Lonomia Genus Caterpillar Envenomation: Clinical and Biological Aspects

Carmen Luisa Arocha-Piñango Belsy Guerrero

Centro de Medicina Experimental, Laboratorio de Fisiopatología, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas, Venezuela

Key Words

Lonomia caterpillars · Hemostasis · Bleeding syndrome · Animal venoms

Abstract

Persons who have been in contact with *Lonomia achelous* or *Lonomia obliqua* caterpillars present external and internal bleeding and opening of recently healed wounds. Hematological tests show normal platelet count, prolonged prothrombin time, activated partial thromboplastin time and thrombin time, totally corrected by normal plasma. Decreased fibrinogen (Fg), factor (F) V, FXIII, plasminogen and α_2 -antiplasmin with increased FVIII:C, von Willebrand factor, Fg degradation products and D dimers. Tissue plasminogen activator, plasminogen activator inhibitor and protein C varied. In *L. achelous* biological fluids, compounds with anticoagulant or procoagulant properties have been identified. In *L. obliqua* bristle extracts, mainly procoagulant activities have been identified. Subcuta-

neous injections of *L. achelous* crude extracts and a semipurified fraction reduce Fg, plasminogen and FXIII in rabbits. Intravenous injections of a very purified fraction of *L. achelous* in rabbits produce lysis of preformed thrombi, a decrease of Fg, plasminogen, α_2 -antiplasmin, FXIII and inhibition of post-thrombolytic thrombus growth. Subcutaneous injections of *L. obliqua* bristle extracts prolong prothrombin time and activated partial thromboplastin time and reduce FXIII. Intravenous injections of crude bristle extract and a purified fraction of *L. obliqua* induce disseminated intravascular coagulation.

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Introduction

In 1967, we reported 5 cases of a severe bleeding syndrome occurring in humans who have been in contact with spiny-hair caterpillars in Venezuela [1]. Since 1972, new patients have been reported from different areas

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C.L. Arocha-Piñango
IVIC, Apartado 21827
Caracas 1020A (Venezuela)
Tel. +58 212 504 1140/1180/1087, Fax +58 212 504 1086
E-Mail carocha@ivic.ve and bguerrer@medicina.ivic.ve

of Venezuela and other South American countries: Brazil, French Guyana [2–9] and also cases from Peru, Paraguay, Argentina and Colombia (congress reports and personal communications).

Lemaire [10] identified the caterpillars from Venezuela as the larvae of the Saturniidae moth *Lonomia achelous* (Cramer), those from the north of Brazil as *Lonomia diabolous* (brown variety of *L. achelous*), and those from the south of Brazil as *Lonomia obliqua* (Walker).

Clinical Aspects

The patients experienced pain and a burning sensation at the site of contact, headache, malaise, and fever in children, followed by obtundation or coma. External and internal bleeding started within a period of 1 h to 10 days after contact [1–3, 6–8]. In South Brazil, about 12% of the patients developed renal insufficiency, whereas in Venezuela, it has been detected only in 1 case [4, 5, 9]. Laboratory tests show anemia, leukocytosis, normal glycemia and liver function, and high values of creatinine and urea in cases of renal insufficiency, as well as prolonged prothrombin time, activated partial thromboplastin time, and thrombin time, which are totally corrected by the addition of normal plasma. The levels of platelets, factors (F) II, FVII, FIX, FX, FXI, FXII, and antithrombin III were normal. However, the tests reflected a marked decrease in fibrinogen (Fg), FV, FXIII, plasminogen (Pg) and α_2 -antiplasmin with a moderate increase in FVIII:C and von Willebrand factor, short euglobulin lysis time, and high titers of Fg degradation products and D dimers. Tissue plasminogen activator, plasminogen activator inhibitor-1 and protein C varied [1–3, 6–8]. Some patients presented thrombin-antithrombin complexes [11].

The treatment has changed in Venezuela according to clinical response and because new drugs have been discovered. The first cases were treated with whole blood or fresh frozen plasma. The patients clinically deteriorated with a decrease in platelets, FII, FV, FVII, FVIII:C, FXIII, Pg and α_2 -antiplasmin, and a slight increase in Fg. Some patients died of cerebral hemorrhage, and those who recovered did so very slowly. In the following years, ϵ -amino caproic acid (Capramol, Choay, France) and aprotinin (Trasylol, Bayer, Germany) began to be used together with replacement therapy. A slight decrease in platelet counts without alteration of the other clotting factors and slow clinical recovery were observed. Years later, only purified human Fg (Immune AG, Austria) together with aprotinin have been used. In some patients, ϵ -amino caproic acid was administered after aprotinin. A very fast clinical recovery and normalization of hemostatic parameters were observed; with the exception of Fg which improved slowly [7, 8]. In Brazil, ϵ -amino caproic acid has been the drug of choice, but recently, the Instituto Butantan in Sao Paulo has developed an anti-*lonomia* antiserum from *L. obliqua* bristle extract. The antiserum has been tested in animals as well as in humans and seems to be effective [12, 13].

Biochemical Studies

Several compounds with anticoagulant or procoagulant activities have been detected in the venom of both *L. achelous* and *L. obliqua* caterpillars (table 1).

Anticoagulant Compounds

The venom of *L. achelous* contains a urokinase-like serine protease (lonomin I) [14, 15] and two serine proteases, named achelase I and II (lonomin II), showing direct fibrinolytic

Table 1. Compounds identified in *L. achelous* and *L. obliqua* venoms

Anticoagulants	<i>L. achelous</i>	plasmin-like (lonomin II) urokinase-like/F XIII protease (lonomin I/lonomin V) FV inhibitor (lonomin VI:i)
	<i>L. obliqua</i>	fibrino(geno)lytic protease
Procoagulants	<i>L. achelous</i>	direct prothrombin activator (lonomin III) FXa-like (lonomin IV) FV activator (lonomin VI:a)
	<i>L. obliqua</i>	FX activator prothrombin activator (Lopap)
Miscellaneous	<i>L. achelous</i>	kallikrein-like (lonomin VII) extracellular matrix protease
	<i>L. obliqua</i>	phospholipase A ₂ -like (lonomia toxin)

ic activity. Their amino acid sequences exhibit high similarity to other lepidopteran larva serine proteinases [16]. Lonomin II degrades Fg, forming fragments different from those produced by plasmin and trypsin with a very rapid degradation of the α -chain [17]. These findings may explain the noninhibitory effect of high levels of Fg degradation products found in the patients as demonstrated by total correction of prothrombin time, activated partial thromboplastin time and thrombin time by normal plasma [1, 7, 8]. The venom of *L. achelous* also contains a serine protease (lonomin V) which produces a dose-dependent decrease in FXIII activity from plasma and platelets and shares many characteristics with lonomin I. It is likely that the same molecule (lonomin I and lonomin V) has both activities. Therefore, we decided to name this protease lonomin I/V [18–21]. Its N-terminal sequence shows 75% homology to the achelases (lonomin II) [unpubl. results]. Finally, the venom of *L. achelous* contains a FV inhibitor (lonomin VI:i) which also seems to be a serine protease [22]. On the other hand, the venom of *L. obliqua* contains a fibrino-(geno)lytic activity which produces fragments

different from plasmin and similar to those reported for *L. achelous* [6, 23].

Procoagulant Compounds

Two types of prothrombin activators are present in *L. achelous*: a direct activation (lonomin III) and a FXa-like (lonomin IV) which have not yet been completely characterized [24]. In addition, there is a FV activator (lonomin VI:a) which seems to be a metalloproteinase [22]. In *L. obliqua*, a calcium-independent FX activator [25] and a calcium-dependent prothrombin activator named *L. obliqua* prothrombin activator protease (Lopap) have been identified (table 1). The N-terminal sequence of Lopap showed no similarity to any other prothrombin activator [26, 27]. This prothrombin activator differs from that of *L. achelous* in that the later is calcium independent [24–27].

Miscellaneous

L. achelous hemolymph, hair secretions or purified fractions and *L. obliqua* crude bristle extracts and purified fractions do not clot purified Fg nor hydrolyze chromogenic substrates specific for thrombin, and do not in-

duce platelet aggregation in vitro [6, 7, 13, 14]. A kallikrein-like compound (lonomin VII) has been identified in *L. achelous* [15] and a protease which hydrolyzes laminin and fibronectin [unpubl. results]. Zymographic studies of *L. achelous* hemolymph and its semipurified fractions show areas of lysis of different molecular weights, some of which are plasminogen dependent [28]. These results correspond to the fibrinolytic activities of lonomin I and lonomin II [14, 16]. *L. achelous* crude hemolymph and a semipurified fraction lyse whole blood clots. This lysis is not inhibited by human plasma, thus indicating that the fibrinolytic physiological inhibitors do not act on them [29]. In *L. obliqua*, a phospholipase A₂-like activity (lonomiatoxin) has also been identified [30]. An antiserum has been prepared at the Instituto Butantan, Sao Paulo, Brazil, in horses immunized with *L. obliqua* bristle extracts [31].

Animal Experiments

L. achelous

Subcutaneous injections of crude venom and lonomin I in rabbits induce a dose-dependent decrease in Fg, plasminogen and FXIII without bleeding manifestations, followed by a rapid return to normal basal values [32]. Intravenous injections of lonomin I/V induce a dose-dependent thrombolysis of preformed thrombi in combination with a decrease in Fg, plasminogen, α_2 -antiplasmin and FXIII, without an increase in Fg degradation products nor any bleeding manifestations [33]. The thrombolytic effect is followed by an inhibition of ¹²⁵I-fibrinogen accretion [34].

L. obliqua

In studies performed in Brazil, subcutaneous injections of *L. obliqua* bristle extracts (Loche) in rabbits cause a prolongation of pro-

thrombin time and activated partial thromboplastin time without any detectable Fg. Similar to the effect of *L. achelous*, the tests returned to normal values within 24–48 h [32]. Intravenous injections of Loche deplete Fg and FXIII, but do not induce lysis of preformed thrombi [35]. Intravenous injections of purified Lopap induce disseminated intravascular coagulation in rats [36].

Conclusion

The presence of fibrinolytic compounds in *L. achelous* venom (plasmin-like and plasminogen activators), a FV inhibitor and a FXIII protease, along with activators of the prothrombinase complex (FII and FV activators and FXa-like), seems to indicate that in the pathogenesis of the clinical picture, two processes coexist: a very severe fibrinolytic syndrome and mild disseminated intravascular coagulation due to the procoagulant agents, which, in most cases, is masked by the former and is manifested when all coagulation factors are infused. *L. obliqua* venom seems to contain mainly activators of the prothrombin complex; therefore, disseminated intravascular coagulation might present as a primary pathological state.

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