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PATHOPHYSIOLOGY OF DENGUE HAEMORRHAGIC FEVER

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ABSTRACT

Dengue is an arthropod-borne infectious disease caused by dengue virus (DENV) infection and transmitted by *Aedes* mosquitoes. Approximately 50–100 million people are infected with DENV each year, resulting in a high economic burden on both governments and individuals. The prevalence is increasing across South East Asia, Africa, America and Western Pacific. DENV infection results in a broad spectrum of clinical symptoms, ranging from mild fever to DHF, and then progress to DSS and death. The pathophysiological parameters for the early recognition of plasma leakage and appropriate fluid therapy.

KEYWORDS: Pathophysiology, Dengue Fever, Dengue Hemorrhage Fever.

INTRODUCTION

Dengue is a mosquito borne disease belong to the *Flaviviridae* family, caused by any one of four closely related dengue viruses (DENV- 1, -2, -3 and -4). Infection with one serotype of DENV provides immunity to that serotype for life, but provides no long-term immunity to other serotype.[1,2] There are 4 serotypes of DENV (DENV-1 through DENV-4) that cause human disease through transmission via the mosquito vectors *Aedes aegypt*i and *Aedes albopictus.*[2]

Dengue Fever (DF) can be with or without hemorrhage, while Dengue Hemorrhagic Fever DHF can be with or without shock, that is called Dengue Shock Syndrome.[3] The WHO criteria for the clinical diagnosis of Dengue Hemorrhage Fever (DHF) requires the presence of acute and continuous fever of 2 to 7 days, haemo-concentration (hematocrit >20% from baseline of patient) and the manifestation of hemorrhagic associated with thrombocytopenia (100.000 cells/c.mm or less). Hemorrhagic manifestations could be skin or mucosal or even a

positive tourniquet test which is commonest.[4]

EPIDEMIOLOGY

Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) is endemic in tropical and subtropical zones and the prevalence is increasing across South-east Asia, the western Pacific, the Americas and Africa. There are more 100 dengue endemic countries in the world. In Asia, dengue fever (DF) and dengue hemorrhagic fever (DHF) affect mainly in children under 15 years old.[5] Approximately 2.5 billion people are at risk of dengue infection every year. It estimated 390 million dengue infection every year, of which 96 million manifests apparently any level of disease severity. In America, 2.35 million cases of dengue were reported in 2015, and more than ten thousand of these cases involved severe hemorrhagic-related clinical symptoms.[2]

Today, dengue virus (DENV) poses a major threat to global public health, and approximately two-fifths of the world's population is at risk of dengue infection.[6,7] DHF has become a public health threat that is associated with remarkable morbidity and mortality, since the first outbreak was reported in 1779 in Jakarta, Indonesia.[8] By the end of 2016, a total of 291,964 outbreak-associated dengue cases had been reported in the literature, mainly from China (27.9%), Singapore (27.0%) and Malaysia (15.1%). The majority (72.4%) of dengue patients were reported in the Western Pacific region, followed by the American region (19.4%), Southeast Asia Region (4.8%), Eastern Mediterranean region (1.5%), European region (1.5%) and African region (0.3%).[8]

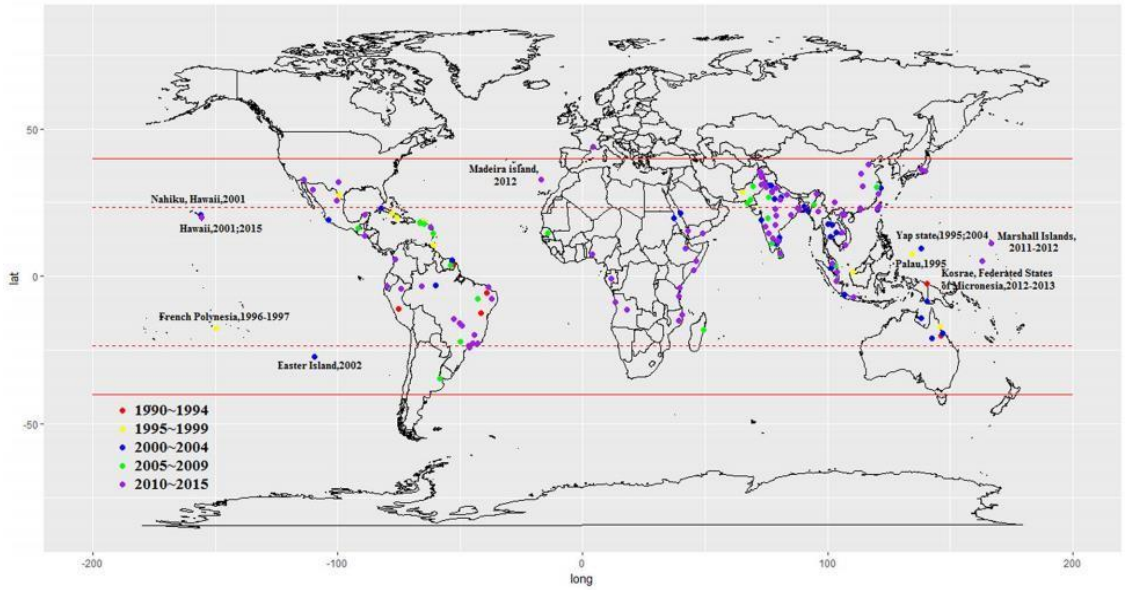

Figure 1: Global Dengue outbreaks distribution from 1990-2015 (Guo C, 2017).

MECHANISM

Although DF and DHF are caused by the same virus, but there is a difference. The main difference is that hemoconcentration that can lead to shock condition. The shock is caused by plasma leak suspected because of the immunological process. In DF, this condition does not occur. Clinical manifestation of DF starts when the virus enters the body. The virus will develop in the bloodstream and will be captured by macrophages. Viremia occurs immediately 2 days before the symptoms occur and end after five days of fever begins. Macrophages will immediately react by catching the virus and processing it so that the macrophages become APC (Antigen Presenting Cells). The antigen attached to this macrophage will activate T- Helper cells and attract other macrophages to phagocytes more viruses. T helper will activate T cytotoxic cells that will lyse macrophages that have phagocytes of the virus.[9] The process causes the release of mediators that stimulate the occurrence systemic symptoms such as fever, joint pain, muscles, malaise and other symptoms.[4]

PLASMA LEAKAGE IN DHF

1. *Pathophysiology*

In DHF there is no vasculitis and hence no injury to the vessel walls, and plasma leakage results from cytokine mediated increase in vascular permeability. The ensuing movement of albumin and the resultant reduction of intravascular oncotic pressure facilitate further loss of fluid from the intravascular compartment. The basic Starling principle still holds true in explaining microvascular ultrafiltration based on the balance of the oncotic and hydrostatic pressures. However, the glycocalyx which is a gelatinous layer lining the vascular endothelium is also implicated in controlling fluid movement by the adherence of albumin molecules in to its matrix, damage of which, leads to loss of albumin into the extravascular compartment. Plasma leakage is specific to the pleural and peritoneal surfaces.[4]

2. Immunopathogenesis

Dengue virus infection causes intense immune activation. Aberrant immune responses such as cytokine overproduction and generation of autoantibody acting against platelets and endothelial cells occur after dengue virus infection. A molecular mimicry between platelets or endothelial cells with the NS-1 or prM of dengue virus would explain the cross-reactive of antiNS1 or anti-prM antibody to host cells, and participate in the attack of platelet and endothelial cells during the disease development. Dengue virus could cause severe

hemophagocytic syndrome. High serum ferritin level, a macrophage activation marker in vivo, was found to be highly elevated in the dengue patients. This suggests that the monocytes or macrophages were activated by cytokines such as IFN-γ during the dengue disease process after dengue virus infection. The activated macrophages would then achieve the phagocytosis of the autoantibody-coated platelet and thus contribute to the development of thrombocytopenia in DHF/DSS. The anti-NS1 and anti-prM cross- reactive antibody to platelets and endothelial cells provide an explanation for the target specificity and unique feature of thrombocytopenia and plasma leakage during the development of DHF/DSS.[10]

3. Hemorrhagic Manifestation in DHF

The pathogenesis of bleeding in DHF is unclear even though well-recognized coagulation disturbances do exist. The clinical hemorrhagic manifestations range from a mere positive tourniquet test, skin petechiae and ecchymoses to epistaxis, and gum bleeding to severe gastrointestinal hemorrhages. Thrombocytopenia is a consistent finding. These hematological abnormalities seem to correlate better with the timing and severity of plasma leakage rather than the clinical hemorrhagic manifestations.[4] Hemorrhage contributes to dengue morbidity and mortality, especially during the severe thrombocytopenia and toxic hemorrhagic stage (3-5 days after illness onset).[11] Thrombocytopenia however correlates poorly with bleeding manifestations. Spontaneous bleeding been uncommon even with counts below 100,000 cells/c.mm. It is strongly associated with the severity of vascular leakage. Counts below 100,000 cells/c.mm or a rapid drop in the platelet count was associated with severe disease.

TREATMENT OF DENGUE INFECTION IN ADULT

There is no specific treatment for dengue. Early recognition of dengue fever like, bleeding and signs of circulatory collapse reduce mortality with dengue. Mild dengue infection may be treated with hydration and antipyretics.[12] Agents like salicylates, non-steroidal anti-inflammatory drugs and traditional medicine that can cause a hepatoxicity must be avoided.[13] To identify the need for intravenous fluid therapy, circulation and vascular leakage must be monitored the value of pulse, blood pressure, hematocrit, urine output and skin perfusion. If shock persist, immediate volume replacement with Ringer's Lactate, physicological saline or Ringer's acetate should be followed by colloid solutions or plasma.[14]

DISCUSSION

Coagulopathy and plasma leakage are the fundamental pathological changes for clinical manifestations, mortality and morbidity in DHF. Plasma leakage progresses rapidly or slowly to cease completely and predictably after 24 to 48 hours of onset, raising the possibility of existence of underlying functional change rather than structural damage and inflammation in the vasculature. The two main fundamental pathological in DHF are plasma leakage and intrinsic coagulopathy. In plasma leakage, the balance of hydrostatic and oncotic pressures is important. The main factor implicated in the development of DHF rather than the relatively innocuous DF in dengue infection is secondary dengue infection but other factors like viral virulence and host characteristics are also important. Severe disease is the result of a complex interaction between the virus and the immune response evoked by the host with secondary infection.

CONCLUSION

Scientist and clinicians have increasingly the understanding of pathophysiology of DF and DHF from several perspective. Further studies are recommended to improve our knowledge of DHF pathogenesis, which is important for developing the effective therapeutic and vaccine against the DENV.

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