HEMATOLOGIC CHANGES IN DENGUE

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Abstract. The pathogenesis of hemostatic changes in dengue patients is not clearly understood. There are evidences suggesting that dengue virus causes pathophysiological changes involving all of the component of hemostasis that result in vasculopathy, thrombocytopenia, thrombopathy, abnormal von Willebrand factor (VWF) multimers, reduction of several coagulation factors, increased antifibrinolytic factors, and consumption of natural anticoagulants. Profound disseminated intravascular coagulation may occur only in severe dengue cases, and this complication leads to uncontrolled bleeding and death. Increased plasma VWF antigen (VWF:Ag) at the febrile phase was found to be the best indicator of progression to severe dengue disease.

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 common hemorrhagic manifestations in DHF/DSS are epistaxis, gingival bleeding, gastrointestinal bleeding, hematuria, and menorrhagia. Although severe hemorrhage remains the major cause of death, the pathogenesis of bleeding in dengue patients is poorly understood (Sosothikul *et al*, 2007).

HEMOSTATIC STUDIES IN DENGUE PATIENTS

The hemostatic changes occurring early in the course of the illness in all severities of dengue infection include the clinical syndromes and their manifestations below.

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Vasculopathy manifests as generalized petechiae and a positive tourniquet test.

Platelet abnormalities manifest as thrombocytopenia, one of the most consistent abnormal hemostatic tests, and this occurs in the febrile phase to reach its lowest levels in the defervescence phase. The platelet count then increases during the convalescent stage to reach its normal values. Many cases have higher platelet counts than the normal ranges during the second week of illness. The clinical severity also correlates with the degree of thrombocytopenia.

The possible mechanisms of thrombocytopenia include decreased production in bone marrow and increased platelet destruction or increased utilization. The decreased production is evidenced by decreased number of marrow megakaryocytes in the early febrile phase. The megakaryocyte number is normal or increased later. The increased platelet destruction is shown by a shortened platelet half-life survival time during the course of illness, which becomes normal later on. Surface counting of radiolabeled platelets revealed increased pooling of platelets in the liver more than in the spleen. In addition to thrombocytopenia, platelet dysfunction is manifested by impaired platelet aggregation to adenosine diphosphate and a concurrent increase in plasma thromboglobulin and platelet factor 4 levels (Srichaikul *et al*, 1989).

Coagulopathy is shown by mild to moderately prolonged partial thromboplastin time and prothrombin time, resulting in reduction of coagulation factors. Fibrinogen is the only factor that almost always decreases mildly to moderately due to increased consumption. Minimal increases of fibrin degradation products are noted intermittently throughout the course of illness. In addition, 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 alterations of the production of cytokines in those cells and alterations of barrier functions, both of 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 infection. 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 the illness. In DHF patients during the febrile phase, von Willebrand factor antigen (VWF:Ag), tissue factor, and plasminogen activator inhibitor (PAI-1) were significantly elevated while platelet counts and ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin repeats) were significantly lower compared with those in DF patients.

In DHF patients during the toxic phase, soluble thrombomodulin, tissue plasminogen activator, and PAI-1 were also significantly increased while ADAMTS 13 and thrombin activatable fibrinolysis inhibitor were significantly lower compared with 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. The level of VWF:Ag is the most important prognostic indicator of dengue severity. (Sosothikul *et al*, 2007).

Besides hematopoietic suppression during dengue infection, there was evidence of the hemophagocytosis of erythroid, myeloid cells, and platelets in bone marrow (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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