Extreme Pain From Brown Recluse Spider Bites: Model for Cytokine-Driven Pain

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Pain from the bite of the brown recluse spider (BRS) can be extreme. One case with extreme pain is reported herein to illustrate the extent of BRS bite distress. We analyze the temporal pattern and severity of pain in cases of BRS bites confirmed both clinically and by detection of BRS venom by enzyme-linked immunosorbent assay (ELISA). We describe a typical time course for pain evolution and chart the pain intensity against anatomic BRS bite locations. These findings support the hypothesis of cytokine release in inflammatory pain.

Report of a Case

A woman in her 20s noted a slight sensation similar to a mosquito bite on the medial knee surface. Within 24 hours, the pain level increased to 8 or 9 on a scale of 0 to 10, causing a noticeable limp with ambulation. Laboratory findings at an emergency department were unremarkable other than a mild left shift in her white blood cell differential count (neutrophils, 81.9% [normal, 40%-80%]). An oxycodone-acetaminophen combination was prescribed.

Less than a week after the bite, her lesion remained painful and pruritic (Figure 1A). The lesion showed 3 loxoscelism features: gravitationally dependent spread, central pallor, and erythema.1 Additionally, 7 negative signs that decrease the likelihood of a BRS bite were all absent: (1) early ulceration (before 1 week), (2) large ulceration (>10-cm diameter), (3) lymphadenopathy, (4) central erythema, (5) purulence, (6) more than 2 lesions, and (7) raised red center.2 Urinalysis findings were normal. ELISA quantization of BRS venom from wound swabs showed a mean (SD) presence of 0.21 (0.13) ng of venom; 2 swabs from the patient to establish an immunoreactivity threshold showed 0.089 ng.3 The patient noted persistent pain (8-9 on a scale of 0-10), only minimally relieved by lidocaine patches, and requested a refill of the oxycodone-acetaminophen combination to enable her to continue working.

About a week after the bite, the patient had persistent itching and additional areas of erythema (Figure 1B). Urine dipstick testing showed a trace of blood and no urobilinogen, a finding interpreted as mild intravascular hemolysis. Additional lidocaine patches and oxycodone-acetaminophen were prescribed.

A month and a half after the initial bite, 2 crusted lesions, one measuring 5 cm, the other 2 cm across the largest dimension, remained unhealed (Figure 1C). Erythema surrounded both lesions; a clear yellow exudate was present. The patient was treated with saline soaks alternated with hydrocolloid moisture-retentive wound dressing (Duoderm GCF; Convatec Inc). The patient complained of severe pain relieved only with oxycodone-acetaminophen. For 2 months, she...
Methods

Data on pain in spider bites were collected as part of National Institutes of Health study SBIR R44 AR-055683 according to a protocol approved by the institutional review board of Phelps County Regional Medical Center, Rolla, Missouri. Photographs, swabs of the bite sites, and clinical data on 175 patients with possible BRS bites were collected. Of these cases, 74 were rated as either probable (n=68) or documented (n=6) by the revised clinical criteria of Rader et al.\(^2\) An experimental ELISA test for BRS venom\(^3\) was performed on 56 of these probable and documented cases. The ELISA result was positive in 46 of these cases. Thus, 46 cases were considered likely BRS bites by both clinical and experimental laboratory criteria. For 23 cases, the patient’s recollection of the pain at the time of the bite and 24 hours later were recorded on a numerical scale of 0 to 10.

Results

The mean (SD) pain score at the time of the bite on the 0 to 10 scale was 2.37 (2.84); after 24 hours, it was 6.74 (2.75). Of the 23 patients with recorded pain scores at the time of the bite, 12 (52%) had pain; 11 (48%) had no pain. Of the 23 patients scored at 24 hours, 22 (96%) had pain.

Mean (SD) ELISA venom quantization for those with a mild pain score (0-3) was 0.13 (0.06) ng. ELISA quantization for those with at least moderate score (4-10) was 0.25 (0.29) ng. The difference suggests a nonsignificant trend of recovering more venom with at least moderate pain. No trend for venom recovery was found among higher pain score subgroups.

The anatomic location of the BRS bites was also considered as a factor affecting severity. The 24-hour pain scores are shown grouped by anatomic region in Figure 2. Pain in 7 BRS bite cases was scored 9 or 10 of 10; anatomic locations for these bites were widespread (Figure 2). Average scores at 24 hours for 23 scored bites were calculated for 5 different anatomic regions. No significant differences in discomfort were found among the anatomic regions, with each region within the standard deviation of the average pain score of 6.74 (2.75).

Discussion

Diagnosis of a BRS bite is often difficult because other diagnoses mimic these bites. Initially asymptomatic, the bites may evolve into very painful, slowly resolving scarring lesions. Two previous studies have recorded the frequency of pain in suspected BRS bite cases; neither study was limited to cases with a high level of certainty. Clowers\(^4\) in Arkansas noted pain in 69% of 39 lesions consistent with BRS bites.\(^4\) The medical record review included cases if the assessment was “probable” or “possible” BRS bite. The criteria for these categories and the number in each category were not discussed.\(^4\) Cacy and Mold\(^5\) in Oklahoma noted pain in 60% of 149 suspected BRS bites. After initial assessment and direct observation of the evolution of the lesions until healed, 9% of the Oklahoma lesions were

continued taking the opioid-analgesic combination, allowing her to continue working. By approximately 3 months after the bite, the lesions had healed.
believed to be definite BRS bites, 40% probable BRS bites, and 22% possible BRS bites.

**Measurement of Severe Pain**

Oldemenger et al, reviewing articles using the 0 to 10 numerical pain scale to establish moderate and extreme pain, found that scores of 5 and 7 were optimal cut points for moderate and severe levels, respectively. Thus the average pain score for spider bites is close to the threshold of severe pain (6.74 vs 7.0). Since only 4 of 23 patients in the present study scored lower than 5, we observed 19 of 23 patients (83%) with at least moderate pain.

There is no universal agreement on the best descriptions for numerical pain ratings 0 to 10. An attempt to describe such scales was compiled from multiple sources by Richards at HealthCentral.com, and the following describe extreme pain:

7 – Severe pain that dominates your senses and significantly limits your ability to perform normal daily activities or maintain social relationships. Interferes with sleep.

8 – Intense pain. Physical activity is severely limited. Conversing requires great effort.

9 – Excruciating pain. Unable to converse. Crying out and/or moaning uncontrollably.

10 – Unspeakable pain. Bedridden and possibly delirious. Very few people will ever experience this level of pain.

For our cases that included comments along with the pain score, overall agreement with this scale is noted: “My tail end was on fire [pain score, 8 of 10].” “Burning, throbbing, feels like a shock [pain score, 9 of 10].” “Constant throb like on fire [pain score, 10 of 10].”

**Cytokine Pain Pattern With Inflammation**

The level of pain was recorded for both the time of the bite and 24 hours later. On a scale of 0 to 10, the mean (SD) pain score at the time of the bite was 2.37 (2.84); after 24 hours, it was 6.74 (2.75). An increase in pain from the time of the bite over the next 24 hours was noted in all but 1 case. For this case, the pain score was 0 at the time of the bite and 0 after 24 hours.

These clinical results showing delay in pain development are in accord with the delay in cytokine release in an experimental study by Gomez et al on the release of a cytokine, interleukin 8 (IL-8), after experimental inoculation of BRS venom in human epithelial cells. The IL-8 level was shown to be over 10 times higher at 8 hours than it was at 0.5 or 2 hours. The amounts released at the earlier times did not differ from background. Interleukin 8 has been associated with pain in several studies and has been proposed as a pain biomarker.

One explanation for the presence of 0 pain in some bites can be found in the same in vivo study by Gomez et al: IL-8 is not released above background when the concentration of BRS venom in the experimental epithelial model is below 0.5 μg/mL, establishing a floor of venom concentration below which cytokine release (and subsequent pain) is not expressed.

Besides cytokine release, BRS venom may cause pain via other peripheral pathways, including direct action on peripheral nerves by sphingomyelinase or even peripheral nerve transport analogous to that of tetanus toxin.

**Central Nervous System (CNS) Mechanism for Severe Inflammatory Pain**

Pain in the cases studied here has been classified as inflammatory owing to associated peripheral tissue damage. Recent research has shown links between chronic pain and cytokine signals to the CNS, in particular astrocytes and satellite glial cells, 2 types of glial cells within the CNS, and in some studies a third type of glial cell—microglia. Cytokines, including interleukins and tumor necrosis factor have been shown to upregulate these glial cells. Thus the time course of the pain, showing marked increase over the first day, is entirely consistent with the direct inflammatory cytokine release found experimentally. These findings could have therapeutic rel-
evance for cytokine-related pain. Minocycline, an inhibitor of microglia, has been shown to reduce inflammatory pain.\textsuperscript{14}

The level of discomfort from different anatomic sites was relatively constant. The bites that were scored 9 or 10 are in widely scattered locations (Figure 2). These findings are consistent with the centrally acting mechanism for inflammatory pain. Incorporating our findings in a recent model of the mechanism for the inflammatory variety,\textsuperscript{12,14} we hypothesize that BRS venom triggers cytokine release, which causes up-regulation of pain receptor glial cells. Pain signals travel via the spinthalamic tract; the thalamus acts as way station for the signal; and finally the cerebrum is made aware of severe pain at a specific site. Because cytokine release is significant for all \textit{Loxosceles reclusa} bites with more than an estimated 0.5 \textmu g of venom, pain is severe after 24 hours; it is largely independent of bite location; and it persists at a high level as long as cytokine levels remain high. After some time, the inflammatory pain subsides, and a more moderate level is driven by chronic tissue injury. Pain in older healing spider bite wounds was not investigated. Anecdotal evidence suggests that discomfort levels with time approach those in chronic leg ulcers: 2.9 of 10.\textsuperscript{15}

\textbf{Limitations}

The ELISA used to detect BRS venom at the bite site is still undergoing modification, as shown in the first case, in which 2 bite-site determinations differed. Overall, 46 of 56 probable cases showed venom at the bite site by ELISA. We considered the possibility that the requirement of a positive ELISA finding in addition to the requirement of clinically probable or documented bites may have changed the average pain scores. For the 10 probable or documented bites with a negative ELISA finding, mean (SD) pain scores at 24 hours were 6.6 (2.3), similar to the score of 6.74 (2.75) found when both positive ELISA result and a clinically probable or documented bite were present. A weakness of this study is the lack of objective measurement of cytokine levels. Inferences regarding the relationship of peripheral pain to CNS mechanisms and the pathways activated by BRS venom are hypothesized but not documented.

\textbf{Clinical Take-Home Points}

1. Pain is a prominent feature of BRS bites and can be very severe, 9 or 10 on a scale of 10 in 7 of 23 cases.
2. Providing relief of discomfort for victims of a BRS bite is an important component of management.
3. Pain from a BRS bite follows a cytokine release pain pattern, starting low at the time of the bite and typically becoming severe after 1 day, regardless of bite location.
4. RICE therapy (rest, ice, compression, and elevation) and lidocaine patches should be tried first for pain relief. Opioid agonists may be a useful treatment adjunct for some patients.
5. Prevent spider bites by keeping the bed away from the wall and checking clothes that have not been worn recently.