HEMOSTATIC STUDIES IN DENGUE PATIENTS

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Abstract. The pathogenesis of hematologic changes in dengue patients is not clearly understood. Consistent hematological findings include vasculopathy, thrombocytopenia, and coagulopathy. There are evidences suggesting that dengue virus causes pathophysiological changes that involve all of the consistent hematologic findings resulting in vasculopathy, reduction in platelet number as well as platelet dysfunction, and reduction of several coagulation factors. Laboratory evidences of disseminated intravascular coagulation (DIC) are also demonstrated in all degrees of severity in dengue patients. Only in severe dengue cases is profound DIC aggravated, leading to uncontrolled bleeding and death. A study to determine the extent of the activation of endothelial cells and the hemostatic system in correlation with clinical severity and also to detect the best prognostic factor for severe dengue showed plasma von Willebrand factor antigen (VWF:Ag) to be the best indicator of progression to severe dengue.

Keywords: dengue, hemostatic studies

INTRODUCTION

Dengue infection, one of the most devastating mosquito-borne viral diseases in humanity, is now an expanding global threat. The disease ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) (Thisyakorn and Thisyakorn, 2015). The pathogenesis of bleeding in dengue patients is poorly understood.

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The hemostatic changes, which have been shown to occur early in the course of illness in all severity of dengue, included the following:

Vasculopathy manifested by generalized petechiae and a positive tourniquet test.

Platelet abnormalities manifested by thrombocytopenia, which was one of the most consistent abnormal hemostatic tests, and this occurred in the febrile phase to reach its lowest values in the defervescence phase. The platelet count then increased during the convalescent stage to reach its normal values. Many cases had platelet counts higher than the normal

ranges during the second week of illness. The clinical severity also correlated with the degree of thrombocytopenia.

The possible causes of thrombocytopenia include megakaryocytic abnormalities, because the degenerative changes and decreased number of marrow megakaryocytes were noted in the early febrile phase. The megakaryocyte number was often normal or increased later on. Isologous platelet kinetic studies have shown a shortened half-life survival during the course of illness, which became normal later on. Surface counting of radiolabeled platelets revealed increased pooling of platelets to the liver more than to the spleen. In a normal spleen, liver platelet-pooling ratios returned to normal in the convalescent stage. This increased pooling of platelets in the liver and possibly their destruction; there might be another contributory factor to the thrombocytopenia noted in dengue patients. In addition to decreased quantity, platelet dysfunction (that is, impaired ADP-induced aggregation and ADP release) was reported.

Coagulopathy shown by mild to moderately prolonged partial thromboplastin time and prothrombin time. Assays of clotting factors showed variable patterns of reduction, mostly of mild to moderate degrees. Fibrinogen was the only factor that almost always decreased mildly to moderately. Minimal increase of fibrin degradation products was noted intermittently throughout the course of illness. In addition, increased consumption of fibrinogen was demonstrated, and euglobulin lysis time was reported to be normal (Mitrakul and Thisyakorn, 1989).

It has been suggested that endothelial cells can be a target for dengue virus infection, leading to alteration of their cytokines production and barrier functions, which may play a central role in dengue pathogenesis (Dalrymple and Mackow, 2011). A prospective cohort study was designed to determine the extent of activation of endothelial cells and the hemostatic system in correlation with dengue clinical severity, as well as to detect the best prognostic factor for severe dengue. Endothelial cell activation, coagulation, anticoagulant and fibrinolysis parameters were measured in 42 children with dengue infections (20 with DF, and 22 with DHF) during the three phases of illness. In DHF patients during the febrile phase, von Willebrand factor antigen (vWF:Ag), tissue factor (TF) and plasminogen activator inhibitor (PAI-1) were significantly elevated while platelet counts and ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin repeats) were significantly low compared to those in DF patients.

In DHF patients during the toxic phase, soluble thrombomodulin (sTM), tissue plasminogen activator (t-PA), and PAI-1 were also significantly increased while ADAMTS 13 and thrombin activatable fibrinolysis inhibitor (TAFIa) were significantly low, compared to those in DF patients. Abnormal vWF multimers were seen only in DHF patients. For endothelial cell injury and release of procoagulant components, activation of the coagulation cascade with thrombin generation increased antifibrinolytic factors and consumption of natural anticoagulants; each appeared to play an important role in the development of hemorrhage in dengue patients. Using logistic regression analysis, plasma VWF:Ag was found to be the best indicator of progression to DHF (Sosothikul *et al*, 2007).

Hematopoietic suppression is a very well known phenomenon that occurred during dengue infection. Bone marrow examinations showed markedly hypocellularity accompanied by decreases in all the hematopoietic cell precursors, namely megakaryocytes, erythroid, and myeloid precursors. Later on, recovery of hematopoiesis occurred, and the bone marrow showed hypercellular, accompanied by an increase in number of megakaryocytes, erythroid, and myeloid precursors. Despite the increase in normal number of megakaryocytes, these cells showed a sign of degeneration. The hemophagocytosis of young and mature erythroid and myeloid cells, including lymphocytes and platelets, were also observed (Srichaikul, 2014).

CONCLUSION

Dengue virus is the causative agent of a wide spectrum of clinical manifestations, ranging from mild acute febrile illness to classical DF, DHF, and DSS. The major pathophysiologic changes in severe dengue include leakage of plasma and abnormal hemostasis. Vasculopathy, platelet abnormalities, and coagulopathy are responsible for abnormal hemostasis in dengue patients.

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