International Journal of Research Studies in Medical and Health Sciences
Volume 6, Issue 7, 2021, PP 19-23
ISSN : 2456-6373
DOI: https://doi.org/10.22259/ijrsmhs.0607003

Dengue: Foreshadowing from Ancient Foe

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BACKGROUND

Although in recent years Bangladesh has achieved a remarkable progress in controlling communicable diseases, the country has still been facing a tremendous pressure in respect of public health problems especially controlling the emerging or re-emerging diseases. Dengue ranks as the most important, rapidly emerged disease in recent years and is endemic in all continents. Approximately, half of the world's population is at risk. Up to 50-100 million infections are now estimated to occur annually in over 100 endemic countries including Bangladesh[1]. Bangladesh is situated in the tropical and sub-tropical regions like other Southeast Asian (SE) countries and like them has become a suitable habitat for the dengue vector and its increased transmission. Dengue is the fastest emerging arboviral infection caused by Dengue virus (DENV). It causes a severe flu-like illness, sometimes potentially lethal complications. Dengue virus is a single stranded positive polarity RNA virus, belongs to the family Flaviviridae. It is transmitted through the bite of an infected female mosquito of *Aedes* species - mainly the species *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*. This mosquito also transmits Chikungunya, Zika and Yellow fever viruses.[2,3]. The Aedes mosquito breeds in fresh stagnant water. Heavy rainfalls in Bangladesh during the monsoon season and unplanned rapid urbanization with thousands of building sites have created the perfect breeding ground for the mosquito-borne virus.

There are four dengue virus serotypes, which are designated as DENV-1, DENV-2, DENV-3, and DENV-4. Infection with anyone of these serotypes confers lifelong immunity to that virus serotype. Although all four serotypes are antigenically similar, yet they elicit cross protection for only few months. Secondary infection with dengue serotype 2 or multiple infection with different serotypes enhance chances of occurring more severe form of diseases.

The first recorded case of probable dengue fever was in a Chinese medical encyclopedia from the Jin Dynasty (265-420 AD) which referred to a "water poison" associated with flying insects. The most plausible early reports of dengue epidemics are from 1779 and 1780, when an epidemic swept across Asia, Africa and North America. The first confirmed case report dates from 1789 and is by Benjamin Rush, who coined the term "break bone fever" because of the symptoms of myalgia and arthralgia.[4] Hemorrhagic dengue was first recognised in the 1953 during dengue epidemics in the Philippines and Thailand.[5] and dengue shock syndrome were first noted in Central and South America in 1981[6].In Bangladesh, dengue occurred sporadically since 1964.[7] Literature shows, the first documented case of dengue like fever occurred in 1964, popularly known as "Dacca fever" which later on serologically proved as dengue fever.[8]Dengue caused a serious public health concern, following a sudden outbreak in 2000 where around 5,551 cases and 93 deaths occurred in the country. In 2019 during the early monsoon dengue outbreak with death in Dhaka started in an alarming way and affected number are almost 101354 and total death is 179 according to DGHS although both numbers are higher according to print and electronic media reports.A recent study in 2017 (until February 2018) in Dhaka, described DENV-2 as the dominant type, but also detected some DENV-1 and DENV-3. In the recent years, despite a small sample size, DENV-3 and DEN -4 accounts for most of the cases[9],[10] and these strains are considered deadly as they cause plasma leakage, respiratory distress and organ impairment in patients.[11]

The virus passes to humans through the bites of an infective female Aedes mosquito, which mainly acquires the virus while feeding on the blood of an infected person. The full life cycle of dengue fever virus involves the role of mosquitoes as a transmitter (or vector) and humans as the main victim and source of

infection. Once humans are infected, humans become the main carriers and multipliers of the virus; serve as a source of the virus for uninfected mosquitoes. The virus circulates in the blood of an infected person for 2 to 7 days, at approximately the same time the person develops a fever. The infected person can transmit the infection via Aedes mosquitoes after the first symptoms appear which normally occur within 4 to 5 days to maximum 12 days.

The pathogenesis of dengue involves a complex interaction between virus and host factors, and remains incompletely understood. The immune system plays a key role in disease pathogenesis. Various mechanisms of severe disease have been suggested, including: (a) Antibody-dependent enhancement or ADE, (b) T-cell mediated immunopathology, (c) Complement activation by virus-antibody complexes and (d) Cytokine abundance. These cytokines along with complement breakdown products (C3a, C5a) activated in DHF/DSS, increases vascular permeability of vascular endothelial cells leading to DSS. Antibody dependent enhancement and inappropriate memory T-cell response are central to the pathogenesis of DHF/DSS. Factors Responsible for DHF/DSS are presence of enhancing and non-neutralizing antibodies, age less than 12 years, female sex, Caucasian race, sequence of infection, infecting serotype(type 3 is most dangerous).Causes of bleeding in dengue syndrome are multifactorial. Proposed causes are abnormal coagulogram, thrombocytopenia, platelet dysfunction, prothrombin complex deficiency secondary to liver involvement, endothelial injury, DIC and prolonged APTT, decreased fibrinogen level, Increased level of fibrinogen degradation product (FDP), Increase level of D-Dimer, consumptive coagulopathy (activation of mononuclear phagocytes), Sequestration of platelet.

Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever, or dengue hemorrhagic fever (DHF) with plasma leakage that may lead to hypovolemic shock Dengue Shock Syndrome (DSS). The World Health Organization (WHO) has coined the term expanded dengue syndrome (EDS) to describe cases, which do not fall into either dengue shock syndrome or dengue hemorrhagic fever. This has incorporated several atypical findings of dengue affecting various organs of the body.

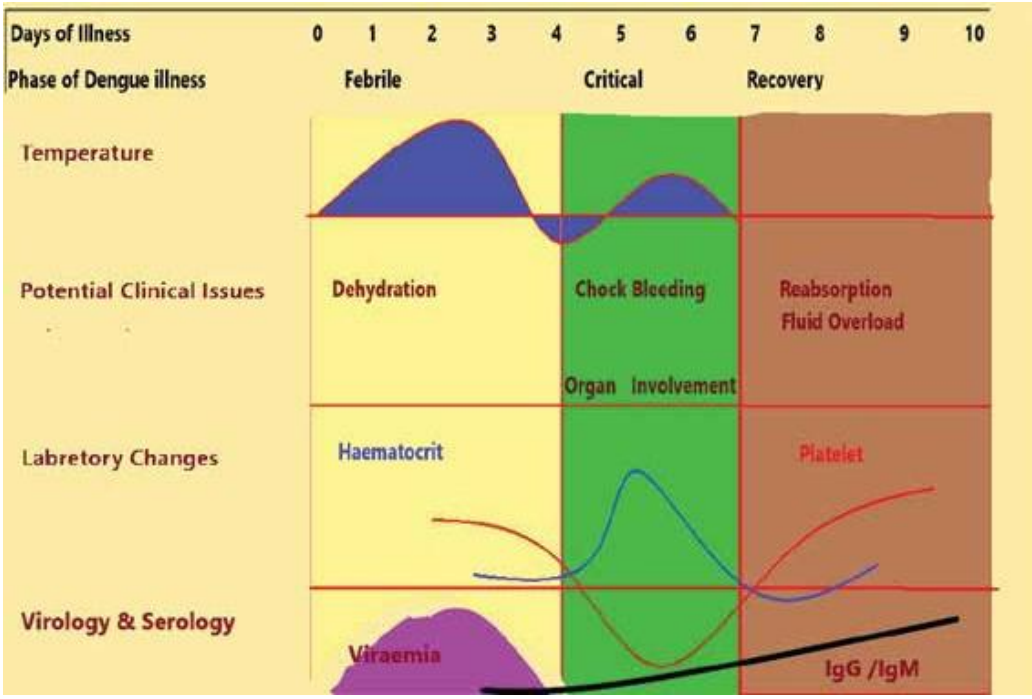

Figure1. *Clinical Course of Dengue Fever*

DHF is characterized by the acute onset of high fever and is associated with signs and symptoms similar to DF in the early febrile phase. Critical phase with plasma leakage is the hallmark of DHF which occurs soon after the end of the febrile phase. Plasma leakage is due to increased capillary permeability. There is a tendency to develop hypovolemic shock (dengue shock syndrome) due to plasma leakage.

DF/DHF patients usually go to critical phase after 3 to 4 days of onset of fever. During this critical phase plasma leakage and high hemoconcentration are documented and patients

may develop hypotension. With the leakage of plasma there will increase in hematocrit. A 20% rise of hematocrit from the baseline is indicative of significant plasma leakage. Abnormal hemostasis and leakage of plasma leads to shock, bleeding, DIC, metabolic acidosis and accumulation of fluid in pleural and abdominal cavity. High morbidity and mortality in DHF/DSS are commonly associated with various organ involvements and metabolic derangement. The period of plasma leakage usually persists for 36-48 hrs. Commonly in DHF, platelet count is less than 100000 per/cmm of blood. Significant loss of plasma leads to hypovolemic shock. Even in these shock cases, prior to intravenous fluid therapy, pleural effusion and ascites may not be detected clinically. Radiographic and ultrasound evidence of plasma leakage precedes clinical detection. A right lateral decubitus chest radiograph to detect pleural effusion and gall bladder walledema is associated with plasma leakage and may precede the clinical detection. Dengue Shock Syndrome is a prevention of Dengue Syndromes when there are criteria of DHF plus signs of circulatory failure, manifested by: rapid and weak pulse, narrow pulse pressure (≤ to 20 mm Hg),hypotension for age, cold clammy skin, restlessness, undetectable pulse and blood pressure.

During the recovery phase the extracellular fluid which was lost due to capillary leakage returns to the circulatory system and signs and symptoms improve. This phase usually after 6-7 days of fever and last for 2-3 days. Longer convalescence may be expected in some of the patients with severe shock, organ involvement and other complications which may require specific treatment. Patient may develop pulmonary oedema due to fluid overload if the fluid replacement is not optimized carefully.

Patients with dengue illness can sometimes develop unusual manifestations such as involvement of liver, kidneys, brain or heart with or without evidence of fluid leakage and therefore do not necessarily fall into the category of DHF named as expanded dengue syndrome or isolated organopathy. These conditions are very rare and management is symptomatic. Such unusual manifestations may be associated with coinfections and comorbidities. However, these manifestations if seen in DHF patients are mostly a result of prolonged shock leading to organ failure

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System	Unusual or atypical manifestation
Neurological	Febrile seizures in young children. Encephalopathy. Encephalitis/aseptic meningitis. Intracranial hemorrhages/thrombosis. Subdural effusions. Monneuropathies/polyneuropathies/Guillane-Barre Syndrome. Transverse myelitis
Gastrointestin	Hepatitis/fulminant hepatic failure. Acalculous cholecystitis. Acute pancreatitis. Hyperplasia of Peyer's patches. Acute parotitis.
Renal	Acute renal failure. Hemolytic uremic syndrome
Cardiac	Conduction abnormalities. Myocarditis. Pericarditis
Respiratory	Acute respiratory distress syndrome. Pulmonary hemorrhage.
Musculoskelet	Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis
Lymphoreticul	Infection associated haemophagocytic syndrome. IAHS or Haemophagocytic lymphohistiocytosis (HLH), idiopathic thrombocytopenic purura(ITP). Spontaneous splenic rupture. Lymph node infarction
Eye	Macular hemorrhage. Impaired visual acuity. Optic neuritis.
Others	Post-infectious fatigue syndrome, depression, hallucinations, psychosis, alopecia

Expanded Dengue Syndrome

In 2021, dengue infection has emerged with changing spectrum of presentations in Bangladesh. Atypical presentations are observed more frequently. There is persistence of fever beyond seven days, absence of fever, only back pain, enteritis as presenting feature, rapid development of pancreatitis, cholecystitis, fulminant hepatic failure, acute renal failure or unusual hemorrhage during febrile phase, development of thrombocytopenia in mid febrile phase and persistence of thrombocytopenia beyond critical phase, high elevation of CRP and D dimer.

The management of DS is based on clinical judgment rather than laboratory evaluations alone. However, few indirect tests may be suggestive of DS from the outset. Complete blood count Including total leucocyte count, total platelet count and hematocrit should be done on first consultation (within first week) of the patient to have the baseline. The change in total white cell count (≤5000 cells/mm3) and ratio of neutrophils to lymphocyte (neutrophils < lymphocytes) is useful to predict the critical period of plasma leakage. This finding precedes thrombocytopenia or rising hematocrit. These changes seen in DF and DHF.Mild thrombocytopenia (100,000 to 150,000 cells/ mm3) is common and about half of all DF patients have platelet count below 100,000 cells/ mm3; A sudden drop in platelet count to below 100,000 occurs before the onset of shock or subsidence of fever. The level of platelet count is correlated with severity of DHF. Severe thrombocytopenia (<100,000/mm3) usually precedes/accompanies overt plasma leakage. A sudden rise in hematocrit is observed simultaneously or shortly after the drop in platelet count. Hemoconc entration or rising hematocrit by 20% from the baseline, e.g. from hematocrit of 35% to ≥42% is objective evidence of leakage of plasma.AST and ALT levels are frequently elevated in both adults and children with DF and DHF.

Regarding dengue diagnostic tests, detection of antigen: NS1 antigen is used in early phase. The ELISA NS1(non-structural protein 1) antigen is positive on first day of illness.This test becomes negative from day 4-5 of illness. Anti-dengue IgM specific antibodies can be detected after 5 days of the onset offever and highest level achieved after 7 days. In primary dengue infection- IgM will be more than IgG early period and sed IgG at 9 or 10th day of fever. In secondary dengue infection- higher elevation of anti-dengue specific IgG antibodies and lower levels of IgM.

Dengue, an emerging disease, will remain in Bangladesh and will continue to constitute a serious public health problem as is happening worldwide. The changing epidemiology should be clearly understood, and constant monitoring is needed, including extending the surveillance areas and addressing the challenges to reduce the impact of the disease on public health and the economy of the country. It may be very challenging to root up the disease from the supply side, and a long-term investment is needed to achieve behavioral changes in the urban population to join the fight against the *Aedes* mosquitoes.

From a public health standpoint, mass mobility events (e.g., Eid exodus, Hajj pilgrimage) can sometimes be reasons for major concern if their location and timing coincide with major outbreak[12]. Such unexpected coincidence could facilitate outbreaks (especially with highly contagious viruses) morphing into an epidemic or even pandemic (depending on other factors like ease of transmission and favorability of climate factors). The ongoing outbreak of coronavirus in Wuhan, China, can be a recent example of this. Transmission and spread of infectious diseases, including dengue and other *Aedes* mosquito-borne diseases (chikungunya and Zika), especially during an outbreak can therefore present an immense challenge for public health safety, as there is no vaccine against dengue.

Prevention and control of dengue in Bangladesh, is not a sole responsibility for any single ministry and or its agencies. It needs effective and timely coordination, collaboration and partnership, among all the concerned ministries and their agencies, led by the Ministry of Health and Family Welfare. Furthermore, strengthening of the existing efforts including capacity building and resource mobilization, and integrated surveillance, sustainable vector control, optimum and active community participation, and adequate monitoring and periodic evaluation throughout the year across the country, considering it an endemic disease, are strongly recommended.. Attempts at conducting risk assessment based on early warning signs therefore need to incorporate social factors and mass movement events along with the climate factors

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Citation: *Dr. Richmond Ronald Gomes, "Dengue: Foreshadowing from Ancient Foe", International Journal of Research Studies in Medical and Health Sciences. 2021; 6(7):19-23. DOI: https://doi.org/10.22259/ ijrsmhs.0607003*