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CASE STUDY

Latrodectus Envenomation in Greece

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Abstract

During the summer period 2011-2012, seven widow spider bites in Greece were reported to the Hellenic Center for Disease Control and Prevention. Widow spiders (in the genus *Latrodectus*) are found all over the world, including Europe, Asia, Africa, Australia, and the US. Alpha-latrotoxin (main mammalian toxin) causes the toxic effects observed in humans. Victims should receive timely medical care to avoid suffering. *Latrodectus* bites are very rarely fatal.

All the patients reported having an insect bite 30 minutes to 2 hours before they arrived at the Emergency Department of the local hospital. Severe muscle cramps, weakness, tremor, abdominal pain, and increased levels of creatinine phosphokinase were present in all patients. The Emergency Operation Center of the Hellenic Center for Disease Control and Prevention was informed immediately in all cases. Antivenin was administered to four patients upon the request of their physicians.

All patients recovered fully. It is essential that health care workers recognize early the symptoms and signs of *Latrodectus* bites to provide the necessary care. The management of mild to moderate *Latrodectus* envenomations is primarily supportive. Hospitalization and possibly antivenin should be reserved for patients exhibiting serious systemic symptoms or inadequate pain control. The most important thing for all of these patients is early pain relief.

Introduction

The spider genus *Latrodectus,* commonly called "widow spider," is found all over the world, including Europe, Asia, Africa, Australia, North America, and South America. The genus includes the black widow spider common in North America: *L mactans*.[1] The term widow spider is used because not all species in the genus *Latrodectus* are black. There are other widow spiders including the brown widow *(Latrodectus geometricus),* the red-legged widow *(Latrodectus bishopi),* the redback spider *(Latrodectus hasselti),* the button spider *(Latrodectus indistinctus), Latrodectus variolus,* and *Latrodectus hesperus. Latrodectus tredecimguttatus* is found in Europe (including Greece) and South America.[2] The adult female *L mactans* is approximately 2 cm in length and is easily identified by its large, shiny, black abdomen with a red-orange hourglass or spot on the ventral abdomen. However, they can have variation in color and markings.[3] *Latrodectus tredecimguttatus* is black in color, similar to most other *Latrodectus* species, and is identified by the 13 spots found on its dorsal abdomen. These spots are usually red in color but may also be yellow or orange. It is otherwise similar to other species in the genus *Latrodectus.* The male *L tredecimguttatus* is smaller, brown, and incapable of envenomating humans. The female sometimes eats the male during or after copulation. Webs are irregular, low-lying, and commonly seen in dark environments such as garages, barns, outhouses, and foliage.[4] Generally, *Latrodectus* bite if they are disturbed, so people should take care when reaching into dark areas to avoid spider bites.

Alpha-latrotoxin is the main mammalian toxin found in the *Latrodectus* venom, with predominantly neurologic and autonomic effects. The toxin opens presynaptic cation channels, causing a massive influx of calcium and increased release of multiple neurotransmitters (primarily acetylcholine). This results in excess stimulation of motor endplates with resultant clinical manifestations.

No deaths caused by *Latrodectus* envenomation have been reported to the American Association of Poison Control Centers since its first annual report in 1983 until 2004.[5] Deaths caused by *Latrodectus* bites were reported in Spain (2001),[6] Greece (2003),[7] and Albania (2006).[8]

The spiders that bit the Greek victims during the summer period 2011-2012 were not caught, so it was not possible for the physicians to identify whether they were *Latrodectus* bites. However, the patients' symptoms were indicative of bites from *Latrodectus* as determined by medical personnel and supported by the positive response to the antivenin, which the Hellenic Poison Information Centre and the medical staff agreed was indicated. The antivenin used (Aracmyn Plus; Instituto Bioclon; Mexico City, Mexico) possesses the necessary mix of antibodies to neutralize the various toxic components found in spider venom. It is produced by the antibodies developed by horses that are immunized with *Latrodectus* venom.[9]

Symptoms of spider envenomation (latrodectism) may include initial localized reaction at the bite site, generally trivial, which may go unnoticed. Commonly, the bite is described as a pinch or pinprick; however, infants may present with unexplained

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crying.[10] Tiny fang marks may be visible, and local effects are usually limited to a small circle of redness, localized diaphoresis, and/or induration around the immediate bite site. A central reddened fang puncture site surrounded by an area of blanching and an outer halo of redness is described as having a target appearance. Systemic symptoms begin within about one hour and may last for a few days.

Abdominal rigidity after the bite may mimic an acute abdomen regarding the symptom's intensity.[4] It is not a true surgical emergency. Neurologic effects, including mild weakness, fasciculations, and ptosis, have been described as well. *Latrodectus* facies, characterized by spasm of facial muscles, edematous eyelids, and lacrimation, may occur. This can be mistaken for an allergic reaction. Pain in the chest, back, and extremity muscles, depending on the bite site, may occur. Respiratory symptoms including chest pain/tightness, shortness of breath, grunting and respiratory distress, bronchorrhea, and pulmonary edema have been described in Europe and South Africa.[4] Other reported symptoms include nausea, vomiting, headache, numbness, agitation, irritability, and priapism.[4]

Latrodectus envenomations may be managed with opioid analgesics and sedative-hypnotics.[11] Antivenin administration may be indicated for patients who have severe envenomation with pain refractory to these measures. Antivenin administration results in resolution of most symptoms half an hour after administration most of the time, and it has been shown to decrease the need for hospitalization.[9] Calcium gluconate, though historically a treatment, has been shown to be less effective than benzodiazepines combined with opioids.[11] Hospitalization and possibly antivenin administration should be reserved for patients exhibiting serious systemic symptoms or inadequate pain control. High-risk factors include age older than 60 years, severe envenomation, pediatric patient, or history of hypertension and coronary artery disease.

Latrodectism can be easily confused with steatodism. Steatodism is the envenomation caused by the spider species *Steatoda*. *Steatoda* resemble *Latrodectus* in size and physical form, owing to being members of the same family (Theridiidae). Although the bite of *Steatoda* spiders is not as serious as that of true widow spiders, several of these spiders do have medically

Table 1. Cases of *Latrodectus* envenomation

Demographics		Clinical symptoms and findings								
Sex	Age, years	Pain	Cardiovascular system	Respiratory symptoms	Other reported symptoms	CPK	CRP	Level of white blood cells	Other	Treatment
Male	24	Acute abdominal pain	ECG: incomplete right bundle branch block	Tachypnea, pulmonary edema	Sweating, salivation, priapism	Elevated	Elevated	Elevated	Elevated troponine (1.6 ng/mL)	Antivenin
Male	66	Severe pain in the legs at the bite point, acute abdomen (pain, flatulence)	Increased systolic pressure (200 mm Hg), signs of cardiac downturn were present without the final manifestation	Dyspnea		Slightly elevated	Elevated	Elevated (20,000/μL)	Impaired renal function (creatinine 1.4-1.6)	Oxygen (venturi mask 30%), diuretic and morphine, antivenin
Male	64	Severe pain at the dorsal surface of the right foot at the bite area, back pain		Mild tachypnea	Sweating					Pethidine
Female	70	Generalized muscle pain to back, chest, and abdomen	Mild hypertension (155/90 mm Hg)						Metabolic acidosis (pH: 7.23)	Opioid analgesics
Male	49	Intense pain at the area of bite (inner surface of the arm), extension of pain to the chest and abdomen	Increased blood pressure (180 mm Hg)		Local swelling at the bite area	Elevated (1423 U/L)		Mild leukocytosis		Oxygen, opioid analgesics, calcium and beta-adrenergic blockers, antivenin
Female	4	Intense pain at the area of bite			Local swelling at the bite area			Mild leukocytosis		Oxygen, opioid analgesics
Male	21	Severe pain in the legs, thoracic pain	Myocarditisaugmentation in T-wave amplitude in leads V3 through V6 without reciprocal changes		General anxiety			Mild leukocytosis	Elevated cardiac enzymes troponin (1.1 ng/mL)	Oxygen, opioid analgesics, antivenin

CPK = creatinine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram.

significant bites. Their bites cause symptoms that have been described as a very minor *Latrodectus* bite. Use of *Latrodectus* antivenin has been shown effective in treating steatodism.[12]

Case Presentations

All patients reported having an insect bite 30 minutes to 2 hours before they arrived at the Emergency Department (ED) of the local hospital. The bite area looked like 2 small holes. Severe pain at the bite area, acute abdomen, severe muscle cramps, weakness, and mild leukocytosis were present in most patients. Respiratory symptoms including chest pain/tightness and tachypnea were present in 3 of them. Other reported symptoms were hypertension, sweating, priapism, elevated creatinine phosphokinase (CPK), elevated C-reactive protein (CRP), pulmonary edema, dyspnea, elevated troponin levels, and metabolic acidosis.

It is interesting that two young males (first and seventh cases) manifested cardiac toxicity. The first patient's electrocardiogram (ECG) showed incomplete right bundle branch block, and he suffered elevated troponin levels; whereas the ECG of the seventh patient showed augmentation T-wave amplitude in leads V3 through V6 without reciprocal changes; he also had elevated troponin levels. Detailed information about each patient's symptoms may be found in Table 1.

The antivenin (Aracmyn Plus) was administered to 4 patients upon the request of their physicians because of the severity of their situation or the presence of underlying diseases. One or 2 vials were administered to patients. The clinical improvement of the patients occurred after half an hour of the antivenin administration. Per the manufacturer, antivenin dose varies from 1 to 5 vials depending on severity of symptoms. The antivenin Aracmyn Plus has completed human Phase 3 trials. Aracmyn Plus is an equine-origin Fab2 product and is considered to be less likely to trigger an allergic reaction.[9] One vial of the antivenin is mixed with 50 mL normal saline and is administered intravenously within 30 minutes.[9]

All patients were administered opioid analgesics for the relief of their intense pain, which is the mainstay of therapy. Readers can find more information about patients' cures in Table 1. We specifically describe here the case of the first victim, who suffered the most severe clinical signs.

Patient A. A man age 24 years came to the ED of our general hospital. The patient was sweating, with acute abdominal pain, salivation, priapism, palpitations, and reduced blood saturation. The ECG showed incomplete right bundle branch block and elevated troponin levels (1.6 ng/mL). CPK and amylase levels were elevated as well. CRP was normal, and the absolute value of white blood cells was 28,000/μL.

The patient reported experiencing intense back pain while he was sleeping, which was severe enough to wake him. After a few minutes, the symptoms appeared. On the basis of the symptoms and the statements and descriptions of the spider by the patient, it was determined that the patient was bitten by *L tredecimguttatus,* one of the European species of *Latrodectus.*

During his hospitalization in the ED, the patient suffered pulmonary edema. He was intubated, sedated, and transferred to the intensive care unit (ICU) of the hospital. ICU physicians contacted the Emergency Operations Center of the Hellenic Center for Disease Control and Prevention to request the antivenin Aracmyn Plus, two vials of which were sent immediately. The first dose of antivenin was administered while the patient was sedated, and the second dose was administered while sedation was interrupted. Half an hour after the administration of the second dose of antivenin, the patient's respiratory function significantly improved.

On the second day of hospitalization in the ICU, the patient was extubated. For his ventilation, a venturi mask was used. Initially, the patient's pulse increased during effort, but this improved by the third day of hospitalization. Cardiovascular and pulmonary systems were in good condition, and he suffered mild fever. CPK and amylase were declining; whereas CRP was increasing. The white blood cells decreased by 21,000/mL. (On the first day of hospitalization, antibiotics were administered to avoid possible local bacterial infection.)

During the third day of hospitalization, CPK, CRP, and amylase remained elevated, whereas transaminases were normal (morning). In the afternoon, CPK increased significantly (4-digit number); amylase was declining. White blood cells declined to 17,000/mL. Twenty-four hours later, CPK was on a downward trend, owing to increasing hydration and diuresis. Amylase and transaminases were increased. The patient's overall health condition was quite good, so he was moved from the ICU to the Internal Medicine Department of the hospital for further observation.

On the sixth day of hospitalization, the patient was discharged with complete recovery.

Discussion

In cases of *Latrodectus* envenomation, it is essential that health care practitioners recognize the signs and symptoms of envenomation as quickly as possible to begin the best care of patients.

To diagnose a *Latrodectus* envenomation, it is important for the physician to see the suspected spider. If this is not possible, *Latrodectus* bites are diagnosed through a bit of detective work. Evidence of the classic "target" lesion can aid the diagnosis. Additionally, other subtle findings on physical examination can be helpful. Physicians often must diagnose *Latrodectus* bites by asking patients about the onset of symptoms, how they discovered their bites, and whether they saw the spider.

Latrodectus bites are distinctive. The site of a bite develops a pale central area with surrounding erythema; often fang marks will be visible.[4] There will probably also be some swelling and redness at the area of the bite.

In the case presented here, the spider was not available for identification, so the diagnosis was made by the clinical and laboratory findings that are reported extensively in Table 1. The victims of *Latrodectus* bites in Greece experienced the typical symptoms of the venomous spider bite. These symptoms were more severe than those caused by steatodism. Thus, physicians determined the identity of the insect that caused the bite and the type of the envenomation. The first case, described here, was the most severe compared with the others reported. It is interesting that the first and the last case reported (two young men) had positive troponins, ECG manifestations indicating that they suffered cardiac toxicity.

The elevated CPK levels in the other patients more likely originated in the skeletal muscle.

Antivenin use appears justified in severe envenomation. It is available and effective, but it is often withheld because of fear of acute hypersensitivity reactions. Because of these concerns about acute hypersensitivity reactions, physicians must weigh the benefits of treating with antivenin for a condition with limited mortality.[13] This is a subject of intense debate within the toxicology community. This controversy stems from a single reported case of fatal hypersensitivity related to spider antivenin administration.[11] Generally, antivenin provides rapid symptomatic improvement—mainly rapid pain relief—as demonstrated in the cases presented here.

Calcium therapy was once considered to be an antidote for *Latrodectus* envenomation.[14] Calcium was thought to stabilize nerve membrane permeability, resulting in decreased neurotransmitter release. Although this effect was demonstrated in vitro and reported in some early clinical series, subsequent experience has not shown effectiveness. Therefore, calcium therapy has lost favor in the medical toxicology community.[11,14]

The traditional therapies for *Latrodectus* envenomation are aimed at providing symptomatic relief while venom effects resolve. Therapies include primarily opioid analgesics and muscle relaxants. In the majority of moderate to severe *Latrodectus* envenomation, patients treated with antivenin experienced a much shorter duration of symptoms and were less likely to be admitted to the hospital than those who did not receive antivenin. Relief of symptoms occurred within an average of 31 minutes of antivenin infusion.[9,11] Administration of antivenin even late in the course of envenomation has been reported to be effective. Multiple allergies, asthma, or past reactions to equine-based products should be considered contraindications. Antivenin therapy is recommended in cases of envenomation during pregnancy because of the risk of venom-induced abortion or other possible harm to the fetus, although the risk is not known.[15] Furthermore, it is not known whether *Latrodectus* antivenin passes into the breast milk. Although most medications pass into breast milk in small amounts, many of them may be used safely while breastfeeding.

Regarding the incidents in Greece, hospitalization was reserved for all patients, and antivenin was reserved for patients exhibiting serious systemic symptoms or inadequate pain control. All the patients who were administered the antivenin required hospitalization, but none of them suffered an allergic reaction. Four of seven symptomatic patients suffering *Latrodectus* envenomation were administered antivenin, and rapid resolution of symptoms was observed within about half an hour after the administration. These cases demonstrate the safe and effective use of Latrodectus antivenin. Antivenin is an important treatment for *Latrodectus* envenomation but has been less successful than those for snake envenomation, with concerns about their effectiveness for latrodectism.[11]

Conclusion

It is very important that health care practitioners recognize the symptoms and signs of *Latrodectus* to provide immediate care to *Latrodectus* bite victims. The management of mild to moderate *Latrodectus* envenomations is primarily supportive. Hospitalization and possibly antivenin administration should be reserved for patients exhibiting serious systemic symptoms or inadequate pain control. Physicians should know that high-risk factors include age older than 60 years, severe envenomation, pediatric patient, or history of hypertension and coronary artery disease. People who report these factors should receive antivenin as soon as possible to avoid suffering envenomation complications (eg, cardiovascular collapse). Finally, the most important goal for all patients is early pain relief. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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