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REVIEW

SPIDERS IN BRAZIL: FROM ARACHNIDISM TO POTENTIAL THERAPEUTIC USE OF THEIR VENOM PART 2 OF 2

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ABSTRACT

Arachnidism, spider envenomation, is an important public health issue in different parts of the world. Its clinical evolution depends on the genus involved. Symptoms and signs range from skin alterations to systemic manifestations. The success of treatment, consisting of serotherapy and other measures, depends on the patient's immediate care. In addition to the potential injury to human hosts, spider venom has been investigated for the therapy of various diseases. Based on these considerations, this article, part 2 of 2, aims to present the main aspects of spider accidents, focusing on clinical findings, diagnosis, differential diagnosis and treatment, as well as highlighting the potential of the venom of these arachnids.

KEY WORDS: spiders; spider bites; spider venom.

INTRODUCTION

Arachnidism, along with the other types of accidents involving venomous animals, is one of the main causes of morbid conditions related to toxins in Brazil (Freitas et al., 2006; Siqueira-Batista et al., 2020). According to data from the Brazilian Ministry of Health, from 2000 to 2017 392,638 accidents caused by spiders were reported nationwide (Brazil, 2019).

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Arachnidism is the designated term for accidents with spiders that inject their venom into human victims, causing a number of clinical alterations, which may be fatal in extremely severe cases. It is noteworthy that clinical evolution of spider accidents is directly related to the spider genus involved, signifying that specific measures are essential for effective treatment.

In Brazil, the three genera of spiders of greatest medical importance are *Latrodectus* (black widow), *Phoneutria* (armed spider) and *Loxosceles* (brown spider) (Silva et al., 2015a). Unfortunately, in most cases the genus of the spider involved in the accident is not known, affecting patient care and notification (Nóbrega et al., 2018). Therefore, it is necessary to gather information regarding the animal, its characteristics, the action of its venom, and associate this data with the signs and symptoms presented by the patient. This characterization is essential for recognition of the condition and for optimizing patient health care and treatment. Spider toxins are beginning to be seen as possible alternatives for the treatment of morbid conditions in human medicine with promising results, despite their potential for damaging tissues and organs.

Therefore, the purpose of this article (part 2 of 2), characterized as a narrative literature review, namely a publication *"that describes and discusses the state of the science of a specific topic or theme from a theoretical and contextual point of view"* and that *"consists of critical analysis of the literature published in books and electronic or paper-based journal articles"* (Rother , 2007, p 2) — is to (1) update the main aspects of arachnidism, particularly its signs and symptoms, diagnosis, differential diagnosis and treatment within the Brazilian territory; and (2) to look into new perspectives regarding therapeutic uses of spider venoms.

CLINICAL ASPECTS

The clinical evolution of accidents caused by venomous spiders varies according to the genus involved (Albuquerque et al., 2018) and factors related to the physical and genetic characteristics of the affected patient. The clinical developments of arachnidism usually involve cutaneous and systemic manifestations (Santana et al., 2020a; Santana et al., 2020b).

Cutaneous symptoms and signs are often similar and may include local pain (varying in intensity, sometimes quite strong), burning, irritation, itching, blistering and ulcerations. On the other hand, the systemic symptoms are fever, pain and muscle contracture, arthralgia, vomiting, sweating, diarrhea, hemolysis, anemia, disseminated intravascular coagulation, (DIC) organ failure and death (Ramos et al., 2015). To better clarify each type of engagement, the clinical conditions can be explained according to the genera of the spiders involved in the accidents.

Loxosceles

This is a genus of arachnid belonging to the Sicariidae family and includes animals whose bite causes cutaneous necrosis, popularly known as brown spiders and accidents usually occur by the accidental crushing of the spider. The venom presents mainly dermonecrotic and hemolytic action resulting in two types of clinical condition: cutaneous (or dermonecrotic) in 84 to 97% of cases, and cutaneous-visceral or (systemic) which comprises between 3 and 16% of the notified cases in Brazil (Kusma, 2008). The development of one or both types of clinical condition, as well as accident severity, depend on several factors that may be related to the specie of the spider involved; the concentration of the inoculated venom, which is usually higher in females; the animal's stage of development; the quantity of the inoculated venom; the patient's age; the genetic characteristics of the individual involved in the accident and other factors, such as the victim's nutritional status, bite location, vulnerability to the venom and the time elapsed between the accident and adequate treatment (Cullen et al., 2018; Trave et al., 2020). Therefore, it is understandable that the symptoms of loxoscelism may vary regarding severity categorized as mild, moderate and severe accidents (Figure 1).

Cutaneous loxoscelism is the most common form, and the bite is, initially, little valued, coursing with low intensity pain (Trave et al., 2020). In a case study carried out by Puerto et al. (2018), cutaneous loxoscelism was found in 81.2% of patients bitten by the *Loxosceles* spider. According to the author, cutaneous loxoscelism is generally benign and patients often present pain, edema and erythema. Regarding the clinical picture, burning is described in 91 to 100% of the cases, and can be noted from the moment of the bite or present variable latency over a period of 5 minutes to 4 hours.

The pain is accompanied by perilesional hyperesthesia, with hard or elastic edema, starting within the first hours after the bite. In 6 to 8 hours, the condition progresses to a vasoconstriction halo and ischemia encompassing the lesion. In about 50% of cases, blistering was also observed, usually without regional lymphadenopathy. The author also highlights the typical appearance of the livedoid plaque, which is visible after 24 hours as a central violet plaque with a pale halo and erythematous border. *"The central ischemic area can evolve to necrosis in three to four days and form a bedsore in four to seven days, giving rise to an ulcer. The bite tends to heal by second intention in 6 to 8 weeks"* (Puerto et al., 2018, p. 267).

Considering the composition of the venom, as seen in Part 1 of this article, formed by several toxic and enzymatic substances, among which: sphingomyelinase-D, hyaluronidases, metalloproteases, peptidases, lipases, collagenases, alkaline phosphatase, in addition to various inorganic components such as calcium and sodium, the skin lesion tends to extend

gravitationally, and may progress to dry necrosis, possibly culminating in the formation of an ulcer of varying depth and extension. Nonspecific manifestations such as fever, general malaise, weakness, nausea, vomiting and myalgia are also reported (Soncini et al., 2012; Montesu et al., 2020).

Figure 1. Arachnidism by *Loxosceles*. Spider bite occurred 64-hours previously on upper right thigh. *"This patient's symptoms included bite site ecchymosis, blistering, jaundice, hemoglobinuria, and a large superficial area of necrosis"*. Source: Centers for Disease Control and Prevention (CDC). Reproduced with permission, as public announcement on the CDC website, which can be found at https://www.cdc.gov/other/imagereuse.html. The original image is available at https://phil.cdc.gov/Details.aspx?pid=6261.

According to Soncini et al. (2012), the condition might evolve to cutaneous-visceral manifestations, the consequence of intravascular hemolysis, normally occurring within the first 72 hours; in fact, the patient may present acute anemia, jaundice, hemoglobinuria, DIC and renal failure (Cullen et al., 2018). It is noteworthy that a direct relationship is not usually established between the venom's hemolytic activity and skin alterations in loxoscelism (Soncini et al., 2012).

Phoneutria

Arthropods of the *Phoneutria* genus are popularly known as armed spiders, whose behavior is considered quite aggressive. In addition, they are invertebrates that move very fast. The venom's main mechanism of action is neurotoxic and is related to the effects of the activation and delayed inactivation of sodium channels, similar to the venom of *Tityus* scorpions (Sant'anna et al., 2021). The clinical condition produced by spiders of this genus normally consists of local manifestations, emphasizing imminent pain of varying intensity (sometimes significant), which can extend to the root of the affected limb, considered the most frequent symptom, affecting more than 90% of patients (Brazil, 2019). Other manifestations observed are edema, erythema and paraesthesia of the bite region with inoculation points, as well as profuse sweating. Local muscle fasciculation may sometimes also occur (de Roodt et al., 2017). Systemic symptoms and signs are rare, affecting around 10% of patients involved in accidents with *Phoneutria* spiders. These are characterized by profuse sweating, tachycardia, systemic arterial hypertension, prostration, vomiting and alterations in the cardiac or respiratory rhythm, pallor, priapism, convulsions, diarrhea, rales on pulmonary auscultation, which indicate the likelihood of pulmonary edema, and signs that suggest shock (Brazil, 2019b; Santana et al., 2020a).

The symptoms and signs of accidents with spiders of the *Phoneutria* genus are described according to three clinical evolution degrees (Brazil, 2019). In mild cases, the most common symptom is intense, sudden local pain that radiates within the first few hours. Local edema (Figure 2) and psychomotor agitation may also occur. In moderate accidents, the manifestations include vomiting, profuse sweating, drooling and fever. Finally, the clinical findings observed in severe accidents are tachycardia, priapism, muscular hypertonia, hypotension or systemic arterial hypertension, acute pulmonary edema, shock and, eventually, death.

Latrodectus

Animals of the *Latrodectus* genus are popularly known as black widows. The venom contains toxins, including α-latrotoxin, which acts upon the autonomic nervous system and nerve endings. The clinical picture consists of three stages (Souza et al., 1998; Brazil, 2021). In the absorption stage, taking place in the hemolymphatic route, symptoms begin within a few minutes and last a maximum of two hours. There is a "pins and needles" sensation at the location of the bite, which may appear as a red dot or be imperceptible. Subsequently, regional myalgia arises, which tends to spread throughout the extremity and the rest of the body (Santana et al., 2020a; Earwood et al., 2020). There is also a decline in the patient's general condition and muscle

contracture may occur. The second stage is characterized by the diffusion or generalization of the envenomation when tachycardia, tachypnea, mydriasis, tearing and sioalorrhea appear; paraesthesias may arise (Souza et al., 1998). It is also at this stage, according to the authors, that temperature rising is detected and there are alternating periods of contractures and mollification. Cutaneous hyperesthesia and osteotendinous hyperreflexia can also be seen in this phase. The last stage, referred to as the decline, designates the beginning of toxin metabolism, when the main clinical characteristics are attenuation of manifestations and decline in general condition, occurring between 48 to 72 hours of evolution, lasting up to six days (Souza et al., 1998).

Figure 2. Arachnidism by *Phoneutria*. Spider bite (arrow) occurred two hours previously on right foot. Note the edema. Source: Centers for Disease Control and Prevention (CDC). Reproduced with permission, as public announcement on the CDC website, which can be found at https://www.cdc.gov/other/imagereuse.html. The original image is available at https://phil.cdc.gov/Details.aspx?pid=6264.

In addition to the stages of envenomation, varying degrees of symptom evolution are observed as pointed out in the Health Surveillance Guide (Brazil, 2019). In mild accidents (1) local low intensity pain, often concomitant with a burning sensation, local sweating, appearance of an erythematous papule and local itching are reported. In (2) moderate cases, abdominal pain, myalgia, agitation, dizziness, generalized sweating, paresthesia of the lower limbs and difficulty walking can be observed. In (3) severe cases, more relevant symptoms and signs are listed, which include tachycardia/bradycardia, systemic arterial hypertension, tachypnea/dyspnoea, priapism, precordial oppression, masseter trismus, nausea and vomiting.

DIAGNOSIS

The diagnosis of accidents involving venomous spiders can be laborious, since the clinical history varies according to the genus of the animal involved; in addition, local and systemic clinical alterations are nonspecific and can lead to a false diagnosis regarding the etiology of the accident (Lopes et al., 2020). Furthermore, depending on the invertebrate involved (e.g. *Loxosceles*); the patient may be unaware of the bite history. Furthermore, laboratory alterations vary from subclinical situations to conditions that evolve with substantial severity according to the venom's toxicity (Santana et al., 2020, Santana et al., 2020b).

Given the above, some data may be relevant for the diagnosis and clinical approach to arachnidism. Identification of the spider by photograph or taking the dead animal to the health care service, description of the spider's characteristics, the type of lesion, the clinical evolution of the symptoms and findings in complementary tests (Lopes et al., 2020).

Thus, it is essential that health professionals recognize the clinical manifestations of arachnidism regarding its different etiologies (Brazil, 2019). In addition, it is necessary to identify changes in the requested laboratory and complementary tests. These changes are often nonspecific, but may be useful diagnostic aids (Warrell, 2019).

In accidents involving the *Loxosceles* genus there are no specific alterations. In the cutaneous form, normally leukocytosis and neutrophilia are observed in the blood count. In the cutaneous-visceral form, disorders such as acute anemia, indirect hyperbilirubinemia (related to hemolysis) are noted. In addition, alterations in the reticulocyte count and haptoglobin dosage (protein produced by the liver, which binds irreversibly to hemoglobin after hemolysis, forming a complex that is removed by Kuppfer cells) are considered sensitive markers for hemolysis, depending on the time of evolution; hemoglobinuria and elevated serum urea and creatinine levels, which suggest kidney damage; thrombocytopenia and alterations in the coagulogram that indicate coagulation disorders (Moranchel-Gárcia et al., 2017). ELISA testing to detect the venom in the affected area has been described; however, such trials have not been used in clinical practice (Lopes et al., 2020).

The disorders found in accidents with *Phoneutria* are similar to the laboratory alterations of scorpionism (Santana et al., 2020a). In the context of cardiac dysfunctions, sinus tachycardia or bradycardia, ventricular repolarization disorders, cardiomegaly, hyperglycemia and hyponatremia are present. In severe accidents involving children, leukocytosis with neutrophilia, hyperglycemia, metabolic acidosis and sinus tachycardia are found (Brazil, 2001). In such cases, it is advisable to evaluate the laboratory profile of arterial gases, blood glucose, electrolytes, as well as monitoring cardiorespiratory conditions.

In the *Latrodectus* genus, the alterations are also nonspecific, comprising mainly hematological (leukocytosis, lymphopenia and eosinopenia), biochemical (elevated blood glucose, C-reactive protein and phosphate), electrocardiographic (atrial fibrillation, atrioventricular block, reduction of QRS and P wave amplitudes, T wave inversion, QT interval prolongation and others) and urinary (hematuria and albuminuria) levels (Roodt et al., 2017).

DIFFERENTIAL DIAGNOSIS

Diagnosis is easier when the genus of the spider is identified, considering the non-specificity of the symptoms and signs under many clinical circumstances. When possible, a description of the animal involved helps to determine adequate and early treatment resulting in the best prognosis (Haddad et al., 2012). When in doubt, it is advisable to try to distinguish arachnidism from other morbid conditions.

In loxoscelic accidents, depending on the evolutionary stage of the lesion, some dermatological conditions such as insect bites, allergic dermatitis, skin abscess, herpetic lesions, gangrenous ectima, necrotizing fasciitis, cutaneous leishmaniasis, gangrenous pyoderma and phytophotodermatosis should be considered (Lopes et al., 2020). Other relevant differential diagnoses include cellulitis, burns, sporotrichosis, cutaneous tuberculosis, cutaneous carcinoma, erysipelas and snake bites (Martins et al., 2014). Hemolytic-uremic syndrome and envenomation by caterpillars (erucism) of the *Lonomia* genus are similar to the systemic (cutaneous-visceral) form of loxoscelism (Siqueira-Batista & Gomes, 2021). The main differential diagnosis in accidents caused by *Phoneutria*, when the animal is not identified, is the scorpionic accident, whose clinical manifestations are similar, and may even be indistinguishable (Sant'anna et al., 2021). Regarding accidents involving spiders, the most common differential diagnosis refers to the clinical conditions produced by the *Lycosa* genus; however, the pain caused by its bite is usually less intense and disappears more quickly (Barbosa et al., 2017). As for latrodectism and other cases of arachnid accidents (including phoneutrism and scorpionism), acute abdominal pain, localized tetanus, poisoning by organophosphate insecticides and intermittent acute porphyria stand out as differential diagnosis (Lazarte et al., 2009).

TREATMENT

Treatment efficiency is directly related to time elapsed between the accident and medical attention. Therefore, the faster the medical assistance, the lower the risk of complications and better the prognosis. Information regarding the type of spider involved in the accident is also a facilitating factor regarding treatment, since this can be correctly directed and initiated immediately, increasing the likelihood of a cure (Ramos et al., 2015).

Specific serotherapy is performed according to the type of accident, where antibodies are used to neutralize the action of the venom. This approach is strictly recommended, considering the severity of the accident and the spider involved. The table below presents information on the treatment for spider accidents, according to the guidelines established by the Brazilian Ministry of Health (Brazil, 2019).

Table. Serotherapy treatment for spider accidents.

Accident	Anti-venom	Severity	Number of ampoules
Phoneutric	Anti-arachnid serum (AAS)	Mild: local pain, edema, erythema, sweating and piloerection	–
		Moderate: intense local pain, sweating, ocasional vomiting, psychomotor agitation, systemic arterial hypertension	2 to 4
		Severe: profuse sweating, sialorrhea, profuse vomiting, priapism, shock, acute pulmonary edema	5 to 10
Loxoscelic	Anti-loxoscelic serum (ALoxS) or AAS	Mild: identified spider, uncharacteristic lesion, absence of systemic involvement	–
		Moderate: regardless of the spider's identification, suggestive or characteristic lesion, nonspecific systemic manifestations (rash, fever), absence of hemolysis	5*
		Severe: characteristic lesion, clinical manifestations and/or laboratory evidence of intravascular hemolysis	10*

*Combination with prednisone is recommended: in adults, 40 mg/day; and in children, 1 mg/kg/day, for 5 days.

Source: Adapted from Brazil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Guia de Vigilância em Saúde: volume único [recurso eletrônico] / Ministério da Saúde. Brasília: Ministério da Saúde, 2021.

Regarding loxoscelism, there is still controversy on the best treatment for skin lesions (Lopes et al., 2020). Different treatment protocols have been proposed, depending on the severity of the injury (Sams et al., 2001; Lopes et al., 2020; Santana et al., 2020a;), which can be classified as mild, moderate and severe, considering, mainly, the presence or absence of necrosis and its extension (Sams et al., 2001; Lopes et al., 2020). In general, the treatment of mild injuries "*includes RICE (rest, ice, compression and elevation), antihistamine, aspirin and tetanus and diphtheria prophylaxis"* (Lopes et al., 2020, p. 10). For moderate injuries, Lopes et al. (2020) believe that the use of analgesics, antibiotics (if there is secondary infection) and, in some cases, dapsone, especially in severe injuries, is indicated. Hyperbaric oxygen therapy and surgical treatment may be necessary in some cases (Swanson & Vetter, 2006; Cetinkaya et al., 2020). Skin lesions are not, as a rule, prevented by the use of serotherapy (Lopes et al., 2020). In the case of systemic implications, supportive therapy may be necessary, including blood transfusion, plasmapheresis, dialysis, as well as hydration and systemic corticosteroids (Lopes et al., 2020).

Drugs such as analgesics, anti-inflammatories, antipyretics and others have also been administered to control symptoms and signs resulting from *Phoneutria* accidents (Brazil, 2019). Medication should be introduced as soon as possible since the patients' main complaint is usually pain. Analgesia can be carried out locally, with trunk block using 2% lidocaine or similar medication, without vasoconstrictors. If there is no prompt response to the anesthetic, it can be administered again after an hour. If the victim still does not show significant pain reduction, 50 to 100 mg of meperidine (children = 1 mg/kg) is suggested (Brazil, 2001; Brazil, 2021).

According to Ryan et al. (2017), severe and persistent pain affects half to two thirds of patients with latrodectism and is the main symptom addressed. Treatment has varied from intravenous calcium gluconate injection to muscle relaxants, *"such as benzodiazepines with opioid analgesia to specific treatment with antivenom, such as red spider antivenom (RBSAV, purified IgG-F (ab) 2) and black widow spider antivenom (whole IgG L. mactans)"* (Ryan et al., 2017, p.2) when available; while chlorpromazine 25 to 50 mg (children, 0.55 mg/kg/dose) at 8 hour intervals can also be used (Brazil, 2021).

PROSPECTS: SPIDER VENOM AS MEDICATION

Although spiders are seen as dangerous and often lethal animals to humans, such invertebrates have been extensively studied recently due to the components of their venom, which appear to have therapeutic properties (Saez & Herzig, 2019). Biochemically, spider venom is composed of small polypeptides, molecules rich in disulfide, with low molecular weight (around 10 kDa mass), high potency and high selectivity compared to traditional small

molecule drugs, which makes these biomolecules ideal for the therapeutic development of new drugs. Another differential regarding these substances is their high selectivity, which allows the active ingredient to reach its therapeutic target in a more direct and effective way, aiding reduction of side effects (Saez & Herzig, 2019).

A lot of promising research is being developed, including some undergoing clinical trials. These studies have demonstrated the great potential to be found in spider toxins, such as the armed spider (*Phoneutria nigriventer*) that presents therapeutic properties for erectile dysfunction (Fernner, 2015). One of these studies from the Federal University of Minas Gerais stands out, in which a peptide with therapeutic action was developed for erectile dysfunction, without the contraindications or warnings of cardiac risk in current medications (example: sildenafil and tadalafil) (Silva et al., 2015b). This new compound was obtained from a peptide that integrates the venom, synthesized from a non-toxic derivative, capable of contributing to different erectile dysfunction modalities. The discovery of this substance came from the finding that one of the effects of spider bites on male animals (including humans) is erection (sometimes priapism) (Nunes et al., 2008).

Another therapeutic action of *P. nigriventer* venom, investigated and discussed in recent years, concerns its analgesic effect. In fact, a purified synthetic peptide, called Phα1β, demonstrated a longer lasting and potent analgesic effect when compared to morphine. In addition, it was also found that such a substance was able to increase the analgesic effect of morphine, reducing adverse reactions and improving drug tolerance (Tonello, 2015).

Some potential therapeutic effects of spider venom are also under research within the oncology field. A study carried out at the State University of Campinas, São Paulo (SP), in rats with glioblastomas, showed encouraging results. In the study, three groups of rodents were compared: (i) one group received PNV (*P. nigriventer* venom component), (ii) one group received methotrexate (MTX) while (iii) the third was the control group. The results showed that after administering the compounds, the group of rats that received the PNV, compared to the other two, evolved with smaller tumors, increased activation of macrophages around the tumor, loss of histopathological characteristics of glioblastoma, weight gain and greater survival (Bonfanti et al., 2020). This and other studies (Barreto dos Santos et al., 2019; Nicoletti et al., 2017) demonstrate the antineoplastic and cytotoxic potential of substances originating from spider venom in cancer therapies.

The biotechnological applications of animal venom — in this case, spiders — are beginning to be seen more clearly (Bonfanti et al., 2020; Herzig et al., 2020; Nicoletti et al., 2017). As there are thousands, perhaps millions, of bioactive peptides in the venom of some of these invertebrates, these are becoming valuable resources for researching new drugs, as is also the case with some snake and scorpion venom (Nentwig, 2013).

FINAL CONSIDERATIONS

The present manuscript — the second part of a set of two articles — aimed to address accidents caused by spiders in Brazil, dealing with aspects related to the clinical condition, diagnosis and treatment of these nosological entities. The relevance of recognizing spider genus whenever possible in an articulated way to aid the clinical course of each morbid incident was highlighted and the different therapeutic approaches were emphasized. Prospects regarding use of spider venom as drugs were also explored, recognizing its potential for the treatment of erectile dysfunction, pain and neoplasms, which makes the systematic study of these invertebrates one of the current uppermost themes in biological sciences and health.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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