MULTIPLE HEMORRHAGIC BRAIN INFARCTS AFTER VIPER ENVENOMATION

EFSTATHIOS J. BOVIATSIS, ANDREAS T. KOUYIALIS, GEORGE PAPATHEODOROU, MARO GAVRA, STEFANOS KORFIAS, AND DAMIANOS E. SAKAS

Department of Neurosurgery Evangelismos General Hospital, University of Athens Medical School, Athens, Greece; Department of Radiology, Piraeus General Hospital, Athens, Greece; Department of Radiology, Evgenidio Hospital, Athens, Greece

Abstract. We report the case of a 65-year-old woman who presented with severe neurologic complications after envenomation by a viper snake. A computed tomography (CT) scan revealed multiple brain hemorrhagic infarcts. Conservative treatment in this case proved to be sufficient and repetitive CT scans displayed a complete resolution of the radiologic findings. Possible mechanisms for the cerebral infarctions are discussed. The mechanism of infarctions in this case was believed to be the vasomotor and coagulation disorders caused by the toxins present in the snake’s venom and was one of the reasons that led to conservative treatment.

INTRODUCTION

Snake envenomation is reported to have a very high mortality and morbidity in some parts of the world, with 1,000 deaths reported each year in Malaysia. Fortunately, this is not the case in European countries, where snakebites are less frequent and not as dangerous, with an annual incidence of approximately 15,000–20,000, resulting in approximately 50 deaths per year.1 Vipera species bites are the most common, mainly by V. berus, followed in decreasing frequency by V. aspis and others (V. ammodytes, V. latastei, V. lebetina, V. xanthina, V. ursinii, and V. seoanei). Most snakebites occur between May and October and affect mainly males, especially on their arms.1

There are approximately 25 Vipera species throughout Europe. In Greece, three species are present: V. ammodytes, V. lebetina, and V. xanthina. Although these species are closely related, they may differ in size and appearance. However, their venom constituents and the treatment strategies for their bites used in field situations and hospitals are very similar. Envenomation by one of these three species is currently a rare occurrence in Greece. Although there are only a few such cases every year in this country, bites by these snakes constitute a serious problem for physicians who lack the necessary experience in diagnosing and treating them.

The case of a 65-year-old woman who was bitten by a viper snake is reported. She was admitted to the Department of Neurosurgery of Evangelismos General Hospital (Athens, Greece) with acute onset of right hemiplegia, confusion, and drowsiness. The importance of initial treatment and the necessity of monitoring coagulation status to prevent fatal cerebral hemorrhage are emphasized.

CASE REPORT

A 65-year-old woman with a history of hypertension and osteoporosis was admitted to a local hospital (Argos District Hospital) with vomiting, dizziness, and drowsiness. She had been bitten by a viper snake on the dorsal surface of her right foot while working in the fields of her home town in Argos, a province of Argolis. A few minutes after being bit, she reported abdominal pain, nausea, and vomiting. The bite site was extremely painful and local erythema and ecchymosis was observed. Four hours later, when her condition worsened, she became drowsy and was taken to Argos District Hospital by her family. On examination, she was found to be hypotensive (blood pressure = 80/50 mm of Hg), with swelling and ecchymosis of the right leg, and generalized petechiae. She had no convulsions, but she was vomiting and had tachypnea. She was considered to be in a state of allergic shock, even though she had no history of this. The patient had no history of snakebites, allergies to horses or goats, or serum sickness, and had never received antivenom. A sensitivity test was performed with an intradermal injection of 0.1 mL of antivenom and no side effects were observed. Fifteen minutes later, she was given an intramuscular injection of 10 mL of viper snake antivenom (Pasteur Institute, Athens, Greece) and 250 mg of hydrocortisone sodium succinate (Solu-Cortef®, Upjohn, Kalamazoo, MI). She was then transferred to Evangelismos General Hospital. No reaction to the antivenom was observed.

On admission to this hospital, the patient was confused and drowsy, but could be aroused easily. Her pupils were symmetrical and the reaction to light was present. There was no evidence of cranial nerve dysfunction. Her fundus oculi was normal when examined by fundoscopy. Her vital signs were stable, with a blood pressure of 100/70 mm of Hg, slight tachycardia (110 beats per second), and tachypnea. There was 3/5 muscle power and increased tendon reflexes on the left side of her body. She had a positive Babinski sign on the left side and hemianopsia on the right side. Clinical examination revealed two hemorrhagic marks on the dorsal surface of her right foot, which was swollen and painful. The bite site was covered with a loose bandage instead of a pressure-immobilization bandage. The patient showed no signs of tetanus, but she received tetanus antitoxin as a prophylactic measure. We immediately started intravenous administration of a crystalloid solution, but since there were no obvious signs of shock or severe blood loss, colloid solutions, plasma, or packed red blood cells were not used. A computed tomography (CT) scan revealed multiple brain hemorrhagic infarcts located in the cerebral hemispheres, surrounded by edema (Figures 1 and 2).

An initial blood sample was obtained during her stay at Argos District Hospital. The results of serologic tests were as follows: hematocrit = 40.9%, hemoglobin level = 13.6 g/dL, white blood cell count = 14,700/mm³ with 88% polymorphonuclear cells and 9.2% lymphocytes, platelet count = 177,000/mm³, muscle-brain creatine phosphokinase = 354 units/L (normal range = 0–23 units/L), creatine kinase = 87 units/L (normal range = 4–173 units/L), glucose = 172 mg/dL (normal range = 76–110 mg/dL), urea = 8 mg/dL (normal range = 10–50 mg/dL), creatine = 1.6 mg/dL (normal range = 0.6–1.4 mg/dL), and aspartate aminotransferase (AST) = 28 units/L (normal range = 1–36 units/L). A second blood test was performed at Evangelismos General Hospital...
and showed a decrease in the platelet count to 70,000/mm³ and an increase in the AST level to 142 units/L. The rest of the values remained unchanged. Her bleeding time and coagulation profile were normal. She had a serum fibrinogen level of 232 mg/dL (normal range 200–400 mg/dL) and a fibrinogen degradation products level of < 9 µg/ml (normal range = 0–0.75 µg/mL). The results of an electrocardiogram (ECG) were within normal limits.

The patient was treated conservatively, with monitoring of her coagulation parameters (prothrombin time, partial thromboplastin time, fibrinogen levels, fibrin degeneration products), serum electrolytes, lactate dehydrogenase, hemoglobin, myoglobin, and urinalysis, both macroscopic and microscopic. The patient’s urine was also monitored for evidence of potentially nephrotoxic hemoglobinuria suggesting hemolysis. In addition, we monitored her urine output to exclude oliguria or anuria and her ECG. During the first week after the snakebite, CT scans were performed, but it was only two weeks later that the hemorrhagic infarcts started to show signs of resolution (Figure 3).

The patient showed a noticeable improvement in her clinical status during her stay in the hospital. Four weeks later at the time of discharge, she was in good condition and could walk without support, but had residual neurologic symptoms (4/5 muscle power on the left side) and hemianopsia on the right side. Her right leg showed marked improvement. It was still swollen, but less painful, and both the erythema and ecchymosis had subsided. She was followed-up for approximately one year and at her examination, muscle power had returned to normal. A final CT scan was performed six months after the envenomation and showed a complete resolution of the hemorrhagic infarcts, which were replaced by low-density cystic areas (Figure 4).

**DISCUSSION**

Snake venom is a complicated mixture of several enzymes and proteins, toxic polypeptides, and inorganic components. It contains more than one toxin, and their combined action has a more potent effect than that of their individual effects. In general, venoms are described as either neurotoxic or hemotoxic. The main compounds of Viperidae venom include 1) proteolytic enzymes, which catalyze the breakdown of tissues structural proteins and lead to pain and swelling at the site of the bite; 2) polypeptide toxins (e.g., viperotoxin), which disrupt the nerve-impulse transmission and may lead to heart or respiratory failure; 3) proteases, which disrupt protein-peptide bonds in tissues, resulting in damage to the wall of blood vessels, hemorrhage, and muscle fiber destruction; 4) phospholipases, which catalyze reactions that harm nerve and muscles; 5) collagenases, which lead to the destruction of connective tissue collagen; and 6) thrombin-like enzymes, which interfere with normal blood clotting.

The manifestations following viper bites depend on the severity of envenomation. In cases of minimal envenomation, only local signs at the bite site are observed, mainly swelling, erythema, and ecchymosis, while systemic manifestations are either insignificant or absent. If there is moderate envenomation, the local signs may also include the presence of blisters and may involve a larger part of the affected location. Systemic symptoms may be present, but are not life-threatening (mild hypotension, tachycardia, and tachypnea). In cases of severe envenomation, the local signs are profound, involving the entire affected location, spread rapidly, and include hemorrhagic edema and tissue necrosis. Systemic manifestations...
are also present and may include abdominal pain, nausea, vomiting, severe hypotension, tachypnea, dyspnea, tachycardia, and neurologic signs and symptoms. There may also be bleeding present, either from the bite site or from mucosal surfaces.

Snake envenomation may cause one or more major complications. Hemorrhagins and hemolysins destroy the walls of blood vessels and along with coagulation defects lead to blood loss severe enough to require a transfusion. Proteolysins result in cell and tissue destruction and tissue loss at the site of the bite. In addition, the necrotizing tissues are a good environment for anaerobic bacteria and may lead to abscess formation. The hemorrhagic activity of the venom causes widespread damage to the capillary walls and may result in pulmonary edema, tachypnea, or dyspnea. Moreover, hemorrhagin-induced hematuria, along with myoglobinuria from muscle destruction, affects renal function and may lead to renal failure. Cardiotoxins present in Viperidae venom may cause depolarization of cardiac muscles and lead to arrhythmias (supraventricular tachycardia). They may also alter heart contraction and in combination with hypotension cause cardiovascular collapse. Singh and others have reported a case of fatal, non-bacterial thrombolic endocarditis following a vpenicure bite.

Most of the vpenoms exhibit both anticoagulant and coagulant effects. The coagulant effect may be a result of arginine esterase hydrolase, an enzyme that is similar in action to thrombin, and which clots fibrinogen and aggregates platelets. These coagulant effects may also be due to the conversion of prothrombin to thrombin, a change catalyzed by proteininases. This triggering of the coagulation cascade in vivo results in the formation of microthrombi, the activation of fibrinolysis, and a bleeding tendency, which could lead to hemorrhagic complications.

Hypotension is a common and serious complication of Viperidae envenomation and should be treated aggressively. Direct action of toxins on the walls of blood vessels and the release of vasogenic agents such as bradykinin and histamine leads to vascular wall permeability deterioration, vasodilation and lowering of peripheral vascular resistance, which results in pooling of blood in the pulmonary and splanchnic vascular beds. Subsequently, hemolysis and leakage of plasma and red blood cells through the damaged capillary endothelium can occur, along with fluid loss through sweating, vomiting, or diarrhea.

Hypotension was present at all times in the patient, from her initial examination at Argos District Hospital (blood pressure = 80/50 mm of Hg) to her transfer to Evangelismos General Hospital (100/70 mm of Hg). This patient had a known history of hypertension since the age of 45. There is a strong possibility that hypertension, if poorly regulated, had damaged the autoregulation mechanism of the cerebral blood supply. Thus, the sudden hypotension caused by the snake venom would place her at increased risk of central nervous system hemorrhage.

The neurologic features of viper snakebites include cranial and peripheral nerve symptoms, drowsiness, confusion, convulsions, fainting, dizziness, weakness, blurred vision, and loss of muscle coordination. Subarachnoid hemorrhage also may be present, along with systemic and neurologic hemorrhagic abnormalities. Tibballs and others reported a case of fatal cerebral hemorrhage following snake envenomation. However, nonhemorrhagic cerebral infraction is quite rare. This has been reported by Ameratunga, in which a Russell’s viper bite caused a middle cerebral artery occlusion. Bashir and Jinkins reported an infraction of the left supraclinoid part of the internal carotid artery after viper envenomation. However, the cause of cerebral arterial occlusion in both of these cases was not clear. These investigators suggested that the cerebral infarction could be related to the vessel-damaging toxin in the venom, possibly acting on a pre-existing abnormality in the blood vessel wall. Other possibilities they considered included low-grade dissemination of intravascular coagulopathy and hypotension.

The patient in this study showed focal neurologic symptoms. However, the decrease in muscle strength, the increase in tendon reflexes, hemianopsia, and the positive Babinski sign were attributed to the cerebral pathology. The brain CT scan revealed multiple hemorrhagic infarcts. The pathogenesis of the infarcts was not clear. The hemorrhagins present in the venom are known to cause destruction of blood vessel walls and vasospasm, followed by vasodilatation of the microvessels and arterioles. It was assumed that the leakage of red blood cells through the damaged brain capillary walls, along with the coagulopathy present, resulted in small hemorrhages in the brain capillary bed.
A second possible mechanism for the formation of multiple infarcts was an embolic infarction. The patient was hypoten-
sive on her arrival at the local hospital, possibly as a result of
the action of venom toxins on the blood vessel wall. Hypoten-
sion, along with the intravascular triggering of the coagulation
cascade, may have resulted to formation of microthrombi that
led to the multiple hemorrhagic infarcts. The multiplicity of
the lesions and the gradual improvement of the patient’s clini-
cal and laboratory status led to the decision for conservative
treatment. Cerebral edema was controlled with the use of
steroids.

Recognition of a snakebite is usually easy. The event as
described by the patient, the fang marks, and the local pain
are sufficient for diagnosis. However, some bites may be dry,
with no envenomation following the injury. Another impor-
tant issue is the snake species involved, since it is very rarely
recognized or caught. This poses some clinical problems re-
garding the severity of the envenoming and the decision to
administer antivenom. In these instances, an enzyme-linked
immunosorbent assay may be helpful. This test can quantify
some venoms in both blood and urine and, along with the
increase in edema that appears within the first two hours of
the bite and the presence of gastrointestinal and cardiovas-
cular disorders, helps assess the severity of poisoning and
decision making concerning specific treatment (antivenom).1

Snake envenomation is currently a rare event in Greece,
with only a few cases reported every year. This leads to a lack
of experience of physicians in treating cases of envenomation
by snakebites. We believe this is one of the reasons for the
high mortality and morbidity rates reported in the literature.
In such cases, immediate medical treatment must be given
without delay. This treatment should include six procedures.

First, the patient should be kept calm and remain as inac-
tive as possible to limit the systemic spread of the venom. The
patient should also be transferred in a horizontal position.

Second, the bite site should be washed thoroughly with
soap and water or disinfecting solutions since snake venom
may contain tetanus-causing bacteria or other anaerobes.

Third, the injured extremity should be immobilized and
kept lower than the heart. Immobilization will reduce both
the spread of venom and reduce pain. It is known that lymph
will circulate slower in an immobilized extremity and help
delay systemic poisoning.

Fourth, in cases in which the bite is located on a limb, a
tourniquet should be applied proximal to the bite and tight
enough to prevent venom absorption both by the superficial
venous and the lymphatic system, which is responsible for
systemic spread of most venoms. This should remain in place
until the decision to administer antivenom is made at the
hospital. The tourniquet should not be extremely tight since
it will lead to interruption of arterial flow and deep vein venom
absorption. Furthermore, a tightly applied tourniquet will en-
courage venom absorption by the products of tissue metabo-
ism and after its removal may lead to rapid deterioration of
the patient. Finally, in cases with rapidly increasing edema,
the tourniquet should be loosened to avoid additional pres-
 sure-induced injury to the limb.

Fifth, making cuts over the fang marks should be avoided,
especially in Viperidae envenomation, which is capable of
producing significant local necrosis. These cuts are not as
effective as previously thought and may result in severe dam-
age if the bite has caused significant local tissue injury. A
suction device, such as the Sawyer vacuum extractor (Sawyer
Products, Safety Harbor, FL), which delivers one atmosphere
of negative pressure to the wound, can be placed over the bite
to help draw venom out of the wound. These devices are often
included in commercial snakebite kits and can help remove
up to 20% of the injected venom within 30 minutes of the bite.
Negative pressure suction devices may mitigate the effect of
envenoming and need for large doses of antivenom, but they
should be applied immediately to be effective.

Sixth, vital signs should be monitored until the patient be-
gins receiving medical care. It is also very important that all
treatment measures under no circumstances delay the trans-
port of the patient to the nearest hospital.

When the patient is transferred to the nearest medical fa-
cility, it is extremely important to obtain early intravenous
access and begin fluid administration to aid in counteracting
hypotension. Crystalloid solutions can be initially used, but in
cases of severe bleeding or shock, colloid solutions, fresh fro-
zened plasma, blood transfusions, and even vasopressors (e.g.,
dopamine) should also be used. Tetanus prophylaxis must be
administered in all cases, since it has been observed that
snake venom may contain tetanus-causing bacteria, and be-
cause there is a strong possibility of wound infection by dust
or even clothes. Blood samples must be obtained for labora-
ory analysis that should include a complete blood count to
evaluate the degree of hemorrhaging, a coagulation profile,
studies of renal and hepatic function, and the determination
of blood type and cross-matching. Urine should be tested for
blood or myoglobin (which would suggest rhabdomyolysis)
and a brisk urine output should be maintained. The patient
must be closely monitored for renal and cardiac functions.
Cardiotoxins may produce cardiac arrhythmias that may re-
quire a temporary pacemaker. Pulmonary function should
also be closely monitored for pulmonary edema and dyspnea,
and the patient may require supplemental oxygen or even
intubation and mechanical ventilation with 100% oxygen.

The basic method for the treatment of envenomation is the
use of one of the specific antivenoms available. An attempt to
locate the appropriate antivenom should be done immedi-
ately, regardless if the envenomation is moderate or severe.
The antivenoms available in Greece are gamma venin-P
(Gerolymatos Pharmaceutical Company, Athens, Greece),
viper snake antivenom (Greek Pasteur Institute), anti-snake
venom serum OLGX21 (Aventis Behring, King of Prussia,
PA), and serum antivenin (Istituto Sieroterapico e Vaccino-
geno Toscano Slavo, Siena, Italy). Each of these antivenoms
contains antibodies against the specific viper venom (e.g., the
Slavo antivenom contains antibodies against the venoms of
V. ammodytes, V. aspis, V. erus, and V. ursini), but they
should be administered only in a hospital because of possible
complications, especially anaphylactic shock. Thus, before ad-
ministration, a detailed history of the patient should be ob-
tained regarding previous snakebites, antivenom administra-
tion, allergies to horses or goats, or previous serum sickness,
followed by an initial sensitivity test.

The ischemic lesions caused by snake envenomation may
occur more frequently than those reported in the literature.
The possible pathogenic mechanism includes vasoconstriction
and ischemia in the brain caused by the venom or the forma-
tion of microthrombi as a result of snake venom–induced
hypotension and coagulopathy. We believe that the treatment
of choice should be conservative in cases in which CT of the
brain shows multiple lesions that do not cause serious medical problems. The small number of snake envenomations reported every year in Greece is responsible for the difficulties in diagnosis and treatment, since physicians lack the necessary experience in dealing with patients affected by snakebites. Education of both public and private practitioners is essential to provide the knowledge needed to treat these patients.

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Authors’ addresses: Efstathios J. Boviatis (E-mail: eboviats@med.uoa.gr), Andreas T. Kouyialis (E-mail: Kouyialis@hotmail.com), Stefanos Korfias, and Damianos E. Sakas, Department of Neurosurgery, Evangelismos General Hospital, 45-47 Ipsilandou Street, Athens 106 76, Greece, Telephone: 30-10-729-1704, Fax: 30-10-721-5281. George Papatheodorou, Department of Radiology, Pireus General Hospital, 3 Petrou Ralli and Mantoubalou Streets, Pireus, Athens, Greece, Telephone: 30-10-4915281. Maro Gavra, Department of Radiology, Evgenidio Hospital, 10 Tzoumerkon Street, Papagou, Athens, Greece, Telephone: 30-10-6518138.

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