Complex regional pain syndrome following southern Pacific rattlesnake (C. oreganus helleri) envenoming

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Abstract
Complex regional pain syndrome (CRPS) has rarely been reported in the setting of snakebite but might be more common than previously reported. We present the third case of CRPS reported in North America and the first resulting from a pit-viper’s bite.

KEYWORDS
CRPS, long-term envenoming syndromes, snakebite

1 | INTRODUCTION

Long-term sequelae of snakebite are poorly understood. CRPS Type II following snakebite by a southern Pacific rattlesnake was diagnosed in a 12-year-old patient. To our knowledge, this is the first report of CRPS in a pediatric patient and one of the first CRPS Type II by Budapest criteria.

Complex Regional Pain Syndrome (CRPS) is known to follow soft tissue injuries and is characterized by persistent pain disproportionate to an initial injury with associated allodynia, autonomic derangement, pseudomotor and skin changes, as well as motor involvement. The sensory disturbances which follow in weeks to months after the injury can be debilitating and require intensive pain management, including physical therapy (Figure 1).

2 | CASE

We present the case of a 12-year-old boy presenting with CRPS type 2 appearing two months following snakebite envenoming. Briefly, an unseen southern Pacific rattlesnake (Crotalus oreganus helleri) bit him near the lateral malleolus as he walked past a tarp in his uncle’s garage in southern California. He described his foot pain from the unknown source as having his foot “lit on fire and run over by a truck.” Search of the garage turned up the snake which was killed and subsequently identified by a local herpetologist (Figure 2). Initial management in the emergency department and subsequent transfer to a tertiary facility comprised intravenous opioids for acute pain management, CroFab® antivenom [Crotalidae polyvalent immune Fab (ovine)], and fluid hydration. Vital signs were within normal limits, and coagulation studies were notable for mildly elevated D-dimer and fibrinogen levels and mild thrombocytopenia, all of which resolved the next day. Control of progressive envenoming signs was achieved following two additional doses of antivenom totaling 14 vials.

Two months following the initial injury, the patient presented to a chronic pain specialist with progressive symptoms ascending the ipsilateral leg just below the
patella in the distribution of the sural nerve. Physical examination was notable for lower extremity edema up to the knee, erythema, hyperalgesia, hot and cold dysesthesia, motor and sudomotor changes in the region overlying the original bite site. These symptoms spread up his leg to the subpatellar area. Budapest Criteria were met for the presence of edema up to the knee, erythema, hyperalgesia, hot and cold dysesthesia, and sudomotor changes.\(^1\) No further testing such as EMG/NCS was performed nor necessary given the clinical diagnosis. The patient was prescribed physical therapy with a pediatric specialist, which comprised of acupuncture, weight bearing, transcutaneous electrical nerve stimulation, and sensory variation. Active use of the affected extremity was encouraged. Four months after envenoming by the pit viper, the patient was able to ambulate and jog, but only after intensive physical therapy.

**FIGURE 1** Complex Regional Pain Syndrome (CRPS) has multiple etiologies, including recent identification of snakebite envenoming as a cause. There are many and varied therapeutic approaches including pharmacological, physical and psychological interventions used alone and in combination.
therapy. In the absence of obvious stigmata from the bite, the patient endured skepticism from classmates and teachers he was exaggerating symptoms at school by staying out of physical education activities, ambulating with crutches and keep his leg elevated in class. Four months after the bite and two months after the start of physical therapy, patient was able to ambulate and jog, and had what he felt was a full recovery.

3 | DISCUSSION

In general, successful management strategies include snake antivenom, gabapentinoids, sympathetic ganglion blockade, physical therapy, graded motor imagery, psychological support and in severe cases, dorsal root ganglion or dorsal column stimulation. At two-year follow-up, the patient was symptom free and without persistent physical or psychological sequelae, but this is not necessarily the norm and psychosocial effects of snakebite need to be addressed as well as the immediate effects of acute envenoming.6–5

The financial implications of snakebite and envenoming pose prominent global health concerns. Despite the availability of antivenom treatment in industrialized nations, the cost of this therapy can bankrupt families without medical insurance.6 The initial cost of this patient’s emergency care totaled more US$70,000, eventually covered by insurance after appeal. These stresses interfere with the psychological wellness of patients as does the uncertainty of recovery time.6,7

Progression to CRPS following snake bites and envenoming has only been reported a handful of times in the medical literature, including cases in Nepal, Turkey, Korea, and Norway—all vipers and one each suspected cases induced by an elapid and colubrid of the genera Micruroides (coral snake) and Leptodeira (cat-eyed snake), respectively.8–15 These disparate geographic locations and two new genera being reported emphasize that venom and/or bites from different genera of snakes can lead to CRPS.13,15 In all of the reported cases of CRPS following viper envenoming we found in the literature, symptoms eventually resolved, but often only after significant interventional pain procedures such as stellate ganglion or lumbar sympathetic blocks. In two cases of distal extremity bite injuries, osteoporosis of the involved digits or joints was observed.8,14 To our knowledge, the current case is the first described in the Americas in a pediatric patient, a population often more vulnerable to the effects of snakebite envenoming.16,17

Snake venom components vary by species, and even intra-species variation has been observed. Myriad substances within venom lead to inflammation, peripheral sensitization, and local adrenergic receptor up-regulation.18 Severe bites from C. oreganus helleri are characterized by mixed neuro- and hemotoxic manifestations such as numbness, severe muscle fasciculation, airway compromise and hemorrhage with thrombocytopenia and consumption.19 In addition to neurological and hematological manifestations, secretory phospholipases (e.g., crototoxin, a dimeric sPLA2) and zinc metalloproteases lead to endothelial damage and leaky capillaries. Snake venom and hemolysin exacerbates tissue edema by damaging cell membranes and red blood cell lysis. Venoms with high content of sPLA2 such as C. oreganus species and Mojave (C. scutulatus) rattlesnakes exhibit both analgesic and nociceptive properties.20 In the case of this bite, the toxidrome included severe pain. Whether toxins in venom per se induce CRPS via direct nerve injury or by altering physiochemical milieu is very poorly characterized and likely under-reported.

4 | CONCLUSION

Emergency medicine providers, primary care physicians and pain physicians should be aware of the potential of snakebites to progress to CRPS. Symptom duration of snakebite and envenoming-related CRPS can last months to years even with intensive therapy and pain management. Successful management strategies employed in the literature include viper antivenom, gabapentinoids, sympathetic ganglion blockade, physical therapy, and psychological support. Isolation of compounds in viper venoms causing tissue and/or nerve injury may provide insight into the pathogenesis of CRPS. With this case, there are now recorded cases of CRPS from the three groups of venomous snakes found in North America.

CONFLICT OF INTEREST
MRL receives salary and has shares in Ophirex, Inc. a Public Benefit Corporation.

AUTHOR CONTRIBUTIONS
HL, RN: Patient care, manuscript, concept; MRL: Patient follow-up, manuscript, concept; HB: Patient follow-up, manuscript.

ETHICAL APPROVAL
This material is the authors’ own original work, which has not been previously published elsewhere. All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.
CONSENT
Patient and parental consent were obtained and photographs and verification of medical bills provided by the family for purposes of publication.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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