IMMUNOPATHOGENESIS OF DENGUE SHOCK SYNDROME

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ABSTRACT

Dengue is the most important emerging tropical viral disease of humans in the world today. It is estimated that there are between 50 and 100 million cases of dengue fever (DF) and about 500.000 cases of dengue haemorrhagic fever (DHF) each year which require hospitalization. Persons of all ages can be infected and develop dengue fever. However, children younger than 15 years typically present with only a nonspecific self-limited febrile illness. Untreated dengue hemorrhagic fever mostly likely progresses to dengue shock syndrome which is defined as dengue fever with signs of circulatory failure. The prognosis depends on prevention or early recognition and treatment with case fatality rate is as high as 12% to 14% once shock has set in. Management of dengue fever requires rest, oral fluids to compensate for losses via diarrhoea or vomiting, antipyretics and analgesics. Patients who present with shock may require central venous pressure monitoring. An arterial line may be required in unstable patients for the assessment of blood gases, electrolytes, and coagulation profile to help identify patients needing ventilatory support.

Keyword: Dengue haemorrhagic fever, dengue shock syndrome, fever

Background

Dengue is the most important human viral disease transmitted by arthropod vectors. Dengue is a homonym for the African Ki denga pepo, which first appeared in English literature during an 1827-1828 caribbean outbreak. Benjamin Rush described the first case of dengue in 1789. DHF and dengue shock syndrome are now leading causes of hospital admissions and deaths among children in Asia.[9]

Aedes aegypti is the principal mosquito vector of dengue. Adult mosquitoes shelter indoors and bite during the daytime. They are adapted to breed around human's residence, in water containers, vases, cans, old tires and other discarded objects. The

secondary vector for dengue virus is *Ae albopictus*, which contributes significantly to transmission in Asia and whose presence is spreading in Latin American countries. Dengue outbreaks have also been attributed to *Ae polynesiensis* and *Ae scutellaris*, but to a lesser extent.[3]

Dengue is the most important emerging tropical viral disease of humans in the world today. It is estimated that there are between 50 and 100 million cases of dengue fever (DF) and about 500.000 cases of dengue haemorrhagic fever (DHF) each year which require hospitalization. Over the last 10-15 years, DF/DHF has become a leading cause of hospitalization and death among children in the South-East Asia Region of WHO.[2]

Persons of all ages can be infected and develop dengue fever. However, children younger than 15 years typically present with only a nonspecific, self-limited, febrile illness. In Southeast Asia, dengue hemorrhagic fever is primarily an illness of children and is the leading cause of hospitalization and death in that population. Elsewhere, the disease affects all ages.[7]

Untreated dengue hemorrhagic fever mostly likely progresses to dengue shock syndrome. Common symptoms in impending shock include abdominal pain, vomiting, and restlessness. Patients also may have symptoms related to circulatory failure.[7]

Dengue shock syndrome is defined as dengue fever with signs of circulatory failure. The prognosis depends on prevention or early recognition and treatment. Case fatality rate is as high as 12% to 14% once shock has set in. Other severe manifestations described with dengue syndrome include hepatic damage, cardiomyopathy and encephalopathy. In a typical case of dengue fever, thrombocytopaenia is seen on day five to six, and the mean duration of thrombocytopaenia is few days.[9]

Standard treatment of DF/DHF has many advantages. Deaths due to DHF can be reduced to less than 1% among hospitalized patients by the widespread use of standard treatment. It also rationalizes hospitalization, reduces the pressure of admissions, and prevents unnecessary blood transfusions.[2]

Management of dengue fever requires rest, oral fluids to compensate for losses via diarrhoea or vomiting, antipyretics, and analgesics. Intravenous fluid may be required for few days since the period of vasculopathy causing plasma leakage may be short, lasting only a few days. Plasma leakage is evidenced by a rising haematocrit. Patients who present with shock may require central venous pressure monitoring. An arterial line may be required in unstable patients for the assessment of blood gases, electrolytes and coagulation profile to help identify patients needing ventilatory support. Insertions of vascular lines should be done under blood products support in view of the thrombocytopaenia and possible coagulopathies.[9]

Dengue Haemorragic Fever

Etiology

Dengue virus belongs to the family Flaviviridae (single-stranded, nonsegmented RNA viruses) and has four serologically distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Dengue virus serotypes are distinguishable by complement-fixation and neutralization tests. Infection with one serotype confers long-term immunity only to that serotype, and therefore persons may be infected up to four times. Humans are the main reservoir for the dengue virus, although nonhuman primates in Asia and Africa may also be infected.[1]

When a person has had been infected by one serotype, a second infection later by another serotype increases the likelihood of suffering from DHF.[4]

Epidemiology

Initially, dengue infections were primarily recorded when they occurred as epidemics in tropical and subtropical countries. But over time, increasing globalization and human movement coupled by the increase in the geographic area where the Aedes aegypti mosquito vector inhabit has promoted dengue virus infection to nearly every corner of the world.[11]

Dengue cases are estimated to occur in up to 100 million individuals annually and the case fatality ratio is 1–5%. DSS occur more frequently in patients experiencing a secondary dengue virus infection than in those experiencing a primary infection. This suggest that the presence of heterotypic dengue virus antibodies is a risk factor for developing DSS in secondary infections.[12]

Clinical Manifestation

All four dengue virus (Den 1, 2, 3 and 4) infections may be asymptomatic or may lead to undifferentiated fever, dengue fever (DF), or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolemic shock, DSS.

As for definition, dengue fever is an acute febrile illness of 2-7 days duration (sometimes with two peaks) with two or more of the following manifestations: (1) headache, (2) retro-orbital pain, (3) myalgia or arthralgia, (4) rash, (5) haemorrhagic manifestation (ptechiae or positive tourniquet test), and (6) leukopenia. Then, DHF is a probable case of dengue and haemorrhagic tendency evidenced by one or more of the

following[2]: (1) Positive tourniquet test, (2) Petechiae, ecchymosis or purpura, (3) Bleeding from mucosa (mostly epistaxis or bleeding from gums), injection sites or other sites, (4) Haematemesis or melena,(5) Thrombocytopenia (platelets 100,000/mm or less), and (6) Evidence of plasma leakage due to increased capillary permeability manifested by one or more of the following: (a) More than 20% rise in haemotocrit for age and sex, (b) More than 20% drop in haemotocrit following treatment with fluids as compared to baseline, (c) Signs of plasma leakage (pleural effusion, ascites or hypoproteinemia).

Some patients with dengue fever go on to develop dengue hemorrhagic fever (DHF), a severe and sometimes fatal form of the disease. Around the time the fever begins to subside (usually 3–7 days after symptom onset), the patient may develop warning signs of severe disease. Warning signs include severe abdominal pain, persistent vomiting, marked change in temperature (from fever to hypothermia), hemorrhagic manifestations, or change in mental status (irritability, confusion, or obtundation). The patient also may have early signs of shock, including restlessness, cold skin, rapid weak pulse, and narrowing of the pulse pressure.[5]

Grading Severity Of DHF

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia and concurrent haemoconcentration differentiates between grades I and II DHF from DF.[2]

Grade I

Fever accompanied by non-constitutional symptoms. The only haemorrhagic manifestation is only positive tourniquet test and/or easily bruising with thrombocytopenia <100.000 and Hct rise ≥ 20%.[2]

Grade II

Spontaneous bleeding in addition to the manifestation of grade I patients, usually in the form of skin or other haemorrhages with thrombocytopenia <100.000 and Hct rise ≥ 20%.[2]

Grade III

Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin, and restlessness with thrombocytopenia <100.000 and Hct rise > 20%.[2]

Grade IV

Profound shock with undetectable blood pressure or pulse with thrombocytopenia <100.000 and Hct rise ≥ 20%.[2]

Dengue Shock Syndrome

Definition

Dengue shock syndrome is defined as dengue fever with signs of circulatory failure. The prognosis depends on prevention or early recognition and treatment. Case fatality rate is as high as 12% to 14% once shock has set in.[9]

To fulfill the case definition for DSS, the four criteria for DHF (fever, haemorrhagic tendencies, thrombocytopaenia, and plasma leakage) must all be present plus evidence of circulatory failure manifested as rapid and weak pulse, narrow pulse pressure (<20 mm Hg) or hypotension for age (this is defined as systolic pressure < 80 mmHg for those less than five years of age, or <90 mmHg for those five years of age and older), cold clammy skin and restlessness.[3]

Immunopathogenesis

DSS occurs when dengue fever/dengue haemorragic fever poorly treated, particularly second infection, and falls into, at least, grade III. Grade III or more of DHF is signed by the occurrence of circulatory failure, such as rapid, weak pulse, narrow pulse pressure, and cold skin. In DSS pathogenesis, there are involvements of virus-antibody complex that will activate pro-inflammatory complements. These activated complements, in turn, will trigger the process of plasma leakage and causing the patient fall into state of hypovolemic shock.[11]

Natural IgM antibodies have been shown to be involved in early recognition of external invaders and elimination of pathogens like bacteria and viruses. In DSS cases, IgM immune complex have been consistently found in the blood vessel walls of dermal papillae or cutaneous rashes of dengue patients. Also, there is an increase level of platelet associated IgM. But, the role of circulating IgM-immune complex in DSS is remains unknown. Perhaps, immune complexes that attach to the surface of platelets may enhance platelet destruction by the reticulo-endothelial system in the liver and the spleen. Result in thrombocytopenia during the shock phase of disease. Therefore, the levels of IgM, notably natural IgM that has specificity for dengue viruses, in an

individual may have an impact on the outcome of dengue infection. These effects that induced by natural IgM also can be induced by IgG in the secondary infection of dengue virus. This counts for the presence of heterotypic antibodies of dengue virus in patient. [11]

DSS are presumed to result from immunopathology possibly caused in part by serotype-cross-reactive T cell responses during secondary heterologous infection. Antiviral activity of $CD8^+$ T cells is mediated by the production of cytokines, including IFN-γ and TNF-α, and direct killing of infected cells. It is found that dengue virus-specific $CD8^+$ T cells produce IFN- γ and TNF- α and demonstrate potent cytotoxic activity in vivo. As dengue virus-specific $CD8^+$ T cells degranulate, it is likely that enzyme-mediated killing contributes to viral clearance.[10]

As for plasma leakage that happens in DSS cases, Chiou-Feng Lin, et al found that Antibodies directed against dengue virus NS1, which called anti endothelial cell antibodies (AECA), would cross react with endothelial cells and cause damage, beside the direct effect of dengue virus. Although, AECA-mediated endothelial cell damage remain poorly defined, it is already known that there are involvement of cytokines (IL-1 and IL-6), chemokines (IL-8 and MCP-1), and adhesion molecules (ICAM-1, VCAM-1, and E-selectin).[6]

Conclusion

According to the explanation about dengue haemorrhagic fever and dengue shock syndrome before, it can be concluded that dengue is the most emerging human viral disease transmitted by arthropod vectors, which can affect almost of all ages. Poorly treated dengue fever or dengue haemorraghic fever can lead into dengue shock

syndrome, which is a life threatening form of dengue haemorragic fever. As for definition, dengue shock syndrome is dengue fever with signs of circulatory failure that manifested as rapid and weak pulse, narrow pulse pressure (<20 mm Hg) or hypotension for age (this is defined as systolic pressure < 80 mmHg for those less than five years of age, or <90 mmHg for those five years of age and older, cold clammy skin and restlessness. Involvement of humoral antibodies in DSS cases will form an immune complex that attach to platelet. This attachment of immune complex will lead to early destruction of platelet by reticulo-endothelial system in liver and spleen. Circulatory failure that occurs in DSS cases, it is caused by damage to the vascular endothelium. This damage is caused by cross reactive antibodies that originally directed to dengue virus NS1.

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