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Gastrointestinal and hepatic manifestations and outcome in dengue multi-organ dysfunction syndrome: data from a tertiary referral center

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ABSTRACT:

Objective: Dengue is a major international public health problem and is endemic in many parts of India. Multiorgan dysfunction is associated with poor outcomes in severe dengue patients. In addition, hepatic and gastrointestinal (GI) involvement are common in dengue. We aimed to study various GI and hepatic manifestations and their outcome in dengue MODS.

Patients and Methods: We performed a cross-sectional observational study on patients in our medicine department. Dengue with multi-organ dysfunction syndrome (MODS) patients based on SOFA score were included. Patients with pre-existing chronic liver disease, chronic kidney disease and coagulation disorders were excluded.

Results: Overall, 69 patients were included in the study. Males were 37 (53.6%). The mean age was 38.7 (±18.73) years. Regarding clinical presentation, anorexia was seen in 58% of patients, abdominal pain and vomiting in 55.1%, gastrointestinal (GI) bleeding in 36.1%, diarrhoea in 21.7%, jaundice in 26.1%, abdominal distension in 5.8% and hepatic encephalopathy in 4.3%. There was no significant correlation between platelet count and GI bleeding and outcome. On LFT examination, abnormal ALT, AST and ALP levels were noted in 68.7%, 88.1%, and 44.8% of patients. Hypoalbuminemia and coagulopathy were seen in 64.2% and 16.4%, respectively. Serum albumin level significantly correlated with outcome. Cholestasis was present in 11 patients, of which nine died. Abdominal ultrasound showed pseudo gallbladder edema in 55.8%, mild ascites in 58.8%, and acalculous cholecystitis in 11.8% of patients.

Conclusions: Anorexia, abdominal pain, vomiting, GI bleeding, and jaundice are common GI and hepatic symptoms. Hypoalbuminemia and cholestasis are predictors of poor outcomes.

Keywords: *Dengue, MODS, Hepatic, Gastrointestinal, Hypoalbuminemia, Cholestasis.*

INTRODUCTION

Dengue fever is a vector-borne viral disease that occurs in tropical countries, particularly in urban and semi-urban areas[1]. Dengue is a major international public health problem[2]. It could be caused by four serotypes of the dengue virus belonging to arboviruses of the genus flaviviruses[3]. The vector for the disease is the *Aedes aegypti* mosquito[3]. Dengue is endemic in many states of India[1]. The disease spectrum may vary from asymptomatic illness to life-threatening diseases like dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)[1].

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Mortality in severe dengue infections is attributed to the development of the multiple organ dysfunction syndrome (MODS). Organ impairment may manifest as hepatic or renal impairment, respiratory failure, myocarditis, encephalopathy, or encephalitis[4-6]. Gastrointestinal (GI) and hepatic manifestations are common in dengue patients. They include hepatic dysfunction, fulminant hepatic failure, shock liver, diffuse peritonitis, acute pancreatitis, ascites, acute inflammatory colitis, splenic rupture, appendicitis, acalculous cholecystitis, and bilateral parotitis[7,8]. Symptoms and signs include nausea, vomiting, jaundice, GI bleeding, abdominal pain, ascites, encephalopathy, hepatomegaly, and splenomegaly.

We aim to study the GI and hepatic manifestations in patients with dengue and MODS in the form of symptoms and signs, laboratory changes, radiological parameters, and outcomes.

PATIENTS AND METHODS

We conducted a cross-sectional observational study including patients evaluated in the Department of Medicine at Sassoon General Hospital between June 2016 and November 2017. All the hospitalized patients in medicine wards and Intensive Care Unit (ICU) who were diagnosed with dengue fever as per WHO criteria[9] with two or more organ systems, i.e., multiorgan involvement defined as per Sequential Organ Failure Assessment (SOFA) score[10], were included. Patients or and those whose relatives refused to give consent for the study and those with pre-existing chronic liver diseases, chronic kidney diseases, chronic heart failure, cerebrovascular accidents, bleeding, and coagulation disorders were excluded based on the clinical history and imaging wherever required. Detailed clinical history was taken, and a physical examination was performed on all patients. Blood investigations, including dengue serology (dengue NS1, IgM), serial hemograms, renal function tests (RFT), liver function tests (LFT), and prothrombin time (PT) were performed. Ultrasound abdomen was performed in indicated patients. Malaria, Leptospira, typhoid, and infections caused by hepatotropic viruses were excluded by doing relevant investigations.

Statistical Analysis

Data were analyzed by statistical software SPSS (Statistical Package for Social Sciences) version 23.0 (IBM Corp., Armonk, NY, USA) and reported as mean with standard deviation for continuous variables and as frequencies and percentages for categorical variables. For continuous variables, a *t*-test was used for normally distributed variables and a Mann-Whitney U test for in-homogenously distributed variables. Categorical variables were compared using the Chi-square test. *p*-value lower than or equal to 0.05 was considered to be statistically significant.

RESULTS

Demography

Overall, 610 serologically confirmed dengue patients were admitted to our hospital during this period, out of which 78 patients (12.8 %) had multiorgan involvement. Of these, 9 patients were excluded, as 4 had pre-existing liver cirrhosis, 3 had chronic kidney disease, and 2 had a past history of cerebrovascular stroke. A total of 69 patients were included. Males were 37 (53.6%), and females were 32 (46.4%). The age varied from 13 to 80 years. The mean age was 38.7 (±18.73) years (Figure 1).

Clinical Manifestations

Fever was the most common symptom, present in 68 (98.6%) patients in our study. Anorexia and abdominal pain and vomiting were the most common GI symptoms

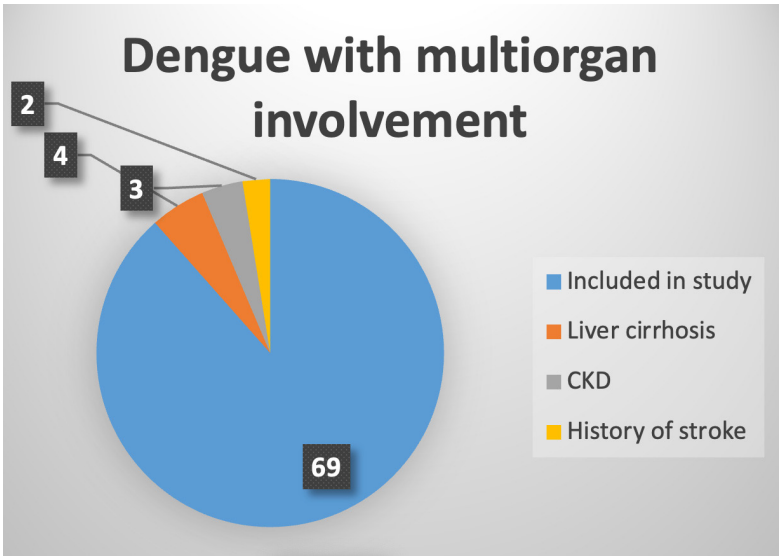

Figure 1. Dengue with multiorgan involvement graph.

in 40 (58%) and 38 (55.1%) patients, respectively. GI bleeding was seen in 25 (36.2%) and diarrhoea in 15 (21.7%) patients. The most common form of GI bleeding was melena, seen in 22 (31.9%) patients, followed by hematemesis in 8 (11.6%) and per rectal bleeding in three (4.3%). Various causes of abdominal pain were acute pancreatitis seen in 2 patients, acalculous cholecystitis in 4, diffuse peritonitis in 1, acute inflammatory colitis in 3, acute hepatitis in 9, and nonspecific in the resting 19 patients. Among hepatic symptoms, jaundice was noted in 18 (26.1%), abdominal distention in 4 (5.8%), and hepatic encephalopathy in 3 (4.3%) patients. Acute liver injury and acute liver failure (ALF) were seen in three patients each.

On physical examination, icterus was present in 18 (26.1%) patients. Abdominal tenderness was observed in 38 (55.1%) patients, with the right hypochondrium as the most common site, followed by epigastrium. Hepatomegaly was present in 18 (26.1%), splenomegaly in 7 (10.1%) and ascites in 4 (5.8%) patients. Table 1 summarizes the clinical findings in dengue MODS.

Liver Function Tests (LFT)

LFT examination was performed in 67 patients in our study. The total number of patients with bilirubin < 2 mg/dl was 46 (68.7%), 10 patients were (14.9%) in the range of 2-5, and 11 patients (16.4%) showed bilirubin > 5 mg/dl. Abnormal aspartate transaminase (AST) (>38 IU/L) and alanine transaminase (ALT) (>41 IU/L) were present in 59 (88.1%) and 46 (68.7%) patients, respectively. ALT >100 IU/L was present in 25 (37.3%) and AST >100 IU/L in 43 (64.2%) patients. ALT and AST, more than five times of upper limit, were seen in 12 (17.9%) and 20 (29.9%) patients, respectively. AST was higher than ALT (i.e., AST/ALT >1) in 85.1% of patients. Alkaline Phosphatase (ALP) was raised (>140 IU/L) in 30 (44.8%) patients. Low serum albumin (<3.5 g/dl) was present in 43 patients (64.2%), and elevated prothrombin time (>15.4 seconds) in 11 (16.4%) patients.

Radiological Imaging

In our study, an ultrasound abdomen was performed on 34 patients. Pseudo Gall bladder edema was present in 19 patients (55.9%), acalculous cholecystitis in 4 (11.8%), hepatomegaly in 6 (17.7%), and splenomegaly in 4 (11.8%) patients. Ascite was present in 20 (58.8%), which was mild in most cases, and pleural effusion (mostly right-sided) in 14 (41.2%) patients. Table 2 describes the GI imaging findings in dengue with MODS.

Outcomes

Platelet count (per microliter) lower than 20,000 was present in 2 (8%) cases, in the range 20,000-50,000 in 17 (68%), in the range 50,000-100,000 in 2 (8%) and >100,000 in 4 (16%) cases with GI bleed. There was no significant correlation between platelet counts and GI bleeding. Overall mortality in our study was 43.5% in this study. Out of 22 patients with Malena, nine (40.9%) patients died; out of 8 patients with hematemesis, 5 (62.5%) died, and out of 3 patients with per rectal bleed, 2 (66.7%) died. There was no significant correlation between GI bleeding and the outcome. Abdominal pain and vomiting were significantly more commonly seen in patients who survived.

In our study, abnormal bilirubin was present in 21 patients, out of which 12 (57.1%) patients died. A total

Table 1. GI and hepatic symptoms and signs in dengue MODS.

Symptoms and Signs	Number of patients N = 69 (%)	Survived N=39 (%)	Dead N=30 (%)	*p*-value
Anorexia	40 (60%)	22 (56.4%)	18 (60%)	NS
Diarrhoea	15 (21.7%)	8 (20.5%)	7 (23.3%)	NS
Abdominal pain and vomiting	38 (55.1%)	27 (69.2%)	11 (36.7%)	<0.05
Gastrointestinal bleeding	25 (36.2%)	14 (35.9%)	11 (36.7%)	NS
Hematemesis	8 (11.6%)	3 (8.7%)	5 (16.7%)	NS
Melena	22 (31.9%)	13 (33.3%)	9 (30%)	NS
Rectal bleeding	3 (4.3%)	1 (2.6%)	2 (6.7%)	NS
Jaundice	18 (26.1%)	9 (23.1%)	9 (30%)	NS
Hepatic encephalopathy	3 (4.3%)	1 (2.6%)	2 (6.7%)	NS
Abdominal distension	4 (5.8%)	2 (5.1%)	2 (6.7%)	NS
Icterus	18 (26.1%)	9 (23.1%)	9 (30%)	NS
Abdominal tenderness	38 (55.1%)	27 (69.2%)	11 (36.7%)	NS
Hepatomegaly	18 (26.1%)	10 (25.6%)	8 (26.7%)	NS
Splenomegaly	7 (10.1%)	3 (8.7%)	4 (13.3%)	NS
Ascites	4 (5.8%)	2 (6.7%)	2 (6.7%)	NS

NS= Not significant.

Table 2. Abdominal ultrasound findings in dengue MODS.

Ultra-sonographic finding	Our study	Santhosh et al[25]
Pseudo Gall Bladder oedema	55.9%	66.7%
Hepatomegaly	17.7%	17.7%
Splenomegaly	11.8%	16.7%
Ascites	58.8%	64.5%

of 25 (42.4%) with raised AST and 21 (45.7%) with increased ALT, and 14 (46.7%) patients with raised ALP died. There was no significant correlation between raised total bilirubin, AST, ALT, and ALP with the outcome. Regarding hypoalbuminemia, 23 (53.48%) out of 43 patients died; on the contrary, only 4 (16.7%) out of 24 patients with normal serum albumin died (p=0.008). Cholestasis was present in 11 patients, of whom 9 died (p=0.01). Two ALF patients out of 3 died.

DISCUSSION

In our study, the male and female ratio was 1.16:1. Male predominance was due to the greater vulnerability of males to mosquito bites due to outdoor work involved in the occupation, recreational activities, and clothing habits[11]. Although older patients are more vulnerable to developing MODS due to comorbidities and more cytokine storm in them leading to systemic inflammatory response syndrome (SIRS)[12,13], our study was more focused on the younger population.

Gastrointestinal Manifestations of Dengue MODS

Anorexia, abdominal pain and vomiting were the most common GI symptoms, followed by GI bleeding and diarrhoea. Abdominal pain was present in 55.1% of patients. Ooi et al[14] and Prashanth et al[15] reported abdominal pain in 47.8% and 33% of patients, respectively. Abdominal pain was mild in the majority of patients. In our study, various causes of abdominal pain were acute pancreatitis, acalculous cholecystitis, diffuse peritonitis, acute inflammatory colitis, acute hepatitis and nonspecific. Cholestasis with gall bladder distension and cystic duct spasm possibly cause acalculous cholecystitis[16]. Diarrhoea was present in 21.7% of patients compared to 35.6% in Ooi et al[14] and 13% in Prashanth et al[15] studies. The mechanisms of diarrhoea include direct or indirect damage to the intestinal epithelium by an inflammatory response, antibiotic-induced intestinal dysbiosis, and virus-induced intestinal flora disorders. GI bleeding was present in 36.2% of patients. Tiwary et al[16] reported GI bleeding in 14.3% of patients. Melena was the most common form of GI bleed. This high incidence of bleeding was due to MODS, which formed our study population. The underlying mechanism for bleeding manifestations is capillary leakage, thrombocytopenia, and platelet dysfunction. GI bleed can occur at any platelet count and is seen in patients with normal or slightly low platelet count.

Hepatic Manifestations of Dengue MODS

The liver is the most common organ involved in the severe form of dengue. Manifestations can vary from an asymptomatic elevation of transaminases to the occurrence of acute liver failure[17]. Hepatic manifestations result from either direct viral toxicity or dysregulated immunologic injury in response to the virus. Hepatocytes and Kupffer cells are prime targets. The E protein has a role in the attachment of the virus[18], and heparan sulfate plays an important role in the virus' intrusion into liver (HepG2) cells. An eventual outcome of hepatocyte infection is cellular apoptosis, and various pathways include viral cytopathy, hypoxic mitochondrial dysfunction, immune response, and accelerated endoplasmic reticular stress[19].

Recurrent infections lead to the enhancement of immune reactions believed to be responsible for severe dengue disease. Dengue infection induces a cytokine storm, and in the initial three days, concentrations of cytokine-like IL-2, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ reach peak levels. In addition, IL-4, IL-5, and IL-10 contribute to later in the course of the disease[20]. In our study, jaundice as presenting complaint was present in 13% of patients. Prashanth et al[15] reported jaundice in 18% of patients. Hepatic encephalopathy occurred in 4.3% of cases secondary to acute liver failure and is associated with high mortality. Cholestasis was seen in 11 patients and was significantly associated with increased mortality. Cholestasis in dengue can be caused due to inflammation by the dengue virus, leading to bile duct obstruction and/or sepsis-related. Clinically significant ascites were seen in 5.8%, and on investigation, it was low protein ascites. Probable causes of ascites are capillary leak leading to third space loss and hypoalbuminemia.

Our study observed abnormal ALT and AST in 68.6% and 88.1% of patients, respectively. Kuo et al[21] reported abnormal ALT and AST in 80% and 90% of patients, respectively. Total bilirubin >2 mg/dl was present in 31.3% of patients, ALT >100 IU/L in 37.3%, and AST >100 IU/L in 64.2% of patients, respectively. A study by Tiwary et al[16] showed that 22.8% of patients had bilirubin >2 mg/dl, 45.7% had ALT >100 IU/L and 68.6% had AST >100 IU/L. ALT and AST more than five times

the upper limit were seen in 7.9% and 29.9% of patients, respectively. AST was more than ALT in 85.1% of patients, and a similar finding was observed in the study conducted by Shukla et al[22].

AST has various sources, including heart, striated muscle, erythrocytes and liver, whilst ALT has primarily hepatic origin[23]. Dengue virus causes acute insult to non-hepatic tissues, resulting in higher AST levels than ALT. Abnormal ALP was found in 45.45% compared to 15.1% found in Saha et al[24].

Hypoalbuminemia was seen in 65.15% of patients and attributed to impaired albumin production by damaged hepatocytes due to dengue virus and septicaemia. Hypoalbuminemia was seen in 76% of patients in Itha et al[8] and in 12.9% of patients in Saha et al[24]. There was no significant correlation between bilirubin, ALT, AST, ALP, and coagulopathy with mortality in our study. However, hypoalbuminemia was significantly associated with high mortality and a marker of poor survival. Mortality was high in our study due to MODS and patients presenting late in the course of the disease to our tertiary referral center.

On abdominal ultrasound, pseudo gall bladder oedema and mild ascites were the most common findings, followed by hepatomegaly, splenomegaly, and acalculous cholecystitis. Santhosh et al[25] reported similar results.

Limitations

Our study had several limitations. First, patients were referred late in the course of the disease and in a severe form to our tertiary care center, leading to poor outcomes in them. Second, chronic liver disease was ruled out based on clinical history, examination, and ultrasound, and not by elastography or liver biopsy. Third, endoscopies were not performed in most patients with GI bleeding. Fourth, other causes of viral hepatitis, including Hepatitis B and C, were not included in all the cases.

CONCLUSIONS

Dengue MODS has varied GI and hepatic manifestations, the most common being anorexia, abdominal pain, vomiting, GI bleeding, diarrhoea, and jaundice. GI bleed can occur even in patients with slightly low or normal platelet count. Acute liver failure in dengue has high mortality due to hepatic encephalopathy. Cholestasis and hypoalbuminemia are predictors of poor outcomes.

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Authors' Contribution:
Sonali Salvi conceptualized and designed this study and also made critical revisions related to the relevant intellectual content of the manuscript. Arun Vaidya designed this study, did the acquisition and interpretation of data and drafted the data. Both authors did supervision, validation, and final approval of the version of the article to be published.

Conflict of Interest:
The authors declare that they have no conflict of interest to declare.

Ethics Approval:
This study was approved by the Ethics Committee of BJ Government Medical College and Sassoon General Hospital, Pune. The ethics approval number was D-0116008-8.

Informed Consent:
All authors declare that written informed consent was obtained from all the patients for this study.

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