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Case Report

Hemorrhagic stroke following viper bites and delayed antivenom administration: three case reports from the Western Brazilian Amazon

***Aline Stephanie Pérez-Gómez*[1],[2], *Wuelton Marcelo Monteiro*[1],[2], *Guilherme Augusto Pivoto João*[1],[2], *Jose Diego de Brito Sousa*[1],[2], *Izabella Picinin Safe*[1],[2], *Marcia Melo Damian*[1],[2], *Jacqueline Almeida Gonçalves Sachett*[1],[2],[3] *and Iran Mendonça da Silva*[1],[2]**

[1]. Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, AM, Brasil.
[2]. Escola Superior de Ciências da Saúde, Universidade do Estado do Amazonas, Manaus, AM, Brasil.
[3]. Fundação Hospital Adriano Jorge, Manaus, AM, Brasil.

Abstract

Snakebites were included by the World Health Organization in their list of neglected diseases. In Latin America, most snakebites are caused by species of the *Viperidae* family, notably by the genus *Bothrops*. *Bothrops atrox* accounts for 90% of the cases of envenoming in the Brazilian Amazon. In this report, we present a series of three cases of snakebites that evolved with hemorrhagic stroke due to delays in the access to antivenom in the Brazilian Amazon, being fundamental for diagnosis to validate the clinical suspicion and make decisions that would improve the treatment and prognosis of the patients.

Keywords: Hemorrhagic Stroke. Viperidae family. Antivenin.

INTRODUCTION

Snake poisonings were recently included by the World Health Organization (WHO) in their list of neglected diseases[1]. Each year, an estimated 5 million cases of envenoming are reported globally[2,3]. In Latin America, there are approximately 129,084 cases per year, most of them caused by species of the *Viperidae* family. In Brazil, from 2011 to 2014, 112,249 incidents were reported, 72% by the genus *Bothrops* spp.[2].

Bothrops venom has proteolytic, coagulant, and hemorrhagic actions[4,5]. Local manifestations are observed mainly as pain, edema, erythema, and systemic manifestations that may include bleeding[6]. Hemorrhagic stroke (HS) is a complication that may be more frequent in patients with pre-existing risk factors, such as diabetes, nephropathies, and cardiovascular diseases[2,6]. In this report, we present a series of three cases of snakebites that evolved with HS due to delays in access to antivenom in the Brazilian Amazon region.

CASE REPORTS

Case 1

A 15-year-old male patient with no comorbidities from the municipality of Rio Preto da Eva-Amazonas experienced a presumed *Bothrops* accident to the dorsal region of the left foot on April 15th, 2017. After the bite, he reported pain, edema, and local erythema without blisters. He was transferred to Thomé de Medeiros Raposo Hospital where a coagulation time (CoT) measurement revealed an incoagulable result. Due to the absence of antivenom in the locality, he was admitted to the Heitor Viera Dourado Tropical Medicine Foundation (FMT-HVD) in Manaus on April 16, 2017.

About 21 hours after the accident, he was sleepy and unresponsive with a Glasgow Coma Scale score of 10/15, and a new CoT measurement persisted in showing an incoagulable

Corresponding author: Prof. Dr. Iran Mendonça da Silva.
e-mail: iramend3@gmail.com
Orcid: 0000-0002-7162-7113
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result (**Table 1**). Due to a convulsive episode and lowered consciousness level, invasive mechanical ventilation was required. The snakebite was classified as severe and 12 ampoules of botropic antivenom (BA) were administered. Physical examination showed non-light-reactive, anisocorial pupils with the left larger than the right; normal cardiopulmonary auscultation; left foot lesions at the snakebite site; mild edema in the ankle without signs of necrosis or infection; and peripheral pulses with preserved perfusion. He remained in the FMT-HVD ICU for 72 hours. Skull CT was performed again. Skull A CT scancomputed tomography (CT) of the skull revealed intraparenchymal hemorrhage in the right frontal region with perilesional edema (**Figure 1**). He was transferred to the FMT-HVD Intensive Care Unit (ICU) of the FMT-HVD, kept maintained under sedation, and withheld from the use of vasoactive drugs.

Case 2

A 78-year-old female patient with no comorbidities from the Werekena tribe, Santa Cruz Village in the municipality of São Gabriel da Cachoeira-Amazonas experienced a presumed *Bothrops* snakebite to the first left-hand pododactyl on October 6, 2017. She reported severe pain, edema, and local erythema without blisters. She was admitted to the emergency clinic after 20 hours with an altered consciousness level and Glasgow Coma Scale score of 11/15. The snakebite was classified as severe, and 12 ampoules of BA were administered; ceftriaxone was administered, and tests showed incoagulable blood.

Three days after admission, her Glasgow Coma Scale score had worsened (8/15); there was hemiparesis to the left and generalized tonic-clonic convulsive attacks for more than 30 minutes. She was sedated, orotracheal intubation was inserted, and she was transferred to the FMT-HVD ICU. Skull CT revealed a hypodense lesion in the right frontal lobe, cortical–subcortical, plus perilesional edema (**Figure 1**). Other examinations are summarized in **Table 1**. On admittance to the FMT-HVD ICU, she was hemodynamically stable, without the use of vasoactive drugs or sedation, and receiving mechanically

TABLE 1: Laboratory tests carried out at FMT-HVD.

Tests	Case 1 April 16th, 2017	Case 2 October 11th, 2017	Case 3 April 7th, 2018	Parameters
Hemoglobin (g/dL)	13.4	9.32	13.61	12.5–15.5
Hematocrit (%)	41.7	27.79	40.18	36–47
Leucocytes (/mm^3)	29.080	13.110	22.010	4000–10.000
Segmented nucleus (%)	88	86	78	40–70
Band cells (%)	0	0	6	
Plaques (/mm^3)	186.000	212.00	190.000	150.000–450.000
Creatinine kinase (U/L)	512	2611	3255	24–190
Creatinine (mg/dL)	1	0.8	0.8	0.5–1.2
Urea (mg/dL)	32	61	20	10–45
Lactic dehydrogenase (U/L)	546	ND	676	211–423
AST (U/L)	32	69	88	2–38
ALT (U/L)	15	30	45	2–44
Sodium (mmol/L)	138	145	140	135–145
Potassium (mmol/L)	4.5	3.3	ND	3.6–5.2
Clotting Time (min)	Unclottable	9	10	5–10
PTA (s)	28.8	16.3	17.8	12.5
INR	2.84	1.39	1.56	1
Glucose (mg/dL)	ND	131	ND	ND

AST: Aspartate aminotransferase; **ALT:** Alanine aminotransferase; **INR:** International Normalized Ratio; **PTA:** Prothrombin time and activity; **ND:** Not done.

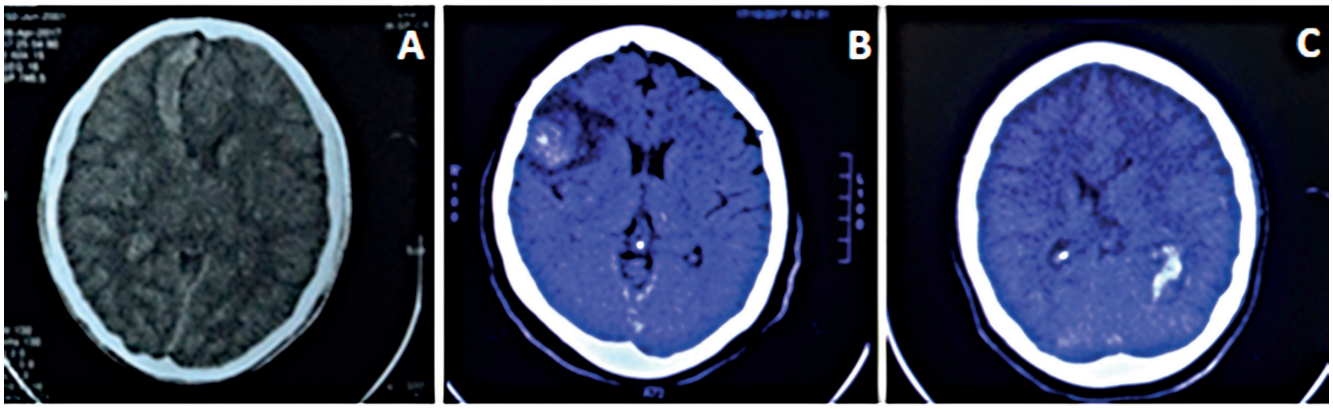

FIGURE 1: CT scans of patients who developed hemorrhagic vascular stroke after presumed botropic accidents. **(A)** Case 1, CT scan of the skull showing intraparenchymal hemorrhage in the right frontal region with perilesional edema. **(B)** Case 2, CT scan of the brain revealing a hypodense lesion in the right frontal lobe, cortical–subcortical, and perilesional edema. **(C)** Case 3, CT scan of the skull demonstrating hyperdensity in the posterior horn of the left lateral ventricle, with dilation of the homolateral temporal horn, related to the hemoventricule. **CT:** computed tomography.

assisted ventilation. She had a Glasgow Coma Scale score of 10/15; was drowsy, but responsive; had blood pressure of 121/66 mmHg; and had photoreceptive and isochoric pupils, left-sided hemiparesis, a swollen left hallux, blisters in the proximal phalanx, and drainage of serous secretion with signs of necrosis in the distal region, besides multiple ulcerated lesions on the skin and the presence of vaginal prolapse. She was extubated, remaining in the ICU for another three days, with improvements in her consciousness level, partial regression of coordination deficit, and no progression of the cerebral lesion nor new bleeding.

She was transferred to the female ward to terminate antibiotic therapy; follow-up of the lesion in the left hallux showed active bleeding and dry necrosis. Evaluations for neurosurgery and vascular surgery led to conservative clinical management of stroke and distal resection of the left hallux due to dry necrosis, respectively. She improved with regression of the hypodense lesion in the right frontal lobe observed on skull CT and clinical improvement and recovery of the left lower limb movements; she was discharged from the FTM-HVD with neurological follow-up.

Case 3

A 20-year-old female patient from the municipality of Lábrea-Amazonas experienced a presumed *Bothrops* snakebite to the fourth left pododactyl on April 6, 2018 in the Japiim Community. She was transferred to the Lábrea Hospital and arrived 20 hours after the accident, reporting chest tightness and pain, a holocranial headache, hematemesis, and syncope. Initial evaluation showed blood pressure of 60/40 mmHg, and CoT measurement showed blood to be uncoagulable. The snakebite was classified as severe, and 10 ampoules of BA were administered with volemic expansion, hydrocortisone, and promethazine. She presented generalized tonic-clonic convulsive attacks. Sedation and physical restraint were required, and air transport for evacuation to Manaus was requested.

She was admitted to the FMT-HVD on April 8th, where skull CT showed hyperdensity in the posterior horn of the left lateral ventricle with dilatation of the homolateral temporal horn, related to the hemoventricle (**Figure 1**) and biochemical tests (**Table 1**). She was then referred to the João Lúcio General Hospital for neurosurgical evaluation and, without surgical indications, she was transferred to the FMT-HVD ICU, where she was treated with anticonvulsants, without sedation or vasoactive drugs. She was hemodynamically stable, drowsy, and non-responsive with a Glasgow Coma Scale score of 10/15, isocoric and photoreceptive pupils, left-sided convergent strabismus, bilateral conjunctival hemorrhage and eyelid ecchymosis, and left-sided hypoesthesia. She presented with edema, erythema, and ecchymosis in the third and fourth left pododactyls; ecchymosis in the lower limbs; and peripheral pulses with preserved perfusion.

Despite progressive improvement, the patient had a persistent headache, and on the third day of hospitalization, showed bilateral nystagmus with neck stiffness (Brudsinsky and Laseggue-negative) and no signs of pyramidal release with sixth right-pair cranial nerve palsy and good visual acuity. Skull CT was performed again, demonstrating thin hypodensity of the deep white substance along the posterior horn of the left lateral ventricle, related to the probable transependymal transudation, in addition to previously observed alterations. The next day, she developed bilateral paresis of the sixth pair of cranial nerves and bilateral convergent strabismus without hemodynamic instability.

Due to clinical stability, she was transferred to the female ward, where she developed left temporal hemianopsia, bilateral retinal hemorrhage, and dry necrosis area in the plantar face of the third and fourth left toes. Amoxicillin-clavulanic acid was administered, and abscess debridement and drainage was performed on the left foot. Based on the persistent headache, neurological evaluation suggested potentiating analgesia and maintaining phenytoin and dexamethasone at full dose with subsequent progressive reduction until its total suspension and ambulatory follow-up. After 18 days of hospitalization with clinical improvement, she was discharged with referral to an outpatient clinic follow-up by the Neurology Service.

DISCUSSION

Delays between the time of envenoming and antivenom administration are often the result of an extensive territorial area, difficulty in transporting the patient, a lack of cold chain distribution for antivenom storage, and practice of traditional treatments, such as the use of medicinal plants[4,5]. Lyophilized serum could be a practical solution to the problem considering that it is not necessary to be conserved in low temperatures[7].

The coagulant activity results from components of venom with activity similar to those of thrombin, which directly hydrolyze fibrinogen to fibrin, and procoagulant activity, which activates the coagulation factors II and X, resulting in the formation of endogenous thrombin[9]. The proteolytic activity induced by venom causes vascular wall injury resulting in bleeding[10]. In hemorrhagic activity, P-I metalloproteinase, especially batroxase, has fibrinolytic and thrombolytic activity and induces bleeding through the digestion of extracellular matrix components[6].

Bothrops snakebites have the potential to cause stroke, represented by the generation of focal neurological deficits, determined by a brain injury, secondary to a vascular mechanism[7]. The observed signs and symptoms that characterized HS in the present cases were acute onset, lack of history of trauma, depression of the level of consciousness, presence of seizures, hemiparesis, and cranial nerve palsy. Meanwhile, the coagulogram was only altered in the first case. However, such an outcome was expected, since the examination was performed in two of the patients, days after administration of the antibotropic serum, and coagulation disorder is usually reversed within the first 24 hours after antivenom administration[8]. We considered the diagnosis of *Bothrops* snakebite because the three cases improved with BA despite the severity of the cases, consistent with the clinical evolution and epidemiology of snakebites.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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