Stroke following *Bothrops* spp. snakebite

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Abstract—*Objective:* To determine the prevalence and subtypes of cerebrovascular complications of *Bothrops* spp. snakebites. *Methods:* The authors studied 309 consecutive patients bitten by *Bothrops* spp. who attended a large general hospital. Special emphasis was placed on the time elapsed between the bite and admission to the hospital, clinical manifestations, laboratory findings, severity of envenomation, CT findings, and outcome. *Results:* Eight of 309 patients (2.6%) developed a cerebrovascular event. Six presented >8 hours after being bitten, and all had clinical and laboratory evidence of severe envenoming. CT revealed intracranial bleeding in seven patients and multiple brain infarcts in one. Hemorrhages were located in the subcortical white matter of the cerebral hemispheres in five patients, in the cerebellum in one, and in the subarachnoid space in one. All patients with intracranial hemorrhage had a bleeding disorder, and the patient with cerebral infarcts may have had angiitis. Five of the eight patients died despite therapy, and the remaining three had irreversible sequelae. *Conclusions:* The prevalence of cerebrovascular complications related to *Bothrops* spp. bites is 2.6%. Intracranial hemorrhages are more frequent than cerebral infarcts. The prognosis of these patients is poor.

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The incidence of snakebites is as high as 500 per 100,000 population in the developing world, with >20,000 deaths a year in some African, Asian, and Latin American countries.[1-3] These may be underestimates as most snakebites occur in rural areas, where people do not seek medical attention because of transport problems or preferences for traditional healers.[4] In the USA, up to 8,000 bites by venomous snakes occur each year.[5,6]

Snake venom is a complex animal poison that contains phospholipase A_2, acetylcholinesterase, hyaluronidase, metalloproteinases, and other enzymes that have either direct neurotoxic effects or procoagulant or fibrinolytic activity.[7] This may contribute to the development of a number of neurologic complications. Both ischemic and hemorrhagic strokes have been linked to the bite of venomous snakes (table 1).[8-14] However, the frequency of these complications is unknown. Here, we present a series of patients bitten by *Bothrops* spp. (the most common venomous snakes in the Pacific coastal region of Central and South America) to study the incidence of snakebite–related stroke and the characteristics of the different stroke subtypes.

Patients and methods. We reviewed the medical records of all cases of snakebite presenting to the Emergency Room of Luis Vernaza Hospital, Guayaquil, Ecuador, between March 2000 and August 2001. We included only those cases where the patient or witnesses provided enough information for identification of the snake as a *Bothrops* spp. (figure 1). Evaluation and treatment of all patients followed the standards of the snakebite management protocol of the Toxicology Service of Luis Vernaza Hospital (table 2). According to severity, all patients presenting with a snakebite were evaluated after admission, and specific therapy was administered during the first hour. The following information was gathered from the records for this study: sex and age of the patient, time elapsed between the bite and admission to the hospital, clinical manifestations, laboratory findings, severity of envenomation, CT findings, and outcome.

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Results. We evaluated 309 patients (252 men, 57 women; mean age 44.3 years, age range 8 to 82 years) bitten by a *Bothrops* spp. during the study period. Time between the bite and admission to the emergency room was <4 hours in 105 patients (34%), between 4 and 8 hours in 88 patients (28.5%), and >8 hours in the remaining 116 patients (37.5%). On admission, 283 patients (91.8%) had pain or swelling at the site of the bite, 227 (73.5%) had abnormal coagulation times, and 137 (44.3%) had evidence of bleeding. According to the Snakebite Severity Score (SSS), 74 patients (24%) were in grade 0, 95 (30.7%) were in grade 1, 129 (41.7%) were in grade 2, and 11 (3.6%) were in grade 3.

Eight patients (2.6%) developed a cerebrovascular event related to the snakebite. Strokes were hemorrhagic in seven patients and ischemic in one (Additional material can be found on the *Neurology* Web site; go to www.neurology.org). These patients were three men and five women with a mean age of 51.9 years (age range 27 to 74 years). All patients had pain and swelling around the bite site, four had evidence of systemic bleeding, and all were in grade 3 of the SSS. On admission, neurologic examination revealed decreased level of consciousness in all patients; six were in a coma, and the remaining two were lethargic. With the exception of one woman who was taking oral contraceptives (Case 1), no other patient had risk factors for cerebrovascular disease.

Six of the patients who developed a cerebrovascular event pre-

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Table 1 *Cerebrovascular complications of snakebites*

Snake	Toxins	Stroke subtypes
Bothrops spp. (equis, terciopelo)	Aspercitin, hemorrhagins, metalloproteinases	Cerebral infarcts, subarachnoid and parenchymal brain hemorrhages
Crotalus viridis (rattlesnake)	Arginine ester hydrolase, thrombin-like enzyme	Cerebral infarcts
Echis carinatus (carpet viper)	Zinc metalloprotein (ecarin), thrombin-like enzyme	Cerebral infarcts
Daboia russelli (Russell's viper)	Proteases	Cerebral infarcts, pituitary hemorrhages
Agkistrodom blomhoffii (Korean viper)	Arginine ester hydrolase, lupus anticoagulant-like proteins, hemorrhagins	Cerebral infarcts
Pseudonaja textilis (brown snake)	Prothrombinase	Parenchymal brain hemorrhages
Notechis scutatus (tiger snake)	Toxic acidic proteins (HTa-I)	Parenchymal brain hemorrhages

sented >8 hours after being bitten. When we compared the prevalence of cerebrovascular disease among our patients according to the time elapsed between the bite and admission to the hospital, we found that only 2 of 193 patients (1.03%) who presented during the first 8 hours after the bite developed a stroke as compared with 6 of 116 patients (5.17%) who were admitted after that time ($p = 0.034$ by Fisher's exact test).

Intracranial hemorrhages were located in the subcortical white matter of the cerebral hemispheres in five patients, in the cerebellum in one, and in the subarachnoid space in one. One of the patients with lobar hemorrhages had multiple foci of bleeding with invasion of the ventricular system, and another had exten-

Figure 1. *(A)* Bothrops asper *(equis, terciopelo); (B)* Bothrops schelegelii *(equis voladora, cabeza de candado, papagayo). These species are responsible for >95% of case of snakebite envenoming in the coastal region of southern Ecuador.*

Table 2 *Snakebite evaluation and management protocol (Luis Vernaza Hospital)*

Initial approach
Record vital signs, ensure an adequate airway, stabilize hemodynamic parameters, administer analgesics if necessary
Snake identification
Direct observation of the snake
Description of the snake by the patient or witnesses
Physical examination
Snake bite inspection: Look for fang marks or local swelling, erythema, ecchymoses, or tissue necrosis
Look for evidence of systemic bleeding
Look for neurologic signs
Complementary examinations
Draw a blood sample for blood cell counts, coagulation tests, electrolytes, creatinine, liver function tests, arterial blood gases
Perform head CT if deterioration of consciousness or focal signs occur
Evaluation of the severity of the envenomation (Snakebite Severity Score)
Grade 0: mild pain or tenderness at the bite
Grade 1: pain and swelling at the bite, perioral paresthesias
Grade 2: edema beyond the area of the bite, systemic bleeding
Grade 3: edema of the entire limb, tissue necrosis, severe coagulopathy, shock
Treatment
Local wound care
Administer polyvalent antivenom as needed
Individualize specific therapeutic agents (antibiotics, osmotic diuretics, etc.)
Correct anemia, thrombocytopenia, and abnormal coagulation tests

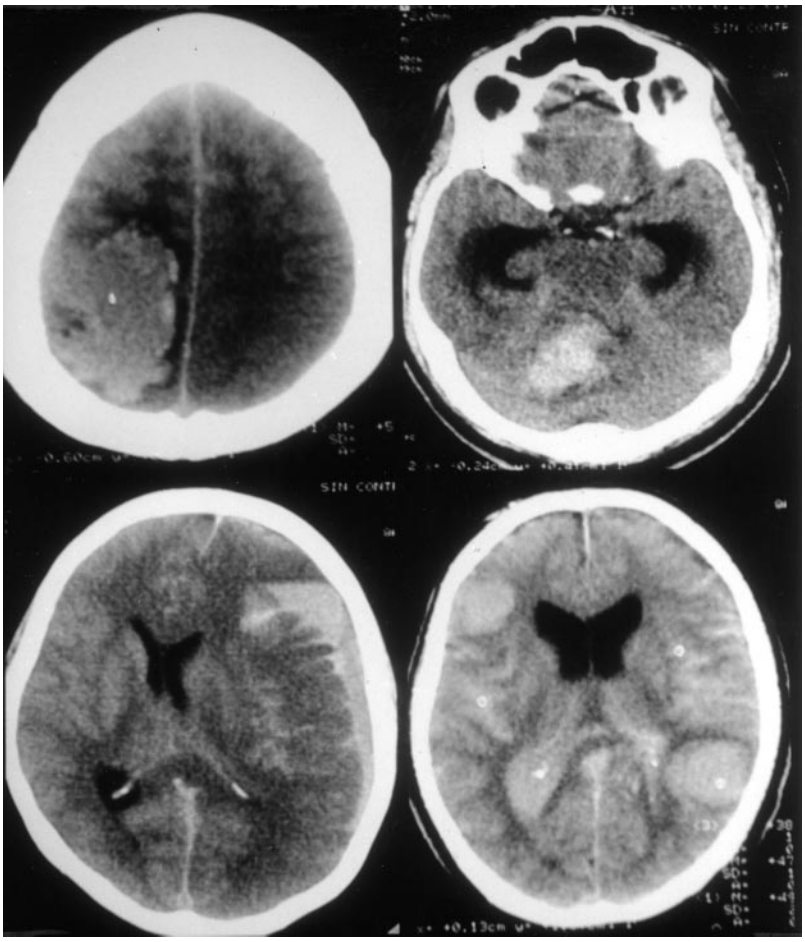

Figure 2. CT showing different patterns of intracranial hemorrhages related to Bothrops *spp. envenoming. Note the low attenuation coefficient of the bleeding due to severe anemia.*

sion of the bleeding into the subdural space. In four patients, the CT attenuation coefficient of the intracranial bleeding was lower than usual owing to severe anemia (figure 2). Six of these seven patients had prolongation of the prothrombin and partial thromboplastin times, six had platelet counts of $<20{,}000/mm^3$, and three had increased fibrin degradation products. The patient with ischemic stroke had simultaneous infarcts in the territory of the left middle cerebral artery, the right posterior cerebral artery, and both superior cerebellar arteries (figure 3). Laboratory examination showed a mild increase in fibrinogen levels, and sonographic evaluation of the heart and neck vessels was normal.

A favorable outcome was seen in 295 of the 309 patients (95.4%) included in this study. Three patients (all with a cerebrovascular event) survived the acute episode but were left with irreversible sequelae, and 11 patients (3.5%) died. The cause of death was directly related to the cerebrovascular event in 5 of 11 patients. In the remaining six, death was caused by hypovolemic shock, acute renal failure, or total body failure. When comparing clinical manifestations, laboratory findings, and outcome, it was clear that patients who developed cerebrovascular complications had more severe clinical pictures and higher mortality rates than those who did not.

Discussion. Venomous snakes may cause neurologic complications due to either neurotoxic or hemotoxic enzymes. Neurotoxic enzymes induce paralysis by blocking transmission at the neuromuscular junction, and hemotoxic enzymes may favor the occurrence of cerebrovascular events through an alteration in coagulation times.[7] As the venom of *Bothrops* spp. does not

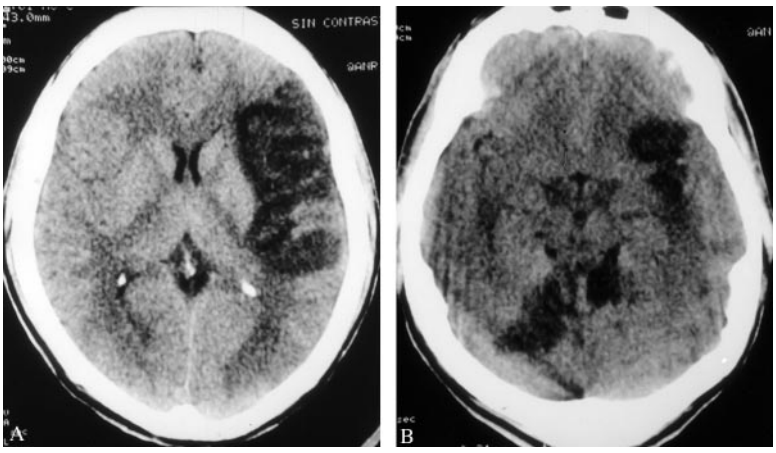

Figure 3. CT of a patient bitten by a Bothrops *spp., taken 5 days after admission, showing infarcts in different cerebral artery territories related to* Bothrops *spp. envenoming.*

have direct neurotoxic properties, the only neurologic complications that could be related to these snakes are cerebrovascular.

The pathophysiology of snakebite-related stroke is complex. The venom of *Bothrops* spp. and other snakes contains aspercitin, metalloproteinases, and hemorrhagins. These substances may cause thrombocytopenia, prolongation of prothrombin and partial thromboplastin times, disseminated intravascular coagulation, and even damage of blood vessel walls.[15,16] As seen in our seven patients with intracranial hemorrhages, such hemostatic disturbances may occur alone or in combination, explaining the bleeding in every case.

Procoagulant activity of some components of the venom, hypovolemic shock, or vascular damage may account for the rare occurrence of snakebite-related cerebral infarcts. Ischemic strokes have been reported after the bite of vipers and rattlesnakes in a handful of cases.[10-13] In addition, a single patient bitten by a *B. lanceolatus* (a rare *Bothrops* spp. geographically restricted to Martinique) developed a brainstem infarct.[17] To our knowledge, cerebral infarcts have not been recognized as a complication of *B. asper* or *B. schelegelii* envenoming. In our patient, the simultaneous occurrence of infarcts in the territory of multiple cerebral arteries, the absence of risk factors for cerebrovascular disease or hypovolemic shock, the increased serum fibrinogen levels, and the normality of the sonographic evaluation of the heart and neck vessels suggest a combination of procoagulant activity induced by the venom and toxic angiitis of intracranial vessels as the possible cause of the infarcts.

The actual prevalence of cerebrovascular complications in patients bitten by *Bothrops* spp. has not been settled. Fifteen patients with intracranial hemorrhages among 294 cases of snakebites have been reported from eastern Ecuador, where the most common venomous snakes are *Bothrops* spp. and *Lachesis muta*.[4] However, neuroimaging studies were not performed in these patients, and the diagnosis was established only on the basis of clinical data. In Brazil, no neurologic complications were observed among 73 children bitten by *Bothrops* spp.[3] In another study from Colombia, 4 cases (only one studied with CT) of intracranial hemorrhages were recognized among 218 patients bitten by *Bothrops* spp.[18] We found a 2.6% prevalence of cerebrovascular complications (87.5% hemorrhagic and 12.5% ischemic) in our series, a more confident number as we performed neuroimaging studies in every patient presenting with deterioration of consciousness or focal neurologic signs (see table 2).

Whereas the prevalence of cerebrovascular complications related to *Bothrops* spp. bites is low, the prognosis of these patients is poor. Five of our eight patients died, and the other three were left with irreversible sequelae despite therapy. Six of these patients presented to the hospital >8 hours after the bite, when hemotoxic effects of the venom cannot be easily neutralized and when the brain has been damaged by the stroke. It has been shown that early administration of metalloproteinase inhibitors and chelating agents or antivenom incubated with the venom prior to injection is effective to reduce the risk of local and systemic hemorrhages after *Bothrops* spp. envenoming.[19,20] In rural areas of developing countries, people should be instructed to seek prompt medical attention after a snakebite to reduce the prevalence of cerebrovascular and other life-threatening complications of this condition.

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