Thrombosis Research 133 (2014) 5–9

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Coagulopathy in malaria

Pantep Angchaisuksiri *

Division of Hematology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form 18 September 2013
Accepted 18 September 2013
Available online 26 September 2013

Keywords:
Coagulopathy
Malaria

ABSTRACT

Blood coagulation activation is frequently found in patients with malaria. Clinically apparent bleeding or disseminated intravascular coagulation (DIC) is associated with very severe disease and a high mortality. Protein C, protein S, and antithrombin levels were found to be low in *P. falciparum*, but were normal in *P. vivax* infection. Plasma levels of plasminogen activator inhibitor-1 were high in cases of *P. falciparum* infection whereas tissue plasminogen activator levels were low. Elevated plasma levels of von Willebrand factor (vWF) and vWF propeptide, thrombomodulin, endothelial microparticles have been reported in *P. falciparum*-infected patients. It has been demonstrated that severe *P. falciparum* infection is associated with acute endothelial cell (EC) activation, abnormal circulating ultralarge vWF multimers, and a significant reduction in plasma ADAMTS13 function. These changes may result in intravascular platelet aggregation, thrombocytopenia, and microvascular disease. It has also been shown that *P. falciparum*-parasitized red blood cells (pRBCs) induce tissue factor (TF) expression in microvascular ECs *in vitro*. Recently, loss of endothelial protein C receptor (EPCR) localized to sites of cytoadherent pRBCs in cerebral malaria has been demonstrated. Severe malaria is associated with parasite binding to EPCR. The cornerstone of the treatment of coagulopathy in malaria is the use of effective anti-malarial agents. DIC with spontaneous systemic bleeding should be treated with screened blood products. Study in Thailand has shown that for patients who presented with parasitemia > 30% and severe systemic complications such as acute renal failure and ARDS, survival was superior in the group who received exchange transfusion. The use of heparin is generally restricted to patients with DIC and extensive deposition of fibrin, as occurs with purpura fulminans or acral ischemia. Antiplatelet agents interfere with the protective effect of platelets against malaria and should be avoided.

Contents

Introduction

Malaria is the most important parasitic disease of humans, affecting more than 500 million people and causing between one and three

* Division of Hematology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand. Tel./fax: +66 2 201 1796.
E-mail address: pantep.ang@mahidol.ac.th.

0049-3848/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.thromres.2013.09.030

million deaths each year. Although malaria is mainly confined to tropical countries, cases of malaria acquired by international travellers from industrialized countries as well as immigrants from endemic countries have increased worldwide [1].

Plasmodium falciparum is the main cause of severe clinical malaria and death. Severe manifestations of *P. falciparum* malaria include impaired consciousness (cerebral malaria), respiratory distress, renal failure, hepatic dysfunction, profound anemia, and abnormal bleeding [2]. Many of these complications are believed at least in part to be related to the coagulopathy and microvascular changes in this disease.

Clinical aspects of coagulopathy in malaria

Coagulation abnormalities are frequently found in patients with severe malaria. Clinically apparent bleeding or disseminated intravascular coagulation (DIC) is associated with very severe disease and a high mortality. Bleeding in severe malaria results from several pathological processes such as thrombocytopenia, consumptive coagulopathy, and impaired clotting factor synthesis.

The reported incidence of bleeding in severe malaria has varied considerably from less than 10% to 25% [3]. In most series the incidence of hemorrhage was low, whereas in one study 83% of patients with pulmonary complications had significant bleeding [4]. In some of these studies, bleeding may have resulted from the coexistent uremia and the use of heparin or dexamethasone. Approximately 5% of adult Thai patients with cerebral malaria manifested spontaneous severe bleeding [5]. In general, bleeding usually occurs late in the course of the disease in patients with renal, pulmonary or hepatic complications and is associated with hyperparasitemia, severe anemia, thrombocytopenia and coagulopathy. DIC is observed in up to 30% of non-immune patients with severe complicated falciparum malaria [3] and indicates a poor outcome. The incidence was higher at 55% in the autopsy cases [6].

Development of symmetrical peripheral gangrene (SPG) and purpura fulminans has also been described in patients with *P. falciparum* malaria and DIC [7–9]. Several factors play a role in the development of tissue necrosis and SPG. Fibrin thrombi were found in skin biopsy specimens of patients with SPG and, postmortem, in the capillaries of various organs, suggesting DIC.

Malarial retinopathy, consisting of retinal abnormalities such as severe macular whitening and retinal hemorrhages, is a newly established diagnostic sign in severe malaria [10]. Its presence and severity are related to risk of death and length of coma in survivors. The number of retinal hemorrhages seen on fundoscopic examination correlates with the number of cerebral hemorrhages in fatal cerebral malaria. In common with cerebral hemorrhages, fibrin thrombi are seen in the small vessel at the center of hemorrhages.

Pathophysiologic mechanisms of coagulopathy in malaria (Table 1)

Table 1
Pathophysiologic mechanisms of coagulopathy in malaria.

- Thrombocytopenia
- Platelet dysfunction
- Coagulation activation
- Defects in inhibitors of coagulation
- Impaired fibrinolysis
- Cytokines
- Endothelial cell activation
- Cytoadherence
- Tissue factor expression

Thrombocytopenia

Thrombocytopenia is the common feature for both *P. falciparum* and *P. vivax* malarias. The incidence of thrombocytopenia in malaria varies from 60%-80% [3]. It is more common and more severe in complicated falciparum infection. In general, thrombocytopenia alone rarely causes bleeding unless it is accompanied by coagulopathy, which is observed only in severe complicated falciparum infection. Possible causes include reduced platelet survival from peripheral destruction (by immune, consumptive, or other mechanisms), enhanced splenic uptake or sequestration, and decreased platelet production. Recently, it was shown that thrombocytopenia in early malaria is associated with vWF-mediated GP1b shedding, a process that may prevent excessive adhesion of platelets and parasitized erythrocytes [11].

Platelet dysfunction

During acute *P. falciparum* and *P. vivax* infection, hyperaggregation and enhanced platelet secretory activity were demonstrated [12]. This *in vitro* study suggested that the interaction between normal platelets and falciparum-infected erythrocytes could induce hypersensitivity of platelets, possibly through the stimulation by ADP released from infected red cells. Antibody bound to platelets as well as the invasion of platelets by malarial parasites may be other responsible mechanisms. The other aspect of platelet dysfunction during malarial infection observed in some patients is the defective aggregation of platelets in response to ADP, epinephrine and collagen but not ristocetin [12]. From electron microscopic study, circulating degranulated platelets were observed during malarial infection. The presentation of the circulating exhausted platelets as a result of persistent *in vivo* activation is most likely a responsible mechanism causing the platelet hypoactivity.

Coagulation activation

During severe complicated malarial infection, the activation of the coagulation system leading to *in vivo* thrombin generation has been demonstrated. The stimulation of the coagulation system is caused by various procoagulants present during malarial infection. The sources of the procoagulants are exposed phosphatidylserine on the cell surface of infected erythrocytes, the lysis of activated platelets together with their secretory products, and the tissue factor (TF) released from damaged vascular endothelial cells [3]. Furthermore, certain substances that are released during severe malarial infection - namely tumor necrosis factor α (TNF α) and histamine - are additional factors that promote fibrin formation [13]. The intrinsic pathway of the coagulation has also been shown to be activated in severe malaria [14]. In turn, this may cause activation of the complement system and release of bradykinin and PMN-derived elastase that could contribute to the pathogenesis of severe malaria.

Activation of the coagulation cascade also occurs in mild malaria. The degree of activation is proportional to disease severity. Several sensitive indices of intravascular coagulation, including decreased plasma antithrombin (AT) activity and increased concentrations of thrombin-antithrombin (TAT) complexes, were proportional to disease severity [15].

Defects in inhibitors of coagulation

Protein C, protein S, and AT levels were found to be low in *P. falciparum*, particularly in complicated cases, but were normal in *P. vivax* infection [16]. The reduction in the levels of protein C, protein S, and AT is attributed to increased consumption due to microvascular thrombosis rather than to reduced synthesis in the liver, as they correlated inversely with levels of TAT complexes. A study in Thailand showed AT levels reached 75% of normal by the 7-10th day of infection [15]. Reduction in protein C level correlated with the coma scale in cerebral malaria, as well as with the more severe clinical course of malaria, and returned back to normal after two weeks [17]. Thus, activation of