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Brown Recluse Spider Envenomation

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Willis Caveness [1] is credited with the first account of toxicity from *Loxosceles reclusa* in 1872 involving a Tennessee man with fever following an insect bite. It was not until 1929 that Schmaus [2] described skin injury associated with the bite. In 1957, Atkins and colleagues [3] proposed that the bite of *L reclusa* caused skin necrosis similar to that of its South American relative *L laeta*. "…[I]t is not unduly presumptive tentatively to assign to *L reclusus* the same relationship with cutaneous arachnoidism [*sic*] in Missouri that *L laeta* bears to that condition in South America" [3]. From the beginning, the diagnosis of brown recluse spider bite was based on supposition much more than fact.

The spider

Of the genus *Loxosceles, L reclusa,* commonly known as the brown recluse spider (BRS), is one of nearly 50 related species endemic to the Unites States and 100 species throughout the world. It first was described in 1940 by Gersch [4]. Other species, such as *L laeta*, *L gaucho*, and *L intermedia*, long have been reported to cause cutaneous and systemic injury in South America. In the United States, *L reclusa* is found in the south from western Florida to the eastern third of Texas and ranges as far north as northern Illinois and southern Iowa (Fig. 1). Southern California and southwest Arizona are home to *L deserta*. Several less known species reside from southwest Texas to the southern half of Arizona, and *L rufescens* is found along the Gulf of Mexico [5].

Brown recluse, also known as fiddleback spiders, are noted for the violin-shaped marking on the cephalothorax (Fig. 2), though some immature spiders

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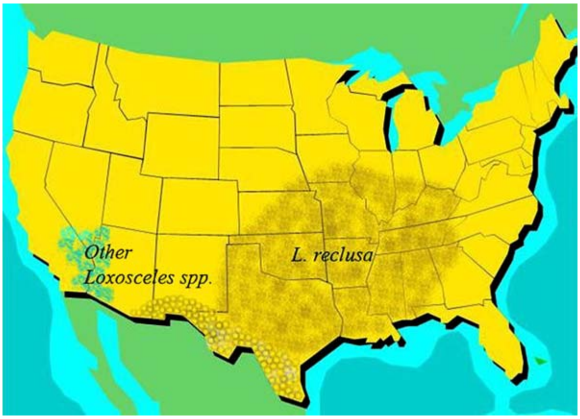

Fig. 1. Reported distribution of *L spp*. in the United States.

may not display that hallmark [5]. Their color ranges from yellow-brown to gray-brown. The adult's leg span is approximately 5 cm with body length of 6 to 11 mm. A helpful identifying feature is the presence of six eyes arranged in three pairs (dyads) as opposed to the more common eight eyes found in most spiders. Although not limited to *L spp*., the number of eyes can be viewed under a microscope to aid in identification (Fig. 3). Legs are long in comparison to body length and have spiked hairs.

BRS may be found indoors or out. They prefer undisturbed areas, such as boxes or furniture in garages or basements. They are nocturnal and avoid areas of human and other animal activity. BRSs generally are nonaggressive and prefer dead prey [6]. Bites typically are defensive and usually occur when the spider is trapped against clothing or bedding. Contrary to popular belief, *Loxosceles* species do not predate human beings. In fact, Vetter and Barger [7] reported on a house infested with *L reclusa*, identifying more than

Fig. 2. *L reclusa* displays violin marking on the cephalothorax.

Fig. 3. *L reclusa* displays classic violin markings on the cephalothorax (*1*), three pairs of eyes (*2*), and hairy legs (*3*). Note several legs are missing.

2000 spiders in a 6-month period without a single known human bite during that time.

The bite

The necrotizing bite of the BRS has been studied intensively. Loxoscelism, necrotic arachnidism, or gangrenocutaneous arachnidism has been used to describe the clinical effects of BRS envenomation and includes the necrotizing lesion and systemic effects, such as fever, chills, rash, joint pains, and hemolysis [8].

Cutaneous effects from confirmed bites usually are found under clothing and on the thigh, lateral torso, or upper arm. Confirmed bites are defined as bites associated with a captured or recovered spider found in close proximity to the bite and correctly identified by a qualified person. They are uncommon on the neck and rare on the hands, feet, or face [9]. Erythema, burning pain, pruritus, and swelling may develop within a few hours of the bite. Less commonly, a hemorrhagic vesicle may develop several hours to days later. If necrosis develops it typically is central, well defined, and surrounded by mixed erythema and vasoconstriction. Similar lesions, however, are associated with many other causes. The vast majority of confirmed bites require no treatment and resolve without incident. Based on confirmed envenomations, the need for surgical intervention seems to be uncommon.

Rees and colleagues [10] reported 17 confirmed bites; a generalized macular rash occurred in 29%. Fig. 4 demonstrates the skin lesions described by Rees. In this case, a 14-year-old girl awoke with pain, redness, and swelling in her left axilla. She found a spider in her bed. Using a colposcope, the spider was identified as an *L reclusa* (see Fig. 3). She developed a generalized

Fig. 4. Bite wound at days 3, 4, and 21 postinfliction.

maculopapular rash that completely resolved 3 weeks after the initial envenomation without any evidence of soft tissue necrosis.

Hemolysis has been associated with numerous case reports of *L reclusa* bites [9,11–24]. Although most of these occurred with unconfirmed bites, some reports with confirmed envenomation have demonstrated that brown recluse venom can cause red cell destruction. In confirmed cases of hemolysis reported by Anderson and colleagues [9] transient renal failure also has occurred.

Fatalities

Few deaths have been reported following *L reclusa* bites [19,21,22,24–27]. The clinical picture is that of rapid cardiovascular collapse with fever and massive hemolysis. Although onset from time of bite is impossible to determine, the reported course ranged from about 18 hours [22,26] to nine days [21]. Autopsy findings include skin lesions with thrombosis of dermal and subcutaneous vessels. Coagulopathy frequently was apparent. Pulmonary edema and renal tubular damage also were reported. Most victims were children and wound or blood cultures were not reported. Although some fatality reports are suggestive of a spider bite, none were confirmed. Toxic Exposure Surveillance System data show eight fatalities attributed to *L reclusa* in the period from 1983 to 2004. In all of these cases the spider was presumed to cause the illness and subsequent death without confirmation, however [28–34]. In reported fatalities, patients presented with signs of hemolysis, including jaundice and dark urine; a retrospective diagnosis of spider bite was made when a skin lesion was identified.

Differential diagnosis

Numerous articles have concluded the skin lesions attributed to BRS bites in fact may be attributable to other causes. These articles warn that the diagnosis of BRS envenomation is purely speculative without a definite witnessing of the spider and subsequent identification of a BRS. In the case of such bites the diagnosis is said to be clinical or presumptive when in fact it is simple conjecture. Box 1 shows a listing of possible causes that should be ruled out before making the diagnosis of BRS bite in the absence of a spider [3,5,8,35–41].

Human reports

A review of multiple case reports of *L spp*. envenomations in the United States reflects the relative percentage of confirmed bites. Confirmed bites required a spider present at the bite site and identified as a brown recluse by an arachnologist, health care provider, or other person trained in such identification (Table 1).

Of 908 cases, only 7.9% were confirmed according to the definition above. Though impossible to analyze reliably, confirmed bites appear to require surgery less often, with only 4% undergoing surgery compared with 12.9% of unconfirmed cases treated surgically.

Animal studies of envenomation

Animal studies of loxoscelism have focused on several areas:

- Identification of venom and its mechanism of action
- Clinical effects of venom
- Diagnostic testing for true BRS bites
- Treatment of envenomation

Experimentally, BRS venom has been obtained by way of electrostimulation and expression from the live spider or by way of dissection of the venom sacs. Venom used in studies may be crude or purified. Unfortunately, many factors, such as gastric or salivary contamination and purification

Box 1. Causes to be ruled out before diagnosis of BRS bite

Angioedema
Ant bite or sting
Bacterial infection (staphylococcal, streptococcal)
Bedsores
Bee sting
Bromoderma use
Burns
Cutaneous anthrax
Cellulitis
Coumadin use
Diabetic ulcer
Drug injections
Ergot alkaloids
Erysipelas
Erythema multiforme
Erythema nodosum
Extravasation of chemotherapeutic agents
Factitious injection
Fat herniation with infarction
Flea bite
Focal vasculitis
Foreign body
Frostbite
Gonococcal hemorrhagic lesion
Heparin use
Herpes simplex infection
Hypersensitivity angiitis
Keratin-mediated response to a fungus
Lyme disease
Lymphoid papulosis
Malignancy causing arterial obstruction
Mosquito bite
Mycobacterial infection
Necrotizing fasciitis
Other arthropods
Periarteritis nodosa
Poison ivy
Poison oak
Purpura fulminans
Pyoderma gangrenosum
Reduviidae spp. bite
Scleroderma

Scorpion sting
Sporotrichosis
Stasis ulcers
Steven-Johnson syndrome
Thromboembolism
Tick bite
Toxic epidermal necrolysis
Trauma

method, lead to difficulty in developing a homogeneous product. In addition, studies often only use a portion of the venom obtained (such as a specific protein fraction). Many investigators test the venom (or protein fractions) obtained by mixing specific concentrations and testing animals for the development of a specific size of lesion before deciding on a dose to administer for the research project. Attempting to quantify the protein content of crude venom by comparison to a bovine standard is also used. In addition, there is significant interspecies variation in response to BRS venom, with rabbits being about 300 times more susceptible than rats [74].

Identification of venom and its mechanism of action

Loxosceles venom has been shown to contain several enzymes, including alkaline phosphatase, 5′ ribonucleotide phosphohydrolase, esterase, protease, and hyaluronidase. Hyaluronidase may be responsible for the spread of lesions. The most important enzyme causing loxoscelism seems to be sphingomyelinase D [75–77]. Sphingomyelinase D degrades sphingomyelin on cellular membranes resulting in lysis and cell death and also causes the release of prostaglandins, activates the complement cascade, stimulates platelet aggregation, and enhances neutrophil chemotaxis [78]. The dermonecrotic portion of venom that contains sphingomyelinase D is found to adhere to platelets suggesting a possible mechanism for BRS-induced coagulopathy [77]. Sphingomyelinase toxins from *Loxosceles* spiders have been shown to induce complement-dependent hemolysis of erythrocytes by way of activation of membrane-bound metalloproteinase [79–81]. The rate of sphingomyelin hydrolysis has been found to be related directly to temperature and to require the presence of divalent calcium. The rate of sphingomyelin hydrolysis is greater in crude venom than in purified fraction containing sphingomyelinase, suggesting a synergistic effect with other venom enzymes [82].

BRS venom adsorbs to cell membranes [10] and hemolyzes human erythrocytes in vitro [83]. Venom does not hemolyze washed erythrocytes in the absence of serum, however, thereby implicating serum factors in the pathophysiology of BRS envenomation [84]. Likewise the addition of complement

Table 1
Case reports of brown recluse spider envenomation

Reference	No. of patients	Unconfirmed	Spider present	Confirmed	Surgery
Arnold [42]	5	5	0	0	3
Berger [43]	2	0	2	2	0
Bey et al [44]	1	0	1	1	0
Borkan et al [45]	34	33	1	1	0
Broughton [46]	1	0	1	1	0
Chu and Rush [11]	1	0	1	1	0
Clowers [47]	39	39	0	0	?
Delozier et al [48]	31	20	?	11	6
Dillaha et al [12]	16	16	3	0	1
Edwards et al [49]	1	0	0	0	1
Eichner [13]	2	2	1	0	1
Goto [50]	1	0	1	1	?
Gross et al [51]	1	0	1	1	0
Hampton Taylor and Olive [52]	1	0	1	1	0
Hansen and Russell [53]	1	0	0	0	0
Hardman et al [54]	1	0	0	0	0
Hillis et al [55]	1	1	0	0	0
Hollabaugh [56]	18	18	0	0	18
Hoover [57]	1	1	0	0	1
Ingber et al [58]	35	35	0	0	5
King and Rees [59]	1	0	1	1	0
Leung [60]	1	1	1	0	0
Masters [61]	1	0	1	1	1
Maynor and Abt [38]	14	14	0	0	1
Murray and Segar [17]	1	1	0	0	0
Rees et al [62]	31	31	?	0	15
Rees et al [10]	17	0	17	17	0
Rees et al [63]	3	2	1	1	3
Ruelle et al [64]	1	1	0	0	0
Sauer [65]	1	1	0	0	0
Schenone and Prats [66]	40	21	25	19	3
Schuman and Caldwell [67]	478	478	0	0	43
Silcox and Miller [20]	1	1	1	0	0
Svendsen [68]	6	6	0	0	0
Taylor and Denny [21]	1	1	0	0	0
Vorse and Seccareccio [105]	1	1	0	0	0
Wasserman and Mydler [23]	5	5	0	0	0
Wesley et al [69]	1	1	0	0	1
Wille and Morrow [70]	1	1	0	0	0
Williams and Khare [24]	2	2	0	0	1
Wright et al [71]	110	98	22	13	3
Yiannais and Winkelman [72]	1	0	0	0	1
Young [73]	1	1	0	0	0
Totals	908	836	82	72	107
Percent of cases		92%	9%	7.9%	11.8%

inhibitors and ethylenediaminetetraacetic acid decreases hemolysis [85–87]. C-reactive protein has been implicated as a cofactor also, possibly by complement activation [84]. Along with complement activation, platelet aggregation occurs in a calcium-dependent fashion [78] requiring serum amyloid P [88]. Hemolysis is not seen with venom-exposed erythrocytes bathed in neonatal serum, and C-reactive protein and serum amyloid P are deficient in neonatal serum [88]. When treated with BRS venom human endothelial cells were found to bind polymorphonuclear cells (PMNs) and activate the release of granules [89].

Clinical effects of venom

The natural course and histology of BRS envenomation has been well studied in animal models. When rabbits were bitten by BRSs, the skin immediately developed hyperemia and within one hour became dusky. No blister was noted and histology at this stage revealed focal aggregations of leukocytes in the dermis with evidence of blood sludging in capillaries. The lesions continued to enlarge and become necrotic over the next 24 hours with histology showing thrombosis of capillary channels and evident necrosis extending through the fascia. By 144 hours (6 days), the zone of necrosis was well demarcated and histology showed necrosis with surrounding inflammatory reaction and granulation tissue at the periphery. By 288 hours (12 days), the eschar was well developed and showed histologic evidence of separation at the margins. At 30 days there was a dense scar with an absence of hair follicles and skin appendages [90]. The extent of dermal inflammation appeared to correlate with the physical diffusion of venom [91]. Polymorphonuclear leukocytes were implicated clearly in the pathogenesis of BRS venom, because rabbits made neutropenic with nitrogen mustard were much less susceptible to toxicity [92].

Dermonecrotic activity of extracted, purified BRS venom was found to be dose dependent in the rabbit, with lesion size proportional to the amount of venom injected (10–40 μg/kg) [77,93,94]. At doses of 60 μg/kg, rabbits developed pulmonary edema and died [94]. The typical lesion became erythematous, warm, and edematous within 12 hours after injection and formed a characteristic central purple papule that developed central necrosis 24 hours afterward. Histologic examination of the lesions showed vascular thrombosis and intense PMN infiltration [94]. Autopsy of the rabbits that died showed interstitial edema and leukocyte infiltration [95].

Guinea pigs administered twice the median lethal dose of BRS venom developed dyspnea, hemoptysis, and chest wall retractions at 6 hours, and became lethargic and developed bloody diarrhea before dying approximately 24 hours after envenomation. Hematologic studies revealed an initial decrease in the white blood cell count followed by a progressive increase, and a progressive decline in platelet count. Serum complement levels were decreased significantly compared with controls (451 $\pm$ 134 CH_{50} units versus 835 ± 134 CH_{50} units, $P < .05$). Autopsy revealed diffuse hemorrhage and vessel thrombosis of lungs, liver, mesentery, and kidneys, with petechial hemorrhages throughout the bowel. Guinea pigs made deficient in complement by treatment with zymosan were resistant to BRS venom [95].

Diagnostic testing

Diagnosis remains difficult at best, with no specific test available to ensure that a lesion is attributable to the bite of a BRS. Passive hemagglutinin inhibition has been reported to test for the presence of BRS venom with a sensitivity of 90% as long as 3 days after envenomation in guinea pigs [96]. The test involves incubation of the subject's wound exudate to a prepared antiserum and then exposure of the mixture to venom-coated O-negative red blood cells. Exudate containing BRS venom causes the red blood cells to settle to the bottom of the test tube. The calculated amount of venom protein to produce a positive result was 0.0037 μg/mL (natural bites in this study injected 5–23 μg of venom) [97].

A lymphocyte transformation test using adsorbed venom protein was found to detect previous exposure to loxosceles venom in a small series of patients [98].

ELISA has been developed to detect antigens from *L intermedia* in Brazil with some prospective validation in hospitalized patients [99]. *L reclusa* ELISA has been developed and found to be specific for BRS venom at low venom levels, although cross-reactivity to other nonloxosceles spider venoms was found at higher levels [100]. In a rabbit model, this assay detected venom up to 7 days after injection [101]. A venom-specific enzyme immunoassay derived from *L deserta* has been used clinically to detect spider venom in a dermal biopsy and hair from a patient 4 days after the development of a skin lesion [102].

Treatment

Animal research has helped us to determine the efficacy of various treatments with experimentally induced envenomations. We must be aware, however, of the inherent limitations in attempting to apply the animal data to humans. Many animal studies use venom preincubated with the treatment agent, or apply the treatment agent either pre-envenomation or shortly afterward, which does not approximate a true clinical scenario. In addition, there is significant variability among animal species in their susceptibility to BRS envenomation. The current mainstay of therapy is supportive care. Even in the rare case of a confirmed bite, treatment should be expectant. Despite multiple trials, early surgical excision [62,94,103,104], electric shock [105], steroids [93–95,104,106], hyperbaric oxygen therapy [38,107–110], colchicine [106], antihistamines [106], vasodilator drugs [111], anticoagulants [94,104,112], prophylactic antibiotics [103], and dapsone [93,104,106,109] remain unproven therapies for BRS envenomation. All have variable degrees of risk. The only treatment modality that consistently has shown success in animal studies of loxosceles envenomation is specific antivenin; however, the treatment seems to be most beneficial either pre-envenomation or shortly thereafter (within 1 hour) [77,93,94,104,112,113]. Intradermal specific antiloxosceles Fab fragments also have been found to attenuate the BRS lesion size up to 4 hours postenvenomation [114]. The potential value of these therapies is limited by the fact that only 10% of people bitten present in the first 12 hours [115] and that antivenin and specific Fab fragments are not available commercially. Furthermore, given the inaccuracy of the brown recluse bite diagnosis, much better documentation of the cause would be required before assuming a risk of administration. For that reason, a reliable test for BRS bite would be useful, but is unavailable at present.

Summary

The bite of the BRS continues to pose a diagnostic and therapeutic challenge. The animal data reveal sphingomyelinase D to be the most important portion of venom and implicate serum factors (such as complement, C reactive protein, and leukocytes) as important cofactors for producing disease. Diagnosis remains difficult at best, with no easily available test to ensure a lesion is attributable to the bite of a BRS. Misdiagnosis of other treatable causes of necrotic skin lesions as BRS bites has presented a challenge also. Treatment of a confirmed brown recluse bite primarily is supportive with appropriate wound care.

Animal studies and the few confirmed human cases have documented that the bite of the brown recluse is much less common than the medical and scientific communities have believed. The data also demonstrate that the bite of the recluse more often than not causes a mild wound, although it can produce a necrotic lesion. There also is support for the rare occurrence of hemolysis. Death reports involving *L reclusa* remain circumstantial. In recent years, Vetter and colleagues [5,116,117] repeatedly have underscored the need for confirmed bites as the evidential basis for our understanding of the spider and its medical significance. Given more than a century of questionable case reports, the medical community must limit BRS envenomation data to well-documented cases and not use the endpoint (ie, lesion or condition) to establish a cause retrospectively.

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