

THE ASSOCIATION BETWEEN SERUM POTASSIUM AT HOSPITAL ADMISSION AND THE CASE-FATALITY RATE OF LEPTOSPIROSIS IN MEN

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SUMMARY

Severe leptospirosis affects predominantly males and presents a high susceptibility to hypokalemic acute renal failure. As hypokalemia and hyperkalemia induce severe complications, it is important to evaluate if the initial serum potassium is an independent risk factor for death in leptospirosis. The medical records of 1016 patients hospitalized with the diagnosis of leptospirosis were reviewed. The analysis was restricted to 442, according to the following criteria: male, 18 years or older, information about death or hospital discharge and recorded values of serum potassium, serum creatinine and duration of symptoms at admission. Potassium values lower than 3.5 mEq/L (hypoK), 3.5-5 mEq/L (normoK) and above 5 mEq/L (hyperK) were detected in 180, 245 and 17 patients, respectively. The death rate increased with serum potassium: 11.1% in the hypoK, 14.7% in the normoK and 47.1% in the hyperK group ($p = 0.002$). In a logistic regression model (normoK as referent), including age, creatinine and duration of symptoms, hypoK was not associated with increased death rate (odds ratio (OR) = 0.80; $p > 0.1$). On the other hand, hyperK showed a significant association with increased risk of death (OR = 3.95, $p = 0.021$). In conclusion, in this sample of men with leptospirosis initial serum potassium was positively and independently correlated with the risk of in-hospital death.

KEYWORDS: Leptospirosis; Potassium; Case-Fatality Rate

INTRODUCTION

Leptospirosis is a worldwide zoonotic disease that affects predominantly men^{2,9}. The case-fatality rate is high, mainly among the elderly, those with the icteric form of the disease, with severe acute renal failure (ARF) and patients who start antibiotic treatment at the late stage of the disease^{3,5,7,9}. The renal involvement in leptospirosis is characterized by acute interstitial nephritis that may be associated with acute tubular necrosis⁴. Predisposition to hypokalemia is another particular feature of the renal involvement in leptospirosis¹. The presence of hypokalemia is more common in patients with ARF due to leptospirosis than in patients with ARF due to other causes¹. A high frequency of ARF with normal or increased urinary output and a defect in the renal tubules are factors that have been related to hypokalemia in patients with leptospirosis¹. As both hypo and hyperkalemia induce severe complications it is important to evaluate if the initial serum potassium is related to in-hospital death in leptospirosis patients, taking into account the influence of other potential risk factors. This study assesses whether serum potassium level at hospital admission is independently associated with death in men with leptospirosis.

METHODS

This is a retrospective analysis using data abstracted from the medical records of 1016 patients with leptospirosis admitted to the Couto Maia

Hospital (HCMaia), located in the city of Salvador, northeast Brasil, between 1993 and 1997. The research protocol was approved by the ethics committee of the HCMaia. Inclusion criteria were: being male older than 17 years, with recorded data on serum potassium, duration of symptoms and creatinine values at hospital admission and with information about the outcome: death or hospital discharge. Leptospirosis diagnosis was based on clinical, laboratory and epidemiological data according to the World Health Organization (WHO) criteria⁶. Six clinical findings (headache, fever, conjunctival suffusion, meningeal signs, myalgia and jaundice), two laboratory alterations (albuminuria and azotemia) and exposure to rats or contaminated water were used to determine a probability score. All patients reached at least 26 points according to the WHO criteria, a limit to define a case as having a high probability of leptospirosis⁶.

The patients were divided into three groups according to their serum potassium value: < 3.5 (hypoK), 3.5-5.0 (normoK) and >5 mEq/L (hyperK). One-way analysis of variance (or its nonparametric equivalent Kruskal-Wallis H) was used to compare quantitative variables across the potassium groups. The t test for independent samples was used for compare means between two groups. The chi-square test (or the Fisher's exact test) was used to compare proportions. Multivariate logistic regression was used to adjust the association between case-fatality rate and the serum potassium levels for age, serum creatinine and duration

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of symptoms attributed to leptospirosis at hospital admission. Age was categorized as < 50 and ≥ 50 years, creatinine as <1.5mg/dL (reference), 1.5-3.0 and >3.0mg/dL and duration of symptoms as <4, 4-6 and ≥ 7 days. Statistical analysis was performed using the SPSS, version 6.0^{10,11} for Windows, and the Computer Programs for Epidemiologists (PEPI), version 3⁸. P values below 0.05 were considered statistically significant.

RESULTS

Among 1016 cases with findings consistent with the diagnostic criteria for leptospirosis, 824 (81.1%) were male and 730 (71.9%) men older than 17 years. After excluding females and patients with missing values, the sample was restricted to 442 patients. Among these 442 patients, 180 (40.7%) were in the hypoK, 245 (55.4%) in the normoK and 17 (3.8%) in the hyperK group (Table 1). In the total group the mean age was 36.8 ± 13.4 years (median = 34 years) and 16.7% were ≥ 50 years. The mean age was significantly higher for the hyperK group (p < 0.05). Icterus at hospital admission was observed in 413 of 435

(94.9%) patients with similar frequency across the potassium groups (p > 0.1). Intravenous penicillin was administered for 78.7% of the patients. The proportion of patients treated by penicillin was smaller in the hyperK group (70.6), than in the hypoK (81.7%) and the normoK (77.1%) groups (p > 0.1). The mean of the initial serum creatinine was 4.6 ± 2.6mg/dl in the total group and significantly (p < 0.05) higher for the hyperK group (7.8 ± 3.5 mg/dl). The mean of symptom duration was 6.1 ± 2.5 days for the whole group and marginally significantly (p = 0.066) higher in the hyperK group (7.4 ± 2.8 days). Duration of symptoms was significantly (p < 0.05) shorter (5.8 ± 2.4 versus 7.4 ± 2.4 days) among patients treated by penicillin (data not shown in the table).

As shown in Table 2, the in-hospital case-fatality rate was 14.5% (64/442). The percent of death was significantly higher (p < 0.05) in patients with ages ≥ 50 (35.1%, 26/74) as compared with those with ages below 50 years (10.3%, 38/368). Serum creatinine was also significantly (p < 0.05) associated with death. None of the 42 patients with creatinine below 1.5 mg/dl died. The percent of death was 4.1%

Table 1
Characteristics of the patients

	Serum Potassium Groups (mEq/l)			Total
	hypoK (<3.5)	normoK (3.5-5.0)	hyperK (>5.0)	
	N = 180	N = 245	N = 17	442
Age (years)				
mean±SD	36.5 ± 11.5	36.1 ± 13.8	50.6 ± 19.5**	36.8 ± 13.4
median	35.0	34.0	46.0	34.0
% Jaundice (N)*	95.5 (170/178)	94.2 (226/240)	100 (17/17)	94.9 (413/435)
% Received Penicillin (N)	81.7 (147/180)	77.1 (189/245)	70.6 (12/17)	78.7 (348/442)
Creatinine (mg/dl)				
mean±SD	4.2 ± 2.2	4.6 ± 2.6	7.8 ± 3.5**	4.6 ± 2.6
median	3.9	4.3	8.3	4.2
Symptoms (days)				
mean±SD	6.0 ± 2.0	6.2 ± 2.7	7.4 ± 2.8***	6.1 ± 2.5
median	6.0	6.0	8.0	6

* Data on icterus were missing for 7 (2 in the hypoK and 5 in the normoK groups); ** p = < 0.05; *** p = 0.066

Table 2
Crude and logistic-regression adjusted associations between potassium and death

Potassium Groups (mEq/l)	Death*		%	Odds Ratio (95% Confidence Interval)	
	yes	no		crude	adjusted**
hypoK (<3.5)	20	160	11.1	0.73 (0.40-1.30)	0.80 (0.43-1.49)
normoK (3.5-5)	36	209	14.7	reference = 1	reference = 1
hyperK (>5)	8	9	47.1	5.16 (1.87-14.25)***	3.95 (1.23-12.66)****
Total	64	378	14.5		

* p for trend in death across the serum potassium groups = 0.005; ** adjusted for age, creatinine level and duration of symptoms; *** p = 0.002; **** p = 0.021

(4/98) and 19.9% (60/302) in the creatinine groups 1.5-3 and >3 mg/dl groups, respectively. The case-fatality rate was lower in the group admitted with less than four days of symptoms (9.3%, 4/43) than in the groups with 4-6 (15.9%, 35/220) and ≥ 7 days (14.0%, 25/179). These differences, however, were not statistically significant ($p > 0.1$). The case-fatality rate was also lower, although statistically not significant ($p > 0.1$), in the anicteric (4.5%, 1/22) than in the icteric group (14.8%, 61/413). These death data by age, creatinine and symptom duration are not shown in the table.

The case-fatality rate of leptospirosis increased significantly (p for trend < 0.05) with the initial level of serum K^+ : 11.1% (20/180), 14.7% (36/245) and 47.1% (8/17) in the hypoK, normoK and hyperK groups, respectively (Table 2). The crude odds of death were more than 5 times higher (odds ratio (OR) = 5.16; 95% CI = 1.87-14.25; $p = 0.002$) in the hyperK as compared with the normoK group. This association between increased serum K^+ and increased mortality remained statistically significant after adjustment for serum creatinine value, age and duration of symptoms. The adjusted odds of death were almost four times higher (OR = 3.95; 95% CI = 1.23-12.66; $p = 0.021$) in the hyperK than in the normoK group.

DISCUSSION

This study expands our knowledge about serum potassium and its relation to in-hospital case-fatality rate of leptospirosis. In this sample, hypokalemia ($K^+ < 3.5$ mEq/l) was found in approximately 41% of men, confirming that it is a very common finding in leptospirosis. SEGURO *et al.*¹³, in São Paulo, studying 56 patients with leptospirosis found hypokalemia in 45%, a very similar finding to those of the present study. Unfortunately, it was not possible to correlate potassium level with the urinary output. According to previous observations, however, the low frequency of hyperkalemia in patients with ARF due to leptospirosis (compared to other causes of ARF) is partly explained by the high frequency of nonoliguric ARF^{12,13}. 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^{13,15}.

The in-hospital case-fatality rate of leptospirosis was positively and significantly associated with the initial serum potassium value. The crude odds of death for patients in the hyperK were significantly higher, over fivefold, than the odds in the normoK group. It should be noted that, compared with normal values of potassium, hypokalemia was not associated with increased risk of death. One potential explanation for this finding is that hypokalemia is an easily treatable alteration. It is also worth noting that the patients of the hypoK and the normoK groups had, on average, lower duration of symptoms than the patients of the hyperK group. A shorter interval between the start of clinically manifested disease and the introduction of the treatment for leptospirosis could also have contributed to a lower death rate observed in the hypoK and normoK groups. It is important to note that the proportion of patients treated by penicillin was smaller (although not significantly different) in the hyperK group. Moreover, patients treated by penicillin had a significantly lower duration of symptoms at admission. These data are consistent with the lack of scientific evidence that the introduction of antibiotics at the late stage of leptospirosis reduces the risk of death. It is plausible to

hypothesize that the hypoK and the normoK groups are comprised of patients to whom we have more to offer to prevent death as compared to the hyperK group.

In addition to a higher duration of symptoms, patients on the hyperK group were, on average, older and had higher levels of serum creatinine. According to the logistic regression analysis, however, the higher risk of death in the hyperK cannot be fully explained by differences in age, renal function and duration of symptoms. In addition to the delay to initiate specific treatment interventions for leptospirosis other potential explanations for the higher risk of death in the hyperK group are congestive heart failure in oliguric and anuric patients and a variety of metabolic alterations associated with hyperkalemia that may contribute to tissue lesion, e.g., metabolic acidosis. The influence of these potential explanatory factors on the association between serum potassium and case-fatality rate of leptospirosis was not assessed in this study and should be viewed as an important questions for future research

Because of the retrospective nature of the study, data on disease outcome and laboratory exams, including the macroscopic slide test, of several patients could not be found. The absence of information on the serologic tests may raise questions about the possibility of misclassification on the diagnosis of leptospirosis with certain diseases, particularly dengue and hantavirus. It is unlikely, however, that diagnostic misclassification with dengue have affected significantly the results, considering that more than 90 percent of the patients were icteric and a large fraction had renal failure, manifestations typical of Weil's disease⁶. It should be observed, that according to the existent data, hantavirus is present in Salvador but symptomatic disease is likely a very rare condition in patients hospitalized at HC Maia¹⁴. The fact that this study was restricted to men limits generalization of the finding to women. This restriction took into account, primarily, the validity of the study. The number of women with reported data on the variables of interest was small. In addition, there was a concern of a differential contribution of the muscle mass to determine specific levels of serum potassium and serum creatinine between males and females with leptospirosis. Studies including larger number of women with leptospirosis are needed to permit valid estimates of the association between levels of potassium and risk of death in this group.

In conclusion, these data suggest that the initial serum potassium value is positively associated with in-hospital case-fatality rate of leptospirosis in men. This association could not be fully explained by differences in age, serum creatinine and duration of symptoms. Although the study was not designed to assess the effect of treatment on mortality, it calls attention to the need for implementation of strategies aimed at identifying patients with leptospirosis at early stage of the disease when the treatment is more effective. It is expected that this kind of intervention will reduce the risk of severe complications of leptospirosis, including hyperkalemia and its associated higher risk of death.

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RESUMO

Associação entre potássio sérico na admissão hospitalar e letalidade da leptospirose em homens

Leptospirose grave afeta predominantemente os homens e apresenta alta susceptibilidade para insuficiência renal aguda com hipocalcemia. Como hipocalcemia e hipercalcemia induzem complicações graves, é importante avaliar se o potássio sérico é um independente fator de risco de morte na leptospirose. Foram revistos os prontuários de 1016 pacientes internados com o diagnóstico de leptospirose. A análise foi restrita a 442, obedecendo os seguintes critérios: sexo masculino, idade igual ou superior a 18 anos, informação sobre morte ou alta hospitalar e registro dos valores do potássio sérico, da creatinina sérica e da duração dos sintomas. Valores de potássio menor do que 3,5 mEq/l (hipoK), 3,5-5 mEq/L (normoK) e superior a 5 mEq/L (hiperK) foram detectados em 180, 245 e 17 pacientes, respectivamente. A mortalidade aumentou com a elevação do potássio: 11,1% no grupo hipoK, 14,7% no normoK e 47,1% no hiperK ($p = 0,002$). Em um modelo de regressão logística (normoK como referência), incluindo idade, creatinina e duração de sintomas, hipoK não se associou com aumento da mortalidade (*odds ratio* (OR) = 0,72; $p > 0,1$). Contrariamente, hiperK foi significativamente associado com risco aumentado de morte (OR = 3,95; $p = 0,021$). Em conclusão, nesta amostra de homens com leptospirose o potássio sérico inicial foi positivamente e independentemente correlacionado com risco de morte hospitalar.

REFERENCES

1. ABDULKADER, R.C.; SEGURO, A.C.; MALHEIRO, P.S.; BURDMANN, E.A. & MARCONDES, M. - Peculiar electrolytic and hormonal abnormalities in acute renal failure due to leptospirosis. *Amer. J. trop. Med. Hyg.*, 54: 1-6, 1996.
2. CICERONI, L.; PINTO, A.; BENEDETTI, E. *et al.* - Human leptospirosis in Italy, 1986-1993. *Europ. J. Epidem.*, 11: 707-710, 1995.
3. DAHER, E.; ZANETTA, D.M.; CAVALCANTE, M.B. & ABDULKADER, R.C. - Risk factors for death and changing patterns in leptospirosis acute renal failure. *Amer. J. trop. Med. Hyg.*, 61: 630-634, 1999.
4. DAVILA DE ARRIAGA, A.J.; ROCHA, A.S.; YASUDA, P.H. & DE BRITO, T. - Morpho-functional patterns of kidney injury in the experimental leptospirosis of the guinea-pig (*L. icterohaemorrhagiae*). *J. Path.*, 138: 145-161, 1982.
5. DUPONT, H.; DUPONT PERDRIZET, D.; PERIE, J.L. *et al.* - Leptospirosis: prognostic factors associated with mortality. *Clin. infect. Dis.*, 25: 720-724, 1997.
6. FAINE, S. - Guidelines for the control of leptospirosis. *Wld. Hlth. Org. Offset Publ.*, 67: 1-171, 1982.
7. FARR, R.W. - Leptospirosis. *Clin. infect. Dis.*, 21: 1-6, 1995.
8. GAHLINGER, P.M. & ABRAMSON, J.H. - Computer Programs for Epidemiologists: PEPI Version 3. Stone Mountain, GA, 1999.
9. KO, A.I.; GALVÃO REIS, M.; RIBEIRO DOURADO, C.M.; JOHNSON JR, W.D. & RILEY, L.W. - Urban epidemic of severe leptospirosis in Brazil. Salvador Leptospirosis Study Group. *Lancet*, 354: 820-825, 1999.
10. NORUSIS, M.J. - SPSS for Windows: advanced Statistics, release 6.0. Chicago, SPSS Inc., 1993.
11. NORUSIS, M.J. - SPSS for Windows: base system user's guide, release 6.0. Chicago, SPSS Inc., 1993.
12. RAMACHANDRAN, S.; RAJAPAKSE, C.N.; PERERA, M.V. & YOGANATHAN, M. - Patterns of acute renal failure in leptospirosis. *J. trop. Med. Hyg.*, 79: 158-160, 1976.
13. SEGURO, A.C.; LOMAR, A.V. & ROCHA, A.S. - Acute renal failure of leptospirosis: nonoliguric and hypokalemic forms. *Nephron*, 55: 146-151, 1990.
14. TRAVASSOS DA ROSA, E.S.; VASCONCELOS, P.F.C.; TAVARES-NETO, J. *et al.* - Prevalence of antibodies to hantaviruses in Salvador, Bahia, Brazil. In: CONGRESSO DA SOCIEDADE BRASILEIRA DE MEDICINA TROPICAL, 31., Brasília, 1995. **Resumos**. p. 185
15. YOUNES-IBRAHIM, M.; BURTH, P.; FARIA, M.V. *et al.* - Inhibition of Na,K-ATPase by an endotoxin extracted from *Leptospira interrogans*: a possible mechanism for the physiopathology of leptospirosis. *C. R. Acad. Sci. (Paris)*, 318: 619-625, 1995.

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