RATTLESNAKE BITES. CLINICAL FEATURES AND COMPLEMENTARY TESTS

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Bites by snakes of the genus *Crotalus* in Brazil are important not only because of their high incidence in certain regions, but also because of their potential production of severe and even fatal clinical pictures.

Six subspecies have been identified which are distributed irregularly throughout the Brazilian territory, the occurrence of snakebites being predominant in the Southeast of the country. The subspecies most commonly encountered in the State of São Paulo is *C. durissus terrificus*.

The frequency of bites by the South American rattlesnake is lower than that of bites by snakes of the genus *Bothrops*. Data provided by the Butantan Institute (Vital Brazil Hospital, 1966-1977) and the Yearly Statistical Data published by the Health Ministry in 1989 reveal that 8 to 10% of poisonous snakebites are caused by rattlesnakes. In the Ribeirão Preto region (data provided by the Center of Intoxication Control) and in the Botucatu region[6], this percentage reaches 20-25%.

Until the beginning of the 1980's, the South American rattlesnake venom was reported to have major activities of the hemolytic and neurotoxic type, the most serious complication of human envenomation being acute tubular necrosis, whose pathogeny was interpreted to be due to the hemolytic effect of the venom associated or not with a direct nephrotoxic effect[15].

Studies initiated in 1982 on victims of rattlesnake envenomation using clinical observation, laboratory tests and biopsy of the member contralateral to the bitten one demonstrated the systemic myotoxic action of *C. durissus terrificus* venom, characterized by aggression to skeletal muscle fibers [4,5,7,12,13,16]. More recently, the analysis of serum levels of the isoenzymes creatine kinase (CK) and

lactate dehydrogenase (LDH), together with the focal involvement of skeletal muscle detected in the biopsies of these patients, has led to the conclusion that the venom may be selective for oxidative type I and/or type IIa fibers [8]. This hypothesis is supported by histochemical data obtained in the analysis of biopsies from two patients, which demonstrated selective atrophy of type I fibers [9].

In 1986, the existence of an enzyme with thrombin-like activity was identified in snake venom. This enzyme has a clotting effect on human plasma *in vitro* and may elicit fibrinogen consumption [14], with reports of afibrinogenemia and absence of blood clotting without platelet consumption [2] being available.

In 1987, the idea of a hemolytic activity of the South American rattlesnake venom in humans was discarded through specific laboratory tests such as serum hemoglobin and haptoglobin measurements and absence of hemoglobin in urine [5].

On the basis of these data, the venom of *C. durissus terrificus* has been reported to have major activities of the neurotoxic and systemic myotoxic type, in addition to a thrombin-like clotting action, to which the main clinical manifestations detected in human poisoning have been attributed.

Clinical signs and symptoms attributed to the neurotoxic activity of the venom: usually evident during the first hours, they are characterized by a myasthenic facies (the ''neurotoxic'' facies of Rosenfeld [15]), anisocoria, uni- or bilateral palpebral ptosis, ophthalmoplegia with possible difficulty in accommodation and diplopia. Less frequent manifestations are velopalatine paralysis with difficulty in swallowing and decreased vomiting reflex, with taste and smell alterations.

Clinical signs and symptoms attributed to the myotoxic activity of the venom: generalized muscle pains may appear early. The reddish or darker (as dark as brown) color of urine is a symptom of later onset reflecting the elimination of myoglobin, a pigment released from muscle tissue, which represents the most evident manifestation of rhabdomyolysis.

Clinical signs and symptoms attributed to the clotting activity of the venom: lack of blood clotting or an increase in clotting time may occur in 30 to 50% of patients, with the occurrence of slight bleeding usually limited to the gingiva [10].

Acute respiratory failure, seldom reported for human snakebite victims, has been observed between the 3rd and 12th day after the bite in patients who develop simultaneous acute renal failure. More recent reports have described patients with respiratory symptoms occurring during the first 24 hours after the bite in the absence of renal failure and lasting no longer than one day [1,11,12]. Impairment of respiratory muscles as a consequence of the neurotoxic and myotoxic activities of the venom has been pointed out as the mechanism of the ventilatory disorders occasionally observed in victims of rattlesnake bites [16,17].

Similarly, limb paralysis and fasciculations and tremors are clinical manifestations of low frequency which are interpreted as being due to the neurotoxic and/or myotoxic activity of the venom.

Since the venom is devoid of ''proteolytic'' activity, only the marks of the fangs are observed at the site of the bite, with discrete or absent edema and/or erythema.

Laboratory Diagnosis

As a result of myolysis, enzymes are released into the blood stream, with elevated CK and LDH levels, as well as aspartate aminotransferase (AST) and aldolase levels. The increase in CK levels occurs early, reaching a peak within the first 24 hours after the bite, whereas LDH levels increase in a slower and more gradual manner.

Analysis of CK and LDH isoenzymes reveals an infarct-like pattern, with an increase in the so-called cardiac fractions CK-MB and LD_1. Electrocardiogram and serial two-dimensional ecocardiogram studies carried out on 4 patients with severe poisoning ruled out the possibility of aggression to the myocardium [8].

Nonspecific blood count changes occurs, with possible leucocytosis with neutrophilia and a leftward shift, at times with the presence of toxic granulations. An increase in clotting time, prothrombin time and partially activated thromboplastin time may occur, as well as a decrease in fibrinogen.

The urinary sediment is usually normal in the absence of renal failure, with the possible presence of discrete proteinuria not accompanied by hematuria.

The presence of myoglobin in urine can be detected by the benzidine test or using urinalysis strips (a positive reaction also for hemoglobin) or by more specific immunochemical methods such as immunoelectrophoresis, immunodiffusion tests and latex myoglobin agglutination test.

When oliguria or anuria sets in, elevated urea, creatinine, uric acid, phosphorus and potassium levels are observed, as well as decreased calcium levels.

The muscle biopsy findings obtained from patients bitten by *C. durissus terrificus* reveal a wide spectrum of ultrastructural alterations involving muscle fibers, such as focal points of myonecrosis with myofibril disintegration, myofilament disorganization and lysis, loss of transversal striations, dilatation of the sarcoplasmic reticulum, formation of contraction bands and mytochondrial edema, side by side with intact fibers in the same muscle [4,5,7,12,13,16].

The clinical and laboratory data described above refer to envenomation caused by *C. durissus terrificus* and *C. durissus collilineatus*. Recently, Fan et al. [18], reported on two snakebite victims from an area in which *C. durissus cascavella* is prevalent, whose clinical and hematological data were similar to those previously reported in the literature.

REFERENCES

1. ALVARES, J.M. Tratamento intensivo da paralisia respiratória no acidente crotálico. Belo Horizonte, 1980. 54p. (Tese de mestrado — Faculdade de Medicina da UFMG).
2. AMARAL, C.F.S.; REZENDE, N.A.; PEDROSA, T.M.G., Da SILVA, O.A.; PEDROSO, E.R.P. Afibrinogenemia secundária a acidente ofídico crotálico *(Crotalus durissus terrificus). Rev. Inst. Med. Trop. S. Paulo, 30*: 288-292, 1988.
3. AMORIM, M. de F. & MELLO, R.F. Nefrose do nefron intermediário no envenenamento crotálico humano. Estudo anátomo-patológico. *Mem. Inst. Butantan, 24*: 281-316, 1952.
4. AZEVEDO-MARQUES, M.M.; CUPO, P., COIMBRA, T.M., HERING, S.E., ROSSI, M.A.; LAURE, C.J. Myonecrosis, myoglobinuria and acute renal failure induced by South American rattlesnake *(C. durissus terrificus)* envenomation in Brazil. *Toxicon, 213*: 631-636, 1985.
5. AZEVEDO-MARQUES, M.M.; HERING, S.E. CUPO, P. Evidence that *Crotalus durissus terrificus* (South American rattlesnake) envenomation in humans causes myolysis rather than hemolysis. *Toxicon, 11*: 1163-1168, 1987.
6. BARRAVIEIRA, B. Curso sobre acidentes por animais peçonhentos; acidentes por serpentes do gênero *Crotalus. Arq. bras. Med., 64:* 14-20, 1990.
7. CUPO, P., AZEVEDO-MARQUES, M.M.; HERING, S.E. Clinical and laboratory features of South American rattlesnake *(C. durissus terrificus)* envenomation in children. *Trans. Royal Soc. trop. Med. Hyg., 82:* 924-929, 1988.
8. CUPO, P.; AZEVEDO MARQUES, M.M.; HERING, S.E. Acute myocardial infarction-like enzyme profile in human victims of *C. durissus terrificus* envenoming. *Trans. Royal Soc. trop. Med. Hyg., 84*: 447-451, 1990.

9. JORGE, M.T.; PEREIRA, J.R.; BONFATI JR., W.; RIBEIRO, L.A.; AMATO NETO, V.; RASSI, I.E.; BOUABCI, A.S Comportamento de enzimas e alterações anátomo-patológicas do músculo esquelético em pacientes picados por serpentes do gênero *Crotalus*. *Rev. Soc. bras. Med. Trop., 19* (suppl.): 27, 1986.
10. KAMIGUTI, A.S. & CARDOSO, J.L.C. Haemostatic changes caused by the venoms of South American snakes. *Toxicon, 27*: 955-963, 1989.
11. LOPEZ, M.; FOSCARINI, L.; ALVARES, J.M.; DINIZ FILHO, I.; MARSA, V.D.; PROCÓPIO, N.P.M. Tratamento intensivo das complicações do acidente ofídico. *Rev. Ass. med. Minas Gerais, 23*: 107-112, 1972.
12. MAGALHÃES, R.A. Contribuição ao estudo da rabdomiólise no acidente ofídico crotálico. Belo Horizonte, 1986. 90p. (Tese de mestrado — Faculdade de Medicina da UFMG).
13. MAGALHÃES, R.A.; RIBEIRO, M.M.F.; REZENDE, N.A.; AMARAL, C.F.S. Rabdomiólise secundária a acidente ofídico crotálico (*C. durissus terrificus*). *Rev. Inst. Med. trop. S. Paulo, 28*: 228-233, 1986.
14. RAW., I.; ROCHA, M.C.; ESTEVES, M.I.; KAMIGUTI, A.S. Isolation and characterization of a thrombin-like enzyme from the venom of *Crotalus durissus terrificus*. *Braz. J. Med. Biol. Res., 19:* 333-338, 1986.
15. ROSENFELD, G. Symptomatology, pathology and treatment of snakebites in South America. In: BUCHERL, W.; BUCKLEY, E.E.; DEULOFEU, V. ed. *Venomous animals and their venoms*. New York, Academic Press, 1971. p. 345-384.
16. ROSSI, M.A.; PERES, L.C.; DEPAOLA, F.; CUPO, P.; HERING, S.E; AZEVEDO-MARQUES, M.M. Electron microscopic study of systemic myonecrosis due to poisoning by tropical rattlesnake *(C. durissus terrificus)* in humans. *Arch. Path. Lab. Med., 113*: 169-173, 1989.
17. VITAL BRAZIL, O. Venenos ofídicos neurotóxicos. *Rev. Ass. Med. Bras., 26:* 212-218, 1980.
18. FAN, H.W.; OLIVEIRA, J.R.F.; MEDEIROS, I.M.; PINHEIRO, E.M.; FRANÇA, F.O.S.; CASTRO, S.; KAMIGUTI, A.S.; CARDOSO, J.L.C. Aspectos regionais do envenenamento crotálico: acidente em área de *Crotalus durissus cascavella*: In CONGRESSO DA SOCIEDADE BRASILEIRA DE MEDICINA TROPICAL, 26. *Resumo 70*, 1990. p.94