Special article
Changes in viper bite poisonings
Novedades en el envenenamiento por mordedura de víbora
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Introduction

Snakebites are rarely reported in the emergency departments of our local hospitals but when a case arrives it always produces great expectancy. For years, clinical manifestations and treatment have been grouped together but recently there have been significant changes in some of the symptoms of envenomation produced by certain snakes in Europe. These changes bring about modifications in the way patients are treated and force us to take serious precautions in controlling their evolution.

New species and new classification

In recent years, new snake species have been discovered in the world. The number of different species has grown to 3432, which has led to a new classification in the order Ophidia and in the respective families, subfamilies, genera, species and subspecies.

Regarding the subfamily Viperinae, which includes the European viper, there have also been changes in the genera in which the different species and subspecies are classified. Table 1 shows the main genera in this subfamily, and the main European species and subspecies, as well as their location.

Epidemiology

The epidemiological work on snakebites by Swaroop and Grab has served as a worldwide reference in epidemiology for decades. But the most up-to-date figures are those presented by Chippaux, which indicate that 5.4 million people are bitten by snakes in the world, causing 2.7 million envenomations and 125,000 deaths every year. In a subsequent meta-analysis, the same author provides figures for Europe (including Turkey and Russia up to the Ural Mountains and Caucasus): of a total of about 8000 cases per year, 1000 are severe and 4 are fatal in Europe.

The Spanish case study that most closely approaches the real problem of snakebites is that presented by the Instituto de la Salud Carlos III (Health Institute Carlos III) as it collected all hospital discharges from 1997 to 2012, with a mean of 133 cases per year and a mortality of 1.2 cases per year. Of all the autonomous communities, Catalonia provides the largest number of cases, followed by Castile and León, Galicia and Andalusia. The distribution of cases shows prevalence in male subjects (68.6%) and an age range of 5–14 years (31% in the whole series) as the target population for these accidents.

Characteristics of the venom

Snake venom is one of the most complex toxins developed by nature. Its composition and activity vary between families, genera, species and even subspecies, but the nearer they are phylogenetically, the more similar their characteristics will be. The macroscopic characteristics of these venoms differ little, although they do differ in protein composition. Methods of protein analysis such as reversed-phase chromatography, two-dimensional electrophoresis, and transcriptome and proteome analyses have revealed that the proteins of these venoms belong to 10–12 families, including enzymes (serine protease, Zn2+-metalloprotease, phospholipase A2, L-amino acid oxidases) and proteins without enzymatic activity (natriuretic peptides, disintegrins, Kunitz-type protease inhibitor, cystatin, C-type lectins and specific of galactose, nerve, vascular and endothelial growth factor and CRISP toxins). These proteins present multiple isoforms and...
Table 1
Species and subspecies of European snakes and geographic areas of distribution.

<table>
<thead>
<tr>
<th>Subfamily Viperinae (genera: Atheris, Bitis, Causus, Cerastes, Daboia, Echis, Eristerophis, Macroviperata, Montatheris, Montivipera, Proatheris, Pseudocerastes, Vipera)</th>
<th>European species</th>
<th>Subspecies</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vipera berus (Balkan viper)</td>
<td>V.b.berus</td>
<td>All Eurasia, from France to the north of the Arctic Circle and to the Pacific Ocean.</td>
<td></td>
</tr>
<tr>
<td>Macroviperata or Daboia lebetina (viper from the East)</td>
<td>MI lebetina</td>
<td>In all Europe, except the Iberian Peninsula and Ireland.</td>
<td></td>
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<tr>
<td></td>
<td>MI ohtusa</td>
<td>Partially excluded from Italy and Greece</td>
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<tr>
<td></td>
<td>MI turanica</td>
<td>North Africa; Middle East and Asia.</td>
<td></td>
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<tr>
<td></td>
<td>MI cernovi</td>
<td>In Europe, in Cyclades islands, Milos and Cyprus</td>
<td></td>
</tr>
<tr>
<td>Montivipera or Daboia xanthina (Turkish viper)</td>
<td>Vipera ammodytes (horned viper)</td>
<td>Eastern zone of Greece, the European part of Turkey and islands of the Aegean Sea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vipera aspis (aspic viper)</td>
<td>Eastern Europe, particularly in the Balkans, Italy,</td>
<td></td>
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<tr>
<td></td>
<td>Vipera latastei (southern简便)</td>
<td>Romania and extended to the south to Greece and the Cyclades. Also in Armenia, Georgia, Turkey and Libya</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vipera seoanei (viper of Seoane)</td>
<td>Of discontinuous distribution, it appears in isolated and generally small populations in South-eastern France, the centre of Italy, Hungary, Romania, Bulgaria, Croatia, Bosnia-Herzegovina, Montenegro, Serbia, Macedonia, central Asia, Turkey and Iran.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vipera ammodytes (horned viper)</td>
<td>North East of the Iberian Peninsula, centre of Europe and the islands of Elbe, Sicily and Montecristo</td>
<td></td>
</tr>
</tbody>
</table>

Contribute to the complexity of the venoms and the diversity of their effects.

Frequently, the venom of European vipers has been described to have cytotoxic and haemotoxic activities, above all affecting the coagulation system, both procoagulant and anticoagulant functions. The venom of the horned viper (Vipera ammodytes) is an exception, characterised by its neurotoxic, cytotoxic and haemotoxic effects. But in the last 20 years, the unusual has become the norm and the neurological manifestations after bites from one of the European asp species (V.aspis, V.aspis zinnikeri) and the Balkan cross adder (V.berus bosniensis) have become the norm. Several countries in the region have noticed the severity of these manifestations. This neurotoxicity is thought to be the action of phospholipase A2 (PLA2)18–24. The different PLA2 isoenzymes may provoke haemolysis, myotoxicity, presynaptic neurotoxicity and postsynaptic neurotoxicity, cardiotoxicity, oedemas and procoagulant and anticoagulant activities. Table 2 shows neurotoxins described in the European species.

The causes of this versatile presentation of protein isoforms and the variations in the effects of the venoms are not clear. It is believed that changes in the ecological niche (human movements that force the animals out of their usual habitats), in food (changes in diet), individual factors (sex, age, season), environmental factors (higher temperatures, changes in precipitation patterns) or maybe hybridization among species obliged to share territories, could determine changes in venom activity. Or perhaps it is only another step in the Darwinian evolution of the species 15–17,25,26.

Clinical Manifestations

The first signs and symptoms of viper envenomation are usually pain and oedema in the region of the bite. Minute by minute, the intensity of pain tends to increase and to radiate towards the root of the extremity, while oedema progresses. These symptoms indicate envenomation. Ecchymosis can be seen at the site of the bite with a similar tendency to progress, not necessarily associated with a clotting disorder but with the capillary-permeability alterations that allows the red blood cells to escape27.

Hour by hour, systemic manifestations can appear. Neurological manifestations usually start to appear in the first 4–12 h, palpebral ptosis being the most frequent symptom28. Other symptoms can include ophthalmoplegia, diplopia, accommodation deficit, and dysarthria, paralysis of the sphincter oris, dysphagia and other general manifestations like lethargy, vertigo, dyspnoea and even paresthesia29,30. In France, a Guillain-Barré syndrome has been described after a vipera aspis bite, although without a full description of the pathogenetic mechanism (direct or indirect neurotoxicity of the venom)29. It is mentioned as a characteristic feature of viper envenomation with neurological manifestations, and usually starts with scarce local symptoms; this should serve as a warning of the possible appearance of neurological manifestations.

New grading of envenomation

The Audebert grading scale to classify the degree of envenomation from the European species is used as a therapeutic guideline31. But the appearance of neurological manifestations has forced a change in the grading of viper envenomations. Thus, regardless of the local reaction, which usually indicates the progression of the symptoms (pain and oedema), the appearance of neurological manifestations directly classifies the envenomation as grade II, with the corresponding consequences regarding treatment (table 3).

Obsolete therapeutic interventions

A consensus exists among professionals from different countries about those practices that should be avoided. Thus, the use of tourniquets, cauterizations, amputations of the injured body part,
incision and suction of the wound (with the mouth, extractors or syringes), the application of homemade remedies (plants, whiskey, gunpowder, dragonfly infusions or bugs mixed with turtle blood) are techniques that must be eradicated, not only because they are not indicated, but also because they are clearly contraindicated. It is surprising that on some health websites consulted to write this review, the use of some of these techniques is still recommended.

**First aid measures**

After a bite, it is essential to ask for help, particularly if signs of progressive, fast envenomation are observed (calling the emergency line 112 is recommended). The patient should be prevented from tiring themselves by walking since this could facilitate a quicker distribution of the venom through the organism. Avoid the consumption of any type of food or stimulating products (either by digestive or respiratory tract, much less intravenously). Any clothing that might apply pressure to the zone near the bite should be removed, as well as any personal jewellery (bracelets, watches, rings, piercings) that could produce a tourniquet effect, in case of oedema.

The objective of local treatment is only to clean and disinfect the injured area. Cleaning should be with soap and water. Any antiseptic that might unnecessarily colour the skin must be avoided. If available, a slightly constricted bandage can be applied following the classic guidelines, i.e., from distal to proximal. Elevation of the limb and application of indirect cold will help to diminish the oedema.

It is important to gather information about the place (province, nearby town or city, surroundings, altitude), the hour of the day, the general description of the snake (the characteristic aspects of the European vipers are a triangular head with multiple, small scales, vertical pupil, zigzag pattern on the back, thick, short body, well-marked short tail, and elusive attitude) to try to identify the species.

**Out-of-hospital treatment**

If first aid is performed in a health or emergency centre, the measures to put into practice will be those previously described. It is important to manage the progression of the envenomation stage, assess the evolution of local pain, oedemas and ecchymosis, as well as the appearance of signs and symptoms of systemic envenomation. In addition, treatment with analgesics and anxiolytics can be started, if necessary. Salicylates should be avoided. The anti-tetanus prophylaxis must be checked and transportation arranged to the nearest hospital or facility with antiphidiom serum.

The use of antibiotics or low-molecular-weight heparin is not recommended. The use of adrenaline, antihistamines and corticosteroids is recommended only in the case of an anaphylactic reaction, which is highly exceptional.

**In-hospital treatment**

Transfer to a hospital for medical assessment and treatment is mandatory in this type of emergency. An initially simple clinical condition could worsen significantly putting the patient at risk. Once in the hospital, the procedure will be to check vital signs, make a physical examination and to run some complementary tests: electrocardiogram, haemogram, haemostasis (platelets, prothrombin time, international normalised ratio [INR], fibrinogen, fibrinogen degradation products [FDP]), biochemical profile (liver and kidney functions) and urine analysis (haematuria and urine protein). The pharmacological treatment will depend on the degree of envenomation and its progression.

- **In grade 0 snakebites**, observation of the patient in the emergency department for a minimum of 6 h is necessary, since neurological manifestations can take several hours to appear. Clean the wound, apply indirect cryotherapy, raise the limb, administer anti-tetanus prophylaxis if applicable, and start antibiotic and analgesia administration if necessary. If there is no progression, admission is not necessary. Rest is recommended for some hours.

<table>
<thead>
<tr>
<th>Grade 0 (no envenomation)</th>
<th>Absence of local or systemic reaction. Only tooth marks and mild or scarce pain. Probable bite of an aglyphous or opisthoglypha snake, or a viper that has not inoculated venom (“dry” bite)</th>
</tr>
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<tbody>
<tr>
<td>Grade I (mild envenomation)</td>
<td>There are tooth marks from the bite, intense pain, moderate local oedema that can progress to blisters, but that do not go beyond the limb. There are no systemic symptoms.</td>
</tr>
<tr>
<td>Grade II (moderate envenomation)</td>
<td>In addition to the grade I injuries, there are oedema progression, ecchymosis, lymphangitis, adenopathys or systemic manifestations such as moderate arterial hypotension, nausea, vomiting, diarrhoea, abdominal pain, dizziness, general discomfort or asymptomatic haemato-haemostatic alterations (leukocytosis, thrombocytopaenia, hypofibrinogenaemia) Neurological symptoms: palpebral ptosis, accommodation deficit, ophthalmoplegia, diplopia, dysarthria, dysphagia, paralyses of the sphincter oris, lethargy, vertigo or paresthesia</td>
</tr>
<tr>
<td>[1.0] Grade III (severe envenomation)</td>
<td>In addition to the grade II lesions, greater regional oedema that can go beyond the injured limb, very intense pain and severe systemic manifestations (rhabdomyolysis, scattered intravascular coagulation, bleeding tendency, acute renal failure, respiratory failure, shock, haemolysis, fluid and electrolyte imbalance) Severe neurological symptoms</td>
</tr>
</tbody>
</table>
and the patient should return for medical assessment in case of any changes.

- **In grade 1 snakebites**, admission to hospital for 24 h to check the evolution of the envenomation (oedema, pain, haematological or neurological alterations). The examination should be repeated periodically. It is recommended that the initial location of oedema should be marked with a marker pen in order to follow its evolution. Clean the wound, immobilize and raise the limb, apply indirect cryotherapy; the patient should rest, preferably in bed; review the anti-tetanus prophylaxis, administer therapy with antibiotics and intravenous treatment for pain if necessary. Complete fasting and serum therapy as a maintenance therapy.

- **In grade II and III snakebites**, patient should be admitted to hospital. Serial blood tests should be performed. Continuous assessment of the local progression of envenomation and of the appearance of possible neurological or haematological complications. Administration of intravenous anti-antidote serum (dissolved in saline) is added to grade I measures. This serum should be administered early to pregnant women and if compartment syndrome develops; in children, the dose will be the same as in adults. Assess patient admission to intensive care unit (ICU) and consider surgical treatment of necrosis in the perilesional area or if compartment syndrome does not respond to the antitoxin serum.

One of the more controversial treatments is antibiotic therapy. It should not be forgotten that the mouth of the reptile hosts germs, among them *Salmonella*, *Clostridium*, *Escherichia coli* and *Klebsiella*, in addition to pentastomid parasites from the family *Porocephalidae*, like *Armillifer armillatus*, *A. moniliformis* and *A. grandidi*, arthropods that inhabit the mouth and respiratory tract of snakes and can pass to humans through the bite. The antibiotic treatment suggested, as first choice, is amoxicillin-clavulanate treatment, replaced by erythromycin or clindamycin in case of allergy.

ViperFab® serum (Laboratory Sanofi-Pasteur, Lyon, France) is used in hospitals in Spain. It was used for the first time at the beginning of 2000 but had already been used in neighbouring countries and its safety had been confirmed. This is a third generation antivenom, i.e., composed of horse antibodies against the venom of several snake species (*V. aspis*, *V. ammodytes* and *V. berus*), subsequently treated with pepsins to obtain the Fab(α) chain from the FC fragment of the antibodies. This last fragment is responsible for the anaphylactic (grade I) and immune-complex (grade III) Reactions. Hence, these complications are no longer expected to appear. For the same reason, it is no longer recommended to perform a hypersensitivity test prior to administering the antidote or corticosteroid treatment after the administration of the antidote to prevent the appearance of serum sickness. The antidote must be administered under strict medical supervision, intravenously in a limb other than that which has been bitten.

**Compartment syndrome after snake envenomation**

Although exceptional, it is possible to develop secondary compartment syndrome after the venom inoculation, with the progressive appearance of the clinical manifestations described as the 6 Ps: *paresthesias, pain, pressure, pallor, paralysis* and *pulslessness*. In these cases, as initial treatment, physical measures are suggested (raising the limb, indirect cryotherapy) and intravenous administration of the anti-antidote serum. Fasciitis is necessary if high intracompartamental pressure persists. Experiments in animals indicate that initial management with anti-antidote serum is the guideline to be followed but no prospective clinical studies have confirmed the effectiveness or value of an extra dose of antivenom for this syndrome.

If compartment syndrome is suspected, the following therapeutic scheme has been proposed. Measure intracompartamental pressure and verify whether or not it is high (>30 mmHg). Apply physical measures, such as raising the injured limb. Administer intravenous mannitol at a dose of 1–2 g/kg and one vial of intravenous anti-antidote serum. Hourly assessment of the evolution and, if these measures failed to normalise pressure within 4 h, urgent fasciotomy is recommended.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**References**


