Rev. Inst. Med. trop. São Paulo
36 (2): 111-114, março-abril, 1994

IS RHABDOMYOLYSIS AN ADDITIONAL FACTOR IN THE PATHOGENESIS OF ACUTE RENAL FAILURE IN LEPTOSPIROSIS?

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SUMMARY

Leptospirosis is an important cause of acute renal failure in our environment. Although several mechanisms are implicated, the role of rhabdomyolysis in the pathogenesis of acute renal failure in leptospirosis has not been analysed. Sixteen patients with the diagnosis of leptospiroses consecutively admitted to the hospital were prospectively studied. The disease was characterized by sudden onset in all patients and, at admission, jaundice, conjunctival suffusion and myalgias. Mild to moderate proteinuria with unremarkable urinary sediment was recorded in 37.5% of the patients and abnormal levels of urea creatinine were found in 87.5% and 74.0%, respectively. Increased levels of aminotranspherase were documented in all 12 and CPK in all 10 patients studied. Serum myoglobin levels greater than 120μg/l recorded in 56.2%. A correlation between myoglobin and renal failure or severity of disease, however, could not be established.

KEYWORDS: Renal failure; Rhabdomyolysis; Leptospirosis.

INTRODUCTION

Leptospirosis is an important cause of acute renal failure in our environment; it is reported to occur in 60% to 70% of the hospitalized patients with this diagnosis [17, 20]. The pathogenetic mechanisms involved in the renal injury are still not well understood: nephrotoxicity directly related to the leptospira itself or to some yet unidentified toxin, nonspecific effects to infection per se, and immunological reactions are some of the proposed mechanisms [18, 21].

The remarkable involvement of the striated muscular system resulting in rhabdomyolysis with myoglobin and muscle enzymes release is well demonstrated in leptospirosis [6, 7, 12]. Its role in the pathogenesis of the acute renal failure, however, has not been examined. The purpose of the present study was to analyse the influence of rhabdomyolysis in the pathogenesis of the acute renal failure in leptospiroses.

PATIENTS AND METHODS

Sixteen patients with the diagnosis of the icterohaemorrhagic form of leptospirosis consecutively admitted to Hospital Couto Maia, Salvador - Bahia, were prospectively studied. All patients had clinical and epidemiological data compatible with, and sorologic reactivity for leptospirosis. At the time of initial evaluation a detailed medical history was obtained, and all patients

The study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq (Grant 400711/85).
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were evaluated by physical examination, urinalysis, complete blood cells count, determinations of serum levels of electrolytes, urea, creatinine, bilirubins, aminotranspherases, creatinephosphokinase (CPK), using standard laboratory procedures. Serum levels of myoglobin were determined by immunochemical method, using commercially available kit (Behringwerke AG, Marburg, Germany); by this method positivity corresponds to a myoglobin concentration above 120µg/l, a value 1.5 time higher than the upper limit of normal [1, 13]. No patient received intramuscular injections before the initial laboratory evaluation.

For the purpose of the present study, duration of symptomatology was defined as a period from the first clinical manifestation noticed by the patient to the hospital admission; acute renal failure was defined as a sudden rise in serum creatinine to levels greater than 1.4mg/dl not reversible by correction of volume status or any other extra-renal abnormalities that may have caused prerenal azotemia. Rhabdomyolysis was defined by the presence of serum myoglobin greater than 120µg/l. The course of each patient was analysed by daily clinical examination and frequent laboratory evaluation.

Statistical significance, defined as $p < 0.05$, was evaluated using Fisher's exact test.

RESULTS

Of 16 patients, 13 were male and 3 female with a mean age of 33.4 ± 18.3 years (variation: 10 to 72 years old). The duration of symptomatology varied from 1 to 12 days (mean of 6.1 ± 2.6 days). All patients exhibited jaundice, conjunctival suffusion and myalgias; mild signs of fluid depletion were recorded in 6 patients, at admission.

Hyperbilirubinemia was present in all studied patients and high serum levels of aminotranspherases in all 12 patients, although 4 of them had normal levels of alanino-aminotranspherase. Serum creatinephosphokinase (CPK) was elevated in all 10 patients studied. Proteinuria of mild to moderate degree (10 to 200mg/dl) with unremarkable urinary sediment was documented in 6 of 16 patients (37.5%). Serum levels of urea greater than 40mg/dl and creatinine greater than 1.4mg/dl were recorded in 87.5% and 74.0% of the patients, respectively (Table 1).

Myoglobin serum concentrations greater than 120µg/l, were documented in 9 of the 16 patients (56.2%), 6 with renal failure and 3 with normal renal function, a difference not significant, statistically ($p = 0.635$). Also, a correlation between myoglobinemia and severity of disease could not be established (Table 2).

TABLE 1

Laboratorial data in patients with leptospirosis

	# Patients n/T	%	Mean ± SD
Proteinuria	6/16	37.5	
Urea > 40mg/dl	14/16	87.5	171.31 ± 146.12
Creatinine > 1.4mg/dl	11/15	74.0	4.17 ± 2.80
Bilirubin > 1.0mg/dl	10/10	100.0	13.90 ± 7.02
ALAT > 30U/l	8/12	66.6	47.52 ± 24.14
ASAT > 30U/l	12/12	100.0	87.00 ± 34.34
CPK > 36IU/l	10/10	100.0	172.40 ± 157.29
Myoglobin > 120µg/l	9/16	56.2	

n = Number of patients with abnormal values.
T = Total number of studied patients.

NORMAL VALUES: Urea - 20 to 40mg/dl
Creatinine - 0.4 to 1.4mg/dl
Bilirubin, total - 0.2 to 1.0mg/dl
Aspartate aminotransferase (ASAT) - 10 to 30U/L
Alanine aminotransferase (ALAT) - 5 to 30U/L
CPK - 0 to 36IU/l.

DISCUSSION

In the present series the clinical and laboratory findings as well as the occurrence of acute renal failure in 68.7% represent a typical population of patients with leptospirosis admitted to hospitals in our environment [17]. Myoglobinemia greater than 120µg/l was found in 9 out of 16 patients, although elevated levels of ASAT and CPK were recorded in all patients who had the levels of these enzymes measured. These data suggest rhabdomyolysis could be more frequent than the 56.2% of patients with myoglobinemia. Though the presence of myoglobin indicates muscular injury [8, 19], as it has a rapid clearance, its serum levels may be minimally elevated or, even, in normal range in patients with well docu-

TABLE 2

Correlation between renal failure and myoglobinemia

Renal Failure	Number Patients	Myoglobinemia
Present	11	6
Absent	5	3
Total	16	9

$p = 0.635$

mented myolysis [15]. In contrast, having a slower clearance, CPK is a much more sensitive marker of muscle injury than myoglobin [9].

The association between rhabdomyolysis and acute renal failure is well known [5, 11, 16] and this etiology has been suggested for the acute renal failure in leptospirosis [10]. Although our patients with rhabdomyolysis met well accepted criteria for such diagnosis [4], a correlation between myolysis, myoglobinemia and renal failure was not found. Nevertheless, some aspects deserve discussion: 1) the pathogenesis of myoglobin nephrotoxicity has not been completly elucidated; it has been estimated that only 1/3 of the patients develop acute renal failure in the setting of rhabdomyolysis [3, 4]. Different studies indicate concomitant metabolic disturbances, hypovolemia and/or hypotension - as frequently found in leptospirosis - contributes to the pathogenesis of the acute renal failure related to rhabdomyolysis [8, 11, 14]. In addition, myoglobinuric renal failure has been diagnosed in patients with higher serum levels of CPK [2], greater than observed in the present series, suggesting a critical toxic level, in serum or tubular fluid, should be reached; 2) it is very difficult to specifically determine the individual role of each factor in a multifactorial pathogenesis of acute renal failure such as in leptospirosis. Although a correlation between myolysis and acute renal failure was not found in the present series, the small number of patients with normal renal function (5 patients) deters definitive conclusion.

Although myoglobinemia had been documented in 56.2% of the patients and acute renal failure in 68.7%, a correlation between them could not be established. A large number of patients, however, needs to be studied to define the role of rhabdomyolysis in the pathogenesis of acute renal failure accompanying leptospirosis.

RESUMO

É a rabdomiólise um fator adicional na patogênese da insuficiência renal aguda na leptospirose?

Leptospirose é uma importante causa de insuficiência renal aguda, em nosso ambiente. Embora vários sejam os mecanismos implicados, o papel da rabdomiólise na patogênese da insuficiência renal aguda na leptospirose ainda não foi analisado. Com esse objetivo, 16 pacientes com o diagnóstico da forma icterohemorrágica da leptospirose consecutivamente admitidos no Hospital Couto Maia, Salvador, Bahia, foram prospectivamente estudados. A doença foi caracterizada por início súbito e, à admissão, icterícia, sufusões hemorrágicas conjuntivais e mialgias. Proteinúria de intensidade média a moderada com sedimento urinário inexpressivo foi observada em 37,5% dos pacientes e níveis séricos elevados de uréia e creatinina em 78,5% e 74,0%, respectivamente. Níveis aumentados de aminotransferase foram documentados em todos os 12 e de CPK em todos os 10 pacientes avaliados para essas enzimas. Níveis séricos maiores que 120μg/l foram observados em 56,2% dos pacientes. Não foram encontradas correlações, entretanto, entre mioglobinemia e insuficiência renal em gravidade da leptospirose.

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Recebido para publicação em 22/06/1993.
Aceito para publicação em 21/01/1994.