CASE REPORT

Further Clinical Evidence for the Existence of Neurotoxicity in a Population of the European Adder (*Vipera berus berus*) in Eastern Hungary: Second Authenticated Case

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We report a recent case of common adder (*Vipera berus*) envenoming causing paralytic signs and symptoms. A 12-year-old girl was bitten by the nominate subspecies of the common adder (*V. berus berus*) in eastern Hungary on May 2, 2012, 22 km away from where the first neurotoxic *V. berus berus* envenoming was reported in 2008. The patient developed unambiguous cranial nerve disturbances, manifested in bilateral impairment characterized by oculomotor paralysis with partial ptosis, gaze paresis, and diplopia. Drowsiness and photophobia were her additional symptoms; both occurred only during the first day of envenoming. Until now among viper envenomings in Europe, photophobia has only been documented by victims of *Vipera aspis*. Supportive and symptomatic treatments were administered during 3 days of hospitalization. Although case reports of *V. berus berus* envenomings are often published, clinical experience with neurotoxicity by this subspecies still remains rare. Population-based and geographic variation of venom composition in *V. berus berus* seems to include neurotoxic envenomings in certain populations. This second authenticated case provides new clinical evidence for the existence of a possible neurotoxic *V. berus berus* population in a restricted geographical area in eastern Hungary.

Key words: neurotoxicity, phospholipase A₂, photophobia, ptosis, regional venom variability

Introduction

Two subspecies of the common adder (*Vipera berus*) occur in Hungary: the nominate subspecies (*V. berus berus*) in the northeastern mountainous area and the eastern lowland corner of Hungary, and the Balkan subspecies, *V. berus bosniensis*, which reaches its northernmost distribution in the lowlands of southwestern Hungary.^{1–3}

The hill country populations of northeastern Hungary are isolated from the lowland adder populations of eastern Hungary. Based on their mitochondrial DNA, these 2 populations belong to 2 different evolutionary

clades.⁴ Although they differ slightly also in morphology^{3,5} and habitat preferences,^{5,6} they are both recognized as *V. berus berus*.^{1,3,5,6}

Variation in snake venom composition is notably influenced by adaptation to available prey species,^{7–10} and can lead to regionally distinct clinical patterns observed in envenomed patients.^{7,11–14} This venom composition diversity—also occurring within species—can lead to regionally distinct clinical patterns on envenomed patients.^{7,14} Intraspecific venom variations have been shown also in some European viperids, eg, in the long-nosed viper (*Vipera ammodytes*) in Croatia¹⁵ and the asp vipers (*Vipera aspis*) in France.¹⁶

The venom of the European viperids has an arsenal of a complex mixture of enzymes. Of the phospholipases A₂ (PLA₂), the post- and presynaptically acting neurotoxins

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(eg, different isoforms of ammodytoxin and vaspin) are the most significant, which can cause peripheral neurotoxic effects on humans.^{16,17} To date in Europe, neurotoxicity in viper envenomings have been described mainly in *V aspis zinnikeri* in northern Spain¹⁸ and southwestern France,¹⁶ in *V aspis aspis* in southeastern France,¹⁶ in *V aspis francisciredi* in Italy,^{19,20} and in *V ammodytes ammodytes* in Croatia.²¹ In 1982, Thouin et al²² mentioned a few negligible neurotoxic cases of *V ammodytes ammodytes* bites in the former Yugoslavia, but did not indicate the exact locality. The bites of certain *V. berus* populations may also cause peripheral neurotoxic effects in humans.²³ Since the 1930s, it has been known that the venom of *V. berus bosniensis* is capable of inducing neurological disturbances dominated by cranial nerve dysfunctions.²⁴ However, the first authenticated case reports and clinically oriented papers about neurotoxic *V. berus bosniensis* envenomings were published only in the last 2 years.^{25,26} Neurological deficits after envenoming by the nominate subspecies of *V. berus* are rarely reported. A few cases of neurotoxic envenoming by *V. berus berus* have been reported in Germany. In these cases, symptoms included ptosis and dysphagia.²⁷ Other, western Transylvanian neurotoxic envenomings were summarized by Malina et al in 2008.²⁸

Here, we present a case of envenoming by *V. berus berus*, in which some of the symptoms were unequivocally consistent with neurotoxicity. This incident occurred near (22 km) the location where the first eastern Hungarian neurotoxic envenoming by *V. berus berus* was documented.²⁹

Case Report

A healthy 12-year-old girl (body weight, 50 kg) was bitten by a snake during a school trip in Túrlevé (Szabolcs-Szatmár-Bereg County), eastern Hungary on May 2, 2012 at approximately 4:30 PM. The girl confidently grabbed the snake, as she believed it was only a harmless grass snake (*Natrix natrix*). The 50- to 60-cm long snake immediately bit her. The culprit specimen had been photographed with a mobile phone by one of her schoolmates (owing to its poor resolution, the photo is omitted, but is on file and available for inspection on request to the senior author). Later, the snake was identified as a melanistic *V. berus berus* specimen by a keeper from the Venomous Snake Department of the Budapest Zoo, and the identification was reconfirmed by a ranger of the Directorate of Hortobágy National Park (Hungary).

Throbbing pain and local swelling developed within minutes after the bite, suggesting that venom had been

injected. The girl received first aid (500 mg of Calcium-Sandoz [calcium] tablet and cold pack) from her teacher and was taken to the local general physician (GP) office. By then she was drowsy and nauseated, but fully conscious. She had no history of snakebite and declared no allergies. The GP requested the transport of the patient to the nearest hospital (Szatmár-Bereg Hospital, Fehérgyarmat). She was transported by ambulance, and admitted to the pediatric ward.

On admission (7:12 PM), the girl's whole left hand was edematous, tense, and painful on palpation. Mild hyperemic discoloration was observed on the dorsum of the hand. There were 2 fang marks approximately 5 to 8 mm apart on the extensor side of the left index finger, and another puncture mark was visible on the finger's radial aspect. The victim was pale, weak, and prostrated and was unable to stand. She repeatedly retched and, on a few occasions, regurgitated. On arrival her blood pressure, heart rate, and respiration rate were 109/70 mm Hg, 99 beats/min, and 13 breaths/min, respectively. She complained of intensive dizziness and was still drowsy but able to be aroused. The sensorium remained clear, and she was able to give adequate answers when questioned. According to the patient, double vision first developed about 20 to 30 minutes after the bite. During the neurological examination, her pupils were moderately dilated, and mild abnormality of pupillary accommodation was detected. Although she could partially open her eyes on request, palpebral ptosis was obvious. The patient described photosensitivity in the presence of ambient light and experienced eye movement difficulties. Medical examination confirmed a bilateral impairment characterized by oculomotor paralysis with partial bilateral ptosis and gaze paresis but no other cranial nerve or additional neurological deficits were observed. The patient preferred remaining in a lying position because it mitigated the intensity of dizziness occurring when sitting or standing.

Immediate routine laboratory tests did not show abnormalities in blood coagulation, assessed by prothrombin (73.3%; normal, 70–100%), international normalized ratio (INR, 1.17; normal, 1.00–1.20), activated prothrombin time (APTT, 23.7 seconds; normal, <42.0 seconds), and thrombin time (TT, 18.80 seconds; normal, <22.0 seconds). Only slight elevations in blood glucose (6.50 mmol/L; normal, 3.30–6.00 mmol/L) and plasma calcium (2.64 mmol/L; normal, 2.15–2.60 mmol/L) were observed. Within approximately 4 hours of postbite supportive therapy, 1 vial (5 mL) of Calcimusc injection (calcium, 100 mg/mL intramuscularly), isotonic saline (Ringer's lactate solution, 500 mL IV), tetanus prophylaxis, corticosteroid (120 mg of methylprednisolone, IV), and antibiotic therapy (850 mg of amoxicillin-clavulanic

acid IV every day) was administered. The latter was maintained longer than 48 hours. Antivenom was not administered because the treating physician considered it unnecessary.

Next morning (May 3, 2012) the retching and regurgitation ceased. Laboratory results showed slight deviations from normal: C-reactive protein, 7.2 mg/L (reference range, <5 mg/L); white blood cells, 17.96 10^3 /L (reference range, 4.5–13.0 10^3 /L); neutrophils, 87% (reference range, 40–74%); lymphocytes, 7% (reference range, 19–41%); and density of urine, 1015.000 (reference range, 1.005–1.020). Some blood coagulation parameters showed an increasing trend as compared with those on the admission day (ie, APTT, 25.7 seconds [normal, <42.0 seconds], TT, 20.90 seconds [normal, <22.0 seconds]), but remained within the normal range. The patient could open her eyes easier, but bilateral ptosis was still present, and the hand edema started to decrease.

On May 4, 2012, the patient showed no systemic symptoms, and the hand edema, as well as hyperemia, was significantly reduced. The cranial nerve palsies resolved, and there were no further peripheral neurotoxic signs and symptoms. She remained stable and was discharged the next day (May 5, 2012) after an uneventful recovery.

Discussion

The composition of snake venom is highly plastic and is influenced by several genetic and non-genetic factors.^{12,29} Knowledge about geographic venom variations is of key importance to clinical toxicologists when selecting the appropriate therapy.^{7,10,12} In Europe, bites of *V aspis* show fascinating variation in the clinical pictures of envenomed patients.^{16,18–20,30,31} Similar diversity of symptoms was reported in studies on the Russell's viper (*Daboia russelii*) envenomings in Asia.^{13,14,32} These clinical reports demonstrate the great medical relevance of the regional venom variability of a given snake species.⁷

A large number of reports have been issued about the clinical aspects of *V. berus* envenoming since Reid's pioneering work.³³ Neurotoxic envenomings from northwestern, northern, and central Europe were seldom recorded.^{27,28,34,35} Individual case reports on neurotoxic signs and symptoms indicate that isolated neurotoxic *V. berus berus* populations might exist in Europe, mostly within the Carpathian basin^{28,36} and in certain parts of Germany.^{27,34,35}

Our case presents further unequivocal evidence for the existence of a neurotoxic population of *V. berus berus* in eastern Hungary. In our patient, oculomotor palsy

manifested as partial bilateral ptosis, gaze palsies, and consequent diplopia. The patient tried to compensate her gaze palsy by turning her head instead of moving her eyes. These neurological signs and symptoms suggest that cranial nerves III, IV, and VI were affected by the paresis. Her ptosis persisted through the second day. Ptosis is one of the early signs of neuromuscular paralysis in snakebites, although it is easily missed in neurotoxic *Vipera* spp envenomings. Patients often develop ptosis lasting less than a day as was reported in *V. berus bosniensis*^{25,26} or *V aspis francisciredi* bites.¹⁹ Gaze paresis, dysphagia, and dysarthria are the most documented and frequent neurological signs of neurotoxic viper envenomings in Europe.^{16,18–21,25,26,28,30,31,36} Photophobia was documented only in *V aspis* bites from a limited area in southeastern France, where neurotoxic envenomings are frequent.³⁰ In our case, this particular clinical feature was assessed subjectively while relying on the description of the patient. According to her, she experienced it only on the first day after the incident. We deem it was related to neurotoxicity. The origin of drowsiness in the envenomings by European viperids is debated. It is considered to be either caused by venom-induced endorphin release,³⁷ vasovagal responses, and central nervous system depression³⁸ or regarded as a neurotoxic symptom, occasionally reported in *V aspis aspis*, *V aspis zinnikeri*,^{30,31} and *V aspis francisciredi* envenomings.¹⁹ Drowsiness also developed in a neurotoxic envenoming by *V. berus* in southeastern Romania in 2012.³⁶ In this case the taxon was erroneously recorded as *V. berus bosniensis* by the authors because only *V. berus berus* occurs in Romania.^{39,40} The weakness and prostration of the girl was most noticeable during the first day of hospitalization. Likely it was a consequence of dehydration owing to repetitive vomiting. Her inability to stand was most probably caused by her weakness, intensive dizziness, and the slight disturbances of fluid retention.

Variation in snake venom composition and its pharmacology have been studied in several species. A number of observations reveal that the effects of the bites inflicted by snakes of the same population can vary.^{14,16,41,42} Intrapopulation venom variability may derive from several different causes: prey specificity, ontogenetic variation, and other ecological pressures.^{43–45} In southeastern France, some specimens of *V aspis* may produce more varied clinical manifestations—mainly in neurological disturbances—on envenomed humans than others as a result of their more complex venom composition, especially because of their higher PLA₂ arsenal variability.¹⁶ Intrapopulation venom variability has already been known in the eastern Hungarian adders.

This is caused by a geographical variation in the biochemical composition (eg, qualitative and quantitative variability of PLA₂ content [Malina and Vasas, unpublished data]) and the neuromuscular activity of the venom (Malina et al, unpublished data). However, neurotoxic manifestations in envenomings occur only occasionally within this region.⁴⁶

Currently there is no officially recommended or widely accepted protocol for snakebite treatment in Hungary. Most Hungarian physicians have limited experience with snakebite therapy owing to the rarity of envenomings by the native species in comparison to other European countries.^{47,48} Consequently, glucocorticoid, antibiotic, and antitetanus therapies are still applied as supportive treatment in cases of snakebite. Although in Hungary glucocorticoids and calcium are administered in most cases of adder bites^{49,50} and bee and wasp stings, these are generally contraindicated practices. Also, the provision of oral calcium is not evidence-based, but Hungarian victims of *V. berus* sometimes apply it as a first aid.^{28,49} Similarly, although cryotherapy is widely contraindicated in snakebites⁵¹ and routine antibiotic prophylaxis has no general supporting evidence,⁵² in Hungary both were,⁴⁹ and still are, administered⁵⁰ in case of adder bites. Other contraindicated first aid methods such as washing of the bite site with potassium permanganate (1%) or hydrogen peroxide (3%) solution is still recommended for *V. berus* envenomings, as the Hungarian medical literature of the last decades shows.^{50,53}

Unfortunately, a false, underestimating conception on the possible consequences of *V. berus* envenoming persists in Hungary. It is often believed that the venom of this taxon is weak and poses little risk for human health.⁴⁸ Hungarian physicians often opt for antivenom therapy inconsistently without well-founded evidence supporting their decision.⁴⁷ Virágh and Tass⁵³ have also highlighted that antivenom is often administered unnecessarily in viper bites, when it is not indicated (eg, dry bites or when only mild local symptoms develop), while it is often not administered in clinically indicated cases. Two antivenoms are available against the venom of *V. berus* in Hungary: the Ipser Europe and the European Viper Venom Antiserum.⁴⁸ The latter was on storage in the hospital where our patient was treated. The treating physician hesitated to administer the antivenom; finally the patient's symptoms ameliorated and did not necessitate the use of it. In our opinion, the early antivenom administration could have lessened the degree of neurotoxic manifestations.

The culprit adder of this incident belongs to an eastern Hungarian *V. berus berus* population different from the one in which the first neurotoxic envenoming was reported in 2008.²⁸ This recent envenoming occurred a

mere 22 km from the previous location. The 2 adder populations are isolated from each other by the River Tisza. Such geographical isolation may lead to venom variability^{7,11,14,32,41}; therefore, physicians need to pay more attention to uncommon features of envenoming that may be attributed to geographic variability.

Although several reviews and case reports on *V. berus* bites are published, clinical experience with neurotoxic envenomings by the nominate subspecies (*V. berus berus*) remains limited. This recent case supports our contention that envenomings by certain populations of this taxon may cause paralytic features. The patient described here presented with moderate local symptoms followed by neurological disturbances primarily manifested as dysfunction of certain cranial nerves. This second authenticated case provides further clinical evidence for the existence of a neurotoxic *V. berus berus* populations in a restricted geographical area in eastern Hungary.

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