



Clinical report

Infant death after nose-horned viper (*Vipera ammodytes ammodytes*) bite in Croatia: A case report

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ABSTRACT

A case of a 45-day-old male infant, bitten on the neck by nose-horned viper (*Vipera ammodytes ammodytes*), is reported. This episode occurred while the baby was on a picnic with his parents in a hill near a town in southern Croatia. In spite of immediate arrival at hospital, where antivenom was administered and all the necessary treatment measures were carried out, the infant died 6 h following the bite. The cause of death was severe and progressive hyperkalaemia, massive intravascular haemolysis, severe coagulopathy and myocardial dysfunction.

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1. Introduction

Venomous snakebites, most common in Asia and Africa, are fortunately less frequent in Europe, where approximately 50 people die annually (World Health Organization, 2001; Menez, 2003). The mean annual snakebite incidence in southern Croatia over the last 21 years was 5.2 per 100,000 inhabitants, and the mortality rate was 0.4% (Lukšić et al., 2006). Nose-horned viper (*Vipera ammodytes* (*V. a.*) *ammodytes*), belonging to the family *Viperidae* and sub-family *Viperinae*, is responsible for the majority of these cases (Lukšić et al., 2006). On rare occasions, *Viperinae* envenoming can

be life threatening, especially in children (Persson, 1995; Warrell, 2005). Tragic death of a 45-day-old male infant, bitten by *V. a. ammodytes*, is reported here.

2. Case report

The 45-day-old male infant without any significant past medical history was bitten by a nose-horned viper (*V. a. ammodytes*) on the neck in the vicinity of the town of Split in southern Croatia. The infant was with his parents and some family friends on a picnic near the town, where they spotted a snake on the ground. Fearing that the snake would crawl closer to children, one of the adults kicked it. Unfortunately, the snake fell directly into the pram with the infant, and bit the baby on the neck. The infant's father applied suction at the bite site and the infant was transported to the Pediatric Intensive Care Unit arriving within 1 h of the bite. On the way to the hospital

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the infant showed signs of profuse sweating and neck swelling. The snake was killed and identified as nose-horned viper (*V. a. ammodytes*).

On arrival at the Intensive Care Unit of the hospital, the infant was in shock, somnolent, Glasgow coma score (GCS) 13, with low body temperature (33.5 °C), low blood pressure (40/26 mmHg), tachycardia (heart rate of 195 beats per minute), and tachypnea (respiratory rate of 35 breaths per minute). A 5-cm diameter area of local oedema with skin discoloration and ecchymosis was present on the neck around the bite. Fang marks were localised submentally and there was no indications that the venom was injected intravenously. Due to the threatening respiratory tract obstruction caused by local oedema, an endotracheal intubation was instantly performed, and a central vein catheter was introduced.

Two doses (20 ml) of Zagreb antivenom were administered immediately upon arrival at the hospital by slow intravenous infusion. At the same time, simultaneously the parenteral infusion of dopamine (11 µg/kg/min) was given, which raised blood pressure to 77/42 mmHg after 5 min, and it was maintained by inotropic support (dopamine (11–22 µg/kg/min) and norepinephrine (0.57–1.71 µg/kg/min) in continuous infusion) under central venous pressure monitoring. There was no adverse reaction to the antivenom applied.

The initial laboratory tests 2 h after the bite showed profound metabolic acidosis (pH 7.09, bicarbonate 7.0 mmol/L, and base excess –21.1 mmol/L), and low oxygen saturation 78.2%. Laboratory parameters consistent with a disseminated intravascular coagulation (DIC) were noted: thrombocytopenia, lowered plasma fibrinogen, prolongation of both prothrombin time (PT) and activated partial thromboplastin time (APTT), and increased D-dimers (Table 1). Coomb's test was negative. Other laboratory findings, including hyperkalaemia and hyperglycemia, are shown in Table 1. The initial electrocardiogram (ECG), approximately one and a half hours after the bite, showed sinus tachycardia of 180/min with normal electrical axis and normal PR, QRS and QT intervals.

Within the third hour after bite the bicarbonate (15 ml), frozen plasma (90 ml) and platelet concentrate (20 ml) were given intravenously. Other treatment measures included ceftriaxone (400 mg), dexamethasone (4 mg), tetanus prophylaxis and intravenous fluids.

Three hours after the bite the infant developed generalised swelling and bruising, lapsed into a coma, GCS was 5, his haemodynamic status worsened gradually, with oliguria, and respiratory failure was noted, requiring a mechanical ventilation support. At that time ECG showed sinus tachycardia at 120/min, lower voltage in standard leads, PR prolongation to 0.14 s and peaked T-waves in the precordial leads.

Further laboratory tests four and a half hours after the bite showed a severe anemia, with drastic progression of DIC, hyperkalaemia, hypernatremia, hyperphosphatemia, hyperglycemia (Table 1) and profound metabolic acidosis (pH 6.80, bicarbonate 4.5 mmol/L, and base excess –26.7 mmol/L). Results of other laboratory investigations are shown in Table 1. Urine was red coloured and urine test strip was positive for haemoglobin/erythrocytes. Fragmented red blood cells on the blood film was not performed, therefore we

Table 1

Results of laboratory investigations in a 45-day-old infant with *V. a. ammodytes* envenoming.

Laboratory investigations	2 h after bite	4.5 h after bite
White cell count ($\times 10^9/L$)	9.8	13.6
Neutrophils (%)	80	81
Erythrocytes ($\times 10^{12}/L$)	3.4	0.7
Hemoglobin (g/L)	107	23
Hematocrit (L/L)	0.31	0.07
Platelets ($\times 10^9/L$)	9	17
Glucose (mmol/L)	27.0	12.4
Blood urea nitrogen (mmol/L)	4.3	4.1
Serum creatinine (µmol/L)	60	70
Sodium (mmol/L)	139	151
Potassium (mmol/L)	5.3	9.0
Chloride (mmol/L)	106	105
Calcium (mmol/L)	1.96	2.35
Phosphate (mmol/L)	3.23	4.9
Magnesium (mmol/L)	1.11	1.32
Bilirubin (µmol/L)	3.6	4.4
Aspartate aminotransferase (U/L)	103	739
Alanine aminotransferase (U/L)	92	416
γ-glutamyl transferase (U/L)	70	44.5
Lactate dehydrogenase (U/L)	619	1983
Creatine kinase (U/L)	491	770
Creatine kinase MB fraction (U/L)	382.2	150.3
Troponin (ng/ml)	0.151	0.241
Plasma fibrinogen (g/L)	1.4	0.6
Prothrombin time (%)	0.10	0.23
Activated partial thromboplastin time (s)	>120	>120
D-dimers (µg/L)	98	2244

cannot differentiate a microangiopathic haemolysis, but instant occurrence and degree of haemolysis was to rapid and severe to be microangiopathic haemolysis alone.

Further treatment involved one dose (10 ml) of Zagreb antivenom infused intravenously (third dose in total, started within the fourth hour after the bite), compatible blood group packed red cells transfusion (100 ml), fresh-frozen plasma (60 ml), bicarbonate (6 ml) and intravenous fluids. The administration of all these drugs did not result in any clinical improvement.

Finally, five and a half hours after the bite, the heart rate continued to slow down to the sinus rhythm of 70/min, lower voltage spread to all standard leads with flattening of the P-waves, prolongation of the PR interval to 0.22 (a first degree atrioventricular block) and widening of the QRS complex to 0.14 s showing a pattern consistent with both right and left branch bundle block, flattened and biphasic T-waves, and depression of the ST-segment of up to 2 mm were at that point seen in both inferior and all precordial leads. At that time in spite of dopamine and noradrenalin infusion, blood pressure decreased to 46/29 mmHg, which continued to fall. Half an hour later asystole occurred, and a cardiopulmonary resuscitation was not successful.

3. Discussion

In this infant, the fatal outcome resulted from a joined effect of severe and progressive hyperkalaemia, massive intravascular haemolysis, severe coagulopathy and myocardial dysfunction. Anaemia, which often follows a viper bite, results from the erythrocyte extravasation and intravascular

haemolysis. In addition to an acute severe haemolysis, we observed a neutrophil leucocytosis and a significant thrombocytopenia, which are also common findings with envenoming (Warrell, 2005; Karlson-Stiber et al., 1997). Most of the snake venoms have both anticoagulant and procoagulant properties (Murthy et al., 1997). The latter may be associated with the facilitation of fibrinogen clotting and platelet aggregation, caused by arginine esterase hydrolase, an enzyme functionally similar to the thrombin. In addition to thrombocytopenia, prolonged PT and APTT, lowered plasma fibrinogen, and raised D-dimers suggested activated intravascular coagulation with consequent fibrinolysis in the present case. The applied treatments were ineffective, and severe coagulopathy consistent with DIC coupled with dramatic haemolysis and anaemia were important factors of the lethal outcome. Pathophysiologically, in contrast to anticoagulation type of coagulopathy with normal fibrinogen level, which may also be caused by a snakebite, in the present case occurred the defibrination type of coagulopathy characterized by prolonged PT coupled with lowering level of fibrinogen (White, 2005).

The *V.a. ammodytes* venom contains cardiovascular toxins that have direct myocytotoxic, adverse electrophysiological, prothrombotic and coronary vasoconstrictive effects (Frangides et al., 2006; Saadeh, 2001). Pathophysiological mechanisms leading to hypotension, and later development of shock, probably have their origin in direct actions of the venom on the vessels' wall. They include hypovolemia due to plasma and erythrocyte leakage through the damaged capillary endothelium, vasodilatation due to bradykinin and other vasoactive factors, and lowering peripheral vascular resistance (Boviatsis et al., 2003; Nayak et al., 1990; Persson, 1995).

Among 11 fractions of the *V. a. ammodytes* venom, two fractions seem to be mediators of a short and slight increase, followed by a decrease in the heart contractility, which may end in an irreversible contracture and systolic arrest (Petković et al., 1983). A similar pattern has been observed for other snake venoms (Cevese et al., 1984; Alloatti et al., 1986, 1991a,b). We have shown that standardized *V. a. ammodytes* venom is capable of inducing a deterioration of cardiac function, decrease in coronary blood flow, and several conduction and electrophysiological disturbances including occurrence of malignant ventricular arrhythmias (Lukšić et al., 2008). In the presence of normal coronary arteries, their thrombotic occlusions (Gaballa et al., 2005; Copley et al., 1973; Kornalik, 1985; Blondheim et al., 1996), or direct myocytotoxic effects (Gaballa et al., 2005; Blondheim et al., 1996) have been reported.

ECG changes observed in the present case, including rhythm disturbances and alterations of normal ECG appearance, are compatible with those usually seen in association with envenomation. These changes are probably consequences of both direct venom cardiotoxicity and hyperkalaemia from the damaged muscles, erythrocytes and other tissues.

Although the increase in troponin levels suggests the presence of a myocardial damage, it may be assumed that hyperkalaemia was more important for the terminal electrophysiological disturbances. Hyperkalaemia is a well recognized life-threatening condition, and its manifestations in

ECG include peaked T-waves, widening of the QRS complex, prolongation of the PR interval, flattening of the P-wave, the ECG changes that were seen in the present case (Parham et al., 2006).

4. Conclusion

The present case report describes a lethal outcome in a 45-day-old infant caused by *V. a. ammodytes* bite as a result of combined effects of mounting hyperkalaemia, massive intravascular haemolysis, severe coagulopathy and myocardial dysfunction.

Nature lovers (mountain hikers, hunters, soldiers, scouts, people who go on picnic and others) should pay close attention to the fact that they can find themselves encountering snakes in certain environments. In case of a snakebite poisoning appropriate first aid should be provided and the victim transported to the nearest medical facility, where the victim can be managed and closely monitored for the development of complications. Hopefully, this will reduce morbidity and mortality, particularly in pediatric patients.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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