis also contribute to disease progression (Cerqueira *et al.,* 2008). Therefore in addition to direct effects of leptospirosis on kidney other parameters like jaundice, dehydration and rhabdomyolysis may also affect the course of renal failure. The early diagnosis and institution of appropriate therapy are the most important points in managing leptospirosis. Several antibiotics can be used for the treatment of leptospirosis. There is no relationship between the type of antibiotic used and renal outcomes (Andrade *et al.,* 2008). Leptospirosis and its resultant complications can be prevented by minimizing occupational exposure, early diagnosis, adequate hydration and renal replacement therapy where indicated.

Conclusion

Oliguric AKI due to leptospirosis is more frequent and more severe than non-oliguric kidney failure among the population in this part of the country. Early recognition and appropriate institution of antibiotics, fluids, inotropic support and initiation of RRT wherever and whenever indicated may have an impact on survival.

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