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Neurologic and hematologic sequalae following a timber rattlesnake *(Crotalus horridus)* envenomation in a dachshund

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ABSTRACT

A 2-year-old female Dachshund had a witnessed timber rattlesnake envenomation. Although rattlesnake envenomations are a common, potentially life-threatening event in companion animals, timber rattlesnake envenomations in the dog are rarely reported. This dog described in this case report had significant hematologic and neurologic clinical derangements consistent with Types A and B rattlesnake venom and a suspected hypersensitivity reaction to the venom. This patient was treated aggressively with antivenom and fully recovered without any persistent neurologic signs at follow-up.

1. Introduction

Most of the veterinary literature describing pit viper envenomation in the dog in the southeastern United States includes incidences involving the copperhead (*Agkistrodon contortrix*), eastern diamondback rattlesnake (*Crotalus adamanteus)* and the water moccasin (*Agkistrodon piscivoris* and *Agkistrodon conanti)* (Pritchard et al., 2014; Schaer, 1984, 2019a). Very little literature describes the consequences of timber rattlesnake envenomation in the dog. This case report describes a severe envenomation by a timber rattlesnake (*Crotalus horridus*) in a 2-year-old female Dachshund dog. Snake identification was made by one of the authors (CW) from a picture taken at the scene of the bite by the owner. The geographic location where this bite occurred is the southernmost range of *C. horridus*. This species is one of the most widespread venomous snakes in North America (Margres et al., 2021). Certain specific populations of the species in southern Georgia and northern Florida are known to have a potent neurotoxin, similar to crotoxin of the South American rattlesnake *(C.durissus)* and the Mojave rattlesnake *(C. scutulatus)* (Margres et al., 2021). Although it is a large snake with a large lethal venom dose, it is usually docile and will avoid human and animal contact unless it feels threatened.

The timber rattlesnake is unique in the variation of its venom components which are restricted to specific geographic locations. These variations are described as Types A, B, A plus B, and C (Rokyta et al., 2013). Type A is primarily a neurotoxin with presynaptic activity at the myoneural junction. This type is geographically localized to the Georgia-north Florida border (Rokyta et al., 2013). Type B has mainly hemotoxic and coagulopathic activity and is distributed amongst the snakes to the north and midwestern parts of the United States and north Florida (Rokyta et al., 2013). Type A plus B venom has a combined action of its components and is present in those snakes along Florida's northern border, and as far south as southern Alachua County (Rokyta et al., 2013). Type C venom is weaker than type A and B venoms based on LD50 in mice. It does not contain hemorrhagic effects or canebrake toxin and decreases in toxicity from A > A + B > B > C (Rokyta et al., 2013).

2. Case

A two-year-old female spayed Dachshund weighing 5.6 kg was examined at a veterinary teaching hospital emergency room (ER) for snake envenomation. The dog was normal and was not receiving any medications prior to the incident, nor had it ever received the rattlesnake vaccine. The rattlesnake was witnessed biting the patient by the

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owner approximately one hour before presentation. The snake was identified as a timber rattlesnake *(Crotalus horridus,* also known as a canebrake rattlesnake) and verified with the 'owner's cell phone photograph (Fig. 1). The bite occurred in Alachua County, Florida.

On presentation, the dog had tachycardia [heart rate (HR)160 bpm] with weak palpable femoral pulses. The mentation was dull, and there was an inability to posture and ambulate. There were two pin-point puncture wounds approximately 3 cm apart over the left eye (OS) with mild swelling (Fig. 2). A fluorescein stain showed no corneal lesions. The menace response and palpebral reflex were persistently absent OS (while normal in the right eye), and the dorsal periorbital region was sensitive and mildly painful. Repeated efforts were made to obtain a blood pressure reading with a doppler and sphygmomanometer, but it was too low to record. The dog had urticaria over her dorsal thoracolumbar skin reflecting possible venom hypersensitivity. Mentation became more dull while an IV catheter was inserted. The dog also developed obvious fasciculations (myokymia) in the vastus lateralis muscles of the hind limbs.

An IV catheter was placed upon arrival and blood samples were drawn. Immediate treatment consisted of an IV bolus (20 ml/kg) of lactated Ringer's solution (LRS) that was repeated once while the antivenom was being prepared for IV administration. Diphenhydramine 2.0 mg/kg was given subcutaneously (SC) for the urticaria. By the time the antivenom was ready for administration, the dog's recorded HR on the ECG showed sinus tachycardia at 220-240bpm despite adequate intravascular volume resuscitation. Point of care ultrasound evaluations showed no free fluid in either body cavity and the gallbladder appeared normal, with no evidence of wall edema, which is typically depicted as a hypoechoic rim around the gallbladder. The dog's condition rapidly deteriorated as the patient became laterally recumbent, developed an obtunded to stuporous mentation, and the onset of yellow/brown-colored diarrhea. The activated clotting time (ACT) was elevated beyond the maximum limits of the machine at 999 s (RI 80–120s). Despite the ACT being prolonged, the patient never developed evidence of hemorrhage. A venous blood gas determination was done, and the results were normal except for lactate of 2.6 mmol/L and a pH of 7.318 (Table 1). Additional point-of-care laboratory results showed a PCV/TS of 70%/8.0 (RI 40–56%/5.9–7.6 g/dL) with hemolysis noted in the supernatant. A hemogram collected after IV fluid resuscitation showed a

Fig. 1. A photograph showing the snake that bit this dog. The inverted "W" or chevron shape and the coloration are typical of a north Florida timber rattlesnake.

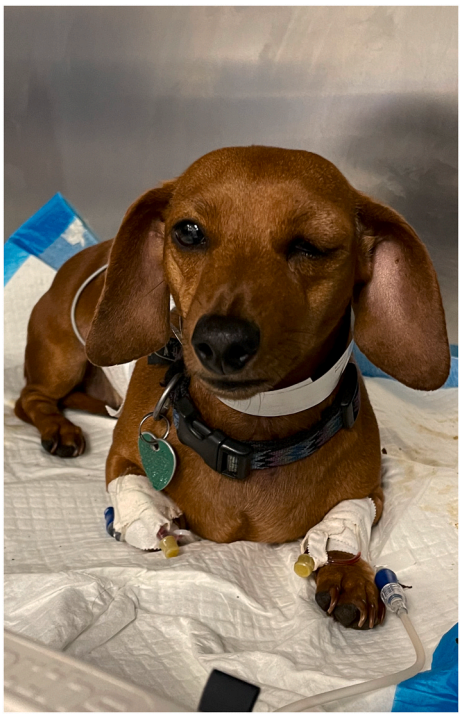

Fig. 2. This image shows the dog during the early stabilization phase on Day 1. The left-sided ocular swelling was devoid of periocular muscle movement which persisted throughout hospitalization.

Table 1
Venous blood gas results.

Test	Result.	Reference Range
pH	7.318	7.33–7.44
PCO_2	37.8	35–45 mmHg
PO_2	49.5	32–62 mmHg
SO_2	81.3	68–92%
Hematocrit	62.3	40–52%
Hemoglobin	20.3	14.1–19 g/dL
Na^+	146	146-151mEq/L
K^+	3.5	3.98–4.41 mEq/L
Cl^-	115	108-116 mEq/L
Ca^{++}	1.25	1.18–1.35 mmol/L
Glucose	129	78–124 mg/dL
Lactate	2.6	0–2 mmol/L
HCO_3^-	19.2	16-24 mEq/L

PCV 59% (RI 40–56%), WBC 13.45 × 10^3 (RI 4.6–11.4) neutrophils 8.37 × 10^3 (RI 2.6–8.0), platelet count 514 × 10^3 (RI 130–328) with clumping noted, and reticulocyte count 101.6 × 10^3 (RI 12.92–86.77). The red blood cell morphology showed echinocytosis and gross hemolysis (Table 2). A serum chemistry panel showed evidence of mild hypokalemia and mild hyperglycemia (Table 3).

Two vials of $F(ab')_2$ antivenom (VenomVet) were given by intravenous bolus over approximately 3 min because of the dog's rapid neurological deterioration and hypotension. Two additional vials were immediately administered over 30 min. Intravenous crystalloid (LRS) was administered at 100 ml/h over 120 min. The HR decreased (150–180 bpm) and the blood pressure normalized at 150 mmHg approximately 30 min after treatment. The ACT remained elevated at 999s. Once stabilized, the dog's mentation improved, and she could sit, stand, and tail wag. A fifth vial of antivenom was administered as a constant rate infusion (CRI) over an additional two hours. After the antivenom CRI, the ACT returned to 72s with a weak clot, and the HR was 100 bpm. The myokymia resolved, and the left periocular swelling lessened. Additional treatments included LRS with 0.1 mEq/kg/hr KCl

Table 2
Complete blood count.

Test	Result	Reference Range
Red Blood Cells (RBC)	7.63 M/uL	5.4–8.1
Hemoglobin	19.7 g/dL	14.1–19.7
Hematocrit (CALC)	54.3%	40.0–56.0
Packed Cell Volume (SPUN)	59% (H)	40.0–56.0
Mean Cell Volume	71.2 fL	64.0–74.0
Mean Corpuscular Hemoglobin Concentration	36.2 g/dL (H)	34.0–36.0
Cellular Hemoglobin Concentration Mean	31.9 g/dL (L)	34.0–37.0
Cell Hemoglobin	22.6	
Mean Corpuscular Hemoglobin	25.8 pg	22.0–26.0
Hemoglobin Distribution Width	1.87	
Red Cell Distribution Width	12.6%	11.7–14.1
Nucleated Red Cells/100	1	
#Reticulocytes	101.6 K/µL (H)	12.92–86.77
Content of Reticulocyte Hemoglobin	26.1 pg	22.8–27.5
White Blood Cells	13.45 K/µL (H)	4.6-11.6
#Band Neutrophils	0 K/ul	
#Neutrophils	8.37 K/µL (H)	2.6-8.0
Toxicity	none seen	
#Lymphocytes	3.56 K/uL	1.0-4.0
#Monocytes	0.67 K/uL	0.1-0.9
#Eosinophils	0.75 K/uL	0.1-1.7
#Basophils	0.07 K/uL	0-0.1
		0–0.1
Platelets	514 K/µL (H)	130-328
Mean Platelet Volume	45.4 fL (H)	7.5-13.3
Plasma Protein	n/a* g/dL	5.8-8.8
Fibrinogen	n/a* g/dL	0.1-0.6
Icterus Index	Hemolyzed	
%Neutrophils	62.2	
%Lymphocytes	26.4%	10-41
%Monocytes	5.0%	1.0-10
%Eosinophils	5.6%	2.0-21
%Basophils	0.5%	0-1.0
Platelets appear	clumped*	

RBC Morphology: 1+ Polychromia, 4+ echinocytes; *n/a reading impaired by hemolysis.

Table 3
Chemistry panel.

Test	Result	Reference Range
Creatine Kinase	137 U/L	49–244
AST	38 U/L	16–53
ALT	50 U/L	23–93
GGT	4 U/L (L)	6–10
ALP	19 U/L	7–116
Total Bilirubin	0.4 mg/dL	0.1–0.4
Glucose	147 mg/dL (H)	78–124
Cholesterol	188 mg/dL	102–340
Triglycerides	103 mg/dL	37–235
Albumin	2.59 g/dL (L)	2.62–3.91
Globulin	2.4 g/dL	1.8–4.0
A/G ratio	1.1	0.7–1.6
Total Protein	5.0 g/dL	5.0–7.4
Blood Urea Nitrogen	15 mg/dL	7–27
Creatinine	0.56 mg/dL (L)	0.6–1.5
Sodium	142.3 mEq/L	141.9–150.6
Potassium	3.4 mEq/L (L)	3.8–5.0
Chloride	109.7 mEq/L	107.8–117.1
Bicarb	21 mEq/L	16–24
Calcium	9.9 mg/dL	8.7–10.4
Phosphorus	3.0 mg/dL	2.2–4.8
Magnesium	1.7 mg/dL	1.7–2.4
Anion Gap	15.0 mEq/L	12.8–22.8
Calculated Osmolality	298.1	

(H) high, (L) low, Aspartate aminotransferase (AST), Alanine transaminase (ALT), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP).

to maintain hydration and to reverse the hypokalemia. Due to left periocular facial nerve paralysis, the dog received frequent Optixcare® eye lubricant every 4 h. The dog also received ampicillin-sulbactam (Unasyn®30 mg/kg IV every 8 h) and pantoprazole 1 mg/kg IV every 12 h for diarrhea assumed to be consequent to the initial poor gastrointestinal perfusion and to prevent bacterial translocation, which resolved after 24–36 h during hospitalization. The dog rapidly improved and remained stable after the first 5 hours of treatment. A repeat ACT and PCV/TS were done on Day 2 and the result was normal [97s (RI 80–120s)] with a strong clot. PCV/TS: 31%/6.1 g/dL with clear serum, indicating hemolysis had resolved. A manual platelet count was estimated at 394,000 platelets, cell morphology was not noted.

An ophthalmology evaluation found no abnormalities with the ocular globe and tear production. By Day 3, continued improvement was accompanied by minimal to no periocular swelling, resolved coagulopathy, and normal ambulation. However, a persistent left-sided periocular branch facial nerve paralysis was attributed to the neurotoxin. At a two-week follow up appointment, there was complete resolution of clinical signs. Facial nerve function appeared fully intact with normal menace response and palpebral reflex upon examination (Fig. 4).

3. Discussion

Envenomation by *Crotalus horridus* can be a life-threatening emergency in both humans and animals (Lavonas et al., 2011) depending on the geographic location of the incident, a combination of hemotoxic and neurotoxic venom can cause rapid clinical deterioration. The venom of *C. horridus* commonly contains snakevenom serine proteinases (SVSPs), phospholipase A (PLA2s), and bradykinin-potentiating and C-type natriuretic peptides (BPP) (Rokyta et al., 2013). Canebrake toxin, which has been isolated from the venom of certain populations of timber rattlesnakes in northern Florida, is a beta neurotoxin that acts presynaptically (Straight and Glenn, 1989). It is primarily a phospholipase A_2 (PLA2) neurotoxin, homologous to Mojave Type A toxin from *Crotalus scutulatus* (Wooldridge et al., 2001) and crotoxin from the South American rattlesnake (*C. durissus terrificus)* (Hendon and Fraenkel-Conrat, 1971). The myokymia may have been due to the action of a crotamine-like component (a beta defensin), or one of the PLA2 presynaptic neurotoxins that can cause muscle spasms (Levine et al., 2023; Brazil et al., 1979).

Rattlesnake venom, in general, is more broadly described as type I or type II, which is based on snake venom metalloprotease (SVMP) content (Mackessy, 2008). Type I venom features higher levels of SVMP activity and has lower toxicity, whereas type II venom has lower SVMP activity

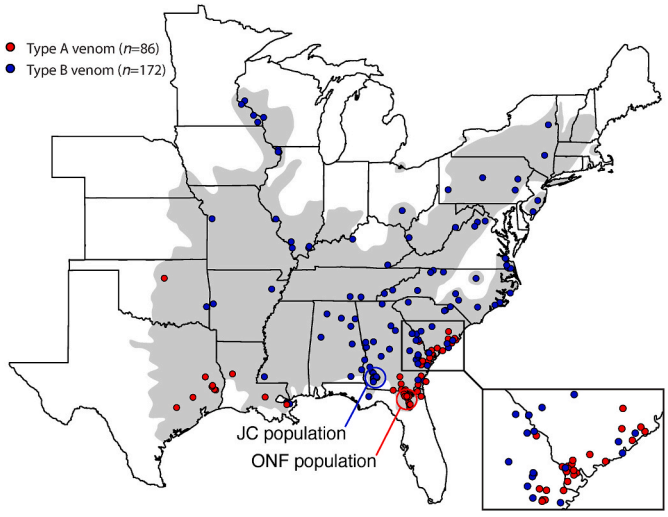

Fig. 3. Historical range (gray) of timber rattlesnake with locations of snakes expressing types A and B venom. Margres, M.J.; Wray, K.P et al. Varying Intensities of Introgression Obscure Incipient Venom-Associated Speciation in the Timber Rattlesnake (*Crotalus horridus*). Toxins **2021**, 13, 782. https://doi.org/10.3390/toxins13110782. Permssion granted through CC BY 4.0 license.

Fig. 4. The patient at the two-week evaluation showing a normal palpebral reflex, which was not present at the time of admission and during hospitalization.

but has higher toxicity. Throughout its range, C. *horridus* is noted to have mostly type I venom; however, southern populations appear to express type II. Type A *C. horridus* venom is considered a type II rattlesnake venom (neurotoxic), whereas Type B is type I (hemotoxic) (Mackessy, 2008). In this particular dog, it is likely the snake's venom contained both A and B timber rattlesnake toxins, as the dog was both neurologically and hematologically affected.

Timber rattlesnakes can have Type A, B, A + B, or C venoms (Rokyta et al., 2013). Type A is neurotoxic (canebrake toxin). It inhibits release of acetylcholine due to cell membrane breakdown of the presynaptic neuron by PLA2, which decreases the ability of neurons to release neurotransmitters (Rokyta et al., 2013; Straight and Glenn, 1989; Chang and Su, 1981). The hemotoxin responsible for clinical hemorrhage in timber rattlesnake envenomations is SVSP, a type B venom. It targets various pathways of the coagulation cascade, including procoagulant effects or consumption of clotting factors such as fibrin formation, factor V activation, kininogenolysis, and platelet aggregation. The SVSP also has anticoagulant activity through fibrinolysis, protein C and plasminogen activation. (Markland, 1998). Type C venom contains neither hemorrhagic nor neurotoxic components and tends to cause less severe effects (Rokyta et al., 2013; Glenn et al., 1994). Motor dysfunction ranging from paresis to paralysis and myokymia are common findings (Brick et al., 1987). The fibrinogen value in this case could not be measured due to hemolysis. The myokymia may also be presented due to hypokalemia and hypomagnesemia, however given the geographical location of the snake bite, the venom components are most likely.

Diphenhydramine is not routinely indicated for snake venom per se, as there is little to no histamine release in response to the toxin (Schottler, 1954; Stone et al., 2013). However, in some studies, diphenhydramine has actually been shown to potentiate the hypotensive effects of venom (Singh, 1980; Benjamin et al., 2020). It also has been determined that diphenhydramine doesn't prevent allergic reactions to antivenom (Nuchprayoon and Garner, 1999). The diphenhydramine in this case was administered subcutaneously as to not cause further hemorrhage by injecting into the muscle, and to not further drop its blood pressure if given intravenously.

This dog had urticaria on its dorsum that the owners noticed soon after envenomation. This resolved soon after the diphenhydramine treatment, thus supporting a type 1 dermatologic hypersensitivity reaction. The urticaria could have been a Type 1 non-IgE mediated hypersensitivity to the venom [12] such as that occurring with mast cell degranulation, immune complex production, or arachidonic acid inhibition (Stone et al., 2013; Reimers et al., 2000; Mendez and Cintra, 1960; Ryan et al., 2021). The owners reported that they live deep in the woods so other etiologies include insect bite or sting, hypersensitivity to a plant, recent bath with new shampoo, or other chemicals. Likewise, the dog had not received the rattlesnake vaccine, which has been documented as a cause for anaphylaxis in snake envenomated dogs (Petras et al., 2018).

The 'dog's rapid hemodynamic and neurological deterioration prompted the decision to bolus the initial dose of antivenom. This is not a common medical practice, but it can be done in cases of severe envenomation where delay may result in increased morbidity and mortality, especially when a neurotoxin is involved (Lavonas et al., 2011; World Health Organization, 2016). This complication along with the dog's compromised cardiovascular status, prompted immediate antivenom infusion. In humans, the initial recommendation for more routine envenomations is 4–6 vials of F(ab) or 10 vials of F(ab')2 antivenom administered IV over an hour, but in cases of severe envenomation with life-threatening shock, a more aggressive delivery rate of antivenom can be employed (Lavonas et al., 2011). This circumstance has likewise been described in the dog and smaller dogs often require more antivenom as there is a higher venom to body weight ratio (Willey and Schaer, 2005; Schaer, 2019b). Determining what dose of antivenom should be based on the patient's clinical signs and laboratory results, and treatment should be continued until clinical abnormalities have resolved.

The commercially available antivenom products available in the Western hemisphere are highly purified and are typically safe with low hypersensitivity rates (Carotenuto et al., 2021; Bassett and Schaer, 2022). Because the patient had prolonged severe hypotension, the choice to place them on gastroprotectants and antibiotics was made. The gastrointestinal tract is the shock organ in the dog, and a poorly perfused gastrointestinal tract can lead to bacterial translocation. Unasyn was chosen for its broad spectrum and anaerobic coverage.

Timber rattlesnake venom is not included in the production of antivenom products used in the United States. However, there can be cross-reactivity amongst various pit viper venoms, allowing them fortuitously to be adequately neutralized with the available polyvalent antivenoms produced in North and South America (Madrigal et al., 2017). The only commercially available antivenom products containing antibodies specifically against Mojave A toxin are Crofab™ and Rattler™, for humans and animals, respectively in the United States. The inclusion of *C. durissus* in the production of VenomVet might have facilitated the neutralization of both the neurotoxic and hemotoxic (Types A and B) components of the venom in this case Wooldridge et al. (2001); Hendon and Fraenkel-Conrat (1971); VenomVet. Advantages of a F(ab')2 product include better volume of distribution, compared to an IgG product, maintenance dosing may not be required, and a decreased cost compared to F(ab) antivenom (Covell et al., 1986; Rucavado et al., 2012; Mascarenas et al., 2020).

The authors hypothesized that the facial nerve paralysis was due to the effects of the venom acting directly on the ocular branch of the facial nerve. This was not likely due to compartment syndrome or muscle damage as there was minimal facial swelling and minimal pain. This palsy is documented in human medicine in both viper and elapid bites. In the viper envenomation, the victim was envenomated by Russell's viper (*Daboia russelii*), and the facial nerve paralysis resolved in three days. In the elapid envenomation, the victim was a child envenomated by a spitting cobra (*Naja mossambica*). The child showed some evidence

of recovery at 4 months. At 7 months, he was able to close his eye again, and 21 months later, he had made a full recovery (Chakrabarti, 2015; Rinkel et al., 2021). This dog was rechecked by ophthalmology two weeks after being discharged. All signs of facial nerve paralysis had resolved (Fig. 3). This supports the hypothesis that as the venom was cleared, the nerves and muscles regained their normal function, which is typical for group II phospholipases A presynaptic neurotoxins (Silva et al., 2017).

4. Conclusion

In conclusion, this dog was adversely affected by the venom of a timber rattlesnake and showed evidence of shock, neurologic dysfunction with myokymia and coagulopathy. The dog was treated aggressively with antivenom and other supportive care and recovered quickly. The facial nerve paralysis may have been associated with the neurotoxin in the venom. Therefore, timely and adequate amounts of antivenom, along with general patient support are recommended for severe envenomations.

Credit author statement

Cory Woliver: Conceptualization, Writing - Original Draft, Visualization, Michael Schaer: Writing - Review & Editing, Supervision.

Ethical statement

The manuscript accompanying this submission is the original work by the authors. This is an original work without conflict of interests.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.toxcx.2023.100156.

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