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Expanded Dengue Syndrome – An ambispective observational study from a tertiary care centre in South India

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Abstract

Objectives –1. To analyse clinical and laboratory profile of patients with Expanded Dengue Syndrome.
2.To classify various Expanded Dengue Syndrome based on system involvement.

Materials and methods- This was an ambispective observational study performed in 206 patients who presented with clinical features of Dengue fever and had serological confirmation as per WHO definition criteria. This study was conducted in Department of General Medicine, Amrita Institute of Medical Sciences, Kochi from the year of March 2017 to March 2020.Patients were categorised into Expanded Dengue Syndrome as per The WHO 2012 criteria. History, Clinical examination and relevant investigations were analysed.

Results - Out of 206 patients,84 were detected to have Expanded Dengue Syndrome. A significant male predilection was noted (65.5%). Maximum patients were observed in the age group of 31-60 years. Among 84 patients, majority of the patients had gastro hepatic manifestations followed by renal involvement. Others include cardiovascular, neurological, co- infections and haematological. Among the biochemical alterations Hyperferritnemia was observed in 43.8% patients followed by transminitis in 40.4% of the study group.

Conclusion - Presence of atypical manifestations should raise suspicion to investigate for Expanded Dengue Syndrome. Early identification and treatment decreases the fatal outcomes associated with some of the manifestations in the spectrum of EDS.

Keywords: Dengue fever,EDS,Transminitis

Introduction

Dengue fever is one of the common vector borne diseases in our country. It is caused by dengue viruses (DENV) of four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) and transmitted by Aedes group of mosquitoes while taking a blood meal [1]. It can have broad range of clinical presentations including a mild febrile illness to a life-threatening shock syndrome.

Dengue fever cases have increased in large proportions in the past few years. All over the world, about 40% of people live in countries where dengue is endemic. Annually 390 million infections and 5,00,000 dengue haemorrhagic fever cases have been reported [2]. Dengue cases in India are also on a sharp rise over past few years.

Classic dengue fever has expanded its horizon by involving various organ systems. Dengue Haemorrhagic Fever comprise of acute onset fever with haemorrhagic manifestations and objective evidence of plasma leakage, whereas dengue shock syndrome encompasses DHF with signs of shock including tachycardia, cold extremities, pulse

pressure less than or equal to 20 mm of Hg with increased diastolic pressure and hypotension. The World Health Organization (WHO) put forwarded the term "expanded dengue syndrome" (EDS) to categorize cases which do not fall into either DHF or DSS, with unusual and atypical manifestations in other organs such as the nervous system, gastro hepatic system, cardiovascular system, the kidneys and the haematological system, which have been increasingly identified and called EDS[3]. These manifestations are more common in infants, elderly population, patients with chronic diseases, patients on steroids and other haematological diseases. Recognition of features of expanded dengue syndrome (EDS) is very important for targeting specific system wise treatment options, in addition to the conventional treatment.

EDS is becoming widespread worldwide with unusual features and increasing severity. There are increasing reports of under-recognized and less frequent manifestations with severe organ involvement. This study provides knowledge of expanded dengue syndrome which helps to catch the diagnosis of EDS early, particularly during the ongoing COVID 19 pandemic.

In this study, we analysed clinical and laboratory profile of dengue patients admitted in Amrita Institute of Medical Sciences, a tertiary care teaching hospital in Kerala, India from the year of March 2017 to March 2020. We conducted this case series to further the knowledge of the clinical presentation and natural history of expanded dengue syndrome.

MATERIALS AND METHODS

This is an ambispective descriptive study conducted in tertiary care teaching hospital in Kerala from 2017 March to 2020 March. All serologically confirmed cases of dengue (including Dengue NS1 antigen, IgM antibody and Tropical fever PCR based panel) as per WHO definition criteria during the above mentioned period were taken in to the study and have been appropriately classified. Clinical and laboratory profile were collected from computerized hospital health records and analysed. Cases of Classical dengue fever, dengue haemorrhagic fever, and dengue shock syndrome were excluded from the study cohort. Institutional review approval (ECASM-AIMS-2021-125 Date – 16-03-20121) was obtained.

As part of hospital protocol for all cases of short febrile illness, Complete blood picture, Renal function tests, Liver function tests, viral markers (HIV, HBsAg, HCV), fasting blood sugar, blood for malaria parasite, WIDAL test, Leptospira IgM ELISA, chest radiograph, and ultrasonography of abdomen and pelvis were done. Other necessary investigations including Cardiac enzymes, Echo cardiogram, computed tomography (CT) brain, magnetic resonance imaging (MRI) brain and spine and cerebrospinal fluid (CSF) examination and bone marrow studies, were done based on the clinical picture. Demographic details of the patients, clinical manifestations, haematological and biochemical parameters and outcome were analysed. Standard treatment and supportive care with intravenous fluids, antibiotics, blood and blood component therapy were given as per institutional protocol. Descriptive statistical tests were used and absolute numbers and percentage were calculated for different categorical variables, such as clinical features, haematological and biochemical parameters.

RESULTS

Overall 206 cases of Dengue fever were diagnosed as per WHO 2012 criteria during the last three years (2017 March to 2020 March) and about 84 cases met the criteria for Expanded Dengue Syndrome and were included in the study. Among them,55 patients (65.5%) were male and 29 patients were female (34.5%)with male to female ratio of 1.9. Their average age was 46.2 years. Majority of the patient belong to the age group of 31 to 60 years, indicative of increased prevalence among younger population (Figure 1).

Analysis of clinical manifestations in our cohort revealed that majority of the patients had gastro hepatic manifestations followed by renal involvement. In our case series 39 (46.3%) patients had different gastro hepatic manifestations. Among the asymptomatic, transaminitis (AST, ALT >300) was the most common presentation which was seen in 34 patients (40.4%) followed by Pancreatitis (4.76%) and acalculous cholecystitis (1.2%). Peak level of Aspartate aminotransferase(AST) was observed at Day 4 of illness and Alanine amino transferase(ALT) peaked at Day 6.AST and ALT levels showed gradual decline after peaking. AST was much higher in comparison to ALT and mean

Volume 5, Issue 2; March-April 2022; Page No 444-450

AST level on Day 4 was 984. In ultrasound abdomen, splenomegaly was seen in 11% of patients and hepatomegaly in 5.95% patients (Table 1,Figure 2).

Renal involvement was found in 17 patients (20.2%) which was the second most common presentation. Further evaluation for the cause of AKI revealed prerenal cause in 28% and intrinsic cause in 72% of study group. Three patients out of 17(17.6%) required Renal Replacement Therapy. Others were managed with adequate hydration and Renoprotective measures. One patient developed refractory metabolic acidosis and later developed MODS and succumbed to illness despite being initiated on Renal replacement therapy(RRT). (Table 1,Figure 2).

Other manifestations include serositis in 14 patients (16.7 %). Eight out of eleven patients had pleural effusion, five had ascites and one patient had pericardial tamponade requiring pericardiocentesis with pig tail drainage and stabilization in Coronary Care Unit(CCU).6 patients (7%) had cardiovascular involvement. Transient sinus bradycardia was observed in two patients, two had myocarditis and two had asymptomatic ST T changes. Both patients with myocarditis had elevated cardiac enzymes and ECG changes. One patient with myocarditis had global LV hypokinesia and regional wall motion abnormality in Echocardiography suggestive of stress cardiomyopathy and he was managed with beta blockers.

Seven patients had co-infections (8.3%). Hepatitis A was the most common co-infection which was seen in four out of seven patients. Other coinfections include Malaria, Adeno virus, Enterovirus and Candida.

Neurological manifestations were observed in 3 patients (3.6%). Cerebellitis, encephalitis and Peripheral neuropathy were the neurological manifestations observed in our patients. (Table 1,Figure 2).Patient with cerebellitis presented with fever, headache and ataxia. Altered sensorium and seizures were the presenting complaints in encephalitis patient. Third case presented with positive sensory symptoms like tingling and paraesthesia. Neuro imaging and Lumbar puncture was done in patients with cerebellitis and encephalitis and among them patient with encephalitis had lymphocytic pleocytosis in CSF analysis and MRI brain revealed hyper intensity in bilateral temporal region and diffusion restriction with no contrast enhancement seen in T1 weighted images. In patient with cerebellitis, CSF examination was normal and MRI showed hyper intensities of bilateral cerebellar parenchyma in T2- weighted images These patients were treated with high dose methyl prednisolone 1 gram for three days and continued on maintenance oral steroids. Spontaneous resolution over a period of one week was observed in person presented with peripheral neuropathy.

Two patients satisfied criteria for HLH (2.38%) among the EDS cases. Both patients had bicytopenia, elevated LDH (> 500), Hyperferritinemia (>5000) and Hypertriglyceridemia (>300) and hepatosplenomegaly in imaging studies. Bone marrow study was done and it showed features suggestive of hemophagocytosis. Patients were pulsed with methyl prednisolone for five days and was started on maintenance oral steroids.44% patients had elevated ferritin more than 1000 (Average 1900). Probable HLH was considered in 7 patients as they did not meet the diagnostic criteria for HLH and were categorized as probable HLH.

The most common electrolyte abnormality observed among these patients was hypocalcaemia. This was seen in 14(16 %) patients. Among them three had very low corrected calcium level < 7 and those patients had protracted clinical course and developed secondary sepsis and MODS.

DISCUSSION

WHO established the term "Expanded Dengue Syndrome" in 2012 to describe cases with atypical manifestations and that do not meet the criteria for either dengue shock syndrome or dengue haemorrhagic fever. Atypical presentations of Expanded Dengue Syndrome include multisystem involvement such as central nervous system, liver, heart and kidney[4]. In this ambispective descriptive study, we analysed 206 dengue patients admitted to our hospital in a period of 3 years and identified 84 cases of Expanded dengue syndrome and characterised their clinical presentation. Gastro hepatic followed by renal involvement was the most common manifestations we have observed in our study.

Volume 5, Issue 2; March-April 2022; Page No 444-450

Transaminitis was found in 30% of patients by Lee et al. [5], whereas it was found in 40.4 % of our cases. Many case studies have documented acalculous cholecystitis. Bhatty et al. reported 27.5 percent of cases with acalculous cholecystitis in a study conducted in the year 2009[6]. In our study, we had only one case of acalculous cholecystitis. Acute pancreatitis is a rare presentation [7,8]. We had only few cases of acute pancreatitis(4 patients), which was diagnosed by elevated serum amylase and lipase (More than three times the upper limit of normal) and ultrasound finding characterised by marked inflammation, reduced echogenicity and peripancreatic collection.

Though sinus bradycardia is the most common CVS manifestation, patients may also have myocarditis, pericarditis, acute myocardial infarction, cardiomyopathy, sinoatrial (SA) node dysfunction, atrio-ventricular (AV) nodal block, and even arrhythmias such as atrial fibrillation, according to previous studies. The incidence of Dengue myocarditis is low because most of the times, patient will be asymptomatic and hence diagnosis will be missed. Complete heart block is also documented [9]. 7% of our patients had cardiac manifestations. We encountered two patients with dengue myocarditis, two had sinus bradycardia and two had ST T changes. Pathophysiology of cardiac involvement in Dengue is still a grey zone and the possible mechanism postulated are virus induced direct injury causing inflammation and possible cytokine storm which resulting in loss of both structural and functional integrity.

Neurological manifestations can involve both central and peripheral nervous system [12]. Patient can present with features of meningoencephalitis, cerebrovascular accidents (both haemorrhagic and ischemic), encephalopathy, seizures or neuropathies. Spinal cord involvement is extremely rare. 3 patients (3.6%) in our study cohort had neurological manifestations. We did not have any patient with intracranial bleed. Cerebellitis, encephalitis and peripheral neuropathy were the neurological manifestations observed in our patients. The pathogenesis in nervous system involvement is unclear. Dengue virus is not primarily a neurotropic virus. But in Encephalitis direct neuronal infiltration of the virus can occur [10,11]. Delayed appearance of neurological disorders usually explained by immune mediated neural injury. Patients with encephalitis have high mortality as shown in recent studies which is reflected in to our study too[13].

Acute kidney injury is a lethal complication of this illness .The renal involvement can vary from asymptomatic rise of the serum creatinine level, acute tubular necrosis, AKI, proteinuria, hemolytic uremic syndrome, and glomerulopathy. Renal involvement was found in 17 patients (20.2%) which was the second most common presentation. Previous studies reported that the AKI in expanded dengue syndrome was associated with significant mortality and prolonged hospital stay and sometimes required initiation of RRT [14,15]. Evaluation for the cause of AKI revealed prerenal and intrinsic cause. Three patients out of 17 required Renal Replacement Therapy. Others were managed with adequate hydration and Renoprotective measures. One patient developed refractory metabolic acidosis and later developed MODS and succumbed to illness.

In our study, protracted clinical course was observed in those patients who had significant hypocalcaemia (<7) and those having renal involvement requiring Renal Replacement Therapy.

In prior studies,Co-infections commonly observed include malaria, Chikungunya, and Zika virus infection[16]. Malaria is the most common coinfection with dengue fever as per other studies which was done worldwide.However,Hepatitis A was the most common coinfection which was seen in four out of seven patients. Co-infections do not contribute to the severity and mortality as per our observation. We had only one patient in our series with malaria coinfection and it could be because of low endemicity in Kerala.

Supportive line of management is the main stay of treatment of Expanded Dengue Syndrome. Early and prompt identification of clinical features of EDS is very important for targeting treatment option and optimum care for the patient. Diagnosis is missed most of the times and therefore, a high index of suspicion is needed for early recognition and appropriate management.

CONCLUSIONS

In 206 patients diagnosed in our case series with Expanded Dengue Syndrome, identification of the spectrum of clinical presentation posed a major

Volume 5, Issue 2; March-April 2022; Page No 444-450

challenge. Presence of atypical manifestations should raise suspicion to investigate for Expanded Dengue Syndrome. The intent is to identify the patient at an early phase to decrease the fatal outcomes associated with some of the diseases in the spectrum of EDS. Spreading vast awareness about atypical manifestations among the health practitioners at large is the need of the our to fight the syndrome which mimic myriad of many clinical conditions.

Figure 1 : Distribution based on age and gender

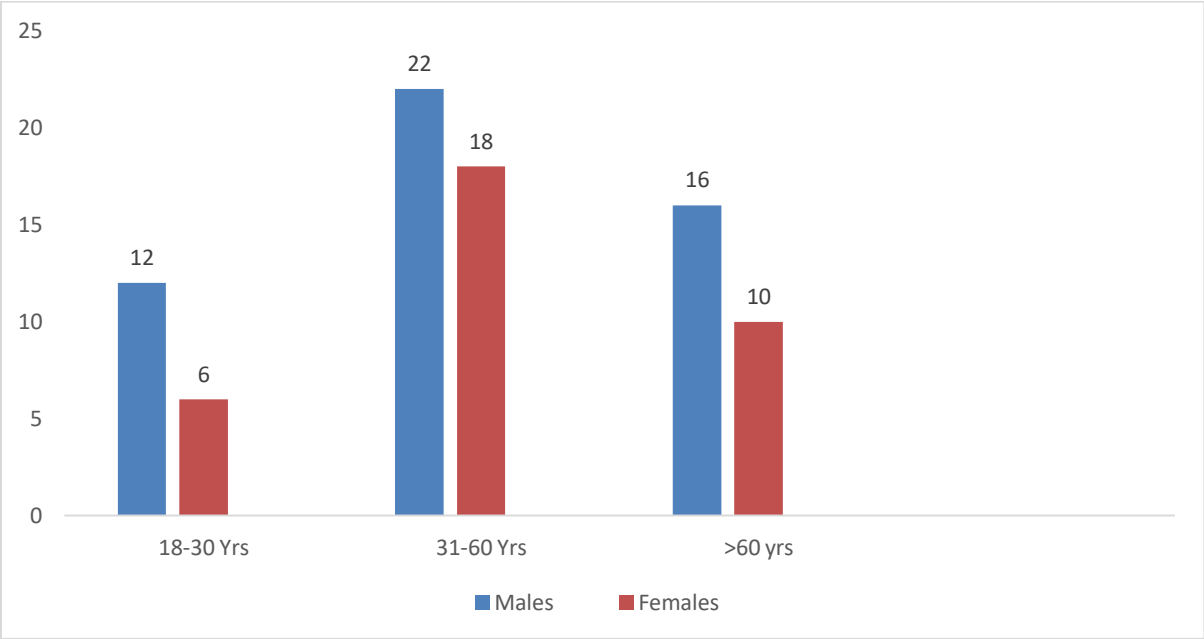
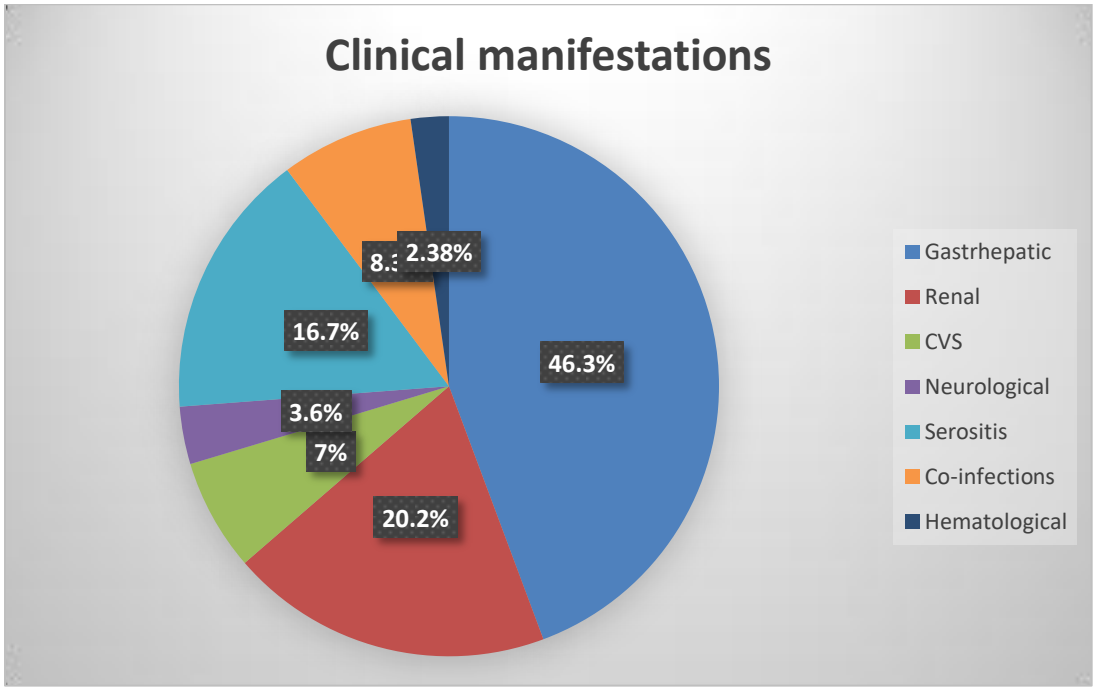


Figure 2 : Clinical manifestations of EDS



Volume 5, Issue 2; March-April 2022; Page No 444-450

Table 1 : Clinical manifestations of EDS

Clinical manifestations	Percentage affected
Gastro hepatic manifestation (46.3%)	
-Transaminitis	- 40.4%(34)
-Acalculous cholecystitis	- 1.2%(1)
-Pancreatitis	- 4.76%(4)
Renal Manifestations(20.2%)	
-Acute Kidney Injury	- 20.2%(17)
Cardiovascular manifestation(7%)	
-Myocarditis	- 4.7%(4)
-Ischemic changes (T inversions and deep q)	- 2.3%(2)
CNS manifestation(3.6%)	
-Encephalitis /Cerebellitis	- 2.4%(2)
-Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	- 1.2%(1)
Serositis(16.7%)	
-Pleural effusion	- 9.5%(8)
-Ascites	- 6%(5)
-Cardiac tamponade	- 1.2%(1)
Coinfection (8.3%)	
-Hepatitis A	- 4.7%(4)
-Others (Malaria,Adeno and ECHO virus)	- 3.6%(3)
Haematological (2.38)	
-HLH	- 2.38%(2)

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Volume 5, Issue 2; March-April 2022; Page No 444-450

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Volume 5, Issue 2; March-April 2022; Page No 444-450