Volume 74, Number 9—September, 1977

Missouri Medicine

JOURNAL OF THE MISSOURI STATE MEDICAL ASSOCIATION

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What's New in Loxoscelism—1978

Case Report

THE MISSOURI FIDDLEBACK SPIDER, known properly as Loxosceles reclusa, is also called the brown recluse spider. This well-known nocturnal house spider is the most dangerous of all North American arachnids.[1] Its bite may cause a cutaneous ulcer, which occasionally can be as large as 40 cm across and may extend well into muscle. When absorbed into the circulation, the venom may cause hemolysis, abnormal clotting, injury to the brain, kidneys and other organs or even death.[2] Pleasantly, the spider tries to avoid humans and, if it can, often will flee across the skin without biting. Most bites result from inadvertently trapping the spider in clothing, e.g., when putting on a bathrobe. Once the spider bites, the resulting injuries still may be trivial; indeed, they usually are trivial.

Since the previous review in 1973,[3] the principal advancements have been in pathophysiology and in knowledge of the chemistry of Loxosceles venom. Clarifications of medical therapy have relied on the collection of well-studied, well-proven cases and concern, mainly, the management of hemolysis. The following brief case report illustrates the use of dialysis for treatment of systemic loxoscelism in a child.

ENTOMOLOGY—THE SPIDER

The brown spider can be identified from small fragments of the body if an expert, experienced entomologist is involved. Patients who squash the spider during the bite might be asked to supply these few remains for study, particularly if the case is to be reported or if the therapy is part of a protocol study. A certain diagnosis of loxoscelism requires positive identification of either the spider or the venom in addition to the usual clinical recognition of "a typical necrotic brown spider bite."

Spiders other than Loxosceles reclusa can cause mild necrotic spider bites, some of which can deceive the expert clinician.[4, 5] In reporting on the therapy of brown spider bites, only proven cases of loxoscelism should be included; or in studying chiracanthism, only proven bites by that spider would be included.

Extermination of Loxosceles from the home is difficult, if not impossible, under the new restraints on the use of insecticides by authority of the Environmental Protection Agency. Simply, the best strategy for humans living in the same house with brown spiders is to warn the spiders when you intrude into their area. Turn on lights, shake out clothing and bedding, open storage areas a while before reaching in and generally show good manners. For the number of infested homes, the incidence of loxoscelism is very low.

THE VENOM

The isolation of the pure, skin-necrotizing fraction (SNF) of Loxosceles venom is very difficult. 99.98% of crude venom consists of spreading factors and other enzymes.[6-8] Compared to other venoms, the pure Loxosceles skin-necrotizing fraction is a large and complex protein molecule of about 30,000 daltons. The structure is not known but may resemble that class of large enzymes which can disassemble complex lipids.[9] Our best approach to im-

Since the author's review of research progress on loxoscelism in MISSOURI MEDICINE in 1973, the principal advancements have been in pathophysiology and in knowledge of the chemistry of Loxosceles venom. This article includes a case report which illustrates the use of dialysis as a new and effective treatment of systemic loxoscelism in a child. The prime indication is protection of the kidneys. The cutaneous loxocelism is then manageable by conservative means. **Dr. Anderson is Chairman and Professor, Division of Dermatology, University of Missouri School of Medicine.**

proved therapy at this time is by a better understanding of the venom. Studies are under way to discover the means by which the venom attacks the erythrocyte and a medication best able to block that attack. Similarly, clinicians need a treatment to be used immediately to prevent rapid injury to the capillaries of the skin at the site of the bite.

PATHOPHYSIOLOGY OF VENOM INJURY TO THE SKIN

Purified venom has been proven to act directly on the cell wall of human strain cells in tissue culture to induce immediate injury and death. The energy systems of the cell are not employed in causing the injury. No mediation through serum or tissue factors is necessary. One principal means of injury by venom to blood vessel walls, erythrocytes and renal glomeruli is certainly this immediate, direct destruction of cell walls. It is with this in vitro system that studies of therapeutic effectiveness can be evaluated most convincingly.

Work in our laboratory in 1973 showed that an immediate cause of necrosis of skin was rapid coagulation and occlusion within the small capillaries touched by venom.[10] This injury to vessels is under way long before the physician has visible evidence of necrosis. Diffusion of venom in human dermis is much more rapid than in rabbits or guinea pigs. Human endothelial cells are very susceptible to injury by small amounts of venom. Once the coagulation process begins, a cascade of other mediators of clotting and inflammation follows, giving complex and variable progress toward a typical necrotic ulcer.

Platelets are trapped in large numbers at the beginning of the vascular coagulation induced by venom in the skin. As coagulation extends, not only does hemolysis result from direct action of the venom but also from mechanical injury to erythrocytes in clots.

What other factors might further aggravate the disseminated intravascular coagulation? We suspect that the venom acts on body fat, freeing nonphysiologic fragments into the circulation which act partly as emboli, partly as abnormal mediators. Observers of the severe brown spider bite have noted that the worst cases seem to involve necrosis into fat pads, often thigh or buttock. Comparable bites in a lean body seem less dangerous to life. These clinical concepts are being evaluated and elaborated by more detailed biochemical studies.

EARLY SURGERY FOR RECLUSE SPIDER BITES

At our institution, brown recluse spider bites are never excised as initial treatment. I am unaware of any persuasive studies to show the merit of early excision. Frequently, in discussing surgical treatment, we find that no certain diagnosis of loxoscelism has been made beyond the clinical impression, and there are no available studies of the immune response to venom before and after excision. No systemic means of evaluating those cases preferred for surgery have been advanced.

Accepting only those cases in which the spider is identified, it is not evident that surgery will be beneficial. Some persuasive evidence that the excised bite was not one of the many trivial ones must be offered. Excision cannot improve on the prognosis of the common, small, brown spider bites which spontaneously heal well. It must be emphasized that for the patient, a great expense and loss of work may be involved in relying on early excision. The size of these added costs and hospitalizations should be stated. For surgery to be acceptable as early therapy, it must be proven that each spider bite selected for early excision was destined to become one of the very rare, large and deep bites. Our best clinical and immunologic techniques cannot assure us on this point, and I am unaware of other accurate predictive procedures.

It is quite typical, both in our animal studies and in natural human spider bites, for a rapidly developing necrotic lesion suddenly to arrest its spread, define a margin and remain a small, easily healed 2 cm lesion. After a skin lesion due to brown spider venom reaches 4 cm in 12 hours (measured across the axis of the avascular core, not across the ecchymosis), I would be suspicious that a severe lesion is developing, but my opinion still would be speculative. I suggest that most of the reports of successful cures of Loxosceles bites by early excision represent the overtreatment of small benign

bites. No treatment would have been preferable, but this is a viewpoint difficult for the surgical therapist to accept. To resolve this disagreement to the satisfaction of the surgical advocates, a series of verified bites might be carefully photographed and measured, and, by a randomizing device, comparable bites assigned either to conservative medical care or to treatment by early excision. A few unbiased observers would verify the data. An accurate comparison in all cases of total costs, days disabled, comfort and healing and final function both of the wound and donor sites would be impressive. No such studies are published and the burden to justify must be with the advocates of the more invasive, more aggressive, more costly procedures.

Late Surgery for Recluse Spider Bites

Many patients with large and deep necrotic spider bites, especially those extending into fat, do benefit from surgical repair of the ulcer after the natural demarcation of the injured dermis has been fully established. Selected spider bites are ready for repair in six to 12 weeks. Earlier attempts to repair often fail because the necrotic ulcer often displays poor healing mechanisms. Repeated, expertly done grafts may fail to "take" or attach as several physicians, themselves the victims of Loxosceles reclusa, have described in detail. When the victim is willing to wait and persist in home therapy perhaps as long as a year, natural healing has always occurred.

Steroid Therapy

From the time of the earliest therapy for brown spider bites with steroids, the impression was that high dose steroids used for three or four days were beneficial. These claims have not been verified. In animal studies, steroids cannot prevent cutaneous necrosis in the rabbit or guinea pig. However, the skin of humans is vastly different from the skin of these animals. My conclusion from clinical experience is that minor amelioration is the most obtained by the treatment of cutaneous loxoscelism with steroids. The important question is the worth of early steroid therapy to prevent systemic loxoscelism. In vitro studies with erythrocytes using purified venom suggest that steroids will prevent hemolysis and, thereby, may block intravascular coagulation.

When should steroids be given? Steroids are not needed at all in mild cutaneous loxoscelism; the results of no therapy, except protection and reassurance, are excellent. Large cutaneous reactions, I believe, are minimized by steroids, but experimental evidence in humans is not obtainable. Preliminary clinical studies suggest that steroids may prevent some of the worst aspects of systemic loxoscelism, but further experience is needed.

In summary, I would prefer to give high-dose steroid therapy for most large bites and always at the first indication of systemic loxoscelism, particularly if I were the patient who had been bitten. In the management of large, deep bites in children which are over fat pads or in the more fatty areas of the skin, I would favor at least three days of treatment with 100 mg of prednisone per day or the equivalent while further observations are made as to kidney injury or hemolysis.

Studies in animals have led to discarding our former practice of injecting steroids into the bite area although this eventually may prove to be a more useful treatment than we can now determine, at least for early bites in humans. Definitive studies in human skin are not possible with this dangerous, painful venom. Until more basic understanding is possible from laboratory investigations, short term/high dose steroid therapy for the more severe forms of loxoscelism is our clear choice of early therapy.

Severe Loxoscelism Managed by Dialysis

Those rare and frightening occasions when a child is bitten by Loxosceles and develops a severe hemolysis, leading quickly to coma, azotemia and anuria, are now more manageable using renal dialysis. These cases have been reported in the literature with death often being the outcome.[11-18] Actually, the usual Loxosceles bite in a child is as benign as those in adults. However, children may lack the protective humoral antibodies of most adults, and large envenomation may prove dangerous. This case illustrates the management of coma due to severe loxoscelism in a child.

Case Report

On a day in late July, the common nocturnal house spider, Loxosceles reclusa, occupied the denim shorts of our patient, a five-year-old boy who had thoughtlessly dropped them to the floor by his bed. In the morning while putting on those shorts, he was stung on the right thigh but dismissed the bite as some trivial scratch, maybe "by a briar." By noontime, the scratch was painful and was described by his mother as "a blue lump." By early evening, the dark blue area was three or four inches across, sunken and surrounded by a widening red band. During the next four hours, the boy's general symptoms worsened alarmingly. A fever of 104F arose with increasing fatigue and pain. He became disoriented, which his mother attributed to the fever. Persistent, severe vomiting developed

despite bed rest and repeated doses of aspirin. At midnight, when he passed grossly dark red urine and first complained of severe flank pain, it was decided he should be hospitalized. During the second day, his hematocrit fell to 20%, his mental status worsened, urine volume declined rapidly and a clotting disorder was evolving. He was transferred to the University of Missouri Medical Center in Columbia in anticipation of renal dialysis.

On admission to the pediatric unit 52 hours after the spider bite, he was in coma. His skin, strikingly pale and cadaver-like in color, was without jaundice. The bite on the right thigh was 24 cm by 20 cm; a blue-black, sunken, hard plaque eroded in the center. Around the bite, from umbilicus to the knee, was a patchy erythema and scattered purpura. Lymph nodes, pulses and reflexes were normal. Blood cells were prepared for the lymphocyte transformation studies, which later confirmed the diagnosis of severe loxoscelism.[8]

Hemolysis and intravascular coagulation were severe as defined by the following tests: hemoglobin 5.0 gm/100 ml; hematocrit, 15%; reticulocytes, 5%; platelets 100,000/cu mm; fibrinogen, 170-185 mg/100 ml in three tests; fibrin split products greater than 100 μg/100 ml; prothrombin time, 10.9 seconds; partial thromboplastin, 40.3 seconds; serum calcium, 7.5 mg/100 ml. Free serum hemoglobin was 320 mg/100 ml and bilirubin was 2.8 mg/100 ml.

Urine was red-black from erythrocytes, free hemoglobin and myoglobin; the quantity of urine declined steadily. Blood pressure had increased to 140/110. The serum blood urea nitrogen was over 100 mg/100 ml and creatine 8.6 mg/100 ml. The white blood cell count remained about 25,000-40,000/cu mm, increasing slowly.

Methyl prednisone therapy was started and cautious efforts were made to correct hyponatremia, to increase fluids and to replace erythrocytes. After 72 hours, however, the kidneys failed to respond and peritoneal dialysis was begun. As dialysis was started, the blood urea nitrogen had reached 180 mg/100 ml. Promptly after dialysis, the boy regained consciousness and in 48 hours was out of bed and active, with his thigh carefully protected from trauma. Dialysis was repeated regularly, and by the 13th day after the spider bite, the kidneys responded and urine output increased toward normal again. By the 21st day, the blood urea nitrogen was 25 mg/100 ml. By the 32nd day, the hemoglobin reached 10 gm/100 ml with the normal white blood cell profile restored. Protein and red blood cells continued to pass the damaged kidneys. Not until six months later was the first wholly normal urine recorded. The complete healing of the necrotic spider bite on the thigh required almost an entire year.

Several points are noted in this case. Initially, the bite evolved typically into a deep ulcer extending into fat, which is a prognostic sign for hemolysis to develop. Rapid evolution of fatigue and fever heralded hemolysis. The early onset of coma was threatening because consumptive coagulopathy may be the cause and heparin treatment may be valuable. The coma remained mild, however, and the coagulopathy was not progressive after the patient received steroids. Azotemia may have been important after 72 hours in maintaining coma. Once hemolysis is completed, in about 48 hours, steroids still may minimize vascular injury, especially in the brain. Proof of this clinical opinion is lacking. From the comfort of retrospective analysis, I would have begun steroid therapy early in the first afternoon and have expected that hemolysis would have been trivial.

The second point is that hemolysis and the ensuing kidney failure disturbed normal blood coagulation, upset acid base balance, impaired glucose metabolism and obstructed normal control of water exchange, especially overloading the extracellular fluid volume. How does dialysis benefit these patients? Dialysis experts might claim that peritoneal dialysis improves these very ill patients more because of the prompt and overall corrective effects on all of these imbalances than because of the usually cited effects of removing uremic poisons and the enzymes of inflammation. Neither hemoglobin nor spider venom is removed in appreciable amounts by dialysis.

Several children with severe loxoscelism have been managed with dialysis, all with excellent results. The prime indication is to protect the kidneys. The initial 48 to 72 hours after the bite are the crucial hours in which to begin dialysis when the indications are well established. Having protected the kidneys and avoided inappropriate coagulation, the cutaneous loxoscelism is then manageable by conservative means at a later time.

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