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## ARTIGOS

# TETANUS AS A CAUSE OF ACUTE RENAL FAILURE: POSSIBLE ROLE OF RHABDOMYOLYSIS

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*To study the frequency and examine the role of rhabdomyolysis in the acute renal failure in tetanus 18 patients with the diagnosis of generalized tetanus consecutively admitted to the infectious disease hospital were evaluated. Of these 14 were male and 4 female with mean age of 31.8± 2.0 years. Except for mild proteinuria recorded in 9 patients, the urinalysis were unremarkable. Serum creatinine higher than 1.4mg/dl was recorded in 39% of the patients, abnormal levels of CPK in 87,5% and serum myoglobin greater than 120µg/l in 39% of the patients. Oliguria was documented in one patient and none required dialysis therapy. No correlation was found between renal failure and myoglobin and/or CPK serum levels. Acute renal failure in tetanus was not infrequent; usually it was non-oliguric, mild and transient and not related to the severity of the disease or to serum levels of myoglobin and/or CPK.*

*Key-words: Tetanus. Rhabdomyolysis. Myoglobin. Acute renal failure.*

Tetanus is a disease caused by tetanospasmin, a potent toxin elaborated at the site of injury by *C. tetani*, an anaerobic, spore-forming, gram-negative rod[21]. Although infrequent in the well-developed countries, tetanus is of particular significance in the third world[16].

The clinical features of tetanus are produced by the neurotoxic activity of tetanospasmin[9 21]. The intense muscular work resulting in rhabdomyolysis with release of myoglobin and muscular enzymes, the profuse sweating, the overactivity of the sympathetic nervous system and the metabolic disturbances that accompany tetanus may cause impairment of the renal function. Acute renal failure has been reported infrequently in tetanus; in a large series of 100 cases it was not observed in any single patient[6], while it was found in only 2 out of 103 children in an 11 years review[22]. In a selected group of patients, however, acute renal failure was found in 14% of them[10]. The purpose of the study was to determine the frequency of acute renal failure and to examine the role of myolysis and myoglobinemia on the renal function in adult patients with generalized tetanus.

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## MATERIAL AND METHODS

Eighteen patients with the diagnosis of generalized tetanus consecutively admitted to Hospital Couto Maia (Infectious Disease Hospital in Salvador-Bahia-Brazil) were prospectively studied. At the time of admission a detailed medical history was obtained, and all patients were evaluated by physical examination, urinalysis, complete blood cell count, determinations of serum levels of electrolytes, urea nitrogen, creatinine, creatinephosphokinase and myoglobin. No patient received intramuscular injections before the initial laboratory evaluation. Serum myoglobin was measured by immunochemical method, using a commercially available kit (Behringwerke AG, Marburg, Germany); by this method, positivity corresponds to a minimum myoglobin concentration of 120 µg/l, a value 1.5 times higher than the upper limit of normal[4 12]. The diagnosis and severity of tetanus were established on the basis of clinical manifestations. For the purpose of the present study, incubation period was the interval between wounding and the first symptom of tetanus; acute renal failure was defined as a rise in serum creatinine to levels higher than 1.4mg/dl, not reversible by correction of volume status or any other extra-renal abnormalities that could cause pre-renal azotemia. All patients were essentially kept in

bed rest; parenteral fluids and medications were given via intravenous infusion. The course of each patient was analysed by daily clinical evaluation, recording fluid balance, urine volume, current medications and frequent laboratory evaluation.

Statistical analysis were done using Fisher's exact test. Statistical significance was defined as $p<0.05$.

## RESULTS

Of the 18 patients enrolled in this study 14 were males and 4 females, with a mean age of $31.8\pm2.0$ years. The patients were studied during the first week of the disease; the incubation period varied from 2 to 14 days (mean: $9.7\pm8.4$ days) and the interval between the onset of symptomatology and hospital admission was $3.0\pm1.9$ days (1 to 5 days). All patients were in general good health before their tetanus and no history of alcohol or drug abuse, or using nephrotoxic drugs could be elicited. A physical examination showed all patients had recognizable wounds, frequently in lower limbs. The tetanus was generalized in all patients and graded as mild in 4 patients, moderate in 9 and severe in 5 (Table 1). Fever, trismus, muscles spasms, opisthotonus and muscle rigidity were present in most patients, during the hospitalization; daily urine output less than 400ml was recorded in only one patient.

In the laboratory evaluation, except for mild proteinuria exhibited by 9 (50%) patients, the urinalysis was unimpressive: no pigmented or red blood cell casts were identified in any patient. Serum creatinine concentrations higher than 1.4mg/dl were recorded in 7 (39%) patients in absence of extra-renal abnormalities that may have caused pre-renal azotemia. Creatinophosphokinase levels above 36 IU were found in 14 from the 16 (87.5%) in whom it was measured. Serum myoglobin concentrations greater than 120$\mu$g/l were detected in 7 (39%) out of 18 patients. The clinical course was characterized by a complete recovery. The mortality of the group was 27.8%; the causes of death were unrelated to renal failure in all, although 3 of the patients with acute renal failure died.

The correlation between acute renal failure and myoglobinemia, as shown in Table 2, was not significant. Also, correlation between acute renal failure and serum levels of CPK or severity of tetanus could not be established.

*Table 1 - Tetanus as a cause of renal failure and rhabdomyolysis: some clinical and laboratorial data.*

| N° | Severity | Proteinuria | Creatinine (mg/dl) | CPK (IU) | Myoglobinemia |
|---|---|---|---|---|---|
| 1 | Mild | + | 0.8 | 249 | + |
| 2 | Mild | Neg | 0.8 | | Neg |
| 3 | Mild* | + | 1.4 | 26 | Neg |
| 4 | Mild | Neg | 1.4 | 166 | + |
| 5 | Mild | Neg | 1.8 | 16 | Neg |
| 6 | Moderate | ++ | 0.7 | 57 | Neg |
| 7 | Moderate | ++ | 0.8 | 109 | + |
| 8 | Moderate | Neg | 1.0 | 171 | + |
| 9 | Moderate | + | 1.2 | 202 | Neg |
| 10 | Moderate | + | 1.4 | 109 | Neg |
| 11 | Moderate* | Neg | 1.6 | 125 | Neg |
| 12 | Moderate | Neg | 1.8 | 68 | Neg |
| 13 | Severe* | Neg | 1.0 | 819 | + |
| 14 | Severe | + | 1.4 | 202 | Neg |
| 15 | Severe* | Neg | 1.5 | 628 | + |
| 16 | Severe | + | 1.5 | | Neg |
| 17 | Severe | Neg | 1.8 | 16 | Neg |
| 18 | Severe* | + | 3.2 | 249 | + |

Normal values: creatinine = 0.4 to 1.4mg/dl
CPK = 0 to 36IU

* = death

*Table 2 - Correlation between myoglobinemia and renal failure in patients with tetanus.*

| Acute renal failure | Number patients | Myoglobinemia positive | negative |
|---|---|---|---|
| Present | 7 | 2 | 5 |
| Absent | 11 | 5 | 6 |
| Total | 18 | 7 | 11 |

p = 0.417

## DISCUSSION

Acute renal failure has not been recognized as a frequent complication of tetanus[6 21 23], except for a very selected series of patients admitted to a respiratory unit where it was diagnosed in up to 14% of them[10 17]. In the present study we recorded acute renal failure, on the basis of sudden increase in serum creatinine in the absence of extra-renal azotemia, in 39% (95% CI, 23 to 60) of patients consecutively admitted to the Infectious Disease Hospital in Salvador-Bahia-Brazil. The patients enrolled in this study were diagnosed as having generalized tetanus graded according to the clinical presentation; minor wounds were the most frequent portal of entry, not differing from other series[1 7].

The high detection of acute renal failure in our series is, probably, related to the sistematically performed urinalysis and determinations of serum creatinine, at admission and during the follow-up. Importantly, only one of the patients presented oliguria; the most frequent form of acute renal failure is non-oliguric and a high degree of suspicion is necessary for the diagnosis of this condition. It is possible that the physicians carring for patients with tetanus have their attention focused on the neurological manifestations of the disease and the mild and transient decrease of renal function goes unnoticed. Acute renal failure has been diagnosed only in the most severely affected patients[15], usually oliguric, denoting a more advanced stage of the disease. Possibly, using a more sensitive marker of renal function the prevalence of acute renal failure probably could be higher than what was reported in the study.

The intense muscular work is generalized tetanus results in rhabdomyolysis, as demonstrated by rising of serum levels of creatinephosphokinase, aldolase, aminotransferases and lactodehydrogenase, in clinical and experimental studies[2 5 8 18 22]. In the present investigation we could not establish a correlation between acute renal failure and rhabdomyolysis as diagnosed by serum concentrations of myoglobin greater than 120ug/l or, even, by elevated serum levels of CPK, a much more sensitive marker of muscular injury[11 14]. Myoglobinuria was not searched for; it correlates poorly with myoglobinemia[12 19]. The role of rhabdomyolysis in the pathogenesis of the acute renal failure in tetanus, however, can not be neglected: the remarkable muscular involvement and myolysis as a consequence of tonic contractions of muscular groups and frequent and generalized clonic contractions in addition to laringeal spasms and profuse sweating cause abnormalities in fluid, electrolytes and acid-base balances. These metabolic abnormalities, in association with the hemodynamic instability secondary to the overactivity of the sympathetic nervous system[13] strongly suggest a multifactorial pathogenesis for the acute renal failure in tetanus. The difficulty in determining the specific role of each individual factor in such a multifactorial pathogenesis is well known[3].

The lack of correlation between acute renal failure and severity or/and mortality of tetanus was not unexpected. Different from other series where the diagnosis of renal failure was done in severely ill patients, monitoring the renal function from time of admission we could detect an impairment of renal function very early in the course of the disease.

In summary, this study recorded acute renal failure in 39% of patients with generalized tetanus. It was, frequently, non-oliguric, mild and transient and not related to the severity of tetanus. Although myolysis, defined by serum increases of muscle enzymes, was frequent (87,5%), a direct correlation between abnormal serum levels of myoglobin and CPK could not be established, suggesting the role of other factors in the pathogenesis of the acute renal failure in tetanus.

## RESUMO

*Com o objetivo de estudar a freqüência de insuficiêncai renal aguda e o papel da rabdomiólise na sua patogênese, 18 pacientes adultos com o diagnóstico de tétano, consecutivamente admitidos no hospital de doenças infecciosas (Hospital Couto Maia, Salvador, BA) foram prospectivamente avaliados. Destes, 14 eram*

*do sexo masculino e 4 do feminino, com idade média de 31,8±2,0 anos. Exceto por proteinúria leve a moderada (<100mg/dl) em 9 pacientes, os sumários de urina foram considerados normais. Creatininas séricas superiores a 1,4mg/dl foram observadas em 39% dos pacientes, níveis elevados de CPK em 87,5% e mioglobina sérica maior que 120µg/dl em 39%. Oligúria foi documentada em apenas um paciente; nenhum paciente requereu tratamento dialítico. Não foram observadas correlações entre insuficiência renal aguda e níveis séricos de mioglobina e/ou CPK. A insuficiência renal aguda no tétano não foi infreqüente; geralmente é não-oligúrica, de pequena gravidade, transitória e não relacionada à severidade da doença ou aos níveis séricos de mioglobina e/ou CPK.*

*Palavras-chaves: Tétano. Rabdomiólise. Mioglobina. Insuficiência renal aguda.*

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