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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[1].

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[2–7].

Epidemiology

The epidemiological work on snakebites by Swaroop and Grab[8] has served as a worldwide reference in epidemiology for decades. But the most up-to-date figures are those presented by Chippaux[9,10], 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[11].

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 Insititute Carlos III)[12,13] 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[14]. 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[15–17], including enzymes (serine protease, Zn^{2+}-metalloprotease, phospholipase A_2, 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

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Table 1
Species and subspecies of European snakes and geographic areas of distribution.

Subfamily *Viperinae* (genera: *Atheris, Bitis, Causus, Cerastes, Daboia, Echis, Eristicophis, Macrovipera, Montatheris, Montivipera, Proatheris, Pseudocerastes, Vipera*)		
European species	Described subspecies	Distribution
Vipera berus (Balkan viper)	*V.b.berus* *V.b.bosniensis* *V.b.sachalinensis*	All Eurasia, from France to the north of the Arctic Circle and to the Pacific Ocean. In all Europe, except the Iberian Peninsula and Ireland. Partially excluded from Italy and Greece
Macrovipera or *Daboia lebetina* (viper from the East)	*Ml lebetina* *Ml obtusa* *Ml turanica* *Ml cernovi* *Ml trasmediterranea*	North Africa, Middle East and Asia. In Europe, in Cyclades islands, Milos and Cyprus
Montivipera or *Daboia xanthina* (Turkish viper)		Eastern zone of Greece, the European part of Turkey and islands of the Aegean Sea
Vipera ammodytes (horned viper)	*Va ammodytes* *Va montandoni* *V.a.meridionalis* *V.a.gregorwallneri* *V.a. transcaucasia*	Eastern Europe, particularly in the Balkans, Italy, Romania and extended to the south to Greece and the Cyclades. Also in Armenia, Georgia, Turkey and Libya
Vipera ursinii (Ursini's viper or meadow viper)		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.
Vipera aspis (aspic viper)	*V.a.aspis* *V.a.zinnikeri* *V.a.francisciredi* *V.a.hugyi* *V.a.atra* *V.a.montecristi*	North East of the Iberian Peninsula, centre of Europe and the islands of Elbe, Sicily and Montecristo
Vípera latastei (snub-nosed viper)	*V.l.latastei* *V. l.gaditana*	The Iberian Peninsula, with the exception of the north
Vípera seoanei (viper of Seoane)	*V.s.seoanei* *V.s.cantabrica*	Green Spain and the northwest of the Iberian Peninsula

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 aspis, V.aspis zinnikeri)* and 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 A_2 (PLA_2)[18–24]. The different PLA_2 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 escape[27].

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 symptom[28]. 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 paresthesia[29,30]. In France, a Guillain-Barré syndrome has been described after a *vipera aspis* bite, although without a full description of the pathogenic mechanism (direct or indirect neurotoxicity of the venom)[28]. 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 guideline[31]. 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,