# A STUDY OF TYPICAL AND ATYPICAL CLINICAL MANIFESTATIONS IN DENGUE PATIENTS

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### ABSTRACT

Dengue viral infections are among the most important mosquito-borne diseases of the Indian subcontinent and have become a major global public health concern. Spread of disease has led to increased recognition of atypical manifestations apart from the classical clinical features of dengue infection. A cross-sectional study of admitted patients suspected to have dengue infection was conducted during the monsoon and postmonsoon seasons in the year 2016. Patients who had serological confirmation of dengue infection were classified according to World Health Organization definitions of dengue fever and dengue Received on : 13-09-2019 Accepted on : 04-10-2019

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hemorrhagic fever. They were observed for typical and atypical manifestations of the disease. Out of 162 confirmed cases of dengue,42 patients had atypical manifestations in the form of hepatic, renal, Gastrointestinal ,cardiac and cutaneous involvement. Haemorrhagic manifestations in the form of epistaxis, malena, gum bleed, hemoptysis, hematemasis, petechial rashes ,hematuria and conjunctival bleed were present in 54% patients. Mortality was 3% due to multi organ dysfunction. Dengue infection poses a huge burden to the health-care system; its spectrum ranges from mild self-limiting illness to severe fatal disease. It can have varied and multi-systemic manifestations which can go unrecognized. Clinicians should have a high index of suspicion for atypical manifestations.

KEYWORDS: Dengue infection, Dengue hemorrhagic fever, Atypical manifestations of dengue fever, AKI in dengue.

# INTRODUCTION

Dengue is fast emerging viral disease in many parts of the world. It is a preventable community health problem with high morbidity and mortality. Vector of disease is aedes aegypti and the causative virus belongs to genus Flavivirus that has four serotypes namely DEN-1, DEN-2, DEN-3 and DEN-4.Reasons for disease proliferation include growing population, rapid urbanization and lack of appropriate sanitary measures. It is estimated that 30-fold increase in incidence has taken place in last five decades (1). Spectrum of disease varies from uncomplicated dengue fever to dengue haemorrhagic fever. Mortality in untreated cases is as high as 20% against 1% in treated cases (2). Adolescents and adults may have either a mild febrile syndrome or the classic incapacitating disease with high fever of acute onset, sometimes with 2 peaks (saddle-backed), severe headache, retro orbital pain, myalgias and bone or joint pains, nausea and vomiting, and rash. Skin haemorrhages (petechiae) are not uncommon. Dengue hemorrhagic fever (DHF) is often a fatal disease and is usually associated with the secondary dengue Infection but can appear during a primary infection, especially in infants who get IgG

dengue antibody from mothers. Clinical diagnosis of dengue haemorrhagic fever is made on the basis of following four criteria (1)Continuous high grade fever lasting 2-7 days (2) Hemorrhagic tendency or positive tourniquet test (3). Thrombocytopenia; platelets < 100,000/microL (4) Evidence of plasma leakage as manifested by hemoconcentration (an increases in hematocrit above 20% above average for age, sex and population), presence of ascitis, pleural effusion (3). Dengue Shock syndrome (DSS) is usually characterized by all of the above four criteria for DHF, plus evidence of circulatory failure manifested by:

- Rapid and weak pulse,
- Narrow pulse pressure (<20 mmHg)

or

- Hypotension for age, and
- Cold, clammy skin and restlessness (3).

World health organization has stated in its position statement of 2019 that, in 2015 Delhi recorded its worst outbreak since 2006 with over 15,000 cases. The year 2016 was characterized by large dengue outbreaks worldwide.



Fig 1: WHO Classification of Dengue Virus Infection

Methodology: Typical and atypical clinical manifestations of dengue

We conducted a cross sectional study at Era's Lucknow Medical college & Hospital during the dengue outbreak occurring in the months of august to november in 2016. All adult patients with acute febrile illness, admitted with symptoms like body ache, arthralgia, headache, retro orbital pain, pain abdomen, nausea and vomiting, bleeding from any site, hypotension or thrombocytopenia were tested for dengue. The study enrolled 356 patients of suspected dengue of whom 162 were confirmed by serum IgM antibodies and/ or NS1 antigen detection. History and clinical examination (including the tourniquet test) were performed. Haematological and biochemical investigations were done at the time of admission and were followed by daily investigations as required until discharge. Signs of plasma leakage were assessed by chest radiograph and abdominal ultrasonography. Specific investigations were performed in patients who presented with neurological involvement, hepatic dysfunction ,cardiac (ECG) pancreatic or dermatologic involvement. Patients were classified as having dengue fever, dengue haemorrhagic fever or dengue shock syndrome in accordance with WHO guidelines.

Approval from institutional ethics committee was taken and an informed consent was obtained from all patients.

# **OBSERVATIONS**

Out of 162 confirmed cases of dengue, 102 were males and 60 were females.54 patients belonged to age group of 18-25 years, 76 to age group of 26-50 years and 32 were more than 50 years of age. Average duration of hospitalization was 5.25 days.117(72%) patients were adjudged to be classical dengue fever whereas 43(27%) belonged to dengue haemorrhagic fever. Mortality rate in our study was 3%(5 patients) and all fatalities were due to multiorgan failure probably due to DSS..

Among the common presenting symptoms, headache and fever was present in all patients, retroorbital pain in 75% patients, nausea and vomiting in 52 % and body ache, itching and rashes were recorded in 90%, 40% and 88% respectively. 57% patients presented as acute gastroenteritis. Hepatomegaly was observed in 70% and transaminitis (elevated SGOT/SGPT) was seen in all the patients (100%). Third space fluid collections in the form of ascites was evident in 59% cases whereas pleural effusion was seen in 61%.Gall bladder wall edema was demonstrated in 78% patients. Haemorrhagic features in the form of epistaxis, malena, gum bleed, hemoptysis, hematemasis, petechial rashes, hematuria and conjunctival bleed were present in 54% patients. These manifestations did not have correlation with platelet counts (fig1).





Apart from these typical signs and symptoms of the disease, 42 patients had atypical clinical presentations or manifestations during their disease course (Table 1, Fig 3).

	Number of patients(n)
Gastrointestinal	
Acute Pancreatitis	4
Esophagitis	1
Subacute intestinal obstruction	3
Hepatobiliary	
Liver Abscess	2
Respiratory	
ARDS	2
Nervous system	
Encephalitis	1
Polyneuropathy with Myelitis	1
Dementia	1
Cardiovascular	
Bradycardia	3
Renal	
Acute Kidney injury	22
Cutaneous	
Cellulitis	1
Leukocytoclastic vasculitis	1
Total	42

Table 1: Atypical Clinical Manifestations of Dengue



### Fig 3: Percentage of Atypical Manifestations (System Wise)

Endoscopically proven esophagitis was seen in 1 patient, 4 patients presented as acute pancreatitis whereas 3 patients as subacute intestinal obstruction. Two patients came with acute pain in right upper quadrant which was found to be liver abscesses. Among the respiratory involvement, two developed adult respiratory distress syndrome. Neurological involvement in the form of encephalitis, polyneuropathy with myelitis and acute onset memory loss were observed in 3 different patients. Cardiovascular complications were seen in the form of symptomatic bradycardia and conduction disturbances in 3 patients. Acute kidney injury was observed in 22 patients. Atypical cutaneous manifestations were seen as cellulitis and leukocytoclastic vasculitis in 2 separate patients.

### DISCUSSION

Dengue assumes importance because of associated morbidity and mortality in DHF cases. Typical symptoms of the disease help in early recognition and management but in recent years various studies have highlighted atypical manifestations of the disease which might have an association as well as causative implication with dengue. In our study among the typical manifestations, headache and fever was present in all 100% patients and retroorbital pain in 75% patients. A laul et al. in their study found that 87% of patients had headache as chief complaint and 41% had typical retro-orbital pain (4).

Abdominal symptoms are important in dengue fever. In present study, 57% patients presented as acute gastroenteritis and nausea and vomiting were documented in 52 %. They were seen in 70% of patients in study by Nimgadda et al (5).

Dengue can cause hepatic injury and elevation of transaminases. Hepatomegaly was observed in 70% and transaminitis was seen in all the patients in our study. In study by A Laul et al.; 57% of patients had elevated ALT and 49% had raised AST (6). Hepatitis presents as right hypochondriac pain, hepatomegaly and raised aminotransferases with liver enzymes peaking after first week of illness and normalizing in three weeks. Haemorrhage, shock, metabolic acidosis and disseminated intravascular coagulation may contribute to severe changes in liver. In patients of chronic liver disease, alcoholic hepatitis and hepatotoxic drug use (e.g. salicyclates, acetaminophen etc.) during dengue infection may predispose to liver injury. The increase in increased aminotransferases has been associated with increased disease severity and might serve as an early indicator of dengue infection (7).

In present study, Gall bladder wall edema was demonstrated in 78% without stones on ultrasonography. In study by A Laul, 57% of patients presented with pain abdomen along with fever and 22% had acalculous cholecystitis with right upper quadrant abdominal pain, abnormal liver function tests, positive Murphy's sign, and thickened gall bladder wall (4). The exact mechanism of acalculous cholecystitis in dengue is not known. It could be due to invasion by dengue virus into the gall bladder wall causing microangiopathic injury and increased vascular permeability. This could be the cause of thickening of gall bladder wall (7). The course of disease is usually self-limiting but, in a few patients, acalculous cholecystitis progresses rapidly to ischemic gangrene and perforation. Cholecystectomy is reserved for such patients who progress to peritonitis. Third space fluid collections in the form of ascites was evident in 59% cases whereas pleural effusion was seen in 61%. In Bangladesh based study by Mia et al. 42% had pleural effusion and 41% of patients developed ascites (8).

Hemorrhagic manifestations are common complications of dengue fever due to decreased platelet count and leakage from blood vessels. Thrombocytopenia may be because of spontaneous aggregation of platelets to virus-infected endothelium, bone marrow suppression, or immune mediated clearance (4). In our study we found that 54% of patients had hemorrhagic manifestations in the form of epistaxis, malena, gum bleed, hemoptysis, hematemasis, petechial rashes, hematuria, menorhhagia and conjunctival bleed. These manifestations did not correlate with platelet counts. Hemorrhagic manifestations were present in 40% of patients in study by Karoli et al. (6).

Early warning signs of dengue like pain in abdomen, persistent vomiting, hepatomegaly, increase in hematocrit and evidence of fluid leak should be observed carefully for timely intervention to prevent shock and severe complications.

Dengue infection has been associated with a variety of renal disorders. Acute renal failure, proteinuria, hematuria, and glomerulonephritis have been reported during or shortly after acute dengue infection. Acute renal failure (ARF) is a potential complication of severe dengue and is mostly associated with hypotension, rhabdomyolysis, or hemolysis (9). Acute kidney injury was observed in 22 patients (13.5 %).Based on the Acute Kidney Injury Network (AKIN) criteria, the results revealed that: fifteen (9%) had mild AKI; five (3%) had moderate AKI; and two (1%) had severe AKI. In a study by Nikita Mehra et al. at a tertiary care centre in southern India 223 patients were retrospectively analysed and acute renal failure (ARF) developed in 24 (10.8%) patients of dengue (10).

Endoscopically proven esophagitis was seen in 1 patient, 4 patients presented as acute pancreatitis. Acute pancreatitis is a rare complication of dengue fever due to possible direct viral cytopathic effect or an autoimmune response by molecular mimicry causing pancreatic outflow obstruction due to edema though exact mechanism is unknown (11). Three patients presented as subacute intestinal obstruction and 2 patients came with acute pain in right upper quadrant which was attributed to liver abscess.

Among the respiratory involvement, two patients developed adult respiratory distress syndrome. Acute lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) are one of the dreaded complications of dengue hemorrhagic fever, secondary to increased alveolar-capillary membrane permeability leading to interstitial and alveolar edema. Adequate tissue perfusion is necessary to prevent progression of dengue shock syndrome to ARDS. However, equally important is to avoid excessive fluid infusion because fluid overload may result in ARDS. Pulmonary haemorrhage is another fatal complication to be suspected in these patients (7).

Neurological involvement in the form of encephalitis, polyneuropathy with myelitis and acute onset memory loss were observed in three different patients. Neurological manifestations like seizures, encephalopathy, encephalitis/aseptic meningitis, intracranial haemorrhages and neuropathies have been reported in the past (12).

These manifestations are secondary to direct tissue invasion of virus, cytokine mediated damage to the blood brain barrier, capillary hemorrhage, DIC, cerebral edema and metabolic derangements like hyponatremia, hypoxia, hepatic encephalopathy and uremic encephalopathy. Although rare, there has been isolated case reports of mononeuropaties, polyneuropaties, Gulliane Barre' syndrome, acute disseminated encephalomyelitis and transverse myelitis (7).

Cardiovascular complications were seen in the form of symptomatic bradycardia and conduction disturbances in three patients. Clinical manifestations of cardiac involvement can vary widely, from silent disease to severe myocarditis resulting in death. Rhythm abnormalities, hypotension, arrhythmias, myocarditis, myocardial depression with symptoms of heart failure and shock, and pericarditis have been reported. Involvement of multiple organs as well as the presence of metabolic derangement can further confuse the picture (13).

Atypical cutaneous manifestations were seen as cellulitis and leukocytoclastic vasculitis in 2 patients. Patients with leukocytoclastic vasculitis have purpuric, palpable lesions, commonly on lowere limbs. Characteristic pathological features include necrosis of small vessels within the dermis, infiltration by polymorphonuclear leukocytes within and around the vessel walls, hemorrhage, and occasionally thrombosis. The mechanism causing tissue damage is hypothesized to be mediated by immune complexes.

#### CONCLUSION

Dengue infection causes significant morbidity and mortality especially in South East Asian regions like India. Timely diagnosis and initiation of medical care is mandatory to prevent risks associated with the disease. Apart from the typical clinical features like fever, headache, retro orbital pain, bodyache etc., certain atypical manifestations of dengue fever are being brought to light .Dengue may have unusual presentations and associations with other disease entities. A high index of suspicion is needed for diagnosis in case of atypical manifestations as this can complicate the clinical course and prove fatal in some cases.

Competing Interests: The authors declare that there is no conflict of interests.

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