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REVIEW ARTICLE

EXPANDED DENGUE SYNDROME: A GROWING CONCERN

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Abstract:
Dengue is not only confined to its classical presentation of high-grade fever, body ache, shock, plasma leakage and thrombocytopenia. Itinvolves multiple organ like brain, heart, liver, abdomen, kidney, lungs, thyroid and causing concerning morbidity and mortality. In this review article we have tried to focus on the different variety of presentation which is now called Expanded Dengue Syndrome. This review article will be helpful to physician to combat Dengue virus where it is endemic.

Keywords: *Expanded Dengue Syndrome, EDS with Neurological Manifestations, EDS with Pulmonary manifestations, Review on EDS, Atypical Dengue, Unusual Dengue*

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Introduction:

Dengue is a major public health concern over a decade now. It is caused by vector borne arbovirus which is transmitted by the female *Aedes*mosquitos. There are 4 serotypes of Dengue Virus (DENV). The global incidence has increased in a concerned manner, causing over 100-400 million infections per year, majority are mild and asymptomatic.[1] High Number of cases were reported in Bangladesh (101,000) in 2019 [1]. In this year between January 1 to November 2022 total 52807 laboratory confirmed Dengue cases and 230 related death were reported in Bangladesh with a case fatality rate of 0.44%[2].WHO took a new target for 2021-2030 to reduce the dengue case fatality rate to 0% by 2030.[3] Overall dengue syndrome comprise of following: Undifferentiated fever, Dengue Fever, Dengue Hemorrhagic fever with our without shock, Expanded Dengue Syndrome.[4]

Dengue can be complicated by other organ such as liver, kidneys, heart and brain which can be manifest as uncommon clinical manifestations that are collectively termed as Expanded Dengue Syndrome (EDS)[5]. Although it can not be predicted but people who underlying co morbidities, associated co-infections or prolonged shock or high risk group such as immunocompromised individuals are susceptible to developing EDS[5].

Methods:

We systematically searched to identify published English literature on expanded dengue syndrome at the national and international level using the search engine Google, PubMed, MEDLINE, MSD Manual, Med Facts, Bangladesh Journals Online (BanglaJOL), and different sets of keywords, viz. atypical dengue, expanded dengue, neurological manifestations of dengue, gastrointestinal involvement of dengue, Cardiac involvement of dengue, Renal involvement of dengue etc. This article aims to review the diverse clinical presentation of expanded dengue syndrome to provide the physician with updated information on this threat to human life.

What is Expanded Dengue Syndrome?

The clinical entity which encompass the cases that do not fall into either dengue shock syndrome or

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dengue hemorrhagic fever[6]. By doing that it was made possible to incorporate different unusual findings of dengue. It can be multisystemic and multifactorial.

Pathogenesis of Dengue:

There are several Proposed mechanisms for severe dengue but the exact mechanism yet to be determined. Among the 4 serotypes, serotype 2 and 3 found to be more lethal[7]. The acknowledged pathological mechanism for typical dengue lies in plasma leakage and bleeding which in turns causes shock and death. In case of severe dengue, extensive T-cell activation along with activation of pro-inflammatory cytokines causes the undesired effect[7].

Cardiac Manifestations:

Many Cardiac Manifestations has been reported in Dengue infection ranging from myocarditis, pericarditis, various form of arrythmias[8,9]. Rhythm abnormalities like sinus tachycardia, second-degree heart block, third-degree heart block, atrial fibrillation to paroxysmal supraventricular tachycardia, all are reported[9]. Also in a study finding revealed that among 81 patient who were included in that study 2 death was due to secondary cardiogenic shock due to myocarditis[9]. Patient can present with feature of myocarditis even as 1st manifestations of dengue and can deteriorate very rapidly[11].

Although true incidence of Cardiac involvement is difficult to guess as different studies use different parameter for diagnosing cardiac involvement[12].

Gastrointestinal Manifestations:

There are many GI manifestations related to Dengue ranging from acute abdomen, acute liver failure, Hepatitis, acute acalculous cholecystitis, Acute Pancreatitis, Spontaneous Splenic rupture, Acute appendicitis, Acute Colonic pseudo obstruction, Splenic necrosis, Upper GI bleeding[12,13,14].

Although its rare but there are reported case of patient presenting with only acute abdomen for that surgical exploration was also needed for exclusion of other causes of acute abdomen[15]. Its not to forgot that acute abdomen is a feature of severe dengue, but as there is many other cause of acute abdomen, in a place where dengue is endemic physician should keep it in mind also.

Minor to moderate elevation of hepatic transaminase enzyme is seen invariably in DHF but not all the case go on to develop fulminant hepatitis and hepatic failure[16]. In a prospective study in india where the other cause of hepatitis excluded shown that among 110 patient tender hepatomegaly and liver function abnormalities were present[17]. The abnormal finding is more related to DHF and SGOT levels were higher than SGPT[18]. But according to a case series described in india with mean peak AST at 2095± 933 Acute liver failure is generally seen within one week of onset of fever [16, 17,18]. Fatalities is not as high as in other causes of hepatic failure[19]. A case was reported in USA about a Bangladeshi immigrant who after travelling from Bangladesh was diagnosed to have DHF with Acute liver failure[20].

Acute pancreatitis in dengue infection is not so common. It Present similarly as other causes[14]. The pathogenesis is unclear but it has been hypothesize that it could be due to direct invasion by virus itself which in turns causes inflammation and destruction of pancreatic cells or by an autoimmune response[15]. There are few case report published regarding the EDS with acute pancreatitis. A case report from Bangladesh showed that, a patient presented with acute pancreatitis along DHF with left pancreatic effusion[21].

Although very rare upper GI bleeding due to dengue also has been reported in south india[22]. A case was reported where colonoscopy revealed diffuse mucosal edema with active bleeding in a patient with DHF[23].

Moreover, DHF can be complicated with multi organ involvement along with acute pancreatitis. A case was reported from Popular Medical College, a 30 year old lady diagnosed with DHF developed hepatitis, pancreatitis, acalculous cholecystitis, coagulation abnormalities and acute renal failure[24].

When spleen rupture without trauma in a normal spleen it is called spontaneous splenic rupture which a very rare and fatal form of expanded dengue syndrome[25]. A case of spontaneous splenic rupture also been reported in bangladesh[26].If there is a strong suspicion with clinical feature of left upper quadrant pain and shock, this condition can be diagnosed easily with USG, MRI or CT of the abdomen[14]. There was only one case report also found that patient had splenic necrosis[14].

Neurological Manifestations:

Neurological manifestations in Dengue is a rare entity. It ranges from encephalitis, meningitis, Transverse myelitis, GBS, Mononeuropathies, Muscle dysfunction[13]. A study published from Bangladesh showed that among 4200 patient enrolled in the study only 5.5% patient had neurological symptoms[76]. The finding corresponds with the different studies done in South east Asia[28-33].

Encephalitis is the most common form of presentation and there is a term called Dengue

encephalitis which is defined as dengue with CNS involvement and the presence of Dengue RNA, IgM or NS1 Antigen in CSF without other neuro invasive organisms[28]. Although it is possible to have features of encephalopathy where CSF can be normal that was shown in a prospective case control study of 27 patients who are children[35].

A case was reported where A 18 year old Srilankan Boy presented with positive dengue serology and convulsions with altered Consciousness. He was diagnosed to have dengue encephalitis by CSF serology[35].

Other manifestations are infrequent. Few cases of intracranial hemorrhages have been found[30]. One interesting thing to note that hemorrhages can be associated with platelet count more than 20k, So it will be not unwise or non justified to a brain imaging in a patient present with altered consciousness level[36].

Autoimmune mediated manifestations such as Acute transverse myelitis, Optic neuritis, ADEM and GBS were also reported[36].

Pulmonary Manifestations:

It is very common to have bilateral pleural effusion in DHF or DSS due to plasma leakage and it is not considered as a part of expanded dengue syndrome[14]. Usually the effusion in dengue resolve spontaneously when the critical phase end[14].

Pneumonia as a part of expanded dengue syndrome not reported profoundly. There is a case report showing that patient developed cavity forming pneumonia by S.aureus following dengue fever as a part of hospital acquired infection[37]. But it was not established that it could be due to dengue virus itself.

On the other hand Acute respiratory distress syndrome is seen in patient of Dengue with multi organ failure. In a retrospective study in Taiwan showed that out of 606 of patient of dengue developed Acute respiratory failure and out of them 8 died. All have co-morbidities, sepsis[38]. But is this ARDS developed due to plasma leakage or as a part of sepsis or due to direct invasion of dengue virus is unclear. In a study in Egypt they reported that among respiratory manifestations pulmonary hemorrhage, ARDS is quite frequent[39].

Renal Manifestations:

Renal manifestations are dengue is seen with minimal importance but it should not be overlooked. There are studies showing that dengue patient may develop AKI with underlying mechanism of hypovolemia, rhabdomyolysis, deposition of immune complex, HUS, direct invasion of virus to kidneys[41-42]. Apart from AKI various form of mild glomerulonephritis were reported[41].

Lymphoreticular Manifestations:

Hemophagocytic lymhphohistiocytosis(HLH) is a rare life alarming condition which is characterized by abnormal immune response[43]. When dengue fever persist beyond 7 days with high ferritin level and spleomegally it should be suspected[44]. Dengue is associated with HLH. A few case is reported in Bangladesh. Among them a case series from Popular medical college was published in 2020 of 3 patients, 2 of them survived with steroid treatment[44]. Among the other causes of HLS, dengue associated HLS has better outcome with corticosteroid[13].

In DHF thrombocytopenia is very common due to plasma leakage. But a rare case of Chronic thrombocytopenia has been described in a case report and also aplastic anemia following dengue has been seen[13, 45].

Thyroid Disorder in EDS:

Subacute thyroiditis is common following any viral infection, post vaccine. Few case were reported about sub acute thyroiditis following dengue. A case was published where a 38-year-old female came with sore throat after dengue[46]. It may open the door of another rare presentation of EDS.

Limitations:

We have reviewed the literature published in English language. So there is a chance that we may miss important article published in other language. Also our focus was finding case reports from Bangladesh and south east Asia perspective may lead to miss some important reports.

Conclusion:

Expanded dengue syndrome is a matter of concern in the endemic area now a days due to high morbidity, increasing hospital stays and mortality. Gastrointestinal, Neurological involvement seems to be the commonest among all the manifestations. Early diagnosis and prompt treatment may save life. So physician treating dengue should remain alert about all these diverse presentation of Dengue.

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