

Dengue Complication in Children

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Abstract: *Dengue is the most common arboviral disease transmitted globally and is also the most important one in terms of morbidity and mortality. It was estimated that annually over 50 million cases of dengue infection and about 400.000 cases of dengue hemorrhagic fever (DHF) occur in Asian countries. Of those with DHF, at least 90% are children younger than 15 years old. The dengue virus has four serotypes and maintains an infection cycle with Aedes aegypti mosquito. While Dengue is self-limited disease, but an increasing number of cases of Dengue infection have been associated with unusual manifestations, these include central nervous system, liver, cardiovascular, and very fatal conditions if patients do not get adequate and well management. The mechanisms leading to severe manifestations of dengue infections are still not completely understood but are likely to be multifactorial, include immune mechanism. This integrated view would like to emphasize the complication of dengue infection in children and how this unusual manifestation can be occurred.*

Keywords: dengue, complication, children, viral

1. Introduction

Dengue is the most common arboviral disease transmitted globally and is also the most important one in terms of morbidity and mortality [1], [2]. The dengue virus, a member of flavivirus group in the family flaviviridae, is a single stranded enveloped RNA virus, 30 nm in diameter. It has four serotypes (DEN 1, DEN 2, DEN 3, DEN 4). It maintains an infection cycle that uses mosquitoes, mostly the *Aedes aegypti* mosquito, a vectors to human hosts, who also serve as sources of viral amplification. *Aedes Aegypti* is a small, highly domesticated, black and white tropical insect that prefers to feed on humans, favoring ankles and the back of the neck. The insect typically lays its eggs in artificial containers that contain water and as a consequence, dengue is frequently an urban-acquired disease [3], [4].

Dengue is a worldwide condition spread throughout the tropical and subtropical zones between 30° North and 40° South. It is endemic in Southeast Asia, the Pacific, East and West Africa, the Caribbean and the America. In 1779-1780, the first reported outbreak of dengue fever occurred almost simultaneously in Asia, North America, and Africa [3], [4]. It has been estimated that at least 2.5 billion people worldwide live in areas where there is a significant risk of infection from the dengue virus. Estimates suggest that annually over 50 million cases of dengue infection and about 400.000 cases of dengue hemorrhagic fever (DHF) occur in Asian countries. Of those with DHF, at least 90% are children younger than 15 years old [5].

Dengue fever is typically a self-limiting disease with a mortality rate of less than 1%. When treated, dengue hemorrhagic fever has a mortality rate of 5%. Untreated, dengue hemorrhagic fever has a mortality rate as high as 50%.³ Based on this data, while dengue is self-limiting disease, but an increasing number of cases of Dengue infection have been associated with unusual manifestations, these include central nervous system, liver, cardiovascular, and very fatal conditions if patients do not get adequate and well management. This integrated view would like to emphasize the complication of dengue hemorrhagic fever in

children and hopefully this integrated view can increase individual and community awareness about this burden disease.

2. Pathogenesis of Dengue Infection

The pathologic process of dengue infection starts with an intimate relationship between the host and the vector that carries the virus. Humans become infected with the virus after an infected mosquito feeds or probes on the susceptible human host. Routes of replication and transmission of Dengue virus:

- 1) Virus transmitted to human in mosquito saliva
- 2) Virus replicates in target organs
- 3) Virus infects white blood cells and lymphatic tissues
- 4) Virus released and circulates in blood
- 5) Second mosquito ingests virus with blood
- 6) Virus replicates in mosquito midgut and other organs, infects salivary glands
- 7) Virus replicates in salivary gland [3].

The mechanisms leading to severe manifestations of (DEN virus) DENV infections are still not completely understood but are likely to be multifactorial. Dengue virus infection begins with inoculation of virus into skin and blood vessels by an infected *Aedes* mosquito. Viral entry and infection of resident dendritic cells in the skin, langerhans cell, and keratinocytes will primarily be infected. The virus subsequently spreads via the blood (primary viremia) and infects tissue macrophages in several organs, especially the macrophages in the spleen. The replication efficiency of DENV in dendritic cell, monocytes, and macrophages, as well as its tropism for and replication efficiency in endothelial cell, bone marrow stromal cells, and liver cells, collectively determine the viral load measured in blood. This viral load represents an important risk factor for development of severe disease [6].

Essentially infection of macrophages, hepatocytes, and endothelial cell influences the hemostatic and the immune response to DENV. Infected cells die predominantly through

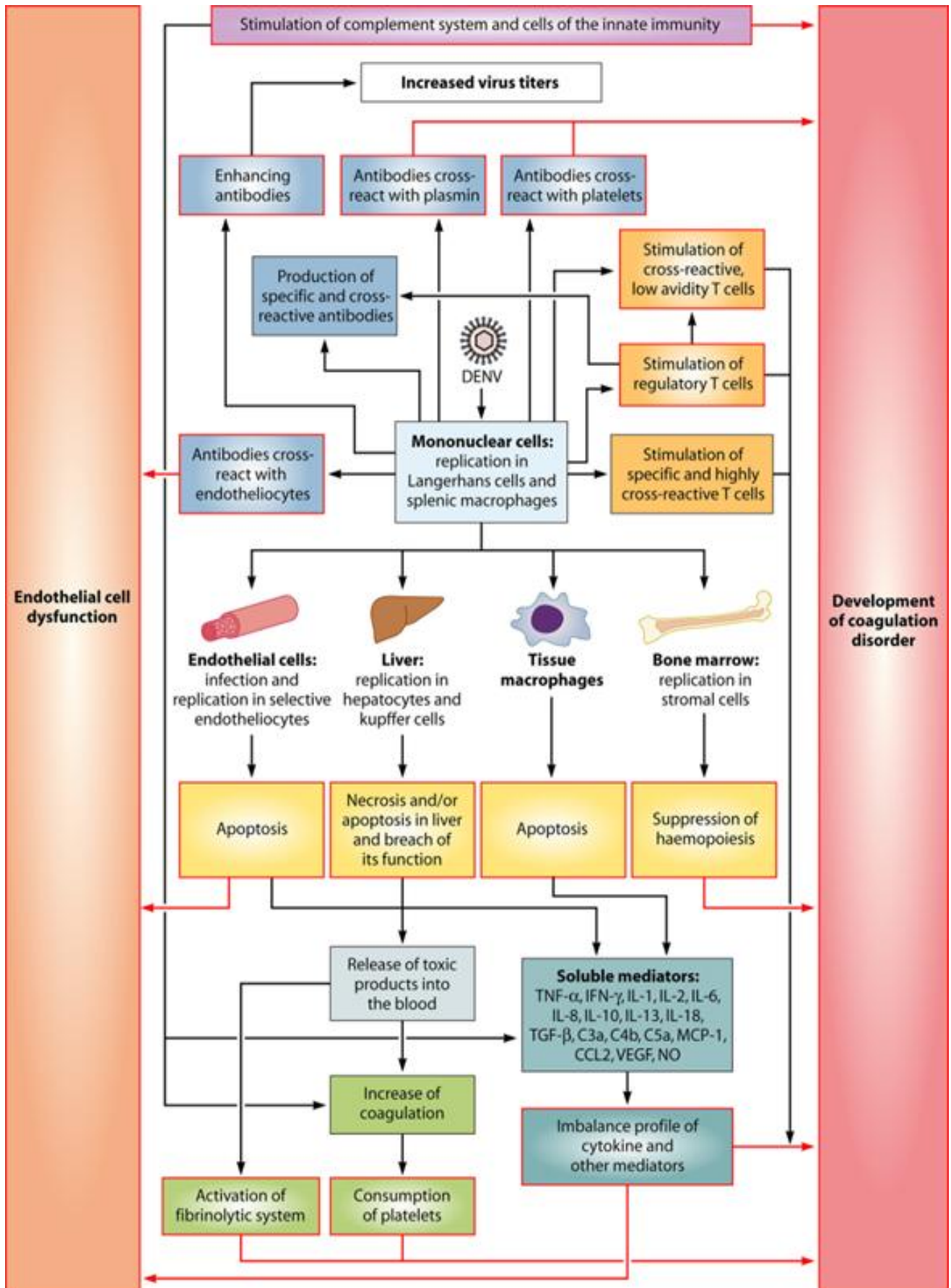


Figure 1: Pathogenesis of Dengue Infection [6]

apoptosis and to a lesser extent through necrosis. Necrosis results in release of toxic products, which activate the coagulation and fibrinolytic systems. Depending on the

extent of infection of bone marrow stromal cells and the levels of IL-6, IL-8, IL-10, and IL-18, hemopoiesis is suppressed, resulting in decreased blood thrombogenicity. Platelets interact closely with endothelial cell, and a normal number of functioning platelets is necessary to maintain vascular stability. A high viral load in blood and possibly viral tropism for endothelial cell, severe thrombocytopenia, and platelet dysfunction may result in increased capillary fragility, clinically manifested as petechiae, easy bruising, and gastrointestinal mucosal bleeding which is characteristic of Dengue Hemorrhagic Fever, as seen in figure 1 [6].

The mechanism of progression from dengue fever to dengue hemorrhagic fever is not clearly understood. However, immune enhancement is the most commonly accepted current explanation. This hypothesis states that individuals who have had a prior infection (primary infection) with 1 of the 4 dengue virus serotypes have circulating non-neutralizing antiviral antibodies. When an individual is infected with another serotype (secondary infection), these non-neutralizing antibodies recognize the dengue virus but do not neutralize or inhibit virus replication. Instead, the Virus and antibody form an antigen-antibody complex. This complex is recognized by receptors on macrophages, which then internalize the immune complex and allow the virus to replicate unchecked (immune enhancement). The affected macrophages release vasoactive mediators that increase vascular permeability, leading to vascular leakage, hypovolemia, and shock. Recent research has demonstrated that this mechanism, along with individual host and viral genome variations, plays an active role in pathogenesis [3], [6].

3. Dengue Complications

3.1 Neurological Complications

Neurological disorder associated with dengue have been reported from twenty five different countries representing Asia Pacific, the Americans, the Mediterranean, and Africa and both sexes are affected by the neurological complications. Case have been reported among ages ranging from 3 months to 60 years. However there is a greater incidence among children. The incidence of neurological symptoms among dengue patients varied from 1% to 25% of all dengue admissions. In Indonesia, 70% virologically confirmed fatal dengue infections presented with one or more neurological signs, and 7% of those admitted for viral encephalitis turned out to be dengue infected [7]. The neurological manifestation can be occurred in include encephalopathy, encephalitis/aseptic meningitis, intracranial hemorrhages/ thrombosis, mononeuropathies/ polyneuropathies/ Guillane-Bare syndrome, Myelitis. These include such as central nervous system phenomena as convulsions, spasticity, change in consciousness and transient pareses. A subtle form of seizure is occasionally observed during the febrile phase in infant. The severity of neurological disease caused by different dengue serotypes, dengue serotypes 2 and 3 have been primarily reported to cause neurological symptoms [4].

3.1.1 Peripheral Polyneuropathies

Peripheral polyneuropathies is a rare complication of dengue virus infection. However, skin itching over the palms and soles, which may be a mild form of polyneuropathy, has been reported in dengue patients. Neuropathologic studies in dengue patients indicated the presence of perivenous demyelinating leukoencephalopathic possible caused by an immuno pathogenic mechanism [8].

3.1.2 Encephalopathy

Encephalopathy is the most common neurological manifestation. It may result from hypotension, cerebral edema, microvascular and frank hemorrhage, hyponatremia, and fulminant hepatic failure which may be part of Reye syndrome. Pathophysiology of neurological involvement may include the following factors: direct tissue lesion caused by the virus because of its neurotropicity, capillary hemorrhage, disseminated intravascular coagulations and metabolic disorders. Water intoxication resulting from the excessive administration of hypotonic solution to treat DHF/DSS patients with hyponatremia may lead to encephalopathy. Previously of neurological manifestations in dengue infection had been referred to as encephalopathy rather than encephalitis, because attempts to demonstrate direct invasion of the central nervous system by dengue virus had failed [7], [9].

3.1.2 Encephalitis

In Dengue encephalitis, virus was detected in cerebrospinal fluid (CSF) by polymerase chain reaction and Ig M antibodies against dengue were present in the CSF. Animal studies done in mice showed that the virus could break down the blood brain barrier leading to CNS invasion. CNS imaging studies in cases of dengue encephalitis have shown that cerebral edema is the predominant finding in the majority patients. Clinical diagnosis of dengue fever along with magnetic resonance of encephalitis and a positive CSF serology, it can be said that this case represents a true case of dengue encephalitis. Mortality in dengue complicated with neurological complication now is increased [7], [9], [10].

3.2 Gastrointestinal Hepatic Complication

Gastrointestinal manifestations of dengue are increasingly being identified and reported such as hepatitis, fulminant hepatic failure, acalculous cholecystitis, acute pancreatitis, acute parotitis, and febrile diarrhea. Dengue virus antigen is found in Kupfer cells and sinusoidal lining cells in the liver. Hepatic manifestations can be characterized by manifestation of acute hepatitis with pain in hypocondrium, hepatomegaly, jaundice, and raised aminotransferase levels.

3.2.1 Hepatitis

In hepatitis, these level of these enzymes peak on the ninth day after onset of symptoms and gradually return to normal levels within 3 weeks. Histopathological findings include centrilobular necrosis, fatty alterations, hyperplasia of the kupfer cells, acidophilic bodies and monocytes alterations of the portal tracts in most cases hepatic involvement prolongs the clinical course of this self-limiting viral infection but it

does not constitute a sign of worse [4]. One important characteristic of hepatic involvement with dengue infection is a greater elevation in AST than ALT levels. The elevation in the level of AST enzymes is normally greater than the elevation of ALT in dengue patients during the first week of infection, may be due to the release of AST from myocyte damage in dengue infection and this information is useful to distinguish between liver failure caused by dengue infection and caused by other etiologies. The use of paracetamol and hepatotoxic drugs (salicylates, acetaminophen) can lead to hepatic damage and trigger or worsen the primary lesion caused by the dengue virus are not indicated in this case. Liver damage was more frequent among women, patient with sequential infection and hemorrhagic cases and infection with dengue serotypes 3 and 4 produced higher liver enzymes levels compared with infections due to other serotypes [2], [5], [11].

3.2.2 Hepatomegaly

Hepatomegaly is the most frequent sign found in dengue shock syndrome (DSS) with values ranging from 30%-79% and remission of hepatosplenomegaly usually 28 days after the onset of the disease. The presence of jaundice in these cases is apparently multifactorial. It can be due to hepatic aggression caused by the dengue virus and/or hypoxia and tissue ischemia. Jaundice was present 12%-62% of patients with DSS [2].

3.2.3 Acute Pancreatitis

Acute pancreatitis is a rare complications of dengue fever. Enlarged pancreas and increase serum amylase and lipase levels were found in 29% of these patients. Pancreas involvement might be due to direct viral invasion or might be due to hypotension in DHF. Acalculous cholecystitis is also rare in dengue fever. Patients present with right upper quadrant abdominal pain, fever, positive Murphy sign, abnormal liver function test, and thickened gall bladder wall without stones on abdominal ultrasonography. The main pathophysiology changes in dengue fever could be due to increased vascular permeability causing plasma leakage and serous effusion with high protein content with cause thickening of gall bladder wall. Thus cholecystectomy is usually not advised in dengue patients unlike other subsets of patient, and could return to normal after several days. Surgical intervention is reserved for patient with diffuse peritonitis [4].

Patient with febrile diarrhea usually followed by hemorrhagic skin lesions. Bilateral parotid gland enlargement in an immunocompetent patient with dengue infection and evidence of dengue virus in saliva has been described as a unique case [4], [12].

3.3 Hematologic Complications

Viral dengue infections may influence hemostasis and can lead to thrombohemorrhagic complications or syndrome such as Disseminated Intravascular Coagulation (DIC), Hemolytic Uremic Syndrome (HUS), Thrombotic Thrombocytopenic Purpura (TTP), or Vasculitis. Symptoms and sign may be dominated by bleeding, thrombosis, or both.

3.3.1 Consumptive Coagulopathy (DIC)

DIC is an acquired disorder in which the hemostatic system is activated, resulting in activation of platelets and the conversion of fibrinogen to fibrin, at the same time there is deposition of fibrin and massive bleeding. This may lead to generalized microvascular thrombosis and Multi Organ Failure (MOF) and to life threatening hemorrhage due to consumption of coagulation factors and activation of the fibrinolytic system. Endothelial cell injury is a common feature of viral dengue infection and can alter hemostasis in direct or indirect manner. This infection may result in a procoagulant state mainly by inducing tissue factor expression on the endothelial surface probably mediated by cytokines such as IL-1, TNF- α , and IL-6. Fibrinolysis may be activated primarily and thus independently of activation of the coagulation cascade or secondarily in response to fibrin formation. In DIC, fibrinolysis was also activated but this activation was relatively weak compared with that of coagulation as a result of persistently high plasminogen activator inhibitor level. This imbalance between coagulation and fibrinolytic may lead to DIC. The mechanism of thrombocytopenia is decreased thrombopoiesis, increased platelet consumption, or combination of both. Endothelial injury by dengue virus may lead to increased adherence and consumption of platelets, pathogenesis of DIC. DIC may contribute to multiorgan failure and associated with high mortality [13], [14].

3.3.2 Nonconsumptive Coagulopathies

DIC as a consumptive coagulopathy with consumption of both platelets and clotting factor, must be distinguished from the nonconsumptive coagulopathies, such as HUS and TTP, characterized by thrombocytopenia, hemolytic anemia, fever, renal abnormalities, and neurologic disturbances. Vasculitis, which may be triggered by infection, is characterized by local or more generalized vascular change, resulting from infarction secondary to occlusion by thrombi of the lumen of small blood vessels in the upper part of the dermis. Vascular occlusion may lead to ischemic tissue injury do to local vascular occlusion or bleeding due to local tissue damage [13].

3.4 Cardiac Complications

Cardiac manifestations of dengue are uncommon but cardiac rhythm disorders such as atrioventricular blocks, atrial fibrillation, sinus node dysfunction and ectopic ventricular beats have been reported during episodes of DHF. Most are asymptomatic and have a benign self-limiting course with resolution of infection. These arrhythmias have been attributed to viral myocarditis, but an exact mechanism has not been elucidated. Pericardial involvement has also been attributed to dengue infection along with myocarditis [4]. Pericarditis is an inflammation and swelling in the membranes that are around the heart. Pericarditis will usually cause a sharp stabbing chest pain. A mild case will sometimes resolve of its own accord, but in severe cases is life threatening [15].

3.5 Renal Complications

Acute renal failure is rare in dengue fever and it mainly presents as shock induced acute tubular necrosis. It was

found to occur in 0.3% cases in a series of 6154 patients with DHF. Acute renal failure and multiple organ failure can also be manifestation of rhabdomyolysis. The role of immune complex in development of renal failure in dengue infection is still unclear. Wiwakinit has discovered that the diameter of dengue virus-immunoglobulin complex is much smaller than the diameter of glomerulus. Thus he postulated that immune complex can be trapped only if previous glomerular lesion causes narrowing of the glomerulus's diameter, and concluded that the immune complex does not play a significant role in pathogenesis of renal failure in dengue infection. Renal failure because of hemolytic uremic syndrome has been described in isolated case report where renal biopsy revealed thrombotic microangiopathy with glomerular and arteriolar microthrombus. Electron microscope demonstrated presence of microtubuloreticular structures suggesting a viral infection. This patient was treated with plasmapheresis, haemodialysis, and anti-hypertensive drugs [4].

3.6 Respiratory Complications

Dengue hemorrhagic fever can result in acute respiratory distress syndrome (ARDS). Dengue virus antigen is found in alveolar lining cells of the lung. Increased permeability of the alveolar capillary membrane results in the edema in the alveoli and interstitial space which lead to pulmonary dysfunction. Vascular extravasation of fluids, electrolytes, protein, and cells can lead to cavity effusions, likes pleural effusion, mainly on the right side. Dengue shock syndrome is reported to be third leading cause of ARDS in the pediatric intensive care setting in dengue endemic area. Early restoration of adequate tissue perfusion is critical to prevent progression of dengue shock syndrome to ARDS. However equal care must be exercised to avoid excessive fluid infusion after adequate volume replacement because fluid overload may result in ARDS. This complication requires early recognition and management for good results. Pulmonary haemorrhage with or without haemoptysis has also been reported in DHF [2], [4].

3.7 Musculoskeletal Complications

Dengue fever has been described classically as break bone fever as it causes severe muscle, joint, and bone pain. Muscular complication including myositis and rhabdomyolysis. Direct invasion of muscle by virus has not been demonstrated and the most likely caused was myotoxic cytokines, particularly TNF. Studies of muscle biopsy specimens have revealed a range of findings from mild lymphocytic infiltrate to foci of severe myonecrosis [4]. The clinical presentation of rhabdomyolysis include symptoms of myalgia, weakness, and dark urine. Predisposing conditions that may lead to rhabdomyolysis include history of seizures, unconsciousness, strenuous exertion frequently associated with altered mental status. Swollen tender muscle or skin changes consistent with pressure injury may be found on clinical examination. Elevated creatine kinase (CK) levels remain the most sensitive indicator to rhabdomyolysis. Meanwhile it has been suggested that all patients with dengue fever should have a dipstick urinalysis to screen for this complication and if

positive, to proceed with a serum CK level. It is also important to remember that the benzidine urinary dipstick doesnot differentiate between myoglobin, hemoglobin, and red blood cells and a CK should be performed if rhabdomyolysis is suspected. This is reasonable as the test is easily available and early diagnosis of rhabdomyolysis can prevent its complication [16]. Rhabdomyolysis can lead to acute renal failure and electrolyte disturbances, if unrecognized. However if recognized early, these complications can be easily prevented [2].

3.8 Lymphoreticular Complications

Dengue virus antigen is found predominantly in cells of the spleen, thymus, and lymph nodes. In DHF, lymphadenopathy is observed in half of the cases and splenomegaly is rarely observed in small infants. Splenic rupture and lymph node infarction in DHF are rare. Physicians should be aware of this fatal complication in areas endemic to dengue. A case of splenic rupture can be misdiagnosed because of misinterpretation of the shock syndrome as in a case of dengue shock syndrome. Splenectomy can be curative. A case of lymph node infarction in association with disseminated intravascular infarction in a serologically proven case of dengue fever have been reported. As malignant lymphoma is the commonest cause of lymph node infarction, this disease should be ruled out using immunochemistry [4].

3.9 Genital Complications

Acute Idiopathic Scrotal Edema (AISE) is rare manifestations of dengue hemorrhagic fever. AISE rarely reported in adults, usually affects children 4-12 years of age and is defined as a self-limited edema and erythema of the scrotum that resolve without sequel in 1-3 days. Patients with AISE are asymptomatic or complain of minimal scrotal discomfort. The conditions is characterized by sudden onset of subcutaneous scrotal edema, erythema, and mild scrotal pain. Typically patients are afebrile or have a low grade fever. With bed rest and scrotal elevations, the conditions is self-limited and symptoms resolve 6-72 hours. The cause of AISE in case with dengue may be caused by plasma leakage from increased vascular permeability as a consequence of dengue hemorrhagic fever. A proposed mechanism of antibody dependent enhancement for dengue hemorrhagic fever is that numerous cytokines including TNF- α , IL-2, IL-6, IL-8, and IFN- γ are released from endothelium, monocytes, and T cells after a secondary infection with a different serotype of dengue virus. Cross reactive antibody, accompanied with cytokine and activated complement, results in clearance of platelet, disruption of the coagulation system and vascular leakage and subsequent dengue hemorrhage fever/dengue shock syndrome [8].

3.10 Ocular Complications

Dengue, generally, is not typically associated with ocular complications. However, with the resurgence of Dengue in Singapore since mid-2004, there have been increasing incidences of dengue-related ocular inflammatory complications [17]. In medical text, manifestations are

related to the bleeding diathesis from thrombocytopenia. Blurring vision occurs one week after onset fever. Clinical features include retinal edema, blot hemorrhage, and vasculitis. Less common features include exudative retinal detachment, cotton wool spots, and anterior uveitis [18].

The pathogenesis of these ocular complications following dengue fever is controversial and as yet unknown. It is probable that the pathogenesis of these ocular manifestations is directly related to the immunopathogenesis of dengue fever. Inflammatory changes in vascular endothelium resulting in vascular leakage, haemorrhage and ischaemia can be seen in cells infected with dengue virus. This has been postulated to be mediated via proinflammatory mediators including IFN- β and tumor necrosis factor (TNF- α) as a result of a shift balance of the cell mediated immunity from Th-1 and Th-2 resulting in CD4/CD8 inversion, through elevated IL-6 and autoantibodies directed against endothelial cells and platelets, or molecular mimicry against dengue viral structural proteins [17].

Prognosis is generally good as the disease is often self-limiting, resolving spontaneously even without treatment. However patients may experience mild relative central scotoma that may persist for month. The use of steroids in treating this inflammatory eye condition is controversial. A heightened awareness of dengue related ophthalmic complications among clinicians involved in the care of patients with dengue would facilitate prompt referral for ophthalmologic assessment and managements [18].

3.11 Iatrogenic Complications

Such complications include sepsis, pneumonia, wound infection and over hydration often occurred in management of dengue patient. The use of contaminated intravenous lines or fluids can result in gram negative sepsis accompanied by fever, shock, and severe hemorrhage; pneumonia, and other infections can cause of fever and complicate convalescence. Over hydration can cause heart or respiratory failure, which may be mistaken to shock. Great care must be taken to prevent iatrogenic complication in the treatment of DHF/DSS, to recognize them quickly if they occur and not to mistake preventable and treatable iatrogenic complications for normal DHF/DSS findings [19].

4. Conclusion

Dengue is a self-limited disease that caused by viral infection. Dengue must be well treated even patient do not show any symptoms (asymptomatic patient). Complications of Dengue can be manifested in many organ, include neurological (encephalopathy, encephalitis/aseptic meningitis, intracranial hemorrhages/thrombosis, mononeuropathies/ polyneuropathies / Guilane-Bare syndrome, Myelitis), Gastrointestinal (hepatitis, fulminant hepatic failure, acalculous cholecystitis, acute pancreatitis, acute parotitis, and febrile diarrhea), Hematology (DIC, HUS, TTP, Vasculitis), Cardiac (atrioventricular blocks, atrial fibrillation, sinus node dysfunction and ectopic ventricular beats), Renal (Acute renal failure, acute tubular

necrosis), Respiratory (ARDS), Muscular (myositis, rhabdomyolysis), Lymphoreticular (lymphadenopathy, spleen rupture), Genital (AISE), and ocular. Such complications include sepsis, pneumonia, wound infection and over hydration are often occurred in management of dengue patient.

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