SERUM ELECTROLYTES, RENAL, HEPATIC AND PANCREATIC FUNCTION IN LEPTOSPIROSIS AND THEIR ASSOCIATION WITH ITS SEVERITY

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ABSTRACT

BACKGROUND

Leptospirosis is an important cause of mortality and morbidity in Kerala. The present study is conducted to evaluate the association of serum electrolytes, parameters of renal, hepatic and pancreatic function with the severity of leptospirosis.

MATERIALS AND METHODS

We enrolled 84 participants in our descriptive study with leptospirosis aged 18 years or above with leptospirosis admitted under General Medicine in 2 years. Pre-existing renal, hepatic and respiratory diseases were excluded. The study was approved by Institutional Ethics Committee and written informed consent was obtained from all study participants. Serum electrolytes, liver function tests, renal function tests, serum amylase, serum lipase and creatinine phosphokinase were done in central laboratory and results were analysed using R®. Parameters are expressed as categorical variables and association was determined using Chi-square test and Fischer's exact test and $p < 0.05$ was considered statistically significant.

RESULTS

Among the participants (n=84), 71% were males, 70% had severe leptospirosis, 72.6% had hyponatremia, 23.8% had hypokalaemia, 40.5% had elevated serum creatinine, 65.5% had elevated blood urea, 56% had elevated serum total bilirubin (T.bil) and 31% had elevated direct bilirubin (D.bil). Aspartate Amino transferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP) and Creatinine Phosphokinase (CPK) were elevated in 61.9%, 47.6%, 44% and 15.5% participants respectively. 8.3% participants had elevated serum amylase and lipase. Significant association with severity of leptospirosis was observed for serum sodium (p=0.001; OR: 7.1, 95% CI 2.4–20.4), serum potassium (p=0.03; OR: 5, 95% CI 1.1-23.7), serum creatinine (p=0.001; OR: 13.6, 95% CI 2.9-63.1), blood urea (p<0.001; OR: 15.5, 95% CI 5–48.6), T.bil (p<0.001), D.bil (p=0.01), AST (p=0.002; OR: 8.3, 95% CI 2.9–23.8), ALT (p=0.03; OR: 4.3, 95% CI 1.5–12.3) and ALP (p=0.001; OR: 6.7, 95% CI 2–21.8). Significant association of serum potassium (p=0.02; OR: 12.2), blood urea (p=0.001; OR: 29.8) and ALP (p=0.04; OR: 8.1) with severity of leptospirosis was observed with multivariate logistic regression.

CONCLUSION

We recommend serum electrolytes, hepatic function tests, renal function tests, serum amylase and lipase to be routinely done in all patients with leptospirosis for early detection and prevention of organ dysfunction.

KEYWORDS

Leptospirosis, Sodium Potassium Hepatic Transaminase, Blood Urea, Serum Creatinine.

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BACKGROUND

Leptospirosis is a potentially fatal zoonotic disease caused by the aerobic spirochete Leptospira spp. and is considered the most widespread zoonosis in the world. The disease has emerged as a potentially fatal infection exemplified by the recent outbreaks in India, Nicaragua, Brazil, United States and Southeast Asia.[1-5] Though this disease is described as ubiquitous it is more prevalent in the tropical regions due to increased survival of Leptospira spp. in warm conditions and due to the favourable climatic conditions for survival and breeding of the most important carrier, the brown rat (Rattus norvegicus). Inadequate sanitation, overcrowding, poor housing and working conditions and the monsoons have contributed to the increase in transmission of disease in these geographic regions. Carriers harbour Leptospira spp. in their renal tubules and shed them in their urine and human infection results from entry of Leptospira spp. from contaminated water through breaks in the skin, intact conjunctiva or mucous membrane. The wide range of symptomatology of leptospirosis from flu-like syndrome to severe life-threatening multiorgan dysfunction, coupled with lack of proper diagnostic test makes the diagnosis

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troublesome. Occupational and accidental exposures occur commonly in the low socio-economic strata imposing a financial burden on the destitute. Leptospirosis patients can develop pulmonary haemorrhage,[6-10] acute kidney injury (AKI),[11] pancreatitis[12] and hepatic dysfunction[13] which contribute to mortality and morbidity. The fatality is high with multiorgan involvement especially pulmonary haemorrhage, AKI, and pancreatitis.[14] Global burden of leptospirosis is 1.03 million and 58,900 fatalities are reported annually.[15] Intensive management and increased recognition of the disease has helped in curtailing the mortality associated with leptospirosis though morbidity has accentuated three fold.[15] The significant mortality associated with leptospirosis is attributed to the enormous ever increasing population of India, expanding urban slums and poor hygienic conditions.[15] The problem gets even more complicated with the lengthy monsoon season coinciding with rodent breeding, waste mismanagement, and absence of a systematic national leptospirosis prevention and control programme. Dual monsoon showers in Kerala also impart a role on the health impact of leptospirosis. Misdiagnosis or delay in diagnosis is common since leptospirosis has overlapping symptomatology with other febrile illness such as dengue fever. Mortality and morbidity associated with leptospirosis can be reduced with early diagnosis, expeditious intervention with adequate hydration and use of appropriate antibiotics. Limited literature is available from Kerala describing the relationship between leptospirosis and its severity with serum electrolytes, hepatic, renal and pancreatic function. Since leptospirosis and its complications are very prevalent in Kerala, this study is conducted.

MATERIALS AND METHODS

Our present descriptive study enrolled 84 participants over 18 years of age with positive IgM for Leptospira spp. using ELISA and satisfying modified Faine's criteria.[16] The study was conducted in Department of General Medicine, Sree Gokulam Medical College and Research Foundation, Venjaramoodu between 2014 and 2016. Participants with pre-existing renal, hepatic and pulmonary disease were excluded. Institutional ethics committee approved the study and written informed consent was obtained from all study participants. Serum electrolytes (sodium and potassium), renal function test (blood urea and serum creatinine), liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum bilirubin (total and direct)), parameters assessing pancreatic function (serum amylase and lipase) and creatinine phosphokinase (CPK) were done in the central laboratory of the institution using standardized techniques and results were collected in separate case record forms. Participants were categorized based on severity of leptospirosis (mild leptospirosis (acute febrile illness with no complications), severe leptospirosis (acute febrile illness with one or more of the following; jaundice, AKI, pulmonary haemorrhage, acute respiratory distress syndrome, neuroleptospirosis, thrombocytopenia, myocarditis, ocular complications or hypokalaemic paralysis,))[16] and based on laboratory results. Sample size was calculated as 84 using the formula $Z\alpha^2P(100-P)/L^2$, Zα-1.96, P-82, L-10%.[17] Data were analyzed using free software R® and parameters were expressed as categorical variables. Tests of significance used were Chi-square test and Fischer's exact test; $p<0.05$ was considered statistically significant. Odds ratio (OR) with 95% confidence interval (CI) was used to express the association in 2x2 tables. Multivariate logistic regression was used to determine the association of variables which showed significant association with severity of leptospirosis.

RESULTS

84 participants enrolled in the study, 71.4% (n=60) were males and 28.6% (n=24) were females. 70.2% (n=59) had severe leptospirosis and 29.8% (n=25) had mild leptospirosis. 27.4% (n=23) participants had normal serum sodium, 72.6% (n=61) had hyponatremia. Among participants with hyponatremia, 98.4% (n=60) had mild hyponatremia and 1.6% (n=1) had moderate hyponatremia. Hypernatremia or severe hyponatremia was not observed among participants. 76.2% (n=64) participants had normal serum potassium, 23.8% (n=20) had hypokalaemia. Among participants with hypokalaemia, 85% (n=17) had mild hypokalaemia and 15% (n=3) had moderate hypokalaemia. None of the participants had hyperkalaemia or severe hypokalaemia. 59.5% (n=50) participants had normal serum creatinine and 40.5% (n=34) had elevated serum creatinine (Table 1). Blood urea, serum total bilirubin (T.bil) and direct bilirubin (D.bil) were elevated in 65.5% (n=55) (Table 2), 56% (n=47) (Table 3) and 31% (n=26) (Table 4) participants respectively.

Serum Creatinine (mg/dl)	n (%)
1.3-2.5	13 (38.2)
2.6-5	19 (55.9)
>7.5	2 (5.9)

Table 1. Stratified Frequency Table for Elevated Serum Creatinine

Blood Urea (mg/dl)	n (%)
<20	29 (34.5)
20-40	23 (27.4)
41-60	10 (11.9)
61-80	7 (8.3)
>80	15 (17.9)

Table 2. Stratified Frequency Table for Blood Urea

T.bil (mg/dl)	n (%)
<1.2	37 (44)
1.3-3	29 (34.5)
3.1-5	9 (10.7)
5.1-7.5	4 (4.8)
7.6-10	2 (2.4)
10-12.5	1 (1.2)
12.6-15	1 (1.2)
>15	1 (1.2)

Table 3. Stratified Frequency Table for Serum T.bil

AST, ALT and ALP were elevated in 61.9% (n=52) (Table 5), 47.6% (n=44) (Table 6) and 44% (n=37) participants respectively. Among participants with elevated ALP, 73% (n=27) had highly elevated ALP. 15.5% (n=13) participants had elevated CPK. Among participants with elevated CPK, 69.2% (n=9) had mild elevation and 30.8% (n=4) had highly elevated CPK. Both serum amylase and lipase were elevated in 8.3% (n=7) participants. Among participants with pancreatic involvement, serum amylase and lipase were highly elevated in 85.7% (n=6) participants. Comparison of baseline parameters between mild and severe leptospirosis is demonstrated in table 7.

D. bil (mg/dl)	n (%)
0.1-0.4	58 (69)
0.5-1	13 (15.5)
1.1-1.5	5 (6)
>1.5	8 (9.5)
Table 4. Stratified Frequency Table for D.bil	

AST (IU/L)	n (%)
<40	32 (38.1)
40-80	33 (39.3)
81-120	8 (9.5)
121-160	2 (2.4)
161-200	5 (6)
>200	4 (4.8)
Table 5. Stratified Frequency Table for AST	

ALT (IU/L)	n (%)
< 65	44 (52.4)
65-105	17 (20.2)
106-145	9 (10.7)
146-185	9 (10.7)
>185	5 (6)
Table 6. Stratified Frequency Table for ALT	

Parameter	Mild Leptospirosis n (%)	Severe Leptospirosis n (%)
Serum sodium < 135 mEq/L	11 (44)	50 (84.7)
Serum potassium < 3.5 mEq/L	2 (8)	18 (30.5)
Serum creatinine > 1.2 mg/dl	2 (8)	32 (54.2)
Blood Urea > 20 mg/dl	6 (24)	49 (83.1)
Serum T. bil > 3 mg/dl	0 (0)	47 (79.7)
Serum D. bil > 0.5 mg/dl	0 (0)	26 (44.1)
Serum AST > 40 IU/L	7 (28)	45 (76.3)
Serum ALT > 65 IU/L	6 (24)	34 (57.6)
Serum ALP > 136 IU/L	4 (16)	33 (55.9)
Serum CPK > 308 U/L	1 (4)	12 (20.3)
Serum amylase > 116 U/L	0 (0)	7 (11.9)
Serum lipase >393 U/L	0 (0)	7 (11.9)
Table 7. Comparison of Baseline Parameters between Mild and Severe Leptospirosis		

Baseline parameters when tested for association with severity of leptospirosis showed no association of CPK (p=0.2), serum amylase (p=0.2) and serum lipase (p=0.2) with severity of leptospirosis. Significant association with severity of leptospirosis was observed for serum sodium (p<0.001) (Table 8), serum potassium (p=0.03) (Table 9), serum creatinine (p<0.001) (Table 10), blood urea (p=0.001) (Table 11), T. bil (p<0.001) (Table 12), D. bil (p<0.001) (Table 13), AST (p=0.002) (Table 14), ALT (p=0.005) (Table 15) and ALP (p=0.001) (Table 16) independently.

Serum Sodium (mEq/L)	Leptospirosis		Total
	Mild	Severe	
≥ 135	14	9	23
<135	11	50	61
Total	25	59	84
Table 8. Association between Serum Sodium and Severity of Leptospirosis			

Significant association was observed (p<0.001; OR: 7.1, 95% CI 2.4–20.4) indicating 7.1 Odds of encountering mild leptospirosis in participants with serum sodium ≥ 135 mEq/L.

Serum Potassium (mEq/L)	Leptospirosis	
	Mild	Severe
≥ 3.5	23	41
<3.5	2	18
Table 9. Association between Serum Potassium and Severity of Leptospirosis		

Significant association was observed (p=0.03; OR: 5, 95% CI 1.1-23.7) indicating 5 Odds of encountering mild leptospirosis among participants with serum potassium ≥ 3.5 mEq/L.

Serum Creatinine (mg/dl)	Leptospirosis	
	Mild	Severe
< 1.3	23	27
≥ 1.3	2	32
Table 10. Association between Serum Creatinine and Severity of Leptospirosis		

Significant association was observed (p<0.001; OR: 13.6, 95% CI 2.9-63.1) indicating 13.6 Odds of encountering mild leptospirosis among participants with serum creatinine < 1.3 mg/dl.

Blood Urea (mg/dl)	Leptospirosis	
	Mild	Severe
≤ 20	19	10
>20	6	49
Table 11. Association between Blood Urea and Severity of Leptospirosis		

Significant association was observed (p=0.001; OR: 15.5, 95% CI 5-48.6) indicating 15.5 Odds of encountering mild leptospirosis among participants with blood urea ≤ 20 mg/dl.

Serum T.bil (mg/dl)	Leptospirosis	
	Mild	Severe
<3	25	12
≥ 3	0	47

Table 12. Association between Serum T.bil and Severity of Leptospirosis

Significant association was observed (p<0.001, OR could not be calculated as one cell of 2x2 table had 0 as value).

Serum D.bil (mg/dl)	Leptospirosis	
	Mild	Severe
<0.5	25	33
≥ 0.5	0	26

Table 13. Association between Serum D.bil and Severity of Leptospirosis

Significant association was observed (p<0.001, OR could not be calculated as one cell of the 2x2 table had 0 as value).

AST (IU/L)	Leptospirosis	
	Mild	Severe
≤40	18	14
>40	7	45

Table 14. Association between AST and Severity of Leptospirosis

Significant association was observed (p=0.002; OR: 8.3, 95% CI 2.9–23.8) indicating 8.3 Odds of encountering mild leptospirosis among participants with AST ≤ 40 IU/L.

ALT (IU/L)	Leptospirosis	
	Mild	Severe
≤ 65	19	25
>65	6	34

Table 15. Association between ALT and Severity of Leptospirosis

Significant association was observed (p=0.005; OR: 4.3, 95% CI 1.5–12.3) indicating 4.3 Odds of encountering mild leptospirosis among participants with ALT ≤ 65 IU/L.

ALP (IU/L)	Leptospirosis	
	Mild	Severe
≤ 136	21	26
>136	4	33

Table 16. Association between ALP and Severity of Leptospirosis

Significant association was observed (p=0.001; OR: 6.7, 95% CI 2–21.8) indicating 6.7 Odds of encountering mild leptospirosis among participants with ALT ≤136 IU/L.

Multivariate logistic regression model demonstrated significant association of serum potassium (p=0.02; OR: 12.2), blood urea (p=0.001; OR: 29.8) and ALP (p=0.04; OR: 8.1) with severity of leptospirosis. Hepatic involvement was seen in 56% (n=47) participants and was the most common organ involved in leptospirosis. 40.5% (n=34) participants had AKI, 8.3% (n=7) had pancreatic involvement and 3.6% (n=3) participants had cardiac involvement.

DISCUSSION

Predominant participants diagnosed with leptospirosis were males which have been previously described[18-21] as due to the higher risk of recreational or occupational exposure to infected animals or contaminated water among men. 70% of participants had severe leptospirosis in contrast to reports of 5-15%[22,23] incidence. This could indicate that Kerala has a higher incidence of severe leptospirosis compared to previous reports or the predominant participants attending hospitals would be with severe leptospirosis. 73% participants had hyponatremia which is commonly associated with leptospirosis[24] but with varying prevalence.[25,26] This is due to natriuresis attributed to increased renal blood flow[27] and elevated vasopressin and intracellular movement of sodium.[27] Contrast to reports suggesting a stronger association of hypernatremia to severity of leptospirosis,[28] none of the participants had hypernatremia. 24% of participants had severe hypokalaemia and the prevalence has been described as 26-45% which is attributed to kaliuresis in leptospirosis.[29] The Leptospira spp. has a direct inhibitory effect on Na^+-K^+-ATPase resulting in reduced reabsorption of Na^+ ions from proximal convoluted tubule, loop of Henle and distal convoluted tubule. This results in increased delivery of Na^+ ions to collecting tubule where epithelial sodium channels reabsorb the Na^+ ions in exchange for K^+ ions leading to kaliuresis.[27] Elevation of serum creatinine has been reported in 27-100% patients,[13,22-23] 41% participants had elevated serum creatinine in our study. The observed difference in prevalence of AKI varies with geographical regions and with different serovars. Renal injury in leptospirosis is due to the direct nephrotoxic action of Leptospira spp., hyperbilirubinemia, rhabdomyolysis and hypovolemia.[30] 65% participants had elevated blood urea which is higher than previous reports of 51% prevalence.[31] This appertains to AKI induced by Leptospira spp. and has been described as a predictor of long-term renal injury[31] in patients with leptospirosis. T.bil was elevated in 56% of participants and the prevalence reported is in 18-92% of leptospirosis patients.[32,33] This is due to disruption of the intercellular junction of hepatocytes and direct hepatocellular damage resulting in leakage of bile and resultant jaundice.[34] 31% participants had elevated D.bil which was lower than previous reports of 66% prevalence.[31] This could be due to the preferential organ involvement with various serovars or

due to enrolment of higher number of severe leptospirosis patients in previous studies. 63%, 48%, and 44% participants had elevated AST, ALT and ALP respectively. Prevalence of elevated AST, ALT, and ALP in leptospirosis patients reported are 27-86%,[31,32] 87%[31] and 96%[31] respectively. This could be due to the varying prevalence of serovars in different geographical areas. 16% participants had elevated CPK, more than threefold elevation of CPK has been reported in 27% patients.[31] Myositis accompanying leptospirosis[35] cause elevated CPK but is not considered as a reliable indicator or predictor of the severity of disease.[31] Only participants with severe leptospirosis had hyperamylasaemia (8.3%) and hyperlipasemia (8.3%). The reported prevalence of hyperamylasaemia is 12.5% in mild leptospirosis and 55% in severe leptospirosis.[32] This is due to AKI[36] and rarely due to pancreatitis caused by Leptospira spp.[37] The difference observed in prevalence could be due to lower virulence of the organism in our region inducing lower rates of AKI and pancreatitis. All patients with pancreatitis were treated with standard supportive care, antibiotics and there was no mortality. Significant association of severity of leptospirosis with serum sodium and serum potassium was observed with higher odds of encountering mild leptospirosis in participants with normal sodium and potassium levels. Reduced expression of sodium hydrogen exchanger 3 (NHE-3) isoform in renal tubules, reduced expression of aquaporin channels in collecting tubule and increased expression of sodium potassium chloride symporter (NKCC-2) in thick ascending limb of loop of Henle by unknown mechanism by Leptospira spp.[38] could explain this association. Predominant sodium reabsorption (65%) occurs in the proximal tubule, reduced expression of NHE-3 leads to reduced reabsorption of sodium causing hyponatremia. Increased delivery of sodium to collecting tubule cause activation of epithelial sodium channels (ENaC) causing increased reabsorption of sodium in exchange for potassium leading to kaliuresis. Increased expression of NKCC-2 is due to increased vasopressin levels.[38] Though NKCC-2 overexpression cause increase in sodium reabsorption, only part of the filtered sodium (~20 ascending limb of loop of Henle and hence cannot compensate the natriuresis. Severity of leptospirosis was associated with blood urea and serum creatinine with higher odds of encountering mild leptospirosis in participants with normal blood urea and serum creatinine. AKI (5-10% patients with leptospirosis)[39] due to tubulointerstitial nephritis caused by Leptospira spp. explains this association. A significant association was observed between severity of leptospirosis and hepatic transaminases with higher odds of encountering mild leptospirosis in participants with normal transaminases. Though liver is not a primary target for Leptospira spp., elevation of AST and ALT has been described in almost all cases of leptospirosis.[35] Weil's disease, a severe icteric form of leptospirosis with renal dysfunction is associated with very high AST and ALT levels. Myositis accompanying leptospirosis[35] caused by the direct toxic effects of Leptospira spp..[40-42] produce parenchymal cell membrane damage and subsequent necrosis which also contribute to the elevated AST. Renal, hepatic and muscular involvement in leptospirosis could contribute to the elevation of ALP as these organs are sources of ALP.[43] No association between pancreatic enzymes and severity of leptospirosis was observed since pancreatic involvement is a rare finding in leptospirosis. Myositis produced by Leptospira spp. can cause elevation in CPK; our study did not demonstrate any association between CPK and severity of leptospirosis. Multivariate logistic regression demonstrated significant association of severity of leptospirosis with serum potassium, blood urea, and ALP. The reasons for this association have been discussed in the text above. The most common organ involved in our study was liver similar to previous reports.[44] Kidney and pancreas were involved in 40.5% and 8.3% participants respectively.

CONCLUSION

In our study, males were predominant and majority participants had severe leptospirosis. 70% had hyponatremia and hypokalaemia was seen in quarter of study participants. Blood urea and serum creatinine were elevated in 65% and 40% participants respectively. Half of the participants had elevated T. bil and a third had elevated D. bil. Hepatic transaminases (AST and ALT) were elevated in 60% and 50% participants respectively. Elevated ALP and CPK were seen in 45% and 15% participants respectively. Pancreatic involvement was seen in 8% of participants. Significant association of severity of leptospirosis with serum electrolytes, parameters of renal function and hepatic transaminases was observed. We recommend that these investigations to be routinely done in all patients with leptospirosis for early detection and prevention of organ dysfunction.

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