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Hemostasis dynamics during coagulopathy resulting from *Echis* envenomation

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ABSTRACT

This work provides a graphic description of the time course of hemostasis tests results during spontaneous evolution of *Echis* envenoming and correction of hemostasis disorders with antivenom therapy.

The dynamics of fibrinogenemia (g L^{-1}), prothrombin time (PT, %), activated partial thromboplastin time (aPTT, patient/normal ratio) and platelet count (Giga L^{-1}) were collected from coagulopathic envenomed patients of a 12 years prospective study in Africa. Sixty patients were included. 47 of them (78%) received an antivenom (33 ± 12 ml) and 13 did not. Thirty patients (50%) presented bleeding. Only one patient died. The time for fibrinogen to be more than 1 g L^{-1} was 181 ± 116 h (7.5 days) in the spontaneous evolution group versus 40 ± 21 h in the antivenom group ($p < 0.0001$). The times for reaching a PT above 50% were 140 ± 64 min (5.8 days) versus 25 ± 15 h ($p < 0.00001$) and for reaching an aPTT less than 1.5 times the normal values, 116 ± 76 h (4.7 days) versus 10 ± 9 h respectively ($p < 0.0002$). Thrombopenia was not a common feature of *Echis* envenomation.

This study is the first one to provide a chart of the evolution of the hemostatic tests during envenomation caused by *Echis* bites. The plots enable to estimate that, in *Echis* envenomation, in the absence of antivenom administration, hemostasis remains severely affected until the 8–10th day of evolution. On the contrary, efficient antivenom against African vipers corrects clotting functions within a few hours.

1. Introduction

Echis is a genus of venomous vipers found in the dry regions of Africa, the Middle East, Pakistan, India and Sri Lanka. The *Echis* species are among the most dangerous snakes in the world. In sub-Saharan Africa, they attribute for more than 20,000 deaths every year, since they are widespread and live in areas lacking modern medical facilities (Chippaux, 2011). *Echis* bites produce a venom-induced coagulopathy (VICC) (Isbister, 2010) resulting in a dramatic fall in fibrinogen concentration.

The only efficient treatment for these hemorrhagic disorders is antivenom (Mion and Larréché, 2009). Antivenom may be unavailable in some developing countries, mainly because of elevated cost. Other limitations include decreased efficacy in some instances (Isbister et al., 2009). In addition, specific antivenom does not exist for some snake species. For these reasons, alternative treatments,

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such as plasmapheresis (Valenta et al., 2011.) or clotting factors (Brown et al., 2009) are still being investigated. In previous studies of these putative treatments, the effectiveness was assessed based on hemostasis evolution. Biological tests results describing the dynamics of hemostasis after envenoming are surprisingly scarce. A recent study precisely reporting the evolution of hemostatic factors during VICC resulting from Australian elapid envenomation (Isbister et al., 2010) resulted in features that vary significantly from viperine envenomation. Concerning *Echis* envenomation, only a few case studies have intermittently provided individual progressions of hemostatic parameters (Mion and Larréché, 2009; Christy et al., 1973; Reid, 1977). For obvious ethical reasons, antivenom trials never include a placebo group, therefore, the natural evolution of envenoming is difficult to grasp.

We undertook this study to provide a realistic description of the time factors for hemostasis disorders during both spontaneous evolutions of *Echis* envenoming and correction of hemostasis with antivenom therapy.

2. Material and methods

2.1. Data

The same investigator (SL) reviewed all statistics from the snakebite database of the French military hospital in Djibouti examining cases of spontaneous (or natural) evolution of viperine syndrome and in cases of antivenom administration. The French Military Health Service ethical commission reviewed and approved the protocol of this prospective study (1994–2006). GM, AB, FP and MP (respectively) recruited all patients for the cohort from 1994 to 2006. The figures used in this analysis were extracted by means of a standardized data collection grid for demographic (age and sex), clinical (bitten area, edema, bleeding features and clinical evolution), and biological tests (fibrinogenemia, prothrombin time, activated partial thromboplastin time and platelet count measured at predefined times). Edema was quantified as mild (local), moderate (regional) or severe (extensive).

2.2. Inclusion criteria

Only coagulopathic patients were included in the study. Coagulopathy was defined as fibrinogen <1 g L^{-1} and at least one of the following laboratory test results: prothrombin time (PT) $\leq$50%, activated partial thromboplastin time (aPTT) $\geq$1.5 times the normal values, or platelets <80 Giga L^{-1}. When aPTT was non-recordable (incoagulable blood), its value was arbitrarily fixed at three times the normal values for graphic representation.

2.3. Laboratory tests

Fibrinogenemia, PT, aPTT and platelet counts were measured in all patients admitted in the Intensive Care Unit for a snakebite. All the laboratory tests were performed at the hospital laboratory within one hour of blood sampling.

Fibrinogen, PT and aPTT measures were performed on START 4 semi-automated coagulation analyzer (Diagnostica Stago, France) as of 1998. Prior to this, the measures were performed on a KC4 semi-automated analyzer (Amelung, Germany) using Dade reagent (Dade Behring, The Netherlands).

The platelet count (G L^{-1}) was measured by commercially available kits on Pentra DF 120 automated analyzer (Horiba ABX, France) as of 1997. Afterward that time, it was performed by a manual visual method by Unopette (Becton Dickinson Vacutainer Systems, NJ). A study in our laboratory checked the correlation between the manual method and the automated method (unpublished data).

2.4. Antivenom administration

Clinical features consistent with *Echis* envenomation (edema and bleeding but no or limited necrosis) were described in a previous paper (Larréché et al., 2011). The snake, sometimes killed or captured, enabled the identification of *Echis pyramidum* (Fig. 1). This viper habitat expands from Algeria to Kenya and it was formerly misclassified as an *Echis carinatus* sub-species (Casewell et al., 2010).

The majority of patients admitted from 1994 to august 2001 were treated with *Echis-Bitis-Naja*® antivenom (20 ml vial, Pasteur-Mérieux, Paris, France), delivered within 20–30 min through an intravenous infusion. At the onset of the study, some patients did not receive any antivenom, because the treating physician believed it was not necessary or, in some rare occasions, it was temporarily out of stock.

From September 2001 on, all envenomed patients, with one exception, received two vials of the FAV-Afrique® antivenom (10 ml vials, Sanofi-Pasteur, Lyon, France), a more recent polyvalent antivenom efficient against *Echis*, *Bitis*, *Naja* and *Dendroaspis* venoms.

Whatever the antivenom, the evolution of bleeding and biology was checked every four hours during the first 12 h after being admitted. If bleeding was still going on or if hemostatic results were not getting better, additional vials were injected at H4, H8 or H12.

2.5. Graphic plots and statistical methods

Plots constructed from parameters values versus time, were expressed in days. Time of serial sampling varied

Fig. 1. *Echis pyramidum*, with the kind authorization of inf-faune (http://www.inf-faune.net/).