RESEARCH ARTICLE

LONOMIC ACCIDENT AND ALLERGIC REACTION TO ANTI-LONOMIC SERUM; CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

A 80-year-old male patient with a clinical picture of macroscopic hematuria, subsequent contact with the family of the Saturniidae family, on admission is documented by prolonged coagulation times, consumption of fibrinogen and elevation of azotees. It was managed with antilonomic serum and is a problem of reaction and allergic reaction required management with corticosteroids, plasma transfusion and tranexamic acid. In this case report, a review of the literature on poison literature, pathophysiology and treatment measures is carried out.

Key words: Lonomic accident; Coagulation; Anti-lonomic serum.

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INTRODUCTION

Lonomic accident, the accident caused by contact with caterpillars or worms of the genus Lononia. During the last years, accidents in humans caused by contact with caterpillars of the genus Lononia have been reported. Since 1967 lonomic accidents have been reported by in different countries of South America, taking importance for the production of a hemorrhagic picture that becomes fatal. The caterpillars of the genus Lononia are light greenish brown and reach a length of up to 6 or 7 centimeters, they have spines that are distributed throughout the body and that break when they come into contact with the skin penetrating it, which favors the entry of the poison, which produces malaise, headache and nausea and between 2 and 72 hours later produces ecchymosis, gingival bleeding, epistaxis, vaginal bleeding, hematuria, gastrointestinal bleeding and intracranial hemorrhage, prolongation of coagulation times and fibrinogen decrease with normal platelet numbers.

Case Report

An 80-year-old male patient from Puerto Gaitán (Meta-Colombia), with no relevant medical history, who presents a clinical course of 4 days of evolution, consisting of pain in the left flank and macroscopic hematuria subsequent to contact with poisonous caterpillar. On admission, the patient is hemodynamically stable, with pain on palpation of the left flank, without signs of peritoneal irritation without any other positive finding. Paraclinics with prothrombine time (PT) that does not clot at 3 minutes, partial thromboplastin time (PTT) 37.3s control 25 s, fibrinogen 92.5 mg / dl, hemoglobin 15.1 gr / dl, hematocrit 44.7% platelets 194,000 ul, uroanalysis with 200 erythrocytes / ul and red blood cells> 25 x field, BUN: 22.7 mg / dl, creatinine 1.08 mg / dl. Anti-lonomic serum (ALS) was administered, with subsequent presentation of acute respiratory distress syndrome secondary to the administration of serum. It is transferred to intensive care unit, with significantly improved with corticosteroid and furosemide administration, did not require intubation. Two days after this event, the patient presented improvement in respiratory parameters, absence of hematuria, normalization of coagulation times and reduction of azote levels.

Poison components

Poison composition: The majority of the caterpillar venom is made up of protease inhibitors, serine protease, lipocalcienas, metalloloprotease, lectins and phospholipases, among others (Maggi et al., 2015).
The venom of the caterpillar has a protein that was called calcium activating protease that converts prothrombin into thrombin (Lopap), it’s a protein with a mass of 69 kDa in its natural form and has a serine-like protease activity activated by calcium ions (Fritzen et al., 2005 and Pinto et al., 2008). Consumption coagulopathy, with an onset of intravascular coagulation and thrombosis in the postcapillary vessels, has been associated with the action of Lopap that has been observed in a study with rats when said protein is administered (Maggi et al., 2015; Reis et al., 1999; Fritzen et al., 2005 and Pinto et al., 2008). It has been shown that Lopap is dose-dependent and capable of producing active thrombin, and according to its dose, calcium ions act as activity enhancers. In a study, Fritzen showed that Lopap increased the production of nitric oxide and other proinflammatory mediators such as prostacyclin 1, interleukin-6, interleukin-8, tumor necrosis factor - alpha, however, it was not able to modulate the expression of the mediators involved in the coagulation and fibrinolysis system or to induce the release of von Willebrand factor or its synthesis by the endothelial cells and neither the modulation of the tissue factor and the cellular plasminogen activator (Reis et al., 1999; Fritzen et al., 2005; Avila et al., 2013 and Nascimento-Silva et al., 2012).

In an Alvarez / Flores study, they identified a protein named stuart-factor activator (Losac), which acts on the activation of factor X (Pinto et al., 2008). This protein triggers the release of nitric oxide and stimulates the growth and inhibition of endothelial cell death. Additionally, Campos and Dias da Silva identified phospholipase A2 activity and its activity depends on the presence of a substrate of phospholipids and calcium ions; this enzyme showed a hemolytic activity (Maggi et al., 2015; Nascimento-Silva et al., 2012 and Medeiros et al., 2014). Berger in his work found a mechanism of calcium-dependent venom that involves arachidonic acid metabolites of the cyclooxygenase pathway and the activation of phosphodiesterase 3A and thus generates platelet aggregation. Additionally, lonofibrase has been described, which is a 35 kDa enzyme that involves a rapid and selective degradation of alpha fibrinogen chains and with less beta efficiency, and has the capacity to cut fibrin and plasmin (Maggi et al., 2015).

**Inflammatory response**

In a study carried out by Nascimento-Silva and collaborators with rats (Nascimento-Silva et al., 2012), it was found that the inflammatory response is activated by direct injury at the endothelial level initially generating activation of the kallikrein-kinin system causing edema, pain and the initial clinical symptoms, the release of prostaglandins, the hypotensive and nociceptive effect. The expression of tumor necrosis factor alpha and nitric oxide release, favored by the release of proinflammatory molecules such as interleukin-8, ICAM-1 and E-selectin (Pinto et al., 2008; Nascimento-Silva et al., 2012; Barrios et al., 2012 and Taylor et al., 2016). On the other hand, interleukin-6 was implicated in the immune response mediated by ICAM-3 and CCL2 that encodes the monocyte chemoattractant protein (Pinto et al., 2008). It was also documented that the activation of endothelial cells after exposure of the poison to non-hemorrhagic doses generated a significant initial vasodilation that increased the expression of adhesion molecules and endothelial interactions with circulating leukocytes with postcapillary venules (Nascimento-Silva et al., 2012). The venom activates the expression of proinflammatory adhesion molecules E-Selectin and VCAM-1 and the induction of leukocyte adhesion and extravasation to the adjacent inflammatory tissue (Fritzen et al., 2005; Nascimento-Silva et al., 2012 and Medeiros et al., 2014). The increase of the vascular permeability generated by the inflammation requires a reorganization of the cytoskeleton necessary for the formation of the cellular gap junctions, likewise the reorganization of the actin is an important component of the inflammatory response and this reorganization given by the venom facilitates the formation of stress fibers that requires anchoring to focal adhesion, such as focal kinase adhesion and signaling proteins (Nascimento-Silva et al., 2012). Focal kinase activation generates an increase in phosphorylation and its subsequent association with actin (Nascimento-Silva et al., 2012).

Vascular injury is associated with greater expression in adhesion molecules, growth factors, cytokines and inducible enzymes by endothelial cells (Fritzen et al., 2005 and Nascimento-Silva et al., 2012). These enzymes not only contribute to the appearance of the reaction through the synthesis of proinflammatory molecules but also to the resolution of the inflammatory response. The appearance of inducible enzymes in endothelial cells is controlled by the activation of NF-kB that is followed by increased expression of COX2, HO-1 (Hemoxigenase-1) and iNOS (nitric oxide synthase), as well as the induction of endothelial cells for the formation of metalloprotein from the tissue matrix (Nascimento-Silva et al., 2012 and Medeiros et al., 2014).

**Pathophysiology**

There are many physiopathological mechanisms that are carried out after the lonomic accident, in vivo study has been difficult, so most studies have been conducted in rats or rabbits and it has been shown that many of the manifestations will depend of the dose received from the poison. Within the alterations in the lonomic accident we can find alterations related with consumption coagulopathy, secondary fibrinolysis, procoagulant activity and anticoagulant simultaneously, thus generating pulmonary hemorrhage, cerebral hemorrhage, renal failure, among others (Nascimento-Silva et al., 2012).

**Coagulation and platelet alterations**

It has been shown that there is plasma reduction of fibrinogen and factor XII and increase in the products of fibrinogen degradation (Pinto et al., 2010). During the poisoning there is an expression of tissue factor increasing the activity of thrombin, plasmin and urokinase which indicates an activation of coagulation and urokinase during fibrinolysis (Fritzen et al., 2005 and Pinto et al., 2010). Platelet aggregation was evidenced 6 hours after exposure with the venom and produces an alteration and inhibition of ADP and collagen, additionally the increase in nitric oxide increased which decreases platelet aggregation (Maggi et al., 2015; Fritzen et al., 2005; Barrios et al., 2012 and Pinto et al., 2010). Additionally, it was found that fibrin and fibrinogen degradation products are involved in platelet hypoaggregation since they bind to the GP Ib-IIa receptor and prevent normal aggregation (Fritzen et al., 2005 and Pinto et al., 2010). The active principles of the venom generate an initial activation of prothrombin and factor X that generate significant amounts of intravascular thrombin that leads to the activation of the coagulation system and the consumption of fibrinogen and other coagulation factors, the olytic fibrin enzymes degrade both fibrinogen and fibrin.
contributing to the reduction of fibrinogen levels and the incoagulability of blood. In addition, olytic enzymes also participate in the generation of FIDP that are probably involved in the disturbance of platelet aggregation (Pinto et al., 2010). Fritzen, conducted a study with a protein from the caterpillar venom extract and showed that it produced an increase in the release of molecules that regulate vascular tone, inhibiting platelet activation and chemotaxis through the direct effect on endothelial cells (Maggi et al., 2015; Fritzen et al., 2005 and Nascimento-Silva et al., 2012).

Intravascular hemolysis

In studies with rats it was documented that caterpillar venom has a cytolitic effect on erythrocytes, causing intravascular hemolysis and anemia (Maggi et al., 2015; Fritzen et al., 2005; Barrios et al., 2012 and Pinto et al., 2010), initially a reduction of erythrocytes and increase of circulating hemoglobin was documented during the first 6 hours. 24 hours after poisoning, there was a decrease in hemoglobin and haptoglobulin and an increase in LDH and unconjugated bilirubin, and in the peripheral blood smear general polychromatography and erythrocyte swelling were found (Maggi et al., 2015; Fritzen et al., 2005 and Pinto et al., 2010). Such hemolytic activity is granted a phospholipase A2 or lonomiatoxin present in the venom, generating a protein degradation of the erythrocyte cell membrane. Hemolytic activity may also be due to microthrombotic deposits in the vasculature as seen in thrombotic microangiopathy (Maggi et al., 2015; Pinto et al., 2008 and Pinto et al., 2010).

Inflammation and vascular disorders.

The contact with the poison of the caterpillar generates pain, burning sensation, edema and erythema. This type of reactions has been found in animal studies that are mediated by prostaglandins, together with other mediators such as bradykinin that could contribute to the general painful nociceptive effect (Pinto et al., 2010). Additionally, an activation was found in the Kallikreina / kinina system (SKK) through the activation of prekallikrein in the plasma and in this sense the SKK seems to be the main responsible of the edema (Maggi et al., 2015; Nascimento-Silva et al., 2012 and Pinto et al., 2010). The venom of the caterpillar has local and systemic effects including the ability to modulate vascular system properties, including hypotension and followed by intracerebral hemorrhage (Medeiros et al., 2014 and Pinto et al., 2010). Studies in animals have found alterations in vascular tone and in the structure of the vessel wall, which is related to intracerebral hemorrhages due to damage to the blood-brain barrier, generating an increase in permeability due to an alteration in the diameter of the vessel secondary to the action of proinflammatory molecules. Also the presence of vacuoles and the generated vasogenic edema could generate hemorrhage in the central nervous system (Nascimento-Silva et al., 2012 and Pinto et al., 2010). The hypotensive effect is related to the SKK, since in studies with rats after administration of aprotinin (SKK inhibitor) the hypotensive effect is completely resolved (Maggi et al., 2015 and Pinto et al., 2010). In conclusion, it is not possible to detail a single toxin that is involved in the systemic and vascular effects, since the procoagulant activity of the venom generates vascular alterations, for which reason the poisoning syndrome is the result of a synergistic action of the compounds (Pinto et al., 2010). The activation of the Kallikreina-kinina system has been described in the action of the poison. A kinin release of all Kininogens is generated, which can be activated by low molecular weight kininogens or by the action of prekallikrein and in this way a decrease in pressure, edema and the aforementioned effects of venom can be seen (Maggi et al., 2015).

Hemorrhagic syndrome

The hemorrhagic syndrome develops after contact with caterpillars and is characterized by low levels of fibrinogen, plasminogen, factor V and factor VIII (Maggi et al., 2015). During the investigations, a serine protease called Lonomin V was identified as responsible for the inactivation of factor XIII from different origins with proteolytic activity on fibrin, fibrinogen and factor XIII (Maggi et al., 2015 and Barrios et al., 2012). The characteristic hemorrhagic syndrome is caused by consumption coagulopathy, which can progress to hypotension (together with the other factors already mentioned), edema, erythema and intravascular hemolysis (Maggi et al., 2015). Among the initial findings is blood coagulation followed by depletion of fibrinogen that was attributed to the presence of factor X and prothrombin activators and coagulation factor II in the venom, and subsequently there is an activation in fibrinolytic activity (Maggi et al., 2015 and Pinto et al., 2008). Additionally, an association of the inflammatory response is found after the activation of TNF-alpha and fibrinogen since this cytokine causes the release of plasminogen activators from the endothelial cells with the subsequent formation of plasmin. In addition, TNF-alpha activates neutrophils that release elastase and both plasmin and elastase degrade fibrinogen (Barrios et al., 2012).

Alterations in gene expression

An alteration in gene expression has been evidenced in different types of cells including fibroblasts, and also an alteration in positive regulation in proinflammatory mediators such as IL-8, IL-6, CCL2, CXCL1 and cyclooxygenase 2, who are quimoatraactive of monocytes, neutrophils, basophils and T cells in the endothelial cells of small blood vessels (Fritzen et al., 2005; Nascimento-Silva et al., 2012 and Pinto et al., 2010). Additionally, there is a gene expression in favor of the soluble receptor urokinase plasminogen activator (gene expression favored by TNF-a) that can contribute to the activation of the indirect fibrinolytic system, this activation generates proteolytic activity and may be responsible for the proteolytic activity of fibrin, the extracellular matrix, activating metalloproteases of the matrix, which facilitates cell migration and tissue remodeling; in addition, it could inactivate the coagulation factors V and VIII (Fritzen et al., 2005; Pinto et al., 2008; Taylor et al., 2016 and Pinto et al., 2010 ). In some studies, an increase in the expression of tissue factor phospholipase was found in the poisoned cells, and it was evidenced that the tissue factor has a procoagulant activity that is not completely neutralized with serum (Pinto et al., 2010).

Transcriptome of the Oblique Lonomy

Four important families of proteins in the venom that could be related to the symptomatology have been identified (Pinto et al., 2010). 1. The serine proteases are the most relevant family associated with activities similar to coagulation factors so they participate in the generation of thrombin by the activation of factor X and prothrombin and in the activation of the
fibrinolytic system contributing to the degradation of fibrinogen and as a result, hemorrhage (Fritzen et al., 2005 and Pinto et al., 2010). 2. Phospholipases are another group that alter hemostasis and effectively affect blood coagulation and platelet aggregation. Phospholipases directly modulate platelet aggregation and destabilize coagulation complexes by phospholipid degradation. 3. Group C lectins have also been found another type of venom, such as snakes, so there is a close relationship between the physiopathological findings related to the hemorrhagic disorder presented. Finally, the serine protease inhibitors, that generate an inhibition in the coagulation factors. These findings and characteristics have been found thanks to the transcriptomic analysis, however, the way in which the proteins of the poison act are still not exactly known (Pinto et al., 2010).

Diagnosis

The diagnosis of lonomiasis is clinical and is based on the presence of coagulopathy or systemic hemorrhage in a previously healthy patient who has had contact with the worms 48 hours before the manifestations, is clearly clinical and must be included in the history (Ávila et al., 2013 and Santos et al., 2017).

Severity of the event

The Ministry of Health of Brazil established 3 degrees of severity:

- Mild: The cases only shows local manifestations (coagulation times altered or not) (Ávila et al., 2013 and Santos et al., 2017 and Sano-Martins et al., 2017).
- Moderate: Local manifestations, bleeding in the skin, membranes, mucous membranes and mild coagulopathy (prolonged coagulation time) (Maggi et al., 2015; Ávila et al., 2013 and Santos et al., 2017 and Sano-Martins et al., 2017).
- Severe: Previously named symptoms associated with visceral or potentially fatal bleeding (acute renal failure (ARF), intracerebral, alveolar or peritoneal hemorrhages) (Maggi et al., 2015; Ávila et al., 2013 and Santos et al., 2017 and Sano-Martins et al., 2017).

Treatment

The treatment of choice for the lonomic accident is the administration of antilonomic serum (SAL), since its development in 1996 in Brazil (Da Silva et al., 1996), since it is able to neutralize the poison and normalize the coagulation times by means of F(ab') antibodies (Avila et al., 2013; Medeiros et al., 2014; Pinto et al., 2010 and Berger et al., 2013). A dose of 10 ml is sufficient for the treatment of a conventional poisoning, studies have shown that a higher dose does not impact the outcomes or the presence of complications, therefore, it is not indicated (Caovilla and José Guardão Barros, 2004). Conventional management, prior to the development of SAL, was the use of antifibrinolytic drugs epsilon-aminocaproic acid (EACA) at an initial dose of 30 mg / kg intravenously followed by 15 mg / kg every 4 hours (main recommendation) or tranexamic acid 15 g / d (oral or intravenous). Where clinical improvement was seen in the clinical manifestations of bleeding (Avila et al., 2013 and Medeiros et al., 2014). But the study done by Gonçalves et al., in 2007; who compared the effectiveness, in animals, of the use of SAL or EACA, the combination of both or the use of saline solution without any other medication; where there is improvement in coagulation and fibrinogen times regardless of the time of administration, without significant difference with the group treated with the combination of EACA and SAL, on the other hand the group treated with EACA or saline did not show improvements in the mentioned parameters previously independent of the time of administration, it can even increase mortality (Gonçalves et al., 2007). It is recommended the use of purified human fibrinogen in those whose fibrinogen values are below 100 g / L, at a dose of 2-4 U / day, evaluating paraclinical parameters. On the other hand, the use of whole blood or fresh frozen plasma is not recommended since there has been a significant increase in mortality, in the case of anemia the use of red blood cells is more advisable (Arocha-Piñango and Guerrero, 2003 and Coll-Sangrona Arocha-Piñango, 1998).

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