

Many Faces of Dengue Fever

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During the havoc caused by ongoing COVID-19 pandemic, Dengue fever (DF) is making headlines along with COVID-19 in many countries of tropics and sub-tropics including Bangladesh. This editorial is an effort to aware our learned readers on the topic, introducing them to the many unusual manifestations of Dengue and highlighting the issue through this academic forum to raise awareness on the subject specially for the policy makers.

The overall picture of dengue fever (DF) and dengue haemorrhagic fever (DHF) is rapidly changing. Worldwide, Dengue is the most rapidly spreading mosquito-borne viral disease. In the last half century, incidence has increased 30-fold with increasing topographical expansion to new regions and, in the present decade, from urban to rural settings. A projected 50 million dengue infections occur every year and an estimated 2.5 billion people live in dengue endemic countries. Furthermore, in recent years the disease has regularly been manifesting with increasing frequency of out-breaks¹.

Dengue is a mosquito borne Flaviviral illness, which has four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). A study in 2017 (until February 2018) in Dhaka, found DENV-2 as the dominant type, but also detected some DENV-1 and DENV-3. In another study, DENV-3 accounted for 46% of the samples in September and October 2018. The principal vector for dengue is *Aedes aegypti*. A less frequent vector, *Ae. albopictus* is known to be indigenous to South East Asia. With the huge outbreak of dengue in Bangladesh in 2000, it has established itself as an important health problem of Bangladesh. In the year 2019 there was significant increase in number of cases of dengue occurring throughout the country and even from the rural areas. Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever, or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolaemic shock, Dengue Shock Syndrome (DSS). This range of

manifestations of dengue virus infection may be defined as Dengue Syndrome²

A primary Dengue Virus infection is the first infection a person suffers. A secondary infection is the second infection caused by a different Dengue virus type. Secondary infections separated in time by more than 18 months represent the highest risk for resulting in a severe clinical outcome³. The majority of secondary infections are subclinical or mild. The determinants of clinical severity remain unclear, though studies indicate a titer-dependent and time-dependent role of cross-protective anti-DENV antibodies. Methods: Data from 2 sequential prospective cohort studies were analyzed for subclinical and symptomatic DENV infections in schoolchildren in Kamphaeng Phet, Thailand (1998-2002 and 2004-2007). The incubation period ranges from 3 to 14 days. Typically symptoms appear within 4 to 7 days after the bite of an infected mosquito⁴. The reported number of imported cases has been rising, and the first domestic dengue outbreak in nearly 70 years was confirmed in 2014, highlighting the need for greater situational awareness and better-informed risk assessment. Methods: Using national disease surveillance data and publically available traveler statistics, we compared monthly and yearly trends in the destination country-specific dengue notification rate per 100,000 Japanese travelers with those of domestic dengue cases in the respective country visited during 2006–2014. Comparisons were made for countries accounting for the majority of importations; yearly comparisons were restricted to countries where respective national surveillance data were publicly available. Results: There were 1007 imported Japanese dengue cases (Bali, Indonesia (n = 202). Three phases can be seen in the setting of Dengue virus infection, a febrile phase, a critical phase, and a recovery phase. However, the critical phase is not witnessed in all cases¹.

It's an acute febrile illness characterized by the presence of fever and two or more of the following: Headache, Retro-orbital or ocular pain, myalgia and/or bone

pain (break-bone fever), arthralgia, rash, haemorrhagic manifestations (eg, positive tourniquet test, petechiae, purpura/ecchymosis, epistaxis, gum bleeding, blood in emesis, urine, or stool, or vaginal bleeding) and leukopenia. Dengue haemorrhagic fever is characterized by fever, thrombocytopenia, haemorrhagic manifestation and evidence of plasma leakage. Lastly, Dengue Shock Syndrome consists of DHF with marked plasma leakage that results in circulatory collapse or shock as evidenced by narrowing pulse pressure or hypotension^{1,2}.

Expanded Dengue Syndrome (EDS) is a term announced by the WHO in 2011 and added to the classification system to incorporate a wide spectrum of atypical manifestations of dengue infection affecting various organ systems including gastrointestinal, hepatic, neurological, pulmonary, renal system & other isolated organ involvements. Certain high-risk groups such as expectant women, infants, elderly groups, and patients with coronary artery disease, haemoglobinopathies, and immunocompromised individuals are particularly susceptible to developing EDS. EDS is becoming widespread globally with unusual features and increased severity. In clinical practice, the occurrence of unusual presentation during the dengue prone season should prompt clinicians to investigate for dengue in suspected cases. Knowledge of expanded dengue helps to confirm the diagnosis of dengue early, especially during ongoing epidemics⁵. Dengue can occur with co-infection, such as Urinary tract infection, sepsis with Hospital Acquired Pneumonia, Community Acquired Pneumonia etc. Dengue with Covid-19 coinfection has recently been reported also⁶.

Different literatures have reported many unusual manifestations of Dengue fever. **Neurological manifestations:** The spectrum of neurological complications ranges from encephalopathy, encephalitis, acute disseminated encephalomyelitis (ADEM), neuro-myelitis -Optica (NMO), optic neuritis, myelitis to Dengue associated stroke. The pathogenesis of neurological indices is associated with direct invasion of the central nervous system by the dengue virus, autoimmune reactions, and metabolic alterations. **Gastrointestinal manifestations:** can manifest as acute

hepatic failure, hepatorenal syndrome, severe bleeding, acute cholecystitis, acute pancreatitis. The pathogenesis of liver involvement in dengue is yet unclear. Direct viral infection of hepatocytes is hypothesized, although immune mechanisms are also believed to play a role.

Renal manifestations: Dengue has been related to various forms of renal involvement. These include electrolyte imbalance, acute kidney injury (AKI), proteinuria, glomerulonephritis, haemolytic uraemic syndrome and acute tubular necrosis. The incidence of renal manifestations varies from 17% to 62%⁷. Hyponatraemia is the most common electrolyte abnormality in DF. The mechanism for AKI is multifactorial, which includes direct viral action on renal tissue, hypoperfusion secondary to shock, and rhabdomyolysis. **Cardiac manifestations:** A diversity of cardiac manifestations has been reported in dengue infection. Cardiac involvement of varying degrees has been described ranging from arrhythmias to myocardial ischaemia, pericarditis and myocarditis. The prevalence of myocarditis in DF ranges from 9% to 15%. A variety of rhythm abnormalities has also been reported⁷. **Respiratory manifestations:** The spectrum of pulmonary involvement can occur in DF, ranges from pleural effusion, pneumonitis, non-cardiogenic pulmonary edema to haemoptysis. In DF, pleural effusion is the most frequent cause of dyspnoea. Usually, it is bilateral and seen in the context of plasma leakage syndrome. **Haematological manifestations:** The foremost abnormalities are cytopenias, hemophagocytic lymphohistocytosis (HLH), disseminated intravascular coagulopathy (DIC).

On a different note, although human beings have witnessed the introduction of several vaccines for SARS-CoV-2 within

a very short period of time, during the long account of Dengue infection, only one vaccine for Dengue, CYD-TDV (Dengvaxia), has been licensed in over 20 countries in Latin America and Southeast Asia. The dengue-vaccine field is encountering numerous hurdles⁸. For now, we have to be optimistic that we will be able to prevent Dengue all together, not only by means of vaccine but also by taking all preventive measures including mosquito control measures. Dengue infection may manifest as an asymptomatic DF, DHF,

and DSS. It is a wide spectrum of disease. Besides, designated terminology, a good number of Dengue patients may present with “many faces” as described by QT Islam et al in their study of dengue fever, being published in this issue of JBCPS. The WHO presented the term “expanded dengue syndrome” to designate cases that do not fall into either DSS or DHF. The most common are cardiac and neurological manifestations. The sensible knowledge about different faces to establish the diagnosis and prompt the appropriate treatment for dengue with unusual manifestations. Clinicians are to be aware of these unusual features so that one can suspect dengue early and take appropriate measures.

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