

IS CK-MB ISOENZYME USEFUL FOR DIAGNOSIS OF CARDIAC INVOLVEMENT IN ICTERIC LEPTOSPIROSIS?

Elizabeth Stankiewicz MACHADO (1), José Guilherme de Faria FERES (2), Luis Augusto FEIJÓ (2), Jarbas ANDRADE (3) & Susie Andries NOGUEIRA (1)

SUMMARY

In the absence of heart failure or cardiogenic shock, cardiac involvement diagnosis in icteric leptospirosis is possible on the basis of abnormal electrocardiograms. As metabolic and electrolytic disorders are frequently seen during acute leptospirosis infection, they may be responsible for some electrocardiograms changes. We conducted a study to assess if creatine phosphokinase isoenzyme determinations are useful in selecting patients with a high cardiac involvement suspicion. Sixty-nine patients were studied prospectively. Ten patients out of 16 with cardiac involvement and 25 without had high CK-MB levels ($p > 0.05$), although mean values of abnormal CK-MB levels were higher in the group with cardiac involvement ($p < 0.05$). Our analysis indicates that serum CK-MB determination does not provide a specific indicator of myocardial involvement in the course of icteric leptospirosis.

KEYWORDS: CK-MB - Cardiac involvement; Icteric leptospirosis.

INTRODUCTION

Cardiac involvement in human leptospirosis is most often subclinical, but severe heart involvement may lead to congestive heart failure and cardiogenic shock with fatal outcome^{5,6}. Studies in our country, based on clinical and electrocardiographic data detected myocardial involvement from 27% to 58% and heart failure in 5% to 11% of the cases^{4,8,11}.

While severe heart involvement is clinically self-evident, mild and often asymptomatic cardiac involvement may be suggested through abnormal electrocardiograms (ECG). Acute renal failure, metabolic and electrolytic disorders from acute icteric leptospirosis, may be responsible for some ECG changes, making diagnosis

less accurate. It is generally believed that elevated CK-MB reflects myocardial injury¹², but noncardiac elevations of CK-MB have been found in several conditions as neuromuscular diseases, hypothyroidism and after vigorous exercises^{1,9,13}.

The aim of this study was to determine CK-MB isoenzyme levels during acute icteric leptospirosis and if it would be useful in detecting patients with high probability of cardiac involvement.

MATERIALS AND METHODS

From May 1, 1990, to January 31, 1992, 69 patients (64 males and 5 females; mean age: 36 years) admitted to the Infectious Diseases Ward, at Clementino Fraga Filho

(1) Serviço de Doenças Infecciosas, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Ilha do Fundão, 21941- Rio de Janeiro, RJ, Brasil.

(2) Departamento de Cardiologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil.

(3) Centro de Referência Nacional de Leptospirose, Instituto Oswaldo Cruz, Rio de Janeiro, RJ, Brasil.

Correspondence to: Elizabeth Stankiewicz Machado, Serviço de Doenças Infecciosas, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Av. Brigadeiro Trompovski s/n, Ilha do Fundão, 21941- Rio de Janeiro, RJ, Brasil. Fax: 55-21-2702193.

University Hospital (UFRJ, Rio de Janeiro) with suspected leptospirosis were followed prospectively to assess the frequency of cardiac involvement and CK-MB behavior in these subjects.

Every day each patient was clinically examined to assess congestive heart failure and the following data were collected: age, sex, heart disease and epidemiologic history as well as presenting symptoms.

ECG study: twelve ECG leads were recorded by commercially available equipment at standard sensitivity (10mm = 1 mV) and at paper speed of 25mm/sec. they were revised by two independent observers. Consensus was required for the data to be accepted.

Diagnosis of leptospirosis was established by a positive macroscopic slide agglutination test for leptospirosis and a microscopic agglutination test using 24 live antigens. Patients were positive for leptospirosis if the microscopic agglutination test showed a four fold rise in titre in two paired blood samples. In patients without paired blood samples, a positive diagnosis was made if there was an initial positive macroscopic slide agglutination test together with a microscopic agglutination test with an titre of at least 1:400.

Creatine phosphokinase determination was performed by optimized method with the use of commercially prepared kits. CK levels exceeding 80 U/l in males and 70 U/l in females at 25°C are considered to be abnormal by this method.

CK-MB was measured by photometric determination. Abnormal values were considered when CK-MB activity exceeded 10 U/l at 25°C

Assessment of renal function was made by determination of serum urea and creatine. Normal values were: creatine: 0.7 to 1.4 mg/dl and urea: 18 to 42 mg/dl.

Sodium and potassium daily dosage was performed in all patients until discharge. Blood-gas determinations were performed in patients with urea and creatine level increase to assess metabolic acidosis presence.

Criteria for cardiac involvement were:

1. Clinical: presence of left ventricular dysfunction or congestive heart failure (dyspnea, orthopnea, gallop sounds and pulmonary rales with or without elevated jugular venous pressure and congestive hepatomegaly).

2. Electrocardiographic

a) Arrhythmia other than sinus bradycardia and sinus tachycardia.

b) T wave inversion was considered a criteria when occurred in at least two ECG leads where T wave is usually positive, and subsequently reserved to normal, without concomitant metabolic or electrolytic disorder.

c) bundle branch block and atrioventricular block were considered if they disappeared during follow up.

STATISTICAL ANALYSIS

Data were analyzed with the use of a computerized data base and analysis program (EPI Info Version 5.0; Centers for Disease Control and Prevention, Atlanta). Chi-square with Yate's correction was used to compare proportions rate of patients and Mann-Whitney test for values not normally distributed. Results were considered to be statistically significant when $P < 0.05$.

RESULTS

Incidence of cardiac involvement: 53 patients had no cardiac involvement (53/69,75.8%). Sixteen patients (16/69,24.2%) had probable cardiac involvement.

Group with cardiac involvement: All patients were males. The mean age was 39 years. No patient had a previous cardiac disease or arterial hypertension. Among the 16 patients in then group, 14 developed a renal failure (87.5%) and 8 (50%) required dialysis.

Eleven patients were included in the group with cardiac involvement due to the presence of arrhythmia during hospitalization (atrial fibrillation or supraventricular tachycardia). In this group, right bundle branch block was presented in 2 patients, left ventricular dysfunction was seen in 3 patients and death in 2. Autopsy was not performed. Only one patient showed potassium serum dosage levels below normal values (2.5 mEq/l) during arrhythmia. There was no indication for peritoneal dialysis in this patient. Blood-gas determinations were obtained in 10 patients with arrhythmia and no one had metabolic acidosis. Peritoneal dialysis was performed in 6 patients. No patients with heart failure symptoms were submitted to dialysis due to hypervolemia. There was no statistical difference between the presence of arrhythmia and the performance of dialysis $P=0.5$.

Five patients without arrhythmia were included in this group due to ECG changes: diffuse T wave inversion that subsequently normalized in follow-up (2 patients), diffuse T wave inversion and a first degree A-V block that disappeared during follow-up (1 patient) and localized ST elevations suggesting acute injury pattern (2 patients). Three patients in this group evolved with renal

failure, two were submitted to peritoneal dialysis. One patient presented mild hypopotassemia during ECG alterations (3.3 mEq/l). Metabolic acidosis was not detected in the three patients with renal failure.

ECG changes was registered between 6 and 12 days from disease onset.

Group without cardiac involvement: 48 males, 5 females. The mean age was 36 years. Arterial hypertension was present in 3 patients, 46 showed renal failure (87%) and 12 were submitted to dialysis (23%).

CK and CK-MB in the study group (Table 1):

Elevated CK levels was present in 46 patients (66.7%), 15 in the group with cardiac involvement (15/16, 93.7%), and 31 without cardiac involvement (31/53, 58.5%), $P=0.02$. Mean CK abnormal values were 718 U/l and 538 U/l for group with cardiac involvement (range of 89 U/l to 5200 U/l) and without cardiac involvement (range of 111 U/l to 3819 U/l) respectively, $P=0.32$.

Elevated CK-MB levels were found in 35 patients (50.7%), 10 in the group with cardiac involvement (10/16, 62.5%) and 25 patients with no cardiac involvement (25/53, 47.1%), $P=0.42$. Mean abnormal values were 50 U/l and 26 U/l, $P=0.047$, respectively.

CK-MB in group with cardiac involvement:

It was possible to have three blood sample determinations in 9 patients, two blood samples in 5 patients and one blood sample in 2. The first blood sample in 15 patients was taken during the first week of disease and 1 patient had blood sample collected in the second week of disease.

Elevated CK-MB was seen in 10 patients in this group (10/16, 62.5%). The range of CK-MB abnormal levels was 19 U/l to 190 U/l. No patient with elevated CK-MB had normal CK values.

Association of elevated CK-MB and ECG changes occurred in 5 patients (four with arrhythmia and 1 with diffuse T wave inversion and first degree A-V block). In 3 patients, elevated CK-MB was noticed before electrocardiographic changes (1, 2 and 5 days - 1 patient with injury pattern and 2 with arrhythmia). In 1 patient measurement was done 24 hr after arrhythmia onset, and another patient, CK level was normal during atrial fibrillation episode and rose 5 days when the rhythm cardiac was already normal.

In the group with probable cardiac involvement and normal CK-MB, determination of CK-MB was done in 5 patients during ECG changes and in one patient, it was determined 5 days after ECG abnormalities.

CK-MB in group without cardiac involvement:

Eighteen patients out of 25 had elevated CK-MB values. In the first week of disease blood samples were taken in 11 patients, in the second week in 12 and in the third week in 2. The range of elevated values was 11 U/l to 81 U/l. It was possible to determine in 10 patients the enzyme rise duration. In 4 the rise lasted 48 hr, in 3 patients it lasted 3 days and the remaining 3 patients 4, 5, and 6 days respectively.

CK-MB in group with renal failure:

Acute renal failure was found in 60 patients in our study group, 32 had high CK-MB. Twenty-six patients had concomitance of renal failure and elevated CK-MB (26/60, 43.3%), and six patients had normal serum urea

TABLE 1

Elevated total CK and CK-MB in patients with and without cardiac involvement

	No.(%) of patients with cardiac involvement	No.(%) of patients without cardiac involvement	P value*
Elevated Total CK	15/16(93.7)	31/53(58.5)	< 0.05
Elevated Total CK-MB	10/16(62.5)	25/53 (47.1)	NS ⁺

* χ^2 with Yates' correction

⁺ $P=0.42$

and creatine values at the time the CK-MB levels were measured.

Three patients out of 9 without acute renal failure during the course of the disease, had elevated CK-MB (33.3%). Together with six patients with normal serum urea and creatine values at the time levels were measured, high CK-MB was seen in nine patients of the group without acute renal failure (60%), $P=0.6$.

DISCUSSION

In spite of the fact that myocarditis definite diagnosis can only be done through histological disorders found in myocardial biopsies, disorders present in our study suggest these are secondary to a real myocarditis. Ten out of 11 arrhythmia patients had no electrolytic or acid-basic disorders to justify their presence. The same was true in the 5 patients with ECG alterations. Heart failure was present in 3 patients with renal failure which could suggest that hypervolemia was responsible for heart alterations but early dialysis in leptospirosis patients in our ward makes this hypothesis remote. Dialysis is prescribed to our patients immediately after no response to hydration is observed, monitoring central blood pressure. Use of sympathomimetic amines (dopamine) in low doses is sometimes prescribed to increase renal flow. If there is no answer the dialytic process is immediately begun. Classic urea and creatine levels are not expected in this cases to begin dialysis. These criteria are responsible for the low pericarditis incidence in our patients, as well as metabolic acidosis, acute electrolytic alterations and hypervolemia.

We have found a higher ratio of elevated total CK activity in the group with probable cardiac involvement suggesting a direct correlation between skeletal and cardiac muscle injury. A previous study¹⁴ did not show an association between these two tissues but only 38 patients with severe Weil's disease were studied and a small sample size may be responsible for the lack of association. Another reason for this disagreement may be myositis incidence in the two groups. This study found 37% of myositis incidence based on high CK activity or unequivocal muscle tenderness while in our group 60% would be classified as having myositis based only on high CK values.

The rate of abnormal CK-MB values in both groups was not statistically significant suggesting that other mechanisms as skeletal muscle involvement or acute renal failure may be involved.

DAWSON & FINE² studied the presence of creatine kinase isoenzyme types in human tissues obtained at au-

topsy and found that kidney was an enzyme source but exclusively of CK-BB. MA et al.¹⁰ described a 28.3% CK-MB rise in 46 male long-term hemodialysis patients. Uremic pericarditis was initially considered to be a possible explanation but no patient with elevated CK-MB had evidence of uremic pericarditis. One possible explanation suggested by the authors was an interference of the assay method by uremic serum, but they found a correlation between the changes in serum CK-MB and CK-MM activity. Even though we did not measure CK-MM activity in our patients we agree with the authors that the probable source of CK-MB isoenzyme may be skeletal muscle involvement, as less than 50% of the patients with acute renal failure had elevated CK-MB.

Rise of CK-MB has been found in patients with myopericarditis⁷ but we do not find pericarditis in any of our patients. This may be accounted for by the fact that all patients with acute renal failure and not responsive to initial hydration have done dialysis.

Reports of increased CK-MB levels in patients after vigorous exercise have been published⁹ indicating a probable muscle source of serum CK-MB. BROWNLOW & ELEVITCH¹ reported the presence of elevated CK-MB levels in six patients with myositis. Although 3 patients had ECG changes that suggested of ischemic changes and cardiac irritability, it was possible to show increase of CK-MB concomitant with exacerbation of dermatomyositis.

Rise of BB-CK could have caused high CK-MB levels but no patient had conditions related to increase of this isoenzyme¹³.

Two patients presented ECG alterations suggestive of injury lesions. DE BRITO et al.¹³ studied myocardium tissue in 20 patients dying from leptospirosis and founded acute coronary arteritis in 70% of the cases. We found a higher level of mean values of elevated CK-MB in the group with probable cardiac involvement. This does not seem, to be related only to muscle damage a both groups had similar mean CK isoenzyme values, so myocardial muscle injury secondary to myocardium ischemia may be responsible for the difference between the two groups.

Based on these results we suggest that measurement of CK-MB is not specific of cardiac involvement in icteric leptospirosis and the ECG still is the main non-invasive diagnosis tool to detect myocardial involvement.

RESUMO

CK-MB: útil no diagnóstico de envolvimento cardíaco na leptospirose icterica

Na ausência de insuficiência cardíaca ou choque cardiogênico, o diagnóstico de envolvimento cardíaco na leptospirose icterica pode ser baseado em alterações electrocardiográficas. Devido ao frequente comprometimento multisistêmico da doença, algumas dessas alterações podem ser secundárias a distúrbios metabólicos ou eletrolíticos.

Realizou-se um estudo para avaliação do significado da enzima CK-MB elevada em casos suspeitos de envolvimento cardíaco.

Sessenta e nove pacientes com leptospirose icterica foram estudados prospectivamente.

Dez dos 16 casos com envolvimento cardíaco e 25 dos 53 pacientes sem envolvimento cardíaco tiveram CK-MB elevada ($p > 0,05$). O valor médio de CK-MB foi maior no grupo com envolvimento cardíaco ($p < 0,05$).

Nossa análise indica que a presença de CK-MB elevada no curso de leptospirose icterica não é indicadora de envolvimento cardíaco.

REFERENCES

1. BROWNLOW, K. & ELEVITCH, F.R. - Serum creatine phosphokinase isoenzyme in myositis. A report of six cases. *J. Amer. med. Ass.*, **230**: 1141-1144, 1974.
2. DAWSON, D.M. & FINE, I.H. - Creatine kinase in human tissues. *Arch. Neurol.*, **16**: 175-180, 1967.
3. DE BRITO, T.; MORAIS, C.F.; YA'SUDA, P.H. et al. - Cardiovascular involvement in human and experimental leptospirosis: pathologic findings and immunohistochemical detection of leptospiral antigen. *Ann. trop. Med. Parasit.*, **81**: 207-214, 1987.
4. ESCOSTEGUY, C.C.; MANSUR, E.M.; ALVES, M.L.M. et al. - Análise do envolvimento cardíaco na leptospirose. *Arq. bras. Med.*, **65**: 42-48, 1991.
5. ESTAVOYER, J.M.; BECQUE, O.; BRIAND, Y.M. & PAGEAUT, G. - Leptospirose grave avec localisation cardiaque. *Nouv. Presse méd.*, **9**: 2579, 1980.
6. GUIRVACH, G.; LEGALL, J.R.; REGNIER, B. & JARDIN, F. - Etats de choc au cours des leptospiroses ictéro-hémorragiques. *Nouv. Presse méd.*, **11**: 837-839, 1982.
7. HEIKKILA, J. & KARJALAINEN, J. - Evaluation of mild acute infectious cardiac involvement. *Brit. Heart J.*, **47**: 381-391, 1982.
8. HERDY, G.V.H.; SILVA, J.J.P.; MARINS, A.B. & FERRARI, A.E.H. - Envolverimento cardíaco na leptospirose grave. *Rev. Soc. bras. Med. trop.*, **24**: 163, 1991.
9. JAFFE, A.S.; GARFINKEL, B.T.; RITTER, C.S. & SOBEL, B.E. - Plasma MB creatine kinase after vigorous exercise in professional athletes. *Amer. J. Cardiol.*, **53**: 856-858, 1984.
10. MA, K.W.; BROWN, D.C.; STEELE, B.W. & FROM, A.H.L. - Serum creatine kinase MB isoenzyme activity in long-term hemodialysis patients. *Arch. intern. Med.*, **141**: 164-166, 1981.
11. MEIRA, D.A.; WAINMAN, J.T.; PILEGGI, F. et al. - Comprometimento miocárdico na leptospirose. Estudo electrocardiográfico e anátomo-patológico. *Arq. bras. Cardiol.*, **18**: 177-194, 1965.
12. ROBERTS, R.; GOWDA, K.S.; LUDBROOK, P.A. & SOBEL, B.E. - Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Amer. J. Cardiol.*, **36**: 433-437, 1975.
13. TSUNG, S.H. - Several conditions causing elevation of serum CK-MB and CK-BB. *Amer. J. clin. Path.*, **75**: 711-715, 1981.
14. WATT, G.; PADRE, L.P.; TUAZON, M. & CALUBAQUIB, C. - Skeletal and cardiac muscle involvement in severe, late leptospirosis. *J. infect. Dis.*, **162**: 266-269, 1990.

Recebido para publicação em 10/10/1994

Aceito para publicação em 19/09/1995